'BRAIN ATTACK'

A new approach to stroke and transient ischaemic attack

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Abstract

This thesis proposes that patients with features of focal neurological dysfunction, of abrupt onset, should be considered as suffering a *brain attack*. Brain attack is a neurological emergency, requiring a prompt and accurate diagnosis before treatment can be commenced. The hypothesis underlying this work was that key reliable and useful parts of the bedside clinical assessment, and currently available brain imaging techniques, could be identified to improve the assessment of patients with suspected acute stroke.

The thesis is divided into three sections. **Section I** reviews the history of stroke and its terminology. A review of the pathophysiology of the ischaemic penumbra demonstrates that 'time is brain' and supports a more urgent approach to stroke. The term brain attack is introduced, its history and applications are traced, and a definition is proposed. A systematic review of previous work examines the accuracy of the clinical diagnosis of stroke and the nature of stroke mimics. The clinical features of stroke in the first few hours are explored using data from the International Stroke Trial. The current contribution and potential of brain imaging – computed tomography (CT), structural and advanced magnetic resonance imaging (MRI) – in the assessment and management of brain attack is reviewed, with particular emphasis on identifying where new information is needed.

Section II explores the clinical features of brain attack. A prospective study of 350 hospital presentations with brain attack is described to determine: 1) the conditions that cause brain attack; 2) if the clinician could distinguish between stroke and mimic; 3) the accuracy of the clinical diagnosis of the cause of brain attack; 4) the reasons for disagreement between the clinical diagnosis and the final diagnosis, and 5) whether the clinical features of patients presenting within the first six hours differed from those presenting later. Univariate analyses identified several key items of history and examination

that differentiated between stroke and mimic. An interrater study, involving 98 patients and four clinicians, was performed to determine the items of history and physical examination that were reliable even when the observer had limited neurological training. A series of diagnostic models (of varying simplicity) are developed using multivariable logistic regression analysis, with strict attention to methodological details. The potential use of the models to differentiate between stroke and mimic at the bedside is discussed.

Section III explores the influence of the CT scan on the diagnosis of brain attack for the 350 patients in the cohort. Routine imaging was frequently normal – particularly in patients where the clinical diagnosis was uncertain – and its sensitivity in the first few hours was highly dependent on the skills of the radiologist. MR may provide more information. The feasibility of scanning acute stroke patients with MR was tested prospectively in 138 MR-eligible patient presentations. The reasons for not scanning patients, and the difficulties and possible risks encountered during scanning are described. The information from MR was explored in 96 patients who underwent diffusion-weighted (DWI) and perfusion imaging (PI), with outcome assessment at three months. The importance of DWI lesion volume and the presence of a DWI-PI 'mismatch' are considered. The current clinical utility of MR, in comparison with CT, is discussed in detail.

Results from this original research should help guide clinicians with an evidence-based, streamlined approach to the emergency assessment of patients with brain attack.

Note: The scans reproduced in this thesis have had identifiers removed (including the left and right markers). All scans are presented with the patient's right on the left of the page.

Declaration

I hereby declare that:

- I composed this thesis
- I made a substantial contribution to the work: I performed the literature reviews and analysis of the data from the International Stroke Trial. I devised, co-ordinated and analysed the brain attack study. I recruited and examined 181/350 patients. I supervised the inter-rater study, saw 53/98 patients, and performed my own analyses of the data. I developed the multivariable predictive models (with support from Dr S.Lewis). I devised, co-ordinated and analysed the imaging studies. I recruited and examined all 96 patients. For the imaging studies, Professor J. Wardlaw examined and coded lesions seen on imaging, and supervised the scientists (Dr M. Bastin, Dr P. Armitage and Ms C. Rivers) who analysed the DWI and PI images. Dr A. Rowat assisted with patient assessment and follow-up.
- All of the work contributing to this thesis was undertaken whilst I was in post in South East Scotland.
- This thesis has not been submitted in candidature for any other degree, postgraduate diploma or professional qualification.

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I received tremendous support from many members of the Department of Clinical Neurosciences. Dr Steff Lewis provided sensible statistical advice. Mrs Sheila Grant entered most of the data in the Brain Attack study. Mrs Vera Soosay designed my database. Mr Paul Chmielnik scanned in all the CT and most of the MR films reproduced in this thesis. Dr Paul Armitage provided the MR perfusion scans. The radiographers at the SHEFC Brain Imaging Research Centre – Mrs Annette Blane, Mrs Evelyn Cowie, and Ms Lorna Cunningham – were most helpful in scanning patients, often under stressful conditions.

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Special thanks are due to my supervisors, Professor Joanna Wardlaw and Dr Richard Lindley, who were a constant source of motivation, inspiration and also managed to keep my sanity intact. Finally, I thank my Australian mentors, Dr Bernard Gilligan, who encouraged me to consider a career in neurology, and Professor Elsdon Storey, who suggested I specialise further in stroke and undertake research.

Dedication: **This thesis is dedicated to my wife Jenny and son Mitchell for their patience, love and support.**

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SECTION I

BRAIN ATTACK – A TERM FOR THE 21ST CENTURY

Chapter 1 : The history of stroke terminology

1.1 Introduction

> "Stroke – a sudden attack of weakness, numbness or hemiplegia caused by cerebral haemorrhage or ischaemia. Also called apoplexy" *New Shorter Oxford English Dictionary, 1993*

The word 'stroke' was first used in a medical sense in the late 16th century. The full term was a 'stroke of apoplexy': a combination of ancient Greek, *apoplexia* – to be struck with violence (McHenry, 1969), and Middle English – implying an unexpected, severe and traumatic event. Throughout time, various terms were used to describe what we now know as stroke. The art of diagnosis changed from seeking to group together conditions with a similar outcome, to attempting to define the underlying pathological process. In this chapter, I will trace the historical developments in classification and diagnosis of stroke and transient ischaemic attack. This chapter serves as the historical rationale for embracing the term *brain attack.*

1.2 Apoplexy – from Hippocrates to the 19th century

1.2.1 The earliest records

The first record of apoplexy was in Hippocratic times (5th century BC). It was defined as a sudden onset of generalised (not focal) brain disturbance, and was invariably fatal. As the aim of the ancient Greek physician was to predict prognosis, diseases as disparate as pulmonary embolism, myocardial infarction and stroke – which may all have a sudden onset and result in coma – were considered to be

'apoplexy'. Despite this, the Hippocratic Writings and Aphorisms gave a remarkably clear description of the apoplexy we now consider as stroke (Clarke, 1963):

> "Apoplexy...occurs most commonly between the ages of forty and sixty...in some cases prodromal symptoms warn of an impending attack...during the spasms the loss of speech for a long time is unfortunate; if present for a short time it proclaims a paralysis of the tongue, of the arm, or of parts situated on the right side."

The Hippocratic physician was aware that apoplexy was a disorder of the brain, and that the paralysis occurred on the side opposite the lesion. Understanding of the function of the brain, or the reason for strokes, was limited because dissection of the human body was precluded by its divine connotations (van Gijn, 2001). At the time, the brain was seen as a gland that cooled the blood and secreted mucous that flowed from the nose (Singer and Underwood, 1962). Apoplexy was explained as an accumulation of black bile in the arteries of the brain, which obstructed the passage of animated spirits from the ventricles.

Following Hippocratic times, there were more refinements in the clinical description of apoplexy. Aretaeus of Cappadocia [81-138 AD] distinguished between paraplegia (a loss of movement and sensation) and paresis (a loss of movement only. Soranus of Ephesus [98-138 AD] distinguished apoplexy (an acute seizure) from paralysis (the long-term sequelae of an episode of apoplexy) (Singer and Underwood, 1962). Paul of Aegina (AD 625 - 690) introduced the term hemiplegia (McHenry, 1969).

1.2.2 17th century – the era of the autopsy

A major advance occurred in the mid 17th century, with the new practice of post mortem examinations. The detailed anatomy of the brain was discovered,

including the vascular network. Willis described the interconnections between the arteries at the base of the brain – later known as the 'circle of Willis' – in 1664 (Singer and Underwood, 1962). Basic pathology was described. Wepfer (**Figure 1.1**) was the first person to associate apoplexy with cerebral haemorrhage. He distinguished between extravasation of blood into the brain and ventricles, and arterial obstruction that prevented the flow of blood (van Gijn, 2001).

Figure 1.1 Johann Jakob Wepfer (1620 – 1695)
Swiss physician and contemporary of Thomas Willis. Studied medicine in Basel, served as army surgeon and physician to Duke Leopold of Wirtenberg. Also known for his early recognition of toxicity from so-called medicinal uses of hemlock, arsenic, and mercury. Image courtesy of the National Library of Medicine.

Clinical description continued to improve. Wepfer noted that those most at risk of apoplexy were "the obese, those whose face and hands are livid, and those whose pulse is constantly unequal", and also observed several patients who recovered (van Gijn, 2001). In 1761 Morgagni, a pioneer of clinico-pathological correlation, demonstrated that the pathological lesion was on the opposite side of the brain to the clinical signs (McHenry, 1969).

1.2.3 19th century

By the early 19th century, clinical diagnosis aimed to identify conditions with common clinical features and causes. Clinical classifications of apoplexy were proposed by Serres in 1819, Abercrombie in 1828, and Hope and Bennett in 1840. Serres divided apoplexy into two types: in the majority (those with paralysis) the brain was involved, and in those without paralysis, the meninges were affected (possibly referring to patients without focal findings). Abercrombie of Edinburgh (**Figure 1.2**) distinguished three classes of apoplexy: primary, where the patient was suddenly struck down, developed convulsions and coma, and if recovery occurred, the patient was often left with paralysis; secondary, which began with headache and vomiting, and if recovery occurred, the patient was less likely to have paralysis; and tertiary, which occurred without coma, but with loss of speech and power on one side of the body, and often with recovery (McHenry, 1969). These classes can be recognised as cerebral haemorrhage, subarachnoid haemorrhage, and vascular occlusion. Hope and Bennett distinguished four forms of apoplexy: transient apoplexy (symptoms last less than a day), primary apoplexy with death or slow recovery, ingravescent apoplexy with partial recovery and relapse, and paraplexic apoplexy (which was apoplexy complicated by paralysis, which they believed was due to raised intracranial pressure) (McHenry, 1969).

Figure 1.2 John Abercrombie (1780 - 1844).
Obtained an MD from University of Edinburgh in 1803, and subsequently practised as a physician in Nicholson Street, Edinburgh. In 1828 he became physician to the king in Scotland, and in 1835 received an honorary degree from Oxford University. Image courtesy of the National Library of Medicine

1.3 The diagnosis of cerebral infarction and haemorrhage

1.3.1 Cerebral haemorrhage

Extravasation of blood into brain parenchyma was recognised by Wepfer and Morgagni, but the cause of this was obscure until the 19th century. In 1825 Baillie associated haemorrhage with hardening of the arteries, which he noted was "a bony or earthy matter deposited in the coat of the arteries" (Schiller, 1970). In 1868, Charcot and Bouchard discovered minute outpouchings of small vessels in the basal ganglia in patients with fatal haemorrhages (Iragui, 1986). They proposed that rupture of these aneurysms resulted in intracerebral haemorrhage, but their view was not uniformly accepted. Debate continued into the 20th century, and was only settled in the 1960s.

It was recognised by Portal in 1781 that it was impossible to distinguish between haemorrhagic and non-haemorrhagic apoplexy in life. This remained true until the invention of computed tomography by Hounsfield in the 1970s.

1.3.2 Cerebral infarction

In 1730, Boerhaave observed that apoplexy could result from interruption of cerebral blood flow by compression of the neck (Schiller, 1970). Rostan [1790-1866] noted that "softening of the brain" (or *ramollissement*) was a separate pathological process to haemorrhage – it was more common than haemorrhage, and its clinical features were often heralded by minor disturbances in limb function, or speech or vision (van Gijn, 2001). Around the same time, Abercrombie (**Figure 1.2**) recognised that brain softening was due to a failure of cerebral circulation as a result of ossification of arteries.

Virchow [1821-1902] firmly established modern thinking about vascular disease. In the mid 19th century, Virchow demonstrated that vascular occlusion produced cerebral infarction, observed that thrombosis was caused by arteriosclerosis (a term he used to describe the process occurring in the vessel wall), and coined the term embolism to describe vessel occlusion where there was no local vessel wall abnormality (McHenry, 1969). Virchow's pupil Cohnheim introduced the word infarction in 1871 (but reserved this for haemorrhagic necrosis, rather than ischaemic necrosis) (van Gijn, 2001). Finally, in 1873 Duret, whilst working in Charcot's laboratory, mapped the areas of distribution of the major intracerebral vessels, and the lesions caused by vascular occlusions (McHenry, 1969).

1.4 Stroke in the twentieth century

1.4.1 Gowers and early 20th century neurology

By the turn of the 20th century, there were two London hospitals devoted to apoplexy and other neurological illnesses (Critchley, 1960). Neurology had acquired a "disease-based approach", with classification of disorders into the now familiar categories of infectious, traumatic, vascular, nutritional, degenerative, demyelinating and hereditary causes (McHenry, 1969). The major elements of stroke – its classification, aetiology, pathology, clinical features and prognosis – had been recognised and recorded.

The leading London neurologist of the time was Gowers (**Figure 1.3**) (Critchley, 1960). Gowers devoted many pages of his Manual of the Diseases of the Nervous System to stroke, which he recognised was "one of the most frequent diseases of the brain" (Gowers, 1893). The clinical features were a result of either sudden interference with the functions of the brain (e.g. loss of consciousness), or the destruction of the nerve elements in the affected area. The commonest cause was vascular occlusion (Gowers, 1893).

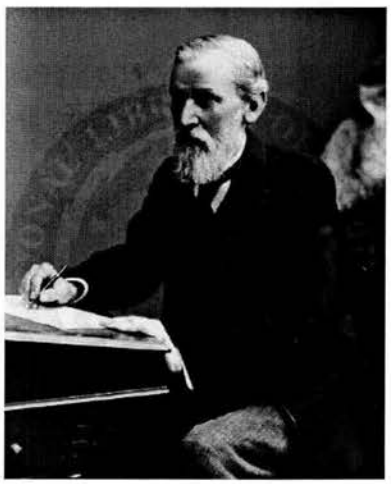


Figure 1.3 Sir William Gowers (1845 – 1915)
Neurologist at the National Hospital, Queen Square. In addition to neurology and neuroanatomy, he had varied interests, including etching and painting (he illustrated all his books), the use of shorthand, and the study of mosses and wild flowers. Image courtesy of the National Library of Medicine.

1.4.2 Birth of the term 'CVA'

At the turn of the 20th century, the common terms were 'stroke' and 'apoplexy' (Gowers, 1893). In the 1930s, a new term – 'cerebrovascular accident' – came into existence. Why another term? Schiller (1970), a medical historian, proposed the following rationale:

> "That rather blurry and pompous piece of nomenclature must have issued from the well-meant tendency to soften the blow to patients and their relatives, also from a desire to replace "stroke", a pithy term that may sound unscientific and lacking gentility. 'Cerebrovascular accident (CVA)' can be traced to the early 1930s - between 1932, to be exact, when it was still absent from the 15th edition of Dorland's Medical Dictionary, and the following edition of 1936 where it first appeared."

By the mid 1950s, the plethora of terms for stroke was hampering research and understanding - a plea was made for more specific terminology at the first Princeton conference on cerebrovascular diseases (Wright, 1955). A major theme of the second Princeton conference was 'problems of nomenclature', in which the leading stroke clinicians of the day – amongst them Millikan, Fisher, Adams, Merritt and Brain – tried to reach consensus (Millikan, 1958). The meeting's result was the publication of 'A classification and outline of cerebrovascular diseases' (Anon., 1958) which attempted to lay out a clear and simple framework.

Despite its banishment from official usage, cerebrovascular accident remained (and remains) popular. On both sides of the continent, physicians with an interest in the area disliked the term. Mulley (1985) stated that it "irritates the stroke physician", Furlan (2000) described its real meaning as a "confused vascular analysis", and van Gijn (2001) eloquently stated:

> "One problem was that sometimes it was used as synonymous with cerebral infarction, at other times as

> denoting stroke in general. In this day and age, the term is a highly specific sign of woolly thinking."

The reader will find no further reference to 'CVA" in this work.

1.4.3 The 1950s – stroke might be a treatable disease

The Framingham study, which commenced in 1949, demonstrated that risk factors such as hypertension, diabetes mellitus, cholesterol, obesity, cigarette smoking and physical activity were clearly associated with premature coronary heart disease. This changed the prevailing view that atherosclerosis was simply an inevitable consequence of ageing. It appeared possible to prevent (and maybe even treat) atheroma of the coronary arteries (Dawber, 1980). Stroke became the next target.

In 1956, Dyken and White (1956) performed the first randomised study of cortisone for acute stroke. Heparin, first used in 1941 (Fraser *et al.*, 1999), attracted much attention in the 1950s and beyond. Some believed that the difficulties of distinguishing between haemorrhage and infarct precluded its safe use (Fields and Lemak, 1989), however reports of its success appeared, and heparin use became widespread. Aspirin was first used in stroke prevention by Craven, but the study's results were not widely disseminated (and it was not until 1971 that interest was rekindled) (Fields & Lemak, 1989).

Other methods of treating strokes, common in the 1950s, were: stellate ganglion block (thought to abolish vasospasm thus increase blood flow to the infarct), carbon dioxide inhalation (to increase blood flow), hypotensive agents and surgery (Rankin, 1957a; Meyer, 1961). There was even mention of pilot studies of

the use of thrombolytic agents for progressing cerebral thrombosis (Millikan *et al.*, 1961)

1.4.4 The difficulty of the clinical diagnosis

For many experts of the day, the need for a more active approach was clear.

> "It is regrettable that the policy of labelling such patients 'cerebrovascular accidents' and committing them to bed without benefit of accurate diagnosis or treatment has been so prevalent in past years" (Meyer, 1961)

However, one of the major problems was that diagnosis was difficult, in the absence of investigations such as brain imaging. Rankin (1957b) noted that:

> "At the onset, when treatment is likely to be of most value, accurate diagnosis is often difficult and sometimes impossible. Later, when the diagnosis is perhaps obvious, permanent damage has already occurred... Diagnosis at the bedside shortly after the onset of symptoms may be exceedingly difficult."

An accurate clinical diagnosis was usually made after several days of careful observation. Cerebral haemorrhage was diagnosed by an onset over minutes, accompanying headache, reduced consciousness, absence of rapid improvement, and bloody CSF (Fisher, 1961a). Cerebral embolism was diagnosed by an abrupt onset, absence of premonitory transient ischaemic attacks (TIAs), rapid improvement, and demonstration of a cardiac source of emboli (Fisher, 1961b). Cerebral thrombosis was diagnosed by the presence of TIAs, older age, evolving onset, and rapid improvement (Fisher, 1961b), and was further divided into 'threatening', 'stroke-in-evolution' (a subacute or progressing stroke, often with slow onset), 'completed stroke' (onset often during sleep, deficit maximal on wakening) and 'chronic cerebral infarction' (which may imitate a space occupying lesion) (Carter, 1972).

Treatments were prescribed for a particular type of stroke (e.g. anticoagulants for evolving strokes) (Carter, 1961). Thus the clinical diagnosis – most accurate after several days of observation – formed the basis for the decision to treat a patient immediately (and often with risky medications). It was little wonder that some clinicians preferred to do nothing.

1.4.5 Simplification of the clinical approach

By the 1970s, it was realised that a cerebral infarct, embolism, or haemorrhage could result in a clinical 'evolving' or 'completed' stroke (Marshall, 1976). Treatment of a completed stroke was deemed not possible, but treatment of progressing or evolving strokes could be attempted with steroids (to reduce oedema), dextran-40 (to aid blood flow) or anticoagulants (Marshall, 1976). There was also growing awareness that the clinical definitions were ambiguous (e.g. 'completed stroke' – some thought it meant that the stroke had stopped worsening, others that the neurological impairment had reached its maximum (Whisnant, 1990)).

The first step towards simplification was the World Health Organisation (WHO) clinical definition of stroke ["rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin" (Hatano, 1976)]. One can speculate that this definition was more useful for epidemiological studies than for the busy clinician. As the clinical features, investigation, treatment and prognosis of subarachnoid haemorrhage are different to other forms of stroke, the clinical utility of the WHO definition was questioned (Bamford, 2001). A sensible modification was to separate SAH and define a stroke as "a clinical syndrome

characterised by an acute loss of focal cerebral function with symptoms lasting more than 24 hours or leading to death, and which is thought to be due to either... haemorrhage or infarction." (Bamford, 2001). This alteration became widely accepted (Mulley, 1985; Rangel, 1986), and has carried through into modern textbooks of stroke (Barnett *et al.*, 1998; Warlow *et al.*, 2001; Bogousslavsky and Caplan, 2001), and will be used in this thesis.

The greatest advance of the 20th century for stroke medicine was the discovery of computerised tomography (CT). Before the era of CT, studies achieved an accurate pathological diagnosis in only about 30% of cases (Marquardsen, 1976). When CT brain scans became available in the 1980s, it was possible to accurately distinguish between haemorrhage and infarct. CT scanning demonstrated that previously held ideas about clinical features were often wrong, leading to a general abandonment of the confusing sub-classifications seen in the previous decades (Toole *et al.*, 1988). With CT, diagnosis and management were aided by an accurate knowledge of what was occurring "inside the head" (McDowell, 2001).

1.5 Defining the transient ischaemic attack (TIA)

References to premonitory symptoms were made by many of the early pioneering physicians (e.g. Hippocrates, Wepfer, Willis, Hope & Bennett). These minor symptoms attracted little interest, as the primary focus for physicians of the time was on apoplexy, with its grave prognosis (Loeb, 1980). Additionally, very early reports did not always differentiate between focal symptoms and general symptoms such as fainting (van Gijn, 2001). Around the end of the 19th century, descriptions of transient stroke-like episodes were common, and in 1914 Ramsay

Hunt called the events "cerebral intermittent claudication" (Hankey and Warlow, 1994). Over the next 40 years, however, little attention was paid to transient episodes of cerebral dysfunction.

Stimulated by the experience of a patient who developed visual loss in the right eye followed by hemiparesis, Fisher (**Figure 1.4**) recognised the importance of transient events as a marker of increased risk of cerebral infarction (Fisher, 1951). Fisher first proposed the term transient ischaemic attack (TIA) in 1957. Other terms used at that time included 'intermittent vascular insufficiency', 'ischaemic recurrent attacks', 'transient cerebral ischaemia' and 'transient ischaemic cerebrovascular attacks'. Fisher's term did not gain widespread acceptance until the fourth Princeton conference of 1965 (Hankey and Warlow, 1994).

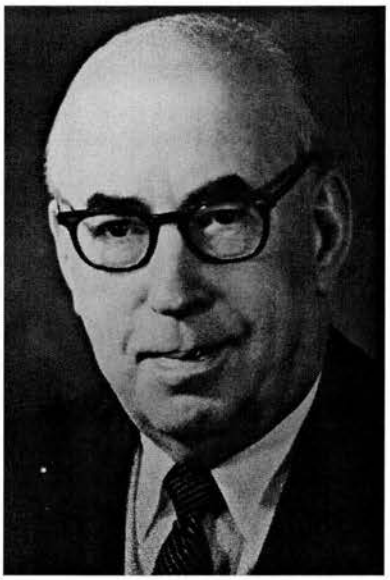


Figure 1.4 C. Miller Fisher (1913 -).
Imprisoned in a German prisoner of war camp for three and a half years during the Second World War. Later, neurologist at the Massachusetts General Hospital, Boston. Major contributions to knowledge of transient ischaemic attacks, lacunar syndromes, also described the Miller-Fisher variant of Guillain-Barre syndrome. Reproduced from Stroke. A practical guide to management, 2nd edition; CP Warlow, MS Dennis, J van Gijn, GJ Hankey, PAG Sandercock, JM Bamford, JM Wardlaw, eds. Oxford: Blackwell Science 2001 with permission.

The accepted duration of TIAs varied greatly over the years: in 1958, it was 1 hour (Committee of the National Institutes of Neurological Diseases and Blindness, 1958), and in 1975, it was 2-30 minutes (Millikan, 1975). In 1978, the World Health Organisation proposed an upper limit of 24 hours (World Health Organisation,

1978). Despite the fact that most cerebral TIAs resolve in less than 60 minutes, this arbitrary definition of symptom duration achieved widespread acceptance (Hankey and Warlow, 1994). In their monograph, Hankey and Warlow (1994) define the transient ischaemic attack as:

> "an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis or embolism associated with arterial, cardiac or haematological disease."

1.5.1 The 'RIND' and other variants

There is a spectrum of symptom duration in cerebrovascular disorders. Symptoms may last from minutes to hours, days, weeks or months (Hankey and Warlow, 1994). Some transient episodes of cerebral ischaemia lasted longer than 24 hours yet still eventually resolved, so terms such as reversible ischaemic neurological deficit ('RIND'), minor ischaemic stroke and 'protracted TIA' were introduced (Hankey and Warlow, 1994). These terms were popular in the 1980s. In the 1990s, they were largely abandoned (Hankey and Warlow, 1994), after considerable debate as to whether there was any point in distinguishing between a TIA and minor ischaemic stroke (Whisnant, 1990)

1.6 The 'decade of the brain'

In 1990 the US Congress signed a resolution declaring the forthcoming ten years to be the 'Decade of the Brain' (Rosenberg and Rowland, 1990). At the commencement of the decade, there was enthusiasm for what could be achieved in stroke:

> "There is a new excitement in stroke research – new technology, new findings, renewed promise of stroke prevention, intervention at the time of stroke to limit destruction, new clinical therapies, and hope that new approaches to restoration after stroke will improve the long-term outlook for patients" (Goldstein, 1990).

The decade of the brain achieved many advances. Sound epidemiological studies in the late 80s and early 90s improved knowledge of the incidence, risk factors and natural history of cerebral infarction and haemorrhage. The Oxfordshire Community Stroke Project developed a simple clinical classification of infarcts that was used in large-scale trials such as the International Stroke Trial (Bamford *et al.*, 1991). Stroke severity scales such as the National Institute of Health Stroke Scale (NIHSS) – the "common language" of acute stroke (Furlan, 2000) – were used in many trials, allowing easier comparisons both within and between trials. Clinical trial methodology improved substantially (Bath *et al.*, 1998), and rigorous studies of neuroprotectants, antiplatelet agents, heparin, oral anticoagulants, and carotid endarterectomy were performed. Evidence-based medicine, aided by systematic reviews and meta-analysis of all available trial results, was introduced (Sandercock, 2001).

1.6.1 Thrombolysis for acute ischaemic stroke

The 1990s can also be seen as the decade of thrombolysis (Starkman & Saver, 1997). Clot dissolution became a theoretical possibility in the early 1950s, after the discovery of the clotting pathway, and streptokinase, a substance produced by bacteria that was capable of accelerating clot lysis. Early studies had an unacceptable risk of complications (Heiss, 1988), prompting a 1980 recommendation

that thrombolysis for acute cerebrovascular disorders is contraindicated (Anonymous, 1980).

In the 1980s, progress was made on several fronts. Understanding of the concept of the ischaemic penumbra increased, which formed the theoretical rationale for reperfusion (Heiss, 1988). Tests in animal models showed that the efficacy of thrombolysis was maximal if given early (within 90 minutes of onset) (Zivin, 1999). The success of trials of thrombolysis in acute myocardial infarction provided a framework for clinical trials of thrombolysis in acute stroke (Baron *et al.*, 1995). But the prevailing attitude of stroke physicians was that treatment of stroke victims within 48 hours of symptom onset was essentially impossible (Sterman *et al.*, 1987).

The decade of the brain changed that attitude. In 1995, the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study reported that recombinant tissue-plasminogen activator (rt-PA) uniformly improved all measures of outcome when given within three hours of onset (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995). rt-PA was subsequently licensed for commercial use in the USA and Canada.

By the end of 1999, over 5,000 patients had been enrolled in 17 randomised-controlled trials of thrombolysis. A Cochrane systematic review of the data showed that treatment with rt-PA up to six hours after onset resulted in 57 fewer dead or disabled patients for every 1000 treated (Wardlaw *et al.*, 2001a). Leading US clinicians had little doubt that rt-PA should be given to any suitable patient presenting within three hours of symptom onset (Grotta, 1997; Zivin, 1999). However, disappointingly few patients were actually treated (Horowitz, 1998), and many issues remained unresolved, such as whether thrombolysis could safely be

given up to six hours after onset, and the interaction between stroke severity and CT appearances and the risks of treatment (Wardlaw *et al.*, 2001a).

By the end of the 1990s, there was little doubt that: (1) there *was* a treatment for acute stroke that was effective for selected patients, and (2) for treatment to be successful, it had to be started as soon as possible. A new era in acute stroke assessment and treatment had begun.

Chapter 2 : The ischaemic penumbra

2.1 Introduction

The recent progress in treating acute ischaemic stroke has been underpinned by advances in knowledge of stroke pathophysiology (Carter, 1961; Marshall, 1976). Infarction is not an all or nothing episode, instantaneous in onset, and irreversibly complete (Hankey, 2001). Instead, occlusion of a blood vessel initiates a series of pathophysiological cascades, involving the vascular system (platelets, coagulation factors, vessel wall, thrombi) and brain tissue, ultimately resulting in neuronal death. In this chapter, I will briefly review the mechanisms that lead to cell death after a vessel is occluded. The major focus will be on the ischaemic penumbra, and how this influences modern management of stroke.

2.2 Cerebral metabolism, blood flow and autoregulation

2.2.1 Cerebral metabolism

The working brain consumes one-third of its energy for maintenance of synaptic transmission, one-third for transporting sodium and potassium ions across the membrane (thus maintaining ionic homeostasis), and one-third for preserving structural integrity (Back *et al.*, 1998). Glucose is the only source of energy, and oxygen is required to convert glucose to ATP with maximal efficiency. The brain is incapable of storing glucose, thus it requires a constant supply of glucose and oxygen (Paczynski *et al.*, 1995; Hankey, 2001).

2.2.2 Cerebral blood flow (CBF)

Resting blood flow to the brain is 50-55ml/100g brain tissue/minute. Total blood flow to the brain constitutes 20% of cardiac output (despite the brain being only 2% of body weight). In the resting brain, metabolism and blood flow are tightly coupled (by unknown mechanisms). The fraction of oxygen extracted from the blood (oxygen extraction fraction, OEF) is also coupled to CBF. Normally, OEF is about 33%, but it can increase significantly if necessary (Hankey, 2001).

2.2.3 Autoregulation

Under normal conditions, CBF is maintained by autoregulation: flow is kept constant despite changes in cerebral perfusion pressure. As *flow = pressure / resistance*, maintaining flow in the face of changes in pressure can be achieved by altering vascular resistance (by dilation or constriction of intracerebral and pial arterioles). Systemic arterial oxygen content, carbon dioxide tension, local pH, and degree of local functional activation of neurones also influence CBF (Paczynski *et al.*, 1995).

Autoregulation functions within the usual blood pressure ranges (higher for those with long-standing hypertension), but when mean arterial blood pressure falls to 50mmHg and below, further dilation of arterioles is not possible and autoregulation fails. Then CBF parallels perfusion pressure, and brain tissue must increase its OEF to sustain aerobic metabolism. In disease states such as stroke, autoregulation is lost (Olsen *et al.*, 1983). CBF becomes 'pressure passive', and sudden drops in blood pressure can predispose to, or worsen, stroke (Hankey, 2001).

2.3 Pathophysiology of ischaemia

2.3.1 Effect of vessel occlusion

Complete arrest of the cerebral circulation leads to irreversible neuronal damage within minutes. Stroke, however is a focal disorder, commencing with occlusion of a single cerebral vessel, and its outcome is far less predictable (Astrup *et al.*, 1981). The presence of collateral blood vessels means that an occlusion will reduce, but not abolish, the delivery of oxygen and glucose to an area of brain tissue. Cells closest to the occluded vessel will infarct after five minutes of severe focal ischaemia. Cells nearest to the collateral vessels are less severely affected than areas close to the occlusion (Pulsinelli, 1992; Siesjo, 1992a).

2.3.2 Critical thresholds of blood flow

The development of infarction is critically dependent on blood flow (Astrup *et al.*, 1981). With initial reductions in CBF (see **Figure 2.1**), cerebral oligaemia occurs: OEF increases to maximal, but oxygen metabolism remains normal. This tissue is not ischaemic, and is not at risk of infarction (Baron, 1999). When CBF reduces to around 50% of normal (20ml/100g brain tissue/minute), electrical failure occurs: cells shut down activities such as synaptic transmission to preserve homeostasis. Electroencephalogram recordings are characteristically suppressed, and evoked potentials attenuated. At this point, a focal neurological deficit will be present (Fisher, 1999). With reduction of CBF to 10ml/100g brain tissue/minute, membrane failure occurs: the cell no longer has enough energy to maintain membrane ion pumps, so sodium and water enter the cell leading to cytotoxic

oedema, and calcium enters the cells leading to failure of mitochondria. This tissue is irreversible damaged (Astrup *et al.*, 1981).

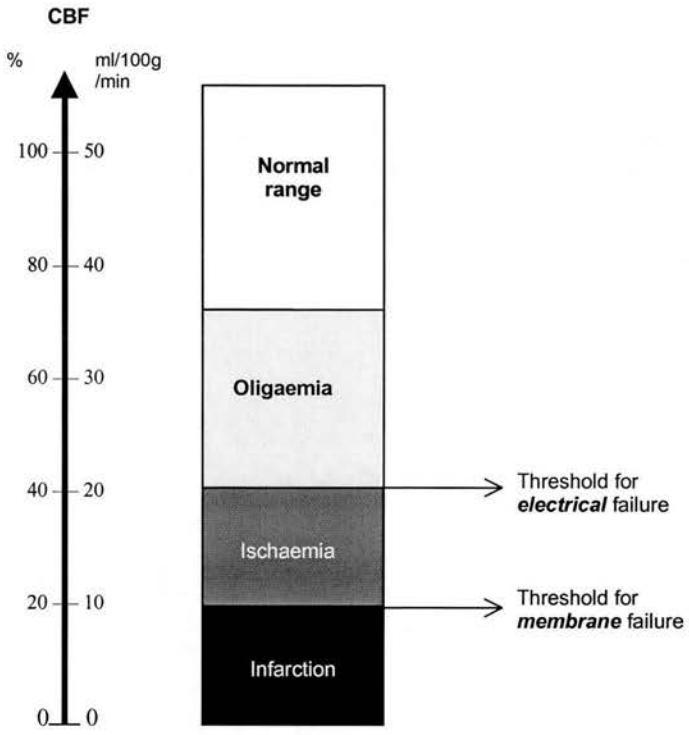


Figure 2.1 Critical blood flow thresholds

Ischaemic brain injury passes through several thresholds, which relate decrements in cerebral blood flow (CBF) to pathological events. In the normal range, CBF is maintained by autoregulation. In oligaemia, there are modest reductions in CBF, but brain tissue maintains normal metabolism by increasing the oxygen extraction fraction. At a CBF of 20ml/100g brain tissue/minute, the threshold of electrical failure is met, the EEG is suppressed, and the tissue is ischaemic. At a CBF of 10ml/100g/minute, the threshold of membrane failure is met, and the cells become infarcted. (Adapted from Hossmann (1988))

Time is also a vital factor in the development of infarction (Baron, 1999). The CBF threshold for membrane failure (infarction) depends on the time elapsed since vessel occlusion – tissue with CBF 15ml/100g/min may withstand three hours of occlusion, but tissue with CBF 10ml/100g/min may withstand only two hours.

2.3.3 *Phases and mediators of cell death*

With prolonged severe reductions in CBF, infarction occurs. There are believed to be four sequential but overlapping cascades that give rise to cell necrosis (Pulsinelli, 1992; Siesjo, 1992b; Paczynski *et al.*, 1995; Hakim, 1998; Garcia *et al.*, 1999; Fisher & Schaebitz, 2000; Hankey, 2001):

1. *Excitotoxicity.* This occurs within minutes, and is a result of uncontrolled release of the neurotransmitter glutamate. High extracellular concentrations of glutamate cause overstimulation of glutamate receptors, allowing even more sodium and calcium to enter the cell. Elevated levels of intracellular calcium activate destructive enzyme systems and generate free radicals.

2. *Peri-infarct depolarisation.* This mechanism occurs minutes to hours after ischaemia. Glutamate and potassium are released into the extracellular space by the ischaemic neurones, and trigger off repetitive depolarisations of adjacent cells. The neurones around the ischaemic area must then consume precious energy in repolarisation, which eventually exhausts, recruiting more cells into the expanding ischaemic lesion.

3. *Inflammation.* This occurs hours to days after the insult. As a result of the influx of calcium into the cell, there is expression of inflammatory cytokines, causing secondary neuronal injury.

4. *Apoptosis.* This mechanism results in further cell death over several days. Ischaemia causes an induction of genes that regulate programmed cell death (through the action of caspases, which destroy cytoskeletal proteins and enzymes essential for cell repair).

2.4 The concept of the ischaemic penumbra

The demonstration of critical thresholds of blood flow to support synaptic transmission and ion homeostasis, and an orderly sequence of events as neuronal blood flow diminishes, led to the concept of the ischaemic penumbra (Astrup *et al.*, 1981). Tissue that loses its electrical function, but maintains its membrane function, is 'between life and death' – if blood flow is restored, it can regain its function (Baron, 1999). Hence tissue in the ischaemic penumbra is destined for infarction, but is still viable – and it can be rescued by appropriate treatment (Ginsberg & Pulsinelli, 1994; Hossmann, 1994; Hakim, 1998; Fisher, 1999).

The term "penumbra" is an analogy to the shaded zone around the centre of a complete solar eclipse (Astrup *et al.*, 1981). In its idealised form the penumbra is a ring of ischaemic but viable tissue surrounding a core of infarcted tissue (see **Figure 2.2**).

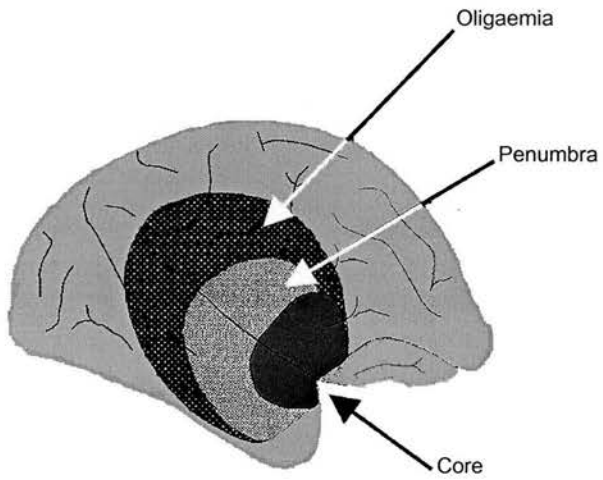


Figure 2.2 The ischaemic penumbra

Idealised diagram showing the topography of the central ischaemic core (in dark grey), the penumbra (light stippled) and the zone of oligaemia (dark stippled). Based on a baboon animal model, following MCA occlusion, and adapted from Baron (1999).

2.4.1 *Does the penumbra exist in humans?*

Initial observations were in animal models – rats, cats, dogs, gerbils and primates – which demonstrated similar blood flow thresholds and response to reperfusion (Hossmann, 1994). However, there are difficulties in translating results of animal studies to humans (Scheinberg, 1991; Furlan *et al.*, 1996). Positron emission tomography (PET) allowed the study of the ischaemic penumbra in humans. The penumbra does exist, and – surprisingly – for much longer than the penumbra seen in animal models (Baron, 1999).

PET has not become a widely used technique (due to limited availability and long scanning times) (Fisher, 1999). Another promising imaging modality for the study of the penumbra in humans is diffusion and perfusion magnetic resonance imaging (MRI). The advantages include its greater availability, shorter scanning times, and ability to be used within minutes of stroke onset. Diffusion weighted imaging (DWI) is sensitive to the movement of water molecules into brain tissue. It is thought that a lesion seen on DWI represents membrane pump failure – the core of an infarct (Warach, 1998). Perfusion imaging detects relative reductions of blood flow to areas of brain. The penumbra is thought to be the region of abnormal perfusion that is larger than the region of abnormal diffusion (Warach, 1998). As shall be discussed in **Chapter 6**, there remains much work to be done before this theory can be considered proven.

2.4.2 *Evolution of the penumbra*

After focal ischaemia, there is a critical reduction of blood flow to an area of brain tissue, but collateral blood flow from adjacent vascular territories maintains

near normal CBF to much of the periphery of the area (Paczynski *et al.*, 1995). For example, in the primate model, occlusion of the middle cerebral artery (MCA) causes maximal reduction in CBF to the sylvian region and anterior basal ganglia. Outside this densely ischaemic region are zones of less severe CBF reduction, ranging from 40-80% of normal, depending on the distance from the ischaemic core and local collateral supply (Paczynski *et al.*, 1995).

Thus, the ischaemic penumbra is a dynamic process. Brain regions outside the zones of severe ischaemia are eventually recruited into the developing infarct. The infarct grows with time at the expense of the surrounding penumbra, which is initially large but then shrinks (**Figure 2.3**). If blood flow can be restored, tissue will be saved, but as time goes by, the volume of salvageable tissue gets smaller (Baron, 1999).

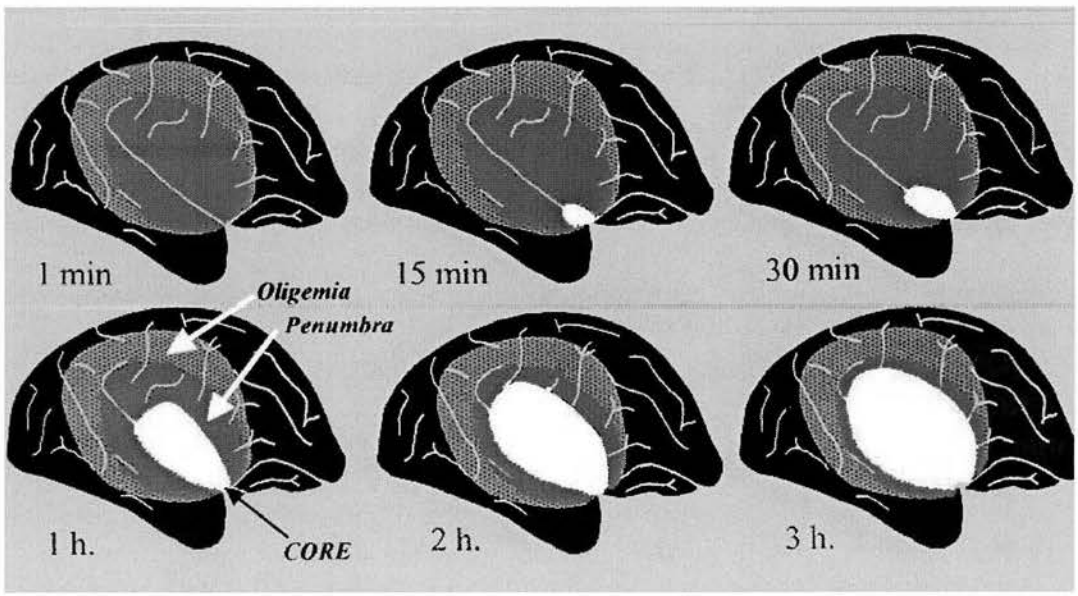


Figure 2.3 The dynamic penumbra.

The grey area represents the penumbra, the white area is the core of the infarct, the mottled grey area is tissue oligaemia, and the black area is normal brain. As time progresses, the core grows into the penumbra – by three hours, there is a large infarct and only a small rim of penumbra. Adapted from Baron (1999)

2.5 The 'therapeutic time window'

The development of effective therapies for acute ischaemic stroke depend on defining: (1) the tissue that is the therapeutic target, and (2) how long the tissue is likely to respond to any treatment (Fisher, 1999). The therapeutic target tissue is the ischaemic penumbra: thrombolysis and neuroprotective agents aim to restore perfusion or attack the mechanisms that lead to cellular necrosis, hence salvage potentially reversible ischaemic tissue (Fisher, 1999).

The time that the therapeutic target is likely to respond to a treatment – the 'therapeutic time window' – is the time that the ischaemic penumbra exists. Work in animal models suggested that the duration of the time window was perhaps as little as 2 hours (Ginsberg & Pulsinelli, 1994). However, PET studies have documented that in some patients, substantial volumes of viable ischaemic tissue exists for up to 16 hours after onset (Furlan *et al.*, 1996). It is not possible to detect whether a patient has potentially salvageable ischaemic tissue by clinical methods (Fisher, 1997). Perhaps MR will be able to identify the ischaemic penumbra and so guide individual treatment in the future.

It seems likely that the time window is not rigid and universal, but is a highly dynamic process that also depends on interactions with factors such as adequacy of collateral blood flow, temperature, blood pressure and systemic metabolic disturbances (Baron *et al.*, 1995; Fisher, 1997). The time window also varies for individual treatments (Baron *et al.*, 1995). An additional factor for thrombolysis is reperfusion injury, whereby restoration of blood flow (beyond a critical time point) may exacerbate ischaemic damage (by increased oedema or free radical production)

(Siesjo, 1992a; Paczynski *et al.*, 1995; Hankey, 2001). It is not known precisely at what time reperfusion injury occurs.

2.6 Summary

- The identification of critical thresholds of blood flow, and the tissue response to reduced blood flow, led to the concept of an ischaemic penumbra
- Current strategies for treatment of acute ischaemic stroke are based on rescuing tissue within the ischaemic penumbra
- The duration of time during which the penumbra exists is likely to be influenced by many factors. An important consideration in thrombolysis is that late treatment may actually increase injury
- Current clinical methods cannot determine if tissue is likely to respond to treatment. It may be possible in the future to determine the state of the penumbra by using advanced imaging
- Until then, the best way of ensuring that there is potentially viable tissue to rescue is for the patient with a stroke to present to hospital as soon as possible after symptom onset
- *Time is brain!*

Chapter 3 : Brain attack

3.1 Introduction

The limitation of the terms stroke and transient ischaemic attack (TIA) is that they are time-based definitions: an accurate label cannot be applied to a patient until 24 hours have elapsed. Yet increasingly, patients present for assessment within hours or even minutes of symptom onset. What should we call these events in the initial few hours? In this chapter, I will present the case for using the term 'brain attack' to describe this clinical state.

3.2 Why another change in terminology?

3.2.1 Pathophysiological rationale

Infarction is not an inevitable and immediate consequence of vessel occlusion, as was previously believed. There is a progression of events, from near normal tissue function, to electrical failure, and finally membrane failure and cell death, that occur both in time and in space. Around a core of tissue destined for infarction is the ischaemic penumbra, which is potentially salvageable. The key factor in these processes is time.

The concept that 'time is brain' has major implications for the clinical approach to acute stroke. For treatment to be given within the therapeutic time window, patients need to present to hospital urgently, the clinical assessment needs to be rapid, and the diagnosis of ischaemic stroke needs to be made accurately.

The terms stroke and transient ischaemic attack offer little assistance to the clinician seeing a patient with focal neurological signs in the first few hours after symptom onset. These diagnoses that can only be made after 24 hours (and it is hoped that successful treatment would convert a 'stroke' to a 'TIA'), but to wait 24 hours ignores the ischaemic penumbra, and may prevent effective treatment.

3.2.2 Historical rationale

The terminology of stroke was developed at a time when our understanding of the pathophysiology of ischaemia was minimal, and treatments were often started 72 hours or more after the onset of symptoms. It was routine practice to observe the patient for a period of time, so the cut-off point of 24 hours to distinguish between stroke and transient ischaemic attack was reasonable. The definitions were helpful for epidemiological studies, and for the therapeutic nihilist.

In the 21st century, patients are assessed – and in some cases treated with potentially dangerous drugs – within a few hours of the onset of symptoms. Traditional time-based definitions of stroke and TIA are now less useful. The problem is: what to label the patient with symptoms of stroke when seen within 24 hours? As Bamford stated (2001):

> "Looked at from the perspective of physicians seeing patients acutely (i.e. within 24 hours from onset of symptoms), there are basically two groups of patients; those whose symptoms have resolved at the time of assessment and therefore can be correctly referred to as TIAs, and those who still have symptoms with or without relevant physical signs. It would seem inappropriate (and potentially confusing) to use the term stroke in this situation and we can see that there may be value in using a new term such as 'brain attack'."

Before embracing the term brain attack, it is important to learn the lessons of recent history. One of the major problems encountered in the early study of stroke treatments was the difficulty in classification. Clinicians attempted to predict the underlying pathology by often quite complex clinical classifications (evolving stroke, threatened stroke, completed stroke, chronic stroke etc.). These terms proved to be unwieldy, with a return to simpler terminology once haemorrhage could be reliably identified with CT scanning. It is clear that for a new term to be of benefit, it needs to be simple, clearly defined, and must serve a useful clinical purpose.

3.3 Early use of the term 'brain attack'

Hachinski (see **Figure 3.1**) first coined the term 'brain attack' in 1974. At his inaugural lecture as a faculty member of the University of Toronto, he concluded with the statement [quoted in Starkman & Saver (1997)]:

> "the day will come when brain attacks will be treated with the same alacrity as heart attacks"

The first printed reference to brain attack appeared in a1986 monograph that examined the relationship between heart disease and brain disease (particularly stroke) (Furlan, 1987). In a chapter titled '*Are heart attacks really brain attacks?*' (Levine *et al.*, 1987), the authors postulated that sudden cardiac death (and other arrhythmias) could be induced by cerebral reactions to psychosocial stressors or acute intracranial events such as a stroke. Activation of a neural neural pathway arising in the orbital frontal cortex and projecting to brainstem cardioregulatory centres was believed to cause sudden cardiac death.

Figure 3.1 Vladimir Hachinski
Trained in Toronto and Montreal, Canada. Pioneered early acute stroke units, and is credited with coining the terms multi-infarct dementia, leukoaraiosis and brain attack. Currently Editor-in-Chief of Stroke. *Image courtesy of Stroke.*

The term remained dormant until 1991, when once again Hachinski used it publicly at a press conference to announce the results of the North American Symptomatic Carotid Endarterectomy Trial. This was reported in the San Francisco Chronicle (Petit, 1991), and thereafter widespread usage followed (Camarata *et al.*, 1994; Hachinski, 1996; Starkman & Saver, 1997; Ellis & Matthews, 1999). The US National Stroke Association began to champion the term in the early 1990s "because it characterises the medical condition and communicates the actual event more clearly to the public than does the word 'stroke'" [NSA website http://www.stroke.org/].

3.4 How is brain attack defined?

Brain attack, as a substitute for the word stroke, has become popular in the lay press and on many patient information websites (and even hospital websites that advertise their own 'brain attack teams'). Despite this public attention, there has been little discussion of the term in the medical literature. No formal definition has ever been given. There are four general ways in which 'brain attack' has been used:

(1) As a synonym for the word stroke. Some authors suggest that brain attack encompasses all conditions previously defined by the World Health Organisation

(infarction, primary intracerebral haemorrhage, and subarachnoid haemorrhage) (Heros *et al.*, 1997), whilst others, including patient support groups such as the NSA, have excluded subarachnoid haemorrhage (National Stroke Association, 1994; Ellis & Matthews, 1999; Wehrmacher *et al.*, 2000). The term is meant to raise awareness of the urgency of the situation for patients, and also to counter the nihilism of paramedic and hospital staff towards stroke that is still prevalent (Wehrmacher *et al.*, 2000).

(2) To refer to brain ischaemia only (Starkman & Saver, 1997; Selman *et al.*, 1997). This is a direct analogy to myocardial ischaemia – the same therapy (thrombolysis) is most effictive if given as soon as possible after symptom onset. Although advocating the use of brain attack, Ellis & Matthews (1999) are highly critical of analogies with myocardial infarction:

> "Those interested in the management of 'stroke' were lulled into intellectual complacency by an uncritical acceptance of analogies with myocardial infarction. Cerebral infarction is a much more complex process and requires a more sophisticated approach; a preliminary and necessary step is the discarding of simplistic terminology (i.e. stroke)"

(3) To refer to a US campaign to recognise stroke as a more urgent condition (Heros *et al.*, 1997). A group of professional, voluntary and governmental entities 'dedicated to reducing the occurrence, disabilities and death associated with stroke' called the 'Brain Attack Coalition' [http://www.stroke-site.org/] aim to increase public knowledge of the early symptoms of stroke. Along with the term brain attack, the Brain Attack Coalition has also introduced 'the three Rs of stroke': **R**educe the risk, **R**ecognize the symptoms, and **R**espond to the symptoms by calling an ambulance [NSA website, http://www.stroke.org/].

(4) As a more specific term to describe the patient who presents with symptoms (or signs) of focal cerebral dysfunction within 24 hours of onset. Rather than a definitive diagnosis, brain attack is a description of a clinical state that awaits further clarification (Ellis & Matthews, 1999). For Bamford (2001), the term highlights the fact that there is a differential diagnosis for the patient's presenting complaint.

In all uses of the term, the need for rapid presentation and assessment is implicit. A brain attack is an emergency, just like a heart attack. Unfortunately, the term suffers from a lack of a clear definition. I favour the fourth use of the term: it serves a useful clinical purpose (describing the patient who cannot presently be classified), highlights the instability of the clinical situation, and alerts the physician to the possibility of masquerading conditions, whilst also embracing the public educational aspects. Brain attack does not pretend to be a diagnosis, which in the hyper-acute situation is an advantage. I see the term as a description, to be applied for a short time until a definitive diagnosis is reached.

3.5 Advantages of using the term 'brain attack'

It should be noted that the following sections refer to *potential* advantages, as no studies have actually assessed the effects of this change in terminology.

3.5.1 Improved public awareness

Stroke is the poor cousin of myocardial infarction. In contrast to heart attack victims, stroke patients do not perceive their symptoms as serious or requiring immediate attention, and often arrive at hospital late (Williams *et al.*, 1997). Just half of the general public can identify one of five warning signs of stroke (Pancioli *et*

al., 1998), whilst 90% can name at least one major sign of myocardial infarction (Heros *et al.*, 1997). Only 29% of the general public – and 50% of stroke patients – know that a stroke is due to an injury of the brain (Wellwood *et al.*, 1994; Heros *et al.*, 1997; Kothari *et al.*, 1997). 'Brain attack' states simply that the problem affects the brain, is sudden and serious, and is a medical emergency (National Stroke Association, 1994).

3.5.2 Counter medical nihilism

There is still widespread nihilism amongst paramedical and medical staff (Heros *et al.*, 1997). Stroke is considered a low priority in emergency transport system protocols and emergency department triage (Heros *et al.*, 1997). The medical assessment of patients with stroke can be painfully slow (Johnston *et al.*, 1999). In the UK, most patients with stroke first contact their general practitioner, but the primary reason general practitioners refer patients to hospital is for nursing care, rather than for treatment (Ebrahim & Harwood, 1999a). 'Brain attack' is devoid of the nihilistic connotations of 'stroke', emphasises that this is a treatable condition, and may help to promote a change in physician attitude (Starkman & Saver, 1997).

3.5.3 Benefits beyond thrombolysis

The main purpose of brain attack has been to increase the number of patients who might receive thrombolysis. However, an aggressive approach to the assessment of all patients is likely to be beneficial (Hachinski, 1996). All patients can benefit from stroke unit care (Stroke Unit Trialists' Collaboration, 2001). Blood pressure needs to be maintained, hyperglycaemia controlled, and hyperthermia treated (Hachinski, 1996). Although trials of neuroprotectants have been

disappointing to date, there may be a role for combined treatment with thrombolysis (Grotta, 1999). Other promising treatments include hypothermia, haemodilution, emergency carotid endarterectomy, middle cerebral artery embolectomy or hemicraniectomy (Heros *et al.*, 1997). Primary intracerebral haemorrhage may benefit from early clot removal (Heros *et al.*, 1997). Where evidence is currently lacking for new treatments, trials may become feasible if large numbers of patients can be randomised within minutes or hours of symptom onset. Prompt intervention holds the best hope for benefit (Hachinski, 1996).

3.5.4 The risks of using brain attack

There may be potential risks of using brain attack. Patients with stroke mimics (e.g. seizure, migrainous aura) could be drawn into fast-track systems and exposed to the risks of acute treatment, if they are diagnosed as brain attack. It is important that brain attack is seen as an interim label rather than a definitive diagnosis.

3.6 Summary

- I propose that 'brain attack' is a useful description of a clinical state in the early stages of suspected cerebrovascular disease
- There has not been a clear definition of brain attack the term. Its use has primarily been to champion a public (and professional) education campaign in the United States
- There are advantages for stroke patients from the change in attitude that using this term would engender

Chapter 4 : A systematic review of the accuracy of the clinical diagnosis of stroke

4.1 Introduction

The clinical assessment is the key process that determines whether the patient with brain attack will receive treatment. In the past, when little was done acutely, an accurate clinical diagnosis within the first few hours was not so important. Thrombolysis has changed that. Yet, as noted by Hachinski (1996), clinical assessment of the patient can be difficult:

> "In contrast to myocardial infarction, which manifests with pain or a limited repertoire of symptoms and signs, stroke can present with bewildering variety, as can its mimics. Inexpert diagnosticians could unintentionally subject some of their patients to the serious risk of thrombolysis without any hope of benefit."

This review is written from the perspective of a hospital-based stroke physician. Typically, a referral to the stroke team or unit is made after a non-specialist doctor (such as an emergency physician or general practitioner, without access to brain imaging) has assessed the patient. This chapter will examine the accuracy of the bedside diagnosis of stroke (using the final diagnosis, determined by the stroke physician after observation and completion of investigations, as the gold standard). The causes and frequencies of conditions that mimic stroke will be described, to determine more precisely what difficulties are encountered in the assessment of brain attack.

4.2 Aims

This review sought to systematically search the literature for data to address the following aims:

(1) To determine the accuracy of the initial bedside diagnosis of stroke versus non-stroke by non-specialist medical practitioners blind to results of investigations

(2) To determine if the misdiagnosis rate was greater in the hyperacute phase of brain attack (within six hours of symptom onset), compared to later stages

(3) To describe the conditions that mimic stroke, and their frequencies

(4) To determine the proportion of mimics that were positively identified by brain imaging

4.3 Methods

4.3.1 Selection of studies

A systematic review of the literature was undertaken to identify appropriate observational studies of the accuracy of the clinical diagnosis of stroke. Included were any studies in which an initial, bedside diagnosis of stroke was made by a medical practitioner with no specific training in neurology or stroke, and later validated by a stroke expert. I used the Cochrane Database of Systematic Reviews methodology to perform an electronic search (Cochrane Stroke Group, 2001). Although this methodology was developed for reviews of randomised controlled treatment trials, the same principles apply to reviews of observational studies (Keir

and Wardlaw, 2000). I used a broad search strategy that consisted of the Cochrane search strategy for stroke, combined with a strategy to detect diagnostic studies and errors/false diagnoses, expanded to maximise the number of hits (**see Appendix 1**). Reference lists of studies obtained were hand-searched, as were abstract books from recent major stroke meetings.

I limited the search to English language studies in Medline, as I had insufficient time to search other databases (e.g. Embase) or translate non-English articles. The search was performed from 1980 to July 2001, to obtain studies where CT scanning had been performed routinely (this was critical for the final diagnosis, *see below*). Case reports, and studies published in abstract form only were excluded.

4.3.2 Assessment of study quality

An important component of a systematic review is to assess the quality of the studies identified (Deeks, 2001). It has been shown that studies with methodological shortcomings overestimate a test's diagnostic accuracy (Lijmer *et al.*, 1999). The initial clinical assessment of a patient with possible stroke by a non-specialist may be viewed as a diagnostic test. However, the stated purpose of the majority of the studies identified was not to assess the accuracy of the clinical assessment. It would be unreasonable to rigidly apply the criteria suggested by Jaeschke and co-workers (1994a; 1994b) to the studies of this review.

I therefore developed my own measures of study quality (see **Table 4.1**), which were based on several sources (Sackett *et al.*, 1985a; Jaeschke *et al.*, 1994a; Jaeschke *et al.*, 1994b; Holloway & Feasby, 1999; Lijmer *et al.*, 1999; Deeks, 2001). Ideally, the study was prospective. The patient sample should have been consecutive

and selected without restrictive exclusion criteria (it is essential that the sample in the study closely resemble clinical practice (Jaeschke *et al.*, 1994a; Holloway & Feasby, 1999)). To ensure that comparisons were uniform, the initial clinical assessment should have been made prior to investigations (particularly brain imaging). The gold standard diagnosis was the final diagnosis, ideally based on both independent expert clinical assessment and all investigation results (rather than just brain imaging, which may be normal). The final diagnosis should have been made after a reasonable period of time had elapsed, although it was difficult to define a 'reasonable' period of time (in some situations only a day may be required, in others, one or more weeks). Finally, a reasonable number (arbitrarily set at 50%) of the patient sample should have had either a brain scan or autopsy. It was not necessary for all patients to undergo brain scanning or autopsy, as many conditions that mimic stroke will not be discovered by a brain scan.

I used these quality measures to comment on the probable reliability of this review, rather than to exclude individual studies.

4.3.3 Data extraction and analysis

I extracted relevant data from the studies. The measure of accuracy used in this review was determined by the fact that in most studies, only patients with an initial diagnosis of stroke were likely to be further evaluated. This allowed the determination of positive predictive value (PPV, = true positives/[true positives + false positives]) but not other accuracy parameters such as specificity or sensitivity. Only those with a final diagnosis of stroke were classed as true positives, not patients with a final diagnosis of transient ischaemic attack or possible stroke. Details of

stroke mimics were tabulated. Frequencies, and their 95% confidence intervals (95% CI), were calculated. Analyses were performed with Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997) and Confidence Interval Analysis software (version 2.0.0, ©Trevor Bryant 2000).

4.4 Results

4.4.1 Study selection

The systematic search strategy identified 38 potentially relevant studies, from a total of 4,982 titles. 13 studies were excluded. Nine of these studies were concerned with paramedic diagnosis of stroke (Bratina *et al.*, 1995; Kothari *et al.*, 1995a; Kidwell *et al.*, 1998; Zweifler *et al.*, 1998a; Smith *et al.*, 1998a; Harbison *et al.*, 1999; Smith *et al.*, 1999; Kidwell *et al.*, 2000; Harbison *et al.*, 2001). Two early studies (Weisberg & Nice, 1977; Britton *et al.*, 1984) were excluded as their primary aim was an evaluation of the usefulness of CT scanning, and the patient sample was therefore biased. An epidemiological study (Lauria *et al.*, 1995) was excluded as notifications to the research team were from neurologists or other consultant physicians once the patient had been hospitalised. One study (Mielke and Hennerici, 2001) was excluded as it was presented in abstract form only – there were insufficient details provided to draw conclusions.

The 25 studies selected (**Table 4.2**) were divided into three categories, according to the source and type of referral. In the first two categories, patients were initially assessed by an emergency physician. Patients were then admitted directly to a stroke unit or (in the United States) referred to a stroke team in nine studies (von Arbin *et al.*, 1979; von Arbin *et al.*, 1981; Norris and Hachinski, 1982; Chambers *et*

al., 1983b; Morris *et al.*, 1993b; Weir *et al.*, 1996b; The members of the Lille Stroke Program, 1997c; Zweifler *et al.*, 1997e; Zweifler *et al.*, 1998c). In eight studies, patients with suspected stroke were admitted to either general medical, geriatric or neurology wards, and a study investigator followed up on these admissions (Allen, 1983a; O'Brien *et al.*, 1987b; Lindley, 1993a; Kothari *et al.*, 1995a; Libman *et al.*, 1995b; Besson *et al.*, 1996a; Ferro *et al.*, 1998a; Allder *et al.*, 1999a).

The remaining nine studies were community-based. The diagnosis of suspected stroke was made by the general practitioner, who then referred the patient to a study investigator or neurovascular clinic (Sandercock *et al.*, 1985a; Ricci *et al.*, 1991; Anderson *et al.*, 1993c; Ellekjaer *et al.*, 1997a; Horn *et al.*, 1997b; Martin *et al.*, 1997d; Ferro *et al.*, 1998a; Kolominsky-Rabas *et al.*, 1998b; Vemmos *et al.*, 1999b). One study (Ferro *et al.*, 1998a) accepted referrals from both general practitioners and emergency room physicians, and presented results from both settings, thus has been treated in this review as two separate studies.

4.4.2 Study quality

Only two studies (Anderson *et al.*, 1993c; Vemmos *et al.*, 1999b) met all quality criteria for this review (see **Table 4.1**). In most studies the patient sample was consecutive (although the community-based part of Ferro et al's study (1998a) received 172 notifications from general practitioners, but only 52 patients were actually referred to be seen by the study neurologists).

Eligibility criteria

Many studies had restrictive eligibility criteria: Ricci et al (1991) included only patients with a definite first ever in a lifetime stroke; Allen (1983a) excluded

patients older than 76 years; O'Brien et al (1987b) required admissions to have had a stable deficit for 24 hours; Besson et al (1996a) required a stable deficit for 72 hours; Horn et al (1997b) excluded patients with reduced consciousness, prior stroke, headache or absence of hemiparesis; Allder et al (1999a) selected only anterior circulation ischaemia; Kolominsky-Rabas et al (1998b) included patients only after several neurological examinations, and Morris et al's (1993b) consecutive series excluded 'those with known non-vascular conditions'.

Timing of brain imaging

The initial (or bedside) diagnosis was made before imaging was performed in most UK studies (although this was not clearly stated in one report – probably because of space restrictions (Weir *et al.*, 1996b)). In some settings, emergency physicians had immediate access to brain imaging (Kothari *et al.*, 1995a; Ferro *et al.*, 1998a), and in others patients were scanned immediately on admission (The members of the Lille Stroke Program, 1997c; Kolominsky-Rabas *et al.*, 1998b).

Definitions of the diagnosis

14/25 studies provided definitions for the diagnosis of stroke (which was usually the World Health Organisation definition (Hatano, 1976)). Few studies provided criteria for deciding that a patient's condition was caused by a non-vascular condition. Four studies presented figures for a final diagnosis of 'possible stroke'. This was defined differently – in one study, patients who lacked laboratory evidence of infarct or haemorrhage were classed as possible stroke (von Arbin *et al.*, 1981), and another study provided a list of conditions that were considered possible stroke (e.g. migraine aura). Two studies provided no definition for possible stroke.

Many studies did not provide adequate details of how the final (or gold standard) diagnosis was reached. One study based the final diagnosis purely on the CT (Besson *et al.*, 1996a), and a further study was heavily influenced by results of advanced MR imaging (i.e. infarct only diagnosed if lesion seen on diffusion-weighted imaging) (Allder *et al.*, 1999a). Two studies used a single neurologist's opinion for the final diagnosis (Zweifler *et al.*, 1997e; Zweifler *et al.*, 1998c), and one study determined the diagnosis by retrospective case notes review (Kothari *et al.*, 1995a).

Were any strokes missed?

The community-based epidemiological studies went to great lengths to ensure that case ascertainment was complete. Only three hospital-based studies examined the issue of patients with true stroke whose initial bedside diagnosis was non-stroke. In two, the proportion of false negative diagnoses was around 1% (von Arbin *et al.*, 1980; Kothari *et al.*, 1995a). However, Zweifler et al's (1998c) study of referrals to a mobile stroke team, set up to provide thrombolysis, found that 60 patients with stroke were not notified to the code stroke team (there were 185 notifications).

4.4.3 Accuracy of the bedside clinical diagnosis

There was wide variation in the accuracy of the bedside clinical diagnosis of stroke (**figure 4.1**). Accuracy was higher for stroke unit admissions or referrals to a stroke team (PPV 88.8%, 95% CI 87.9 – 89.7), and general or neurology ward admissions (PPV 88.9%, 95% CI 87.5 – 90.4), than for community-based studies (PPV 72.4%, 95% CI 71.2 – 73.7). Mean positive predictive value for all 25 studies was 81.9% (95% CI 81.1-82.6%).

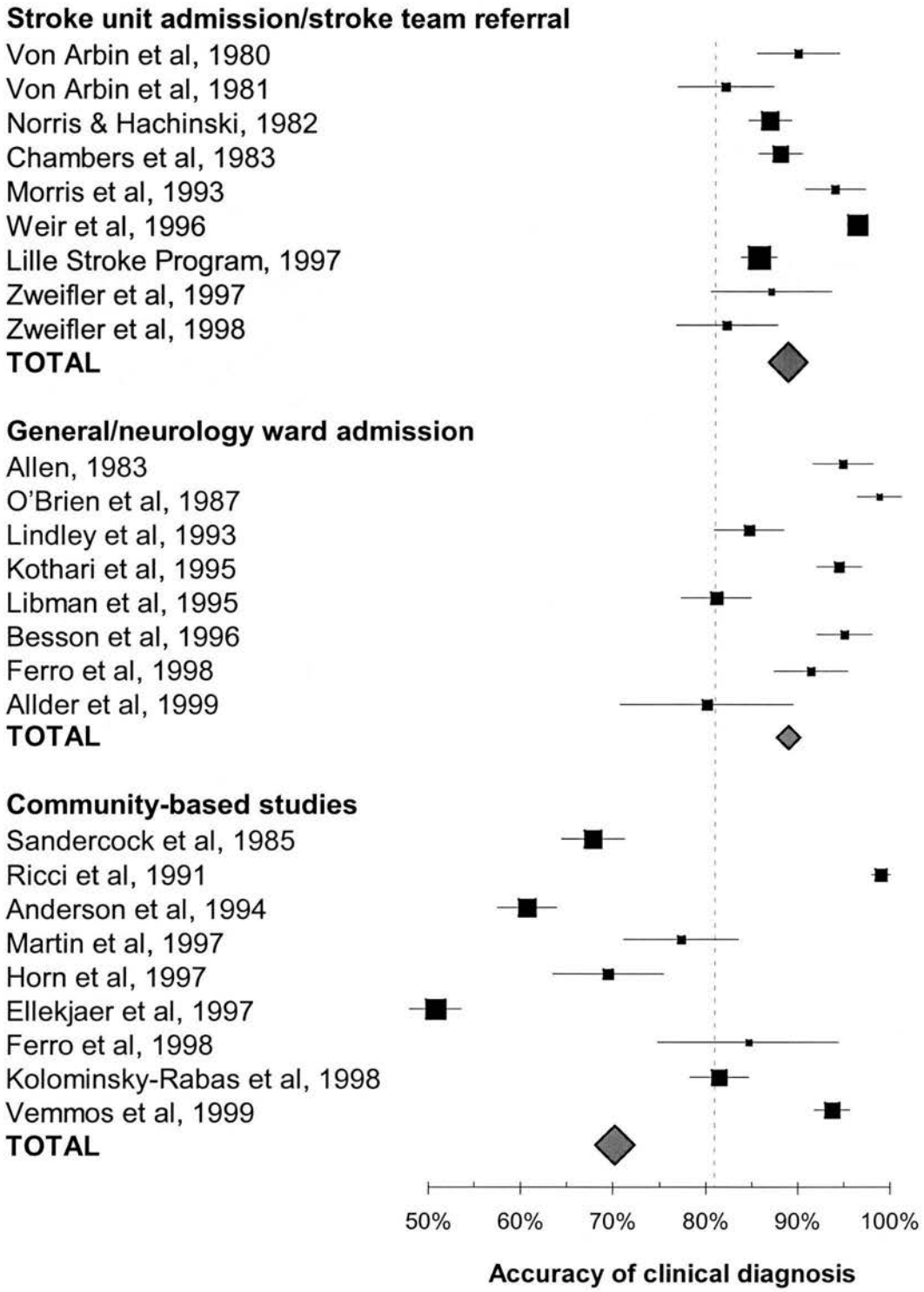


Figure 4.1 Accuracy of the initial diagnosis of stroke

Dotted vertical line is the mean positive predictive value for all studies (80.9%). Each study is represented by a square box, with 95% confidence intervals provided. Size of the box is proportional to the number of patients within each study. Subtotals (diamonds) are given for each of the three settings.

Seven studies provided figures for transient ischaemic attacks, which accounted for between 10% (Allder *et al.*, 1999a) and 18% (Kolominsky-Rabas *et al.*, 1998b) of the total in these studies.

Studies that reported the highest accuracy of referrals to a stroke unit (Morris *et al.*, 1993b; Weir *et al.*, 1996b) accepted patients 'in whom known non-vascular conditions had been excluded'. Although the patient sample was consecutive, it is not clear how much selection had occurred before referral to the stroke unit. Similarly, accuracy for general/neurology ward admissions was highest in those studies with restrictive entry criteria (Allen, 1983a; O'Brien *et al.*, 1987b; Besson *et al.*, 1996a). Kothari et al's study (1995a), often cited as evidence that the emergency physician's diagnosis of stroke is highly accurate, reported that the initial diagnosis was correct in 322/341 admissions (94%). However, patients received a CT scan in the emergency department, a phone consultation with a neurologist could be obtained, and the emergency physician had to present the case to the emergency department faculty before the decision was made to admit the patient (Kothari, 1996).

Community studies had lower accuracy than hospital-based studies. In the studies of Ellekjaer et al (1997a) and Anderson et al (1993c), general practitioners were encouraged to refer as many patients as possible, even if the symptoms were dubious. Conversely, Ricci et al (1991), found only four mimics amongst 379 patients, an accuracy of 99%. This study registered only those with first-ever-in-a-lifetime-stroke, and it was unclear how many patients were screened (and thus excluded) to obtain the final 379 *registered* patients.

4.4.4 Stroke mimics

The final diagnosis was definite stroke in 9,113 / 11,259 patients in total. Thus 2,146 patients had a final diagnosis other than stroke: there were 1,265 mimics, and the remainder were TIAs, possible strokes, or patients excluded from the study for various reasons. Seven of 25 studies (28%) provided no details of stroke mimics and 12 studies provided an incomplete list of mimics.

The frequencies (and their 95% confidence intervals) of stroke mimics are presented in **Figure 4.2**. The five major causes were: seizures (14.2% of mimics), toxic/metabolic disturbances (11.2%), sequelae of prior stroke (11.2%), space occupying lesions (11.2%), and syncope/presyncope (10.4%). The miscellaneous category accounted for 16% of all mimics (see **Table 4.3**). These included diverse conditions such as cardiac disorders, spinal cord lesions, multiple sclerosis, and rare neurological problems.

Clinical factors that increased the likelihood of an incorrect initial diagnosis included: inability to obtain a good history (Allen, 1983a; Sandercock *et al.*, 1985a; Ferro *et al.*, 1998a), absence of vascular risk factors (Ferro *et al.*, 1998a), reduced level of consciousness (Libman *et al.*, 1995b) and younger age of patient (Kothari *et al.*, 1995a). Physicians with better clinical skills made fewer errors than junior physicians (Norris and Hachinski, 1982).

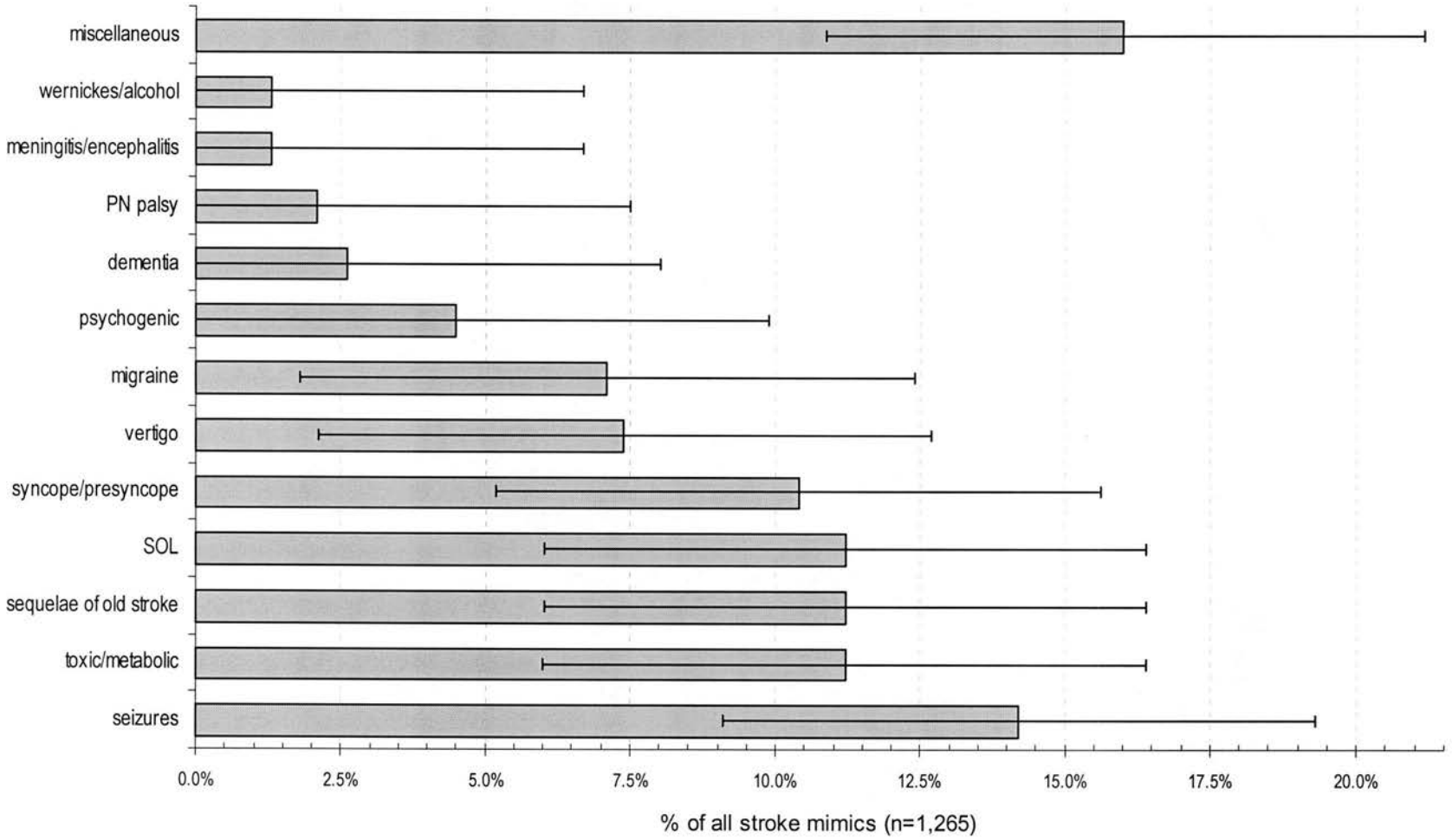


Figure 4.2 Stroke mimics

PN palsy: peripheral nerve palsy; SOL: space occupying lesion (tumour, subdural or abscess)

4.4.5 *The initial diagnosis in studies where a brain scan was available*

In four studies, the initial clinical diagnosis was made after a CT brain scan had been performed (Kothari *et al.*, 1995a; The members of the Lille Stroke Program, 1997c; Ferro *et al.*, 1998a; Kolominsky-Rabas *et al.*, 1998b). The mean PPV for the studies in which the initial diagnosis was made after scanning was 86.4% (95% CI 84.9-87.7%). For the studies where the clinical diagnosis was made before the CT scan, the mean PPV was 79.5% (95% CI 78.7-80.3%). The difference in means was significant (6.9% difference, 95% CI 5.2-8.4%).

4.4.6 *'Hyperacute stroke'*

Only 729/11,053 (6.6%) patients were recruited in the hyperacute phase of stroke (symptom onset less than six hours). Horn et al (1997b) recruited all 229 patients within six hours of onset to a community-based study. Despite rigid selection criteria, general practitioners achieved only 69% accuracy (but 96% if possible strokes were included). Allder et al's (1999a) hospital-based study recruited 70 patients with symptoms of anterior circulation ischaemia within six hours of onset. 57 / 70 (81%) had a final diagnosis of stroke. Five other studies (Morris *et al.*, 1993b; Libman *et al.*, 1995b; Zweifler *et al.*, 1997e; Ferro *et al.*, 1998a; Zweifler *et al.*, 1998c) reported the proportion of hyperacute stroke patients seen (which ranged from 25% to 57%), but did not provide figures for the accuracy of the initial diagnosis in those seen early. Ferro et al (1998a) found that time was not a significant influence on the accuracy of the initial assessment by emergency physicians, but numbers were small (46 seen within six hours/185).

4.5 Discussion

There is consistent evidence that large numbers of patients arrive at hospital within the first few hours of symptom onset (Harper *et al.*, 1992; Barsan *et al.*, 1994; Johnston *et al.*, 1999; Lacy *et al.*, 2001). Despite this, few patients receive time-critical treatments such as thrombolysis. The major barrier appears to be the long delay for the patient to be assessed in the emergency department (Evenson *et al.*, 2001; Barber *et al.*, 2001a).

A confident clinical diagnosis allows the clinician to rapidly arrange further investigations and treatment. The present delays are probably due to the uncertainty of junior doctors (the first contact point in emergency rooms) who are not comfortable dealing with acute neurological patients (Johnston *et al.*, 1999). For the experienced stroke clinician the diagnosis may seem easy, but is it so for the non-specialist doctor seeing a patient within minutes or hours of symptom onset?

An earlier review of the clinical assessment of stroke (Goldstein & Matchar, 1994) identified only two studies of the accuracy of the clinical diagnosis. The present review identified twenty-five. The accuracy of the bedside diagnosis of stroke by a non-specialist varied between 51% and 99%, depending on the source of referral, the presence of restrictive entry criteria, and the availability (to the referring doctor) of specialised tests. It is important to note that the community-based studies attempted to capture all strokes, thus GPs were encouraged to refer all possible strokes. These studies may have overestimated the number of mimics, but they do provide useful information (as an 'upper limit' of what the hospital-based doctor might expect). Overall, almost 20% of patients referred to a stroke physician were incorrectly diagnosed.

Methodological limitations of the included studies

I aimed to include many studies to provide a broad picture of what stroke clinicians can expect to be referred. There was considerable variation in the quality of the studies – few met all of the criteria developed for this review. In accordance with others (Lijmer *et al.*, 1999), we observed that studies with outlying results often contained sources of bias. Identifying these biases – patient exclusions, scan before the bedside diagnosis, etc. – allows a better understanding of the data.

I was surprised that only four studies included possible stroke as a final diagnosis. In one, 28% of all referrals were classed as possible stroke (Horn *et al.*, 2001). It is a fact of clinical life that there is uncertainty: as Sackett and colleagues state (1985b), "certainty is a delusion". How were all the other studies able to be so precise (particularly when few described how they determined what was a non-stroke)?

4.5.1 Limitations of the present review

The search strategy of the present review was limited to Medline and English language articles, which may have introduced bias. Although a recent study found that systematic reviews restricted to one language did not yield biased conclusions (Moher *et al.*, 2000), ideally all studies should be included in a systematic review. It is said that Medline lacks comprehensive references in the fields of psychology, medical sociology and non-clinical pharmacology (Greenhalgh, 1997). Other databases that can be searched include Embase, which focuses on drugs and pharmacology, and CINAHL, which covers nursing and allied health fields. Embase is more time consuming and less accessible than Medline (Woods & Trewheellar,

1998). However, using multiple databases identifies more studies, and is ideal for a comprehensive review (Woods & Trewheellar, 1998; Topfer *et al.*, 1999; Minozzi *et al.*, 2000).

The measure of accuracy used in this review was the positive predictive value (PPV). PPV depends on the prevalence of the disease being studied, so is not an ideal measure of test performance (Sackett *et al.*, 1985b; Ebrahim & Harwood, 1999a). Unfortunately, insufficient data were provided to determine sensitivity, specificity and likelihood ratios for the individual studies. Most studies did not follow patients admitted with a non-stroke diagnosis (i.e. true and false negatives). However, the aim of this review was to identify studies in a variety of settings (thus different prevalence of stroke mimics) to provide a robust overall estimate of the nature and proportion of mimics that a stroke physician will encounter.

4.5.2 Implications of the review

Stroke physicians should encourage referrals

It is possible to increase the accuracy of referrals by stipulating rigid criteria (such as a definite hemiparesis). However, this would come at the expense of missing patients with true stroke, as was observed (Zweifler *et al.*, 1998c). To ensure that patients might receive the benefit of acute care, stroke physicians should actively encourage the referral of *all* patients with possible stroke (no matter how vague the symptoms). We must be prepared for a high rate of diagnostic error.

Improved clinical skills

In addition, stroke physicians need to provide better training to junior doctors. Many stroke mimics (e.g. sudden onset multiple sclerosis or encephalitis) are neurological disorders that are rarely seen by a non-specialist. As was shown by Norris & Hachinski (1982), greater experience and clinical skill resulted in better accuracy. However, only one study (Libman *et al.*, 1995b) examined the clinical clues that suggested a mimic.

An alternative approach would be to involve the stroke specialist at an earlier stage (Hachinski, 1996; Adams, Jr., 1998). Recent evidence suggests that US hospitals that have a stroke neurologist are more likely to treat acute stroke patients with thrombolysis (Reed *et al.*, 2001). However, this is impractical for the many smaller centres that do not have the resources to provide a mobile stroke team. Improved methods of clinical diagnosis are still required.

The CT brain scan is normal in most mimics

The present review found that studies with access to immediate brain scanning were significantly more accurate that those in which the scan was performed later. There were other sources of bias in these studies that may also have influenced accuracy, such as early assessment by a stroke specialist. It may be optimistic to believe that improved imaging – though desirable – is the answer. In the 11.2% with a space-occupying lesion, and the few with subarachnoid haemorrhage, and possibly dementia, the scan may be helpful. The scan may also be misleading (e.g. if the patient has suffered a previous stroke).

More research is needed

Patients with symptoms that eventually resolve (i.e. transient ischaemic attacks) are a particular problem in the clinical assessment of hyperacute stroke. This review suggests that up to 18% of patients turn out to have had a TIA. Ideally, the clinician could identify such patients before commencing treatment. In addition, few studies have examined patients in the hyperacute phase of stroke. One might anticipate that the diagnosis in the first few hours would be difficult, but the available data from the present review cannot be extrapolated to routine clinical practice.

More clinical research is required. Studies should try to avoid the biases identified in this report – in particular, the patient sample should reflect routine practice, and the definitions and methods of reaching the final diagnosis should be specified. There is a need for further research into the features that suggest a mimic is likely, and the features of hyperacute stroke that are most reliable.

4.6 Summary

- Accuracy of the non-specialist clinical diagnosis of stroke is around 81%, but may be as low as 51% or as high as 99% depending on the setting, selection criteria, and investigations available
- Few of the studies identified aimed to address the issue of accuracy, and thus contained major biases
- There are a large number of stroke mimics. There is a need for better training of junior doctors in the clinical skills required to diagnose brain attack

- Brain imaging, though helpful, should not be relied on excessively as imaging will be normal for most stroke mimics
- Further methodologically sound clinical studies are required

Table 4.1: Quality measures of included studies

Quality measure	Number clearly specified (n=26)
▪ Prospective study design	22 (85%)
▪ Consecutive patient sample	25 (96%)
▪ Patient sample lacked restrictive exclusions	18 (69%)
▪ Initial clinical assessment was made before investigations	20 (77%)
▪ Final (or gold standard) diagnosis based on both an independent expert's clinical assessment and all investigation results	17 (65%)
▪ Final diagnosis made after a reasonable period of time had elapsed	15 (58%)
▪ A reasonable number of patients had a brain scan or autopsy	16 (62%)

Table 4.2: Characteristics of included studies

Study	Design	Setting	Total n	Final diagnoses	Notes
Von Arbin et al, (1980)	P	Consec admissions to SU	169	152 True stroke 17 Non-stroke	Admission criteria: 'recent and sudden onset of focal neurological deficit'; 39% had autopsy or 'extensive investigations in S.U.'
Von Arbin et al, (1981)	P	Consec admissions to SU	206	169 True stroke 6 Non-stroke 8 Possible stroke 23 TIA	Primary aim of study was classification of stroke type; 20% had autopsy and/or CT
Norris & Hachinski, (1982)	P	Consec admissions to SU	821	713 True stroke 108 Non-stroke	30% had CT; patients admitted to S.U. after being seen by neurology resident
Allen (1983a)	P	Consec admissions to general ward with stroke	174	165 True stroke 9 Non-stroke	Excluded patients aged over 76; compared the general physician's opinion before CT/autopsy with final diagnosis
Chambers et al, (1983b)	P	Consec admissions to SU	700	616 True stroke 84 Non-stroke	
Sandercock et al, (1985a)	P	Community epidemiological study	736	499 True stroke 74 TIA 134 Non-stroke	42% had CT or autopsy 29 'referred in error'

Study	Design	Setting	Total n	Final diagnoses	Notes
O'Brien et al, (1987b)	P	Consec admissions to geriatric unit	81	80 True stroke 1 Non-stroke	Criteria for admission: deficit for at least 24 hours
Ricci et al, (1991)	P	Community epidemiological study	379	375 True stroke 4 Non-stroke	Criteria for inclusion: first ever in a lifetime stroke
Lindley et al, (1993a)	P	Consec general ward admissions	350	296 True stroke 54 Non-stroke	IST pilot phase
Morris et al, (1993b)	R	Consec admissions to SU	200	188 True stroke 12 Non-stroke	Patients with 'known non-vascular conditions' not admitted to S.U.
Anderson et al, (1993c)	P	Community epidemiology study	883	536 True stroke 224 Non-stroke 123 TIA	
Kothari et al, (1995a)	R	Consec stroke admissions through E.D.	441	322 True stroke 19 Non-stroke 70 TIA 30 SAH	All patients had CT in E.D., were discussed with panel of E.D. consultants, some patients were discussed with neurologist
Libman et al, (1995b)	R	Consec stroke admissions through E.D.	411	333 True stroke 78 Non-stroke	Criteria for selection: sudden onset of focal deficit for at least one hour

Study	Design	Setting	Total n	Final diagnoses	Notes
Besson et al, (1996a)	P	Consec admissions through E.D.	200	190 True stroke 10 Non-stroke	Criteria for admission: unilateral weakness >72 hours, final diagnosis based on CT only
Weir et al, (1996b)	R	Consec admissions to SU	1029	992 True stroke 37 Non-stroke	Criteria for selection: sudden onset of focal deficit for at least one hour
Ellekjaer et al, (1997a)	P	Community-based epidemiological study	1169	593 True stroke 262 Non-stroke 168 TIA 56 Possible stroke	Details of 90 patients not recorded
Horn et al, (1997b)	P	Consec GP referrals to a trial	229	159 True stroke 7 Non-stroke 63 Possible stroke	VENUS trial. Exclusion criteria: reduced consciousness, prior stroke, headache, absence of hemiparesis (Horn *et al.*, 2001)
Lille Stroke Program, (1997c)	P	Consec admissions to SU	1250	1071 True stroke 113 Non-stroke 66 Possible stroke	Patients admitted to S.U. following CT scan
Martin et al, (1997d)	P	Consec referrals to an out-patient neurovascular clinic	176	136 True stroke 40 Non-stroke	TIA referrals excluded. Final diagnosis based only on neurologist's opinion (proportion of patients who had CT not stated)
Zweifler et al, (1997e)	P	Consec referrals to stroke team ('code stroke')	100	87 True stroke 13 Non-stroke	Final diagnosis based on initial evaluation by neurologist

Study	Design	Setting	Total n	Final diagnoses	Notes
Ferro et al, (1998a)	P	Community-hospital study – GP diagnosis	52	44 True stroke 8 Non-stroke	GPs notified 174 strokes, but only referred 52
Ferro et al, (1998a)	P	E.D. diagnosis	185	169 True stroke 16 Non-stroke	Emergency physicians had access to CT scanner
Kolominsky-Rabas et al, (1998b)	P	Community-based epidemiological study	571	465 True stroke 3 Non-stroke 103 TIA	Patients had multiple neurological assessments before enrolment
Zweifler et al, (1998c)	P	Consec referrals to a stroke team ('code stroke')	185	152 True stroke 33 Non-stroke	This study was performed after NINDS rt-PA study results released, 2 month overlap with 1997 study. 60 admissions with stroke did not trigger 'code stroke' system
Allder et al, (1999a)	P	Consecutive anterior circulation strokes	70	57 True stroke 6 Non-stroke 7 TIA	
Vemmos et al, (1999b)	P	Community-based epidemiological study	592	555 True stroke 37 Non-stroke 15 excluded	Most referred in hospital

Legend:
P – prospective; SU – stroke unit; Consec – consecutive; TIA – transient ischaemic attack; R – retrospective; E.D. – Emergency department SAH – subarachnoid haemorrhage

Table 4.3: The 'miscellaneous' causes of stroke mimics

	Number
Cardiac cause (ischaemia, heart failure etc.)	24
Spinal cord lesion	13
Multiple sclerosis	12
Transient global amnesia	11
Parkinson's disease	8
Subarachnoid haemorrhage	6
Trauma	4
Hypertensive encephalopathy	3
Myasthenia gravis	3
Acute confusional state	2
Aortic dissection	2
Herpes encephalitis	2
Motor neuron disease	2
Parasthesia of unknown cause	2
Vertebral artery dissection	1
Friedreich's ataxia	1
Multiple systems atrophy	1
Cerebral sarcoidosis	1
Normal pressure hydrocephalus	1
Sleep apnoea	1
Perforated duodenal ulcer	1
Weakness of unknown cause	1
Arm stiffness of unknown cause	1
Arm pain of unknown cause	1
Sudden death	*13*
No details provided	*76*
Total	**193**

Chapter 5 : The clinical features of hyperacute stroke – an analysis of the International Stroke Trial

5.1 Introduction

Stroke is a medical emergency, but the diagnosis of hyperacute ischaemic stroke can be difficult for the inexperienced doctor. Better understanding of the clinical features common to patients presenting very early is required, as there is no good reason to assume that patients presenting early are the same as those presenting later.

I used data from the International Stroke Trial (IST) to explore the clinical features of patients with hyperacute stroke, compared to patients presenting later. The IST was used for this analysis as it enrolled large numbers of patients assessed within the first few hours, as well as those who reached hospital at later times (up to 48 hours after onset), and in different countries where different health resources might influence time to presentation.

5.2 Aims

The aim of this analysis was to assess the frequency of different clinical features among patients recruited into the IST at different times after stroke onset.

5.3 Methods

Methodology of the IST

The IST was the largest available dataset that contained details of patients with acute, presumed ischaemic stroke assessed up to 48 hours after symptom onset. The trial sought to evaluate the efficacy of antithrombotic therapy, started as soon as possible after onset of ischaemic stroke. Full details of the protocol have been published elsewhere (International Stroke Trial Pilot Study Collaborative Group, 1996; International Stroke Trial Collaborative Group, 1997). Data collected at assessment included: age, gender, time since symptom onset, whether symptoms were first noted on waking from sleep, conscious level, systolic blood pressure, presence of atrial fibrillation, seven key neurological signs, and stroke subtype (after Bamford et al (1991)). I applied a validated model (Slattery & Sandercock, 1996) which used the neurological deficit at assessment to calculate a baseline stroke severity score. The greater the number of deficits (aphasia, hemiparesis etc), the higher the baseline severity score. Outcome was measured by (1) the proportion of patients dead at 14 days (early deaths were notified to the trial office), and (2) the proportion dead or dependent in daily activities at six months (functional outcome was assessed by postal questionnaire (International Stroke Trial Pilot Study Collaborative Group, 1996)).

Computed tomography (CT) or Magnetic resonance (MR) brain imaging was to be performed where possible before randomisation (and was mandatory for patients in coma). If brain imaging were not immediately available, and the clinician felt that haemorrhagic stroke was unlikely, the patient could be randomised in the study (with imaging to be performed as soon as possible after enrolment). This was

allowed on the basis that the benefit of antithrombotic therapy might be time-dependent and hence early randomisation would offer scope for greater benefit.

The final diagnosis of the event that led to the patient's inclusion in the trial was based on all of the available clinical, radiological (and autopsy) data. As anticipated, a small proportion of patients (5%) proved to have a non-stroke condition or intracranial haemorrhage as the final diagnosis. The primary analysis of the IST was an intention-to-treat analysis, so these patients were retained in the database. In this report, I have combined data from the treatment and control patients, and the findings therefore do not describe variation between the groups in the efficacy of aspirin or heparin

Methodology of the present analysis

I compared the baseline clinical features, stroke subtype classification, stroke severity, final diagnosis, early deaths and six-month outcome of patients assessed within three hours, four to six hours and seven to 48 hours. I plotted median severity (and interquartile range) of patients assessed and randomised into the IST at three hourly intervals for the first 12 hours, and six hourly thereafter, to explore the relationship between severity and time to randomisation (as stroke severity was not normally distributed). I analysed the relationship between severity and time by linear regression (using time from onset to assessment as a continuous variable).

Comparisons between countries

I hypothesised that there would be no major differences in the features of patients assessed early between countries, despite differences in healthcare systems. I examined measures of severity for each country that randomised over 500 patients

to give a reasonable sample. By excluding countries that recruited fewer patients, I wished to avoid the extreme variability that can occur with small sample sizes (Weir *et al.*, 2001).

Statistical analyses

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997) and SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999).

5.4 Results

5.4.1 Baseline characteristics and outcome

The IST enrolled 19,435 patients in 36 countries, of whom 3,165 (19%) were assessed and treated within six hours, and 843 (4.3%) within three hours. Almost all of the clinical features assessed among patients randomised within three hours, and between four and six hours, were significantly different to those randomised between seven and 48 hours (χ^2 test for trend) (see **Table 5.1**). The most important differences were that patients assessed within three hours were more likely to have cortical signs, reduced consciousness and total anterior circulation syndrome (TACS) than patients assessed later.

Patients assessed early had worse baseline stroke severity. **Figure 5.1** shows a trend for severity to decrease as time to assessment increased, particularly over the first 12 hours. When analysed by linear regression, the trend was significant but the strength of the association was weak (r^2=0.015, p<0.0001).

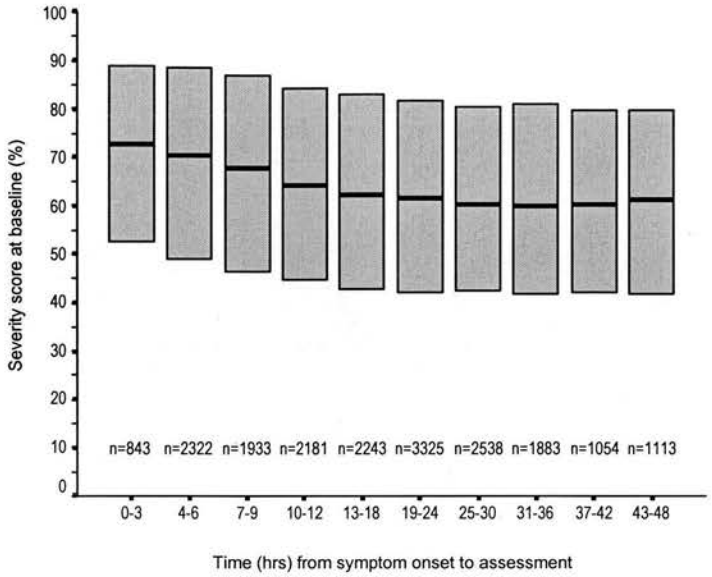


Figure 5.1 Baseline stroke severity score in the IST, subdivided by time to randomisation. *Severity score (expressed as the % likelihood of a poor outcome) was determined by the neurological deficit at baseline. The boxes represent the inter-quartile range and the thick black line the median severity score for patients within each time interval.*

5.4.2 Final diagnosis and outcome

Patients were randomised into the IST if the *clinical* diagnosis were acute ischaemic stroke. In two thirds, the clinical diagnosis had been confirmed as definite ischaemic stroke by neuroimaging prior to randomisation. If the patient were conscious, enrolment was permitted whilst the scan was being arranged. 403/843 (48%) of patients recruited within three hours had a CT scan before randomisation, compared with 1,279/2,322 (55%) recruited between four and six hours, and 11,342/16,270 (70%) recruited between seven and 48 hours ($p<0.0001$, χ^2 test for trend).

Among those not scanned until after randomisation, as expected, there were some patients with haemorrhagic stroke (n=538). 51/440 (12%) of patients recruited within three hours, 110/1,043 (11%) of patients recruited four to six hours, and

377/4,928 (7.7%) of patients recruited after six hours (in all cases before the CT scan) had an intracerebral haemorrhage, (p=0.0004, χ^2 test for trend) (**Table 5.2**).

More patients assessed within three hours died within 14 days of stroke or were either dead or dependent at six months (**Table 5.2**).

5.4.3 Comparisons between countries

There were nine countries that individually recruited more than 500 patients in the IST. **Table 5.3** shows the proportions of patients randomised within six hours, which varied between seven and 25% of all patients recruited by each country. Patients randomised early had worse baseline severity scores than those recruited later in all countries; although this finding was not significant in Norway, Sweden and Argentina (Mann-Whitney U test). These three countries recruited only a few early patients, thus there is the possibility of type II error explaining the lack of statistical significance. Clinical evidence of an extensive cortical infarction (TACS) was more frequently observed in patients randomised within six hours in all countries except Norway and Sweden ($p<0.001$, χ^2 tests).

5.5 Discussion

The IST enrolled 3165 patients within six hours (and 843 patients within three hours) of onset, the largest group of prospectively recruited hyperacute stroke patients ever reported. The data were systematically collected, came from a variety of settings, and follow-up was 99% complete. Although there are limitations to the IST data, the clear finding of the present analysis is that patients with features of severe stroke arrived at hospital and were assessed earlier. This was seen in seven of

the nine major recruiting countries, and is therefore likely to be independent of regional variations in healthcare provision.

Comparison with other studies

These findings in 19,435 patients confirm previous smaller single centre (Jorgensen *et al.*, 1996; Goldstein *et al.*, 2001) and multicentre (Davalos *et al.*, 1995; Barber *et al.*, 2001a) studies which showed that the clinical features of patients with suspected hyperacute stroke were different to those presenting later. In addition, the present study clarifies the results of other earlier studies, which did not measure severity directly (Kay *et al.*, 1992; Anderson *et al.*, 1995; Wang *et al.*, 1997; Smith *et al.*, 1998b; Lacy *et al.*, 2001). This analysis refutes the findings of two moderate-sized studies which found that severity was not a significant factor in early presentation (Harper *et al.*, 1992; Barsan *et al.*, 1994).

5.5.1 Limitations of the present study

The limitations of the data presented here are that they were collected in a randomised-controlled trial, rather than an epidemiological study, and were purposefully kept brief, as there is evidence that one barrier to recruitment is excessive data collection (Ross *et al.*, 1999). The exact time of admission to hospital (and other details of pre- or in-hospital delays) was not known. One of the now standard stroke severity scales (such as the National Institute of Health Stroke Scale) was not used in the IST. Therefore we approached the assessment of stroke severity from several angles: we used a validated model to assign a baseline 'severity score' to each patient, we looked at individual clinical variables such as coma, stroke

subtype and cortical neurological signs, and we looked at outcome. All pointed to the same conclusion.

Given the large sample size of the IST, even small differences between groups were found to be statistically significant. For example, the linear regression analysis of baseline severity score and time found an r^2 value of 0.015, suggesting that although significant, the strength of the relationship observed was small. In this report, changes that were clinically significant have been highlighted.

5.5.2 Implications of the present study

Training

Clinicians should be aware that the features of patients who present early are likely to be different to 'average' stroke, and that bedside diagnosis may be more difficult. Clinical algorithms to aid early diagnosis are needed, which could be used to educate non-specialist staff as well as stroke physicians and neurologists. Most acute stroke patients are cared for by non-specialist staff (Mitchell *et al.*, 1996), who may not be familiar with the clinical features of the hyperacute syndrome.

Organisation of stroke services

In the IST, there was a strong tendency for patients who later turned out to have haemorrhagic stroke to be (inadvertently) randomised earlier. Since such patients may be 'fast-tracked' for thrombolysis (until the CT scan is performed), hyperacute stroke services will need to be designed to cope with increased numbers of patients with acute intracerebral haemorrhage. Care must be taken to ensure that

these patients are not neglected in the rush to thrombolyse the ischaemic stroke patient.

The impact of stroke severity on time to presentation is relevant to audit of stroke service performance and observational cohort studies. Audits that assess the performance of different acute stroke services must allow for the fact that patients presenting earlier are likely to be more severe (otherwise, stroke units that manage a larger proportion of early-presenting patients will appear to perform worse than units that manage more late-presenting patients) (Weir and Dennis, 2001).

Design of clinical trials

For randomised controlled trials, these data emphasise the importance of employing both time and stroke severity as stratification (or minimisation) variables. For example, in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study, there was substantial imbalance in stroke severity among those recruited between 91 and 180 minutes, which could potentially have biased the estimate of treatment effect (Marler *et al.*, 2000). Such imbalance will not necessarily be corrected by standard statistical covariate adjustment techniques (Mann, 2002).

5.6 Summary

- The IST data have significant limitations that permit only cautious conclusions to be drawn
- This report highlights the differences in patients assessed within hours of onset, compared to patients assessed later. The finding of greater stroke

severity in those assessed early was consistent across several different clinical measures, and in patients enrolled throughout the world.

- The findings have important implications for the provision of stroke services, training of staff, and the design and interpretation of observational studies and randomised-controlled trials.

Table 5.1 Clinical features at baseline among 19,435 patients, assessed within 3 hours (n=843), 4-6 hours (n=2,322) and 7-48 hours (n=16,270) after onset

	Features among patients randomised:						
Clinical Feature	**0-3 hours**	**(%)**	**4-6 hours**	**(%)**	**7-48 hours**	**(%)**	***P****
Male	459 / 843	**(54)**	1258 / 2322	**(54)**	8690 / 16270	**(53)**	N.S.
Age 80 and over	232 / 843	**(28)**	662 / 2322	**(29)**	4238 / 16270	**(26)**	0.03
Asleep at onset	155 / 843	**(18)**	651 / 2322	**(28)**	4879 / 16270	**(30)**	<0.0001
Reduced consciousness	281 / 843	**(33)**	701 / 2322	**(30)**	3532 / 16270	**(22)**	<0.0001
Systolic BP>185	168 / 843	**(20)**	482 / 2322	**(21)**	2824 / 16270	**(17)**	<0.0001
In Atrial Fibrillation†	181 / 821	**(22)**	466 / 2227	**(21)**	2522 / 15403	**(16)**	<0.0001
Cortical Signs:‡							
Aphasia	462 / 813	**(57)**	1186 / 2232	**(53)**	6861 / 15806	**(43)**	<0.0001
Neglect	163 / 630	**(26)**	462 / 1786	**(26)**	2553 / 13571	**(19)**	<0.0001
Hemianopia	156 / 597	**(26)**	424 / 1688	**(25)**	2516 / 13205	**(19)**	<0.0001
Any cortical sign	580 / 843	**(69)**	1495 / 2322	**(64)**	8940 / 16270	**(55)**	<0.0001
Stroke Subtype: ‡§							
TACS	301 / 841	**(36)**	727 / 2315	**(31)**	3610 / 16222	**(22)**	<0.0001
PACS	357 / 841	**(42)**	926 / 2315	**(40)**	6572 / 16222	**(41)**	N.S.
LACS	121 / 841	**(14)**	428 / 2315	**(18)**	4108 / 16222	**(25)**	<0.0001
POCS	62 / 841	**(7)**	234 / 2315	**(10)**	1932 / 16222	**(12)**	<0.0001

** Significance determined by χ^2 test for trend. N.S. – not significant, p>0.05.*

† The presence of atrial fibrillation was not recorded in the 984 patients randomised in the pilot phase of the trial.

‡ total number of patients where the sign or stroke subtype could be determined

Table 5.2: Outcome for 19,435 patients, assessed within 3 hours (n=843), 4-6 hours (n=2322) and 7-48 hours (n=16270) after onset

Outcome	Feature among patients randomised: 0-3 hrs	(%)	4-6 hrs	(%)	7-48 hrs	(%)	P^*
Final Diagnosis:							
Intracerebral haemorrhage	54/843	**(6.4)**	115/2322	**(5.0)**	430/16270	**(2.6)**	<.001
Randomised after CT†	3/403	**(0.7)**	5/1279	**(0.4)**	53/11342	**(0.5)**	N.S.
Randomised without CT†	51/440	**(11.6)**	110/1043	**(10.5)**	377/4928	**(7.7)**	<.001
Non-stroke lesion	24/843	**(2.8)**	77/2322	**(3.3)**	319/16270	**(2.0)**	<.001
Deaths within 14 days	114/843	**(13.5)**	278/2322	**(12.0)**	1389/16270	**(8.5)**	<.001
Dead or dependent at 6 months‡	590/836	**(70.6)**	1563/2305	**(67.8)**	9972/16144	**(61.8)**	<.001

** P value determined by χ^2 test for trend. N.S. – not significant, p>0.05.*
† Patients were enrolled in the IST if the randomising doctor felt the clinical diagnosis was acute ischaemic stroke. If the patient were conscious, and there was likely to be a delay before CT brain scan could be performed, enrolment was permitted whilst the scan was being arranged. The intracerebral haemorrhages have been subdivided by whether the patient was scanned immediately before randomisation or after randomisation.
‡ A small number of patients were lost to follow-up (less than 1%)

Table 5.3: Measures of severity in patients recruited early among nine countries that contributed over 500 patients to the IST

	Proportion of patients randomised 0-6 hours		Median severity score† among patients randomised:	
Country	**n/N**	**(%)**	**0-6hrs**	**7-48hrs**
Argentina	49/545	**(9.0)**	65	56
Australia	102/597	**(17)**	76	58
Italy	739/3437	**(22)**	67	59
Netherlands	176/728	**(24)**	66	57
Norway	52/526	**(10)**	68	65
Poland	157/759	**(21)**	73	61
Sweden	46/636	**(7.2)**	68	60
Switzerland	407/1631	**(25)**	77	72
UK	888/6257	**(14)**	78	68
Total	*2616/15116*	*(17)*	*72*	*64*

† Severity score predicted the likelihood of a poor outcome (death or dependence) for each patient based on initial neurological deficits (expressed as percentage likelihood of a poor outcome). The difference between groups was significant for all countries except Argentina, Norway and Sweden (Mann-Whitney U *test, difference between mean severity scores).*

Chapter 6 : The potential of imaging in hyperacute stroke

6.1 Introduction

Imaging is fundamental to the assessment and management of acute stroke. In the past, the main purpose of imaging was to differentiate haemorrhage from infarct. Whilst this remains vital, recent research using computed tomography (CT) and magnetic resonance (MR) has suggested that imaging can confirm the diagnosis of infarction within hours (or even minutes) of symptom onset, and possibly assist in the selection of treatment for acute ischaemic stroke.

In this chapter, I will review the use of CT, structural MR (T2, gradient echo sequences etc) and advanced MR (diffusion and perfusion sequences) to diagnose acute stroke. This thesis is not concerned with the complex technical details of different imaging techniques, but rather how best to apply them to solve common clinical problems. Hence each section will provide the clinician with brief – but essential – technical background.

6.2 Brain imaging is required to differentiate haemorrhage from infarction

The initial step in the diagnosis of brain attack is to determine whether the event is a result of a vascular process (Bamford, 2001). The second step is to distinguish between ischaemic stroke and primary intracerebral haemorrhage (PICH). This is an important distinction, as the causes, prognosis and management of PICH is vastly different to ischaemic stroke (Qureshi *et al.*, 2001). The gold standard for

making the distinction is brain imaging (either CT or MR) (Mohr & Donnan, 1998; Wardlaw, 2001).

6.2.1 Clinical scoring methods

Our early knowledge of the clinical features of PICH came from the post-mortem examination, which emphasised that PICH was a catastrophic event. CT scanning revolutionised the approach to PICH (Caplan, 1994). It allowed precise clinico-pathological correlation of the whole spectrum of disease, including the milder clinical syndromes (usually due to capsular haemorrhages) which were difficult to distinguish from infarcts (Kinkel & Jacobs, 1976; Harrison, 1980). Several scoring methods, based on clinical features, were developed to differentiate PICH from infarction when CT scanning was unavailable. These are the Guy's Hospital score (Allen, 1983a), the Siriraj stroke score (Poungvarin *et al.*, 1991) and a simpler scale proposed by Besson et al (1995). The score was determined by combining clinical features that increase the likelihood of PICH (e.g. elevated diastolic blood pressure) with features that reduce the likelihood of the event being haemorrhagic (e.g. markers of atheroma elsewhere).

When tested in prospective validation studies, the results were less impressive than the original studies (Sandercock *et al.*, 1985b; Celani *et al.*, 1992; Weir *et al.*, 1994; Hawkins *et al.*, 1995). The scoring systems were unwieldy and difficult to perform at the bedside, even for the experienced stroke clinician (Weir *et al.*, 1994; Ebrahim & Harwood, 1999a; Wardlaw, 2001). For those with a low pre-test probability of haemorrhage, clinical scoring systems will misclassify small haemorrhages as infarcts in up to 10% of patients (Wardlaw, 2001). The level of

accuracy achieved by scoring methods is unacceptable for high-risk decisions such as thrombolysis – brain imaging is mandatory (Mohr & Donnan, 1998).

6.2.2 CSF examination

Before routine CT scanning, lumbar puncture was usually performed to diagnose cerebral haemorrhage (particularly when anticoagulation was contemplated) (Fishman, 1992). Following PICH, the typical changes in CSF are: blood-stained fluid (which may be obvious to the naked eye), raised white cell count (due to blood-induced meningeal irritation), raised protein and low glucose. Similar changes may be seen after cerebral infarcts, though less commonly (Fishman, 1992).

Clear CSF does not exclude a small PICH (up to 20% of patients with haemorrhage have normal CSF (Harrison, 1980)), nor does bloody CSF exclude an infarct (up to 10% of infarcts will have xanthochromic or slightly bloody CSF) (Fishman, 1992). A traumatic tap can simulate a haemorrhage, and it can be dangerous to perform lumbar puncture when there is raised intracranial pressure. CSF examination is thus a useless method of distinguishing between haemorrhage and infarction (Harrison, 1980; Fishman, 1992; Mohr & Donnan, 1998).

6.2.3 CT evidence of haemorrhage

Technical details

The basic principle of the x-ray image is that a beam of radiation is attenuated to some degree as it passes through body tissues. Dense tissues such as bone attenuate more x-rays than less dense tissue such as brain. The intensity of the exiting radiation is measured with sensitive photographic film. In computed

tomography (CT), thin beams of x-rays are emitted from multiple different directions, and the intensity of the exiting radiation is measured by detectors (rather than on film). A computer integrates the information to construct images in cross-section (Hounsfield, 1973; New *et al.*, 1974; Ketonen & Berg, 1997; Gilman, 1998).

The attenuation of a body tissue is determined by the density and atomic number of that tissue, and is measured in Hounsfield units (HU) (Dul & Drayer, 1994). In a CT scan of the brain, bone (or metal) has the highest density [1000 HU], then blood [80-85 HU], gray matter [35-40 HU], white matter [25-30 HU], cerebrospinal fluid [0 HU] and finally fat [-100 HU] (Dul & Drayer, 1994; Ketonen & Berg, 1997).

On CT, an intracerebral haematoma appears hyperdense (white, see **Figure 6.1**). Increased density on CT is a result of both the haemoglobin content and the protein matrix of the clotted blood. Haemorrhages are visible in patients with anaemia, thrombocytopenia or abnormal clotting syndromes (Pierce *et al.*, 1994). In the first few hours, an ICH appears slightly less dense than it will ultimately appear on CT, as blood has extravasated but not yet clotted (Dul & Drayer, 1994). Over the next few hours to days, the process of clot retraction produces a well-defined, homogeneous, hyperdense mass (Savoiardo & Grisoli, 1998). After three or four days, as haemoglobin is broken down, the density of the haematoma decreases (initially at the periphery and later in the centre) (Savoiardo & Grisoli, 1998). After a few weeks – depending on the size of the haematoma – it can appear identical to an infarct of the same age (Dennis *et al.*, 1987) (**Figure 6.2**).

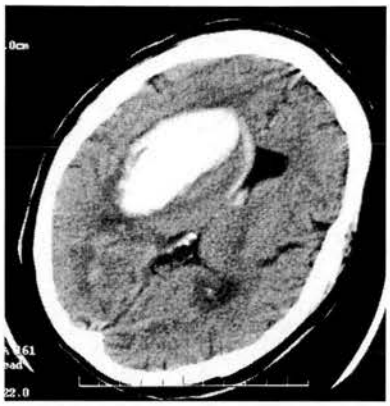


Figure 6.1 An acute intracerebral haematoma on CT

There is extension of blood into the lateral ventricles

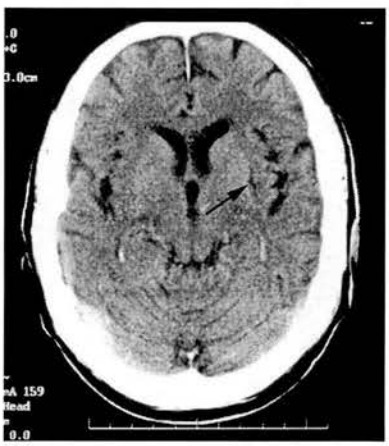


Figure 6.2 An old PICH appears identical to an old infarct

Patient presented with a right hemiparesis six months earlier, arrow points to the remains of the old bleed. Although old haemorrhages tend to be more slit-like than old infarcts, the reliability of this sign is unknown.

How often is the CT positive?

Early reports suggested that a CT diagnosis of PICH was highly accurate and correlated with autopsy findings (Paxton & Ambrose, 1974; Scott *et al.*, 1974; Kinkel & Jacobs, 1976; Weisberg, 1979; Tohgi *et al.*, 1981). As far as we know, all haemorrhages large enough to cause symptoms will be seen on CT when imaged in the first few days (Savoiardo & Grisoli, 1998; von Kummer & Patel, 1999; Wardlaw,

2001). The haematoma will be visible on CT immediately [as seen in patients who have had an ICH whilst being scanned (Franke *et al.*, 1990)].

There are a few pitfalls in the CT diagnosis of haemorrhage. CT appearances that can be confused with haemorrhage include calcification (both physiological and pathological), high-density tumours or colloid cysts. However, the clinical details of a patient with a tumour or colloid cyst will usually be different. Careful analysis of the attenuation coefficient of the lesion may be required to distinguish calcium from blood (Dul & Drayer, 1994).

6.3 CT for acute ischaemic stroke

CT is now widely available – 92% of consultants caring for patients with stroke in the UK have access to a CT scanner (Ebrahim & Redfern, 1999) – and relatively cheap. An unenhanced CT scan of the brain (5-mm slices through the posterior fossa, 10-mm slices throughout the rest of the brain) takes only five minutes. Fast CT provides diagnostic information even in restless, uncooperative patients, and allows access to critically ill patients during scanning.

6.3.1 Limitations of the CT

The main limitations of CT are:

(1) Beam-hardening artefact – this produces alternating dark and bright lines on the CT film. It arises when soft tissue is adjacent to bone, as the computer is unable to compensate for the sudden marked change in densities. Beam hardening particularly affects the posterior fossa, reducing the sensitivity to lesions of the cerebellum and brainstem.

(2) Small lesions are less visible than larger infarcts on CT. Between 35 to 49% of patients with lacunar infarcts have a lesion on CT (Bamford *et al.*, 1987; Norrving & Cronqvist, 1989; Arboix *et al.*, 1990a; Chamorro *et al.*, 1991). In the International Stroke Trial (IST), 41% of patients with lacunar syndromes had a relevant lesion when scanned within 48 hours of onset (compared with 61% of patients with total anterior circulation syndromes) (Hand & Wardlaw, 2001).

(3) 'Fogging' of an infarct – this occurs in the second week, when the density of the infarct gradually increases to become isodense with normal brain tissue, and after swelling has subsided. The infarct may be impossible to see on CT, or its size may be underestimated (Savoiardo & Grisoli, 1998; Wardlaw, 2001). The frequency of 'fogging' varies from 100% (Becker *et al.*, 1979) to 54% (Skriver & Olsen, 1981) depending on the study. Eventually, when the process of tissue breakdown is completed, the infarct is replaced by fluid-filled cystic spaces (Savoiardo & Grisoli, 1998).

6.3.2 What influences the likelihood of seeing an infarct on CT?

Early reports indicated that abnormalities on CT could be seen with cerebral infarcts as well as bleeds (Paxton & Ambrose, 1974; Kinkel & Jacobs, 1976). The quality of scans was poor, which limited the ability to visualise small infarcts and the subtle abnormalities of early infarcts (Wardlaw, 2001). Despite this, it was recognised that infarcts resulted in reduced density of the involved brain tissue, often with surrounding oedema.

In the past, CT was thought to be insensitive to ischaemic changes in the first 24 hours (Wardlaw *et al.*, 1999). Even now, an infarct may never be seen in up to

50% of patients (Wardlaw, 2001). Signs of infarction on CT within the first six hours of stroke are often subtle but become more obvious and better demarcated over the first few days (**Figure 6.3**).

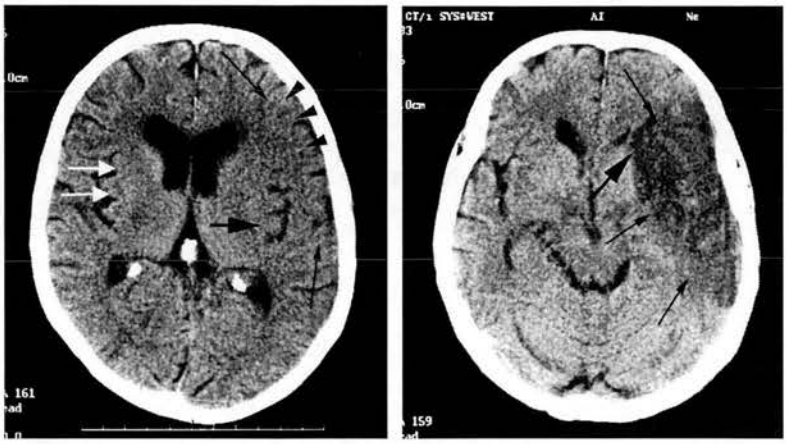


Figure 6.3 subtle early signs of ischaemia evolving into an obvious infarct

Early CT on left (4hrs from onset) shows loss of the insular ribbon (large black arrow, white arrows show normal insular ribbon) and early effacement of sulci (thin arrows show limits of effacement, arrow heads show obscured sulci). CT six days later (right) reveals obvious hypodensity in the left middle cerebral artery territory (thin arrows) and compression of the lateral ventricle by swelling (large arrow) in addition to the sulci.

Established infarction

When visible, an established infarct (i.e. one that is a day or so old) appears as a wedge-shaped or rounded hypodensity within a recognised vascular territory (**Figure 6.3**). Swelling may be seen within the lesion, reaching its peak around the third to fifth day. The likelihood of seeing a relevant infarct depends on time to scanning, and stroke severity. The later a patient is scanned, and the more extensive the clinical syndrome, the greater the chance of seeing an infarct. In the International Stroke Trial (IST), an infarct was seen in 33% of patients scanned within six hours, and in 58% of those scanned 24-48 hours after onset. 61% with a total anterior circulation infarct had a visible infarct, compared with 41% of those with a lacunar

syndrome (see **Figure 6.4**) (Hand & Wardlaw, 2001). There is a weak independent association of visible infarction with poor outcome – a patient with a visible infarct has a slightly worse prognosis than an otherwise identical patient with no visible infarct (Wardlaw *et al.*, 1998).

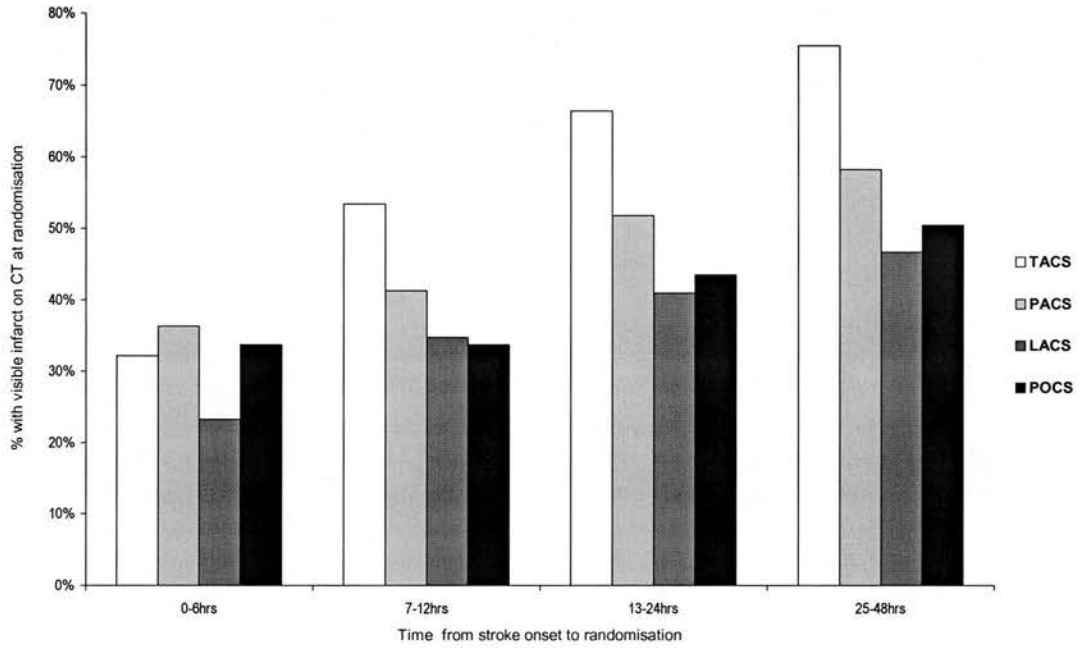


Figure 6.4 The effect of time and stroke severity in determining the presence of a visible infarct, amongst 12,802 patients randomised into the International Stroke Trial immediately following CT

Vertical bars represent the proportion of patients with a visible infarct in each time interval, subdivided by stroke subtype (used here as a measure of stroke severity). TACS – total anterior circulation syndrome; PACS – partial anterior circulation syndrome, LACS – lacunar syndrome; POCS – posterior circulation syndrome.

Early CT signs of infarction

With advances in modern CT technology, and more patients presenting for early assessment, signs of ischaemia may be seen on a scan within hours of stroke onset. The characteristic changes are a loss of tissue density, resulting in loss of distinction between grey and white matter, and swelling. The pathological process that explains the CT signs is an influx of water into affected ischaemic cells. The

grey matter is affected first, as neuronal cell bodies are more sensitive to ischaemia than axons or other cells in white matter tracts (Beauchamp & Bryan, 1997).

The 'Hyperdense Middle Cerebral Artery Sign' (HMCAS)

This is not strictly a sign of early infarction, but reflects occlusion of the middle cerebral artery (MCA) by acute thrombus or embolism (von Kummer *et al.*, 1995). The CT appearance (**Figure 6.5**) is an increased density of part of the MCA compared with other parts of the vessel or its contralateral counterpart (and not attributable to calcification). Although most frequent in the MCA, any artery may appear hyperdense when it contains fresh thrombus (even the lenticulostriate arteries (Wardlaw *et al.*, 2001b)). In the distal MCA, it has been called the hyperdense sylvian fissure 'dot' sign (Barber *et al.*, 2001b) (**Figure 6.6**).

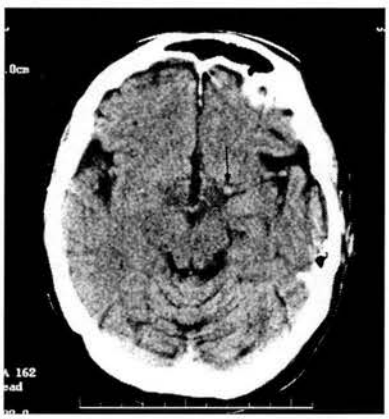


Figure 6.5 Hyperdense middle cerebral artery
A 79 year old man with right sided weakness, aphasia and right hemianopia. CT scan at 5.25 hrs shows a left HMCAS (arrow).

Basal Ganglia

Loss of definition of grey matter is most obvious at the interface of grey and white matter in the basal ganglia. The distinction between caudate nucleus and anterior limb of internal capsule, globus pallidus and genu of internal capsule, and

putamen and external capsule, is blurred or lost (**Figure 6.6**). Within the first few hours, the ischaemic grey matter becomes a similar density to the adjacent white matter. Later, the grey and white matter become even more hypodense, so that the whole area is darker than surrounding brain tissue. Swelling is seen as compression of the adjacent ventricle (**Figures 6.3 & 6.7**).

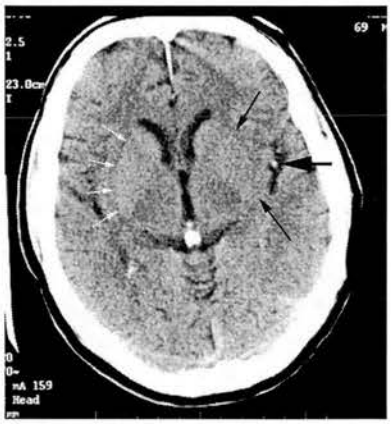


Figure 6.6 Hyperdense sylvian fissure dot sign and loss of the outline of the basal ganglia.
A 69 year old man fell out of bed, and was found to have right sided weakness and aphasia. CT at 4hrs shows a hyperdense sylvian fissure dot sign (large arrow), and loss of the outline of the basal ganglia (thin black arrows, normal outline of contralateral basal ganglia marked by white arrows). The patient made a full recovery and was discharged four days later (follow-up CT showed a small hypodensity of the left insular cortex).

Cortical surface

Swelling of the cortex results in effacement (loss of visibility) of the sulci in the territory of the involved artery, most easily seen by comparing sulci in corresponding parts of each hemisphere (**Figures 6.3 & 6.7**). Loss of definition between grey and white matter may be seen at the boundary between cortex and white matter, in particular involving the insular cortex between the sylvian fissure and external capsule. Loss of definition of the insular cortex results in 'loss of the insular ribbon' (**Figure 6.3**). Subsequently both grey and white matter become more hypodense than normal white matter, so more obviously abnormal.

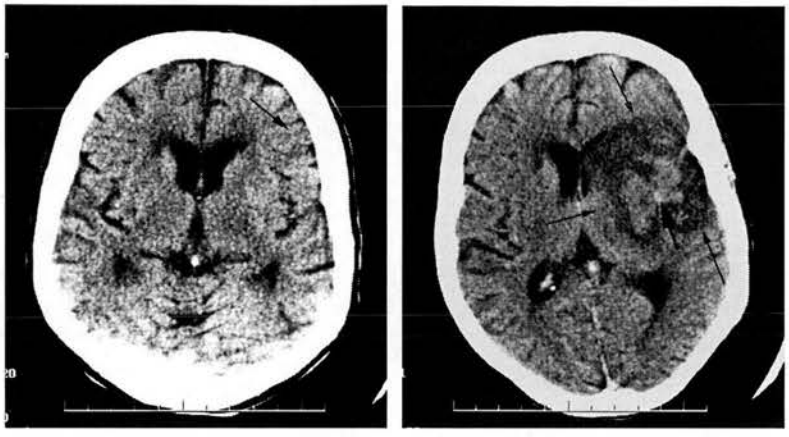


Figure 6.7 An 80 year old woman developed mild right sided weakness, then deteriorated 2.5 hours later with dense weakness and aphasia.

CT on left (3.3 hrs after onset) shows very subtle loss of grey-white differentiation in the anterior division of left middle cerebral artery (black arrow). CT 48 hours later (on right) shows an established infarct (thin arrows) with compression of the lateral ventricle and haemorrhagic transformation (thick arrow) within a larger island of surviving tissue. The patient died three months later.

6.3.3 Making a positive diagnosis: how often do early changes occur?

Early studies reported that hypodensity and/or swelling were seen in 82% of patients with hemispheric stroke scanned within six hours (von Kummer *et al.*, 1996). 46% of patients had parenchymal hypodensity, and 21% had focal swelling on the initial scan in the European Cooperative Acute Stroke Study (ECASS) (in the opinion of the expert CT reading panel, who were not blind to the follow-up scans) (von Kummer *et al.*, 1995). Conversely, the NINDS rt-PA trial, which enrolled patients within three hours, had a 5.7% frequency of clear-cut early CT findings (von Kummer & Patel, 1999).

The frequency of the HMCAS varies from 50% in some series of anterior circulation infarcts (Bastianello *et al.*, 1991; von Kummer *et al.*, 1994), to 5% in a recent Canadian study (Barber *et al.*, 2001b). An equal number of patients may not demonstrate the HMCAS despite angiographically proven MCA occlusion (Leys *et*

al., 1992; von Kummer *et al.*, 1994). A hyperdense *distal* MCA is reported to occur in 16% of thrombolysis-eligible patients (Barber *et al.*, 2001b). When studied serially, the HMCAS usually disappears in a few days (Bastianello *et al.*, 1991).

It is difficult to be certain of the true frequency of early signs of infarction. It all depends on the severity of stroke in the particular patient group, the size and position of the infarct, how quickly patients are scanned, the expertise of the radiologist, the quality of the scanner, and so on. A study that reports high frequencies probably reflects the interests of the research group and the mix of patients admitted to its service, and may not be easily extrapolated to the rest of the world. Early signs of infarction, and the presence of visible clot in a large cerebral vessel, are helpful to confirm the clinical diagnosis when present.

6.3.4 Unresolved issues of early CT signs of infarction

Enthusiasm for making an early positive diagnosis on CT needs to be balanced by an understanding of the problems involved. Confusion has arisen through the use of multiple terms for early infarct signs that describe two basic pathological processes, ischaemia and swelling (**Table 6.1**) (Wardlaw, 2001). In one study, 5/15 doctors even observed an invented sign ('dense cortical sulci') on CT, suggesting that knowledge of early infarct signs was poor (Wardlaw *et al.*, 1999). There needs to be simplification, as well as clear and universally agreed definitions for early CT signs of infarction.

How reliable are early signs of infarction?

Even amongst neuroradiologists with an interest in stroke, agreement for early signs is moderate at best (Marks *et al.*, 1999; Kalafut *et al.*, 2000). There are

not– and will probably never be – enough neuroradiologists to provide timely reports to clinicians (Brillman *et al.*, 1997). Unfortunately, the reliability amongst general radiologists, stroke clinicians and emergency physicians in detecting early signs of infarction is poor, barely better than would be achieved by chance alone(Wardlaw *et al.*, 1999; Grotta *et al.*, 1999; Kalafut *et al.*, 2000; Barber *et al.*, 2000).

There have been some recent attempts to improve reliability of early scan interpretation. One study formalised the interpretation of the 1/3 rule (by applying a series of imagined templates) (Silver *et al.*, 2001), and another developed a systematic quantitative scoring system for ischaemic changes in the MCA territory ('ASPECTS') (Barber *et al.*, 2000). Both studies report impressive interobserver reliability, but are based on small numbers of patients treated with intravenous thrombolysis. Neither scale can be used for the many infarcts that occur outside MCA territory.

What does it all mean?

When seen in the proximal vessel, the HMCAS is associated with severe brain ischaemia and poor outcome, but has no independent prognostic significance (Manelfe *et al.*, 1999). A distal HMCAS may be associated with small volumes of infarcted tissue and a better prognosis than the proximal sign (Barber *et al.*, 2001b). Several studies have shown that early infarct signs have a strong univariate association with stroke severity and outcome (Moulin *et al.*, 1996; von Kummer *et al.*, 2001), but do not independently predict outcome in multivariate analyses (Mendizabal *et al.*, 2001). It is likely that early infarct signs, as with established infarct signs, probably have weak independent prognostic significance. However this, and the magnitude of any independent association, is still to be determined.

Current thinking is that these early CT changes reflect the pathophysiology of the infarct (von Kummer & Weber, 1997; Buchan, 2001). Early evidence of infarction involving a large part of the cerebral hemisphere is thought to represent major, irreversible ischaemic damage, where reperfusion is unlikely to be helpful. When the CT changes are more subtle, evidence from positron emission tomography studies (albeit of very small sample size) have suggested that there is a small core of tissue destined to infarct, surrounded by a larger area of critically hypoperfused (yet still viable) brain tissue (Grond *et al.*, 1997). The current thinking is that reperfusion is likely to be of benefit in this situation, and that those with normal CT scans may recover rapidly, or develop delayed infarction (von Kummer & Hacke, 2000). However, despite strongly polarised opinions of some experts, all of this conjecture remains to be proven.

6.4 Structural MR for acute stroke

In this section, I will summarise the technical principles underlying MR, and discuss the potential of specific sequences that examine the structure of the brain ('structural' MR). There has been huge enthusiasm for the (relatively) new imaging modality of MR. However, this enthusiasm has not yet been matched by appropriate availability. In the UK 93% of consultants who care for stroke have access to an MR scanner, but 85% of consultants scan fewer than 10% of their patients, and only 10% of consultants are able to scan patients within the same or next day (Ebrahim & Redfern, 1999).

6.4.1 Technical details of MR in general

The theory underlying MR imaging is extremely complex, and beyond the scope of this thesis. The following is a brief summary of the basic principles and techniques of MR (to help discuss stroke imaging for the clinician).

How does it work?

When the human body is placed in a strong constant magnetic field, the protons within the tissues align. If a radiofrequency pulse is applied, the protons become excited. When the pulse is turned off, the protons relax to their previous state over milliseconds, giving off energy that is detected as the MR signal (and is called the 'spin echo'). The signal is converted into digital images through computerised Fourier transformation. For images of the brain, a coil is placed over the head, which provides the radiofrequency pulses and detects the resultant MR signal (Moseley, 1988; Ketonen & Berg, 1997; Gilman, 1998; DeLaPaz & Mohr, 1998).

The T1 and T2 time constants

In general, tissues with the highest proton content (fat and water) produce more signal than tissues with low proton content (bone). Simplistically, a conventional MR image is a measure of the amount of fat and water within different regions (Ketonen & Berg, 1997). The radiofrequency pulse sequences can be varied to produce images with different tissue contrast. The parameters altered are the repetition time of the radiofrequency pulses (TR) and the time after these pulses that a spin echo returns (TE). T1 and T2 are time constants that describe the rate of proton relaxation after a radiofrequency pulse; varying the TR and/or the TE

'weights' images to show mainly the T1 or T2 tissue property (see **Figure 6.8** and **Table 6.2**) (Ketonen & Berg, 1997; DeLaPaz & Mohr, 1998).

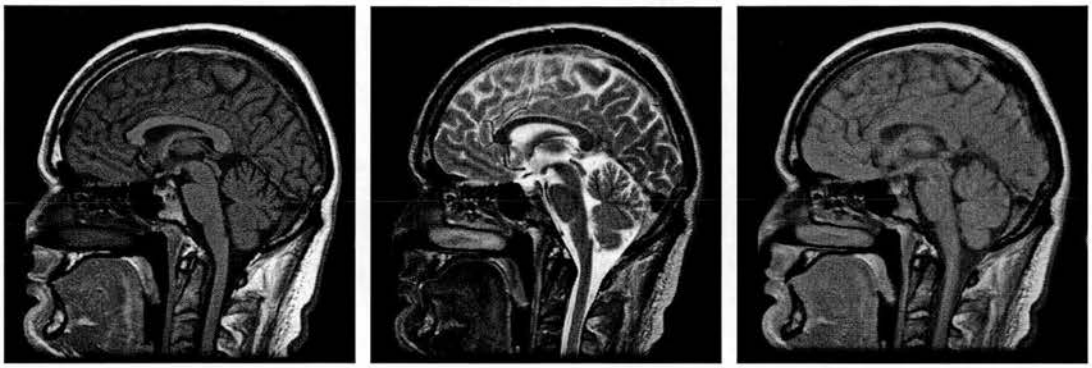


Figure 6.8 Saggital views of a normal (the author's!) brain
T1 weighted image on left (note CSF black), T2 image in middle (note CSF white), and proton density on the right.

Magnetic susceptibility

Tissues placed within a magnetic field generate their own magnetic field, which may enhance or reduce the effect of the externally applied field (Dul & Drayer, 1994). Paramagnetic substances such as gadolinium, calcium and blood products (iron in haemosiderin, deoxyhaemoglobin, or methaemoglobin) disrupt the local magnetic field, resulting in low signal on T1-weighted images. Intravenous gadolinium, a common MR contrast agent, can be used to enhance the arterial signal in the acute stages of infarction, to define areas of blood-brain barrier breakdown, and to image the regional perfusion of the brain (DeLaPaz & Mohr, 1998).

MR artefacts and limitations

Although MR provides outstanding tissue definition (Dul & Drayer, 1994), there are several technical limitations with which to be familiar. MR is insensitive to bone or densely calcified tissues (which contain little fat or water) (Ketonen & Berg, 1997). Artefacts occur at interfaces between tissues with different magnetic

properties, and may result in focal distortion or bright bands being seen on the MR image. Chemical shift artefact is common at water-fat interfaces (e.g. the orbit), and susceptibility artefact is seen in the paranasal sinus region, the skull base and pituitary gland (Ketonen & Berg, 1997).

MR is extremely sensitive, but not very specific (Hommel, 1995). Normal anatomy can easily be mistaken for pathology (e.g. enlarged Virchow-Robin spaces), and non-vascular pathology may be mistaken for infarcts (e.g. gliosis, myelin loss, 'unidentified bright objects') (Ketonen & Berg, 1997) (Kertesz *et al.*, 1987; Hommel, 1995).

6.4.2 Structural MR imaging sequences

A routine MR brain imaging sequence consists of some combination of a midline saggital localising view of the brain, a T1 weighted axial image, a T2 axial image and a proton density or fluid attenuated inversion recovery (FLAIR) image covering the whole brain (DeLaPaz & Mohr, 1998; Wardlaw, 2001). The exact sequence performed depends on the preference of the neuroradiologist. The images obtained with routine sequences provide information about the structure of the brain, and will be referred to as structural MR.

The evolution of an infarct on structural MR

The earliest change of ischaemia is absence of the normal flow void in the affected artery (the equivalent of the hyperdense middle cerebral artery sign). Within hours there may be subtle swelling of cortical gyri seen on T1-weighted images. T2 signal changes are quite unusual before eight hours, but are usually seen by 24 hours.

T1 signal changes take longer to develop, and are more difficult to see (dark as opposed to bright) so are less commonly observed (see **Table 6.3**).

Following the acute changes, the infarct gradually enlarges (in up to 1/3) and swelling becomes pronounced. The CT equivalent of fogging, an increase in the T1 signal, and reduction in the T2 hyperintensity, may be seen by two to three weeks — which can make the infarct difficult to identify (Pereira *et al.*, 1997). This fact has probably been under recognised. Later, the infarct shrinks as the affected tissue atrophies. This is accompanied by ex-vacuo dilatation of the ipsilateral ventricle and adjacent sulci, and often Wallerian degeneration of the corticospinal tracts (seen as increased signal on T2-weighted images of the brainstem) (Yuh *et al.*, 1991; DeLaPaz & Mohr, 1998; Wardlaw, 2001).

The appearance of haemorrhage

Acute haemorrhage may be difficult to detect with structural MR (T1, T2 or proton density images) (Dul & Drayer, 1994). When imaged within the first few hours, PICH has a characteristic appearance on T2 images: a centre of isointense signal, a periphery of hypointensity and a rim of oedema (see **Figure 6.9**) (Schellinger *et al.*, 1999; Linfante *et al.*, 1999). This is because the main constituent of the bleed is oxygenated haemoglobin, which has a signal intensity equivalent or slightly reduced relative to normal brain tissue, but over hours to days, the oxygenated haemoglobin is converted to de-oxygenated haemoglobin (starting at the periphery). Deoxyhaemoglobin is paramagnetic, so results in signal loss on T2 images (Dul & Drayer, 1994).

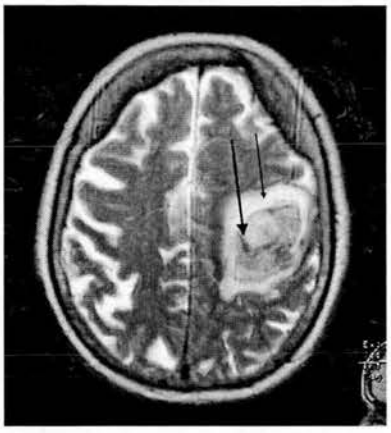


Figure 6.9 Acute haemorrhage on T2

MR at 12 hours after onset. There are some darker lines at the periphery of the bleed (deoxyhaemoglobin, large arrow), and surrounding oedema (thin arrow).

After a few days, and up to a few weeks, deoxyhaemoglobin is converted into methaemoglobin, which has different MR characteristics. Thus the subacute PICH will appear as marked hyperintense signal on T1-weighted images (and dark on T2-weighted images). After several weeks, the methaemoglobin is converted to haemosiderin, and appearances are changed once again – this time signal is low on T1, and very low on T2 images (Dul & Drayer, 1994).

The gradient echo sequence (GRE)

A more recent sequence called gradient echo (also known as susceptibility-weighted, or 'Flash2D'T2) is exquisitely sensitive to breakdown products of blood. In this sequence, gradient shifts rather than radiofrequency pulses are used to generate the spin echo; consequently the sequence is more sensitive to tissue magnetic field inhomogeneities. It is capable of detecting prior ICH more reliably than spin echo or fast spin echo T2 images (Wardlaw, 2001), is very sensitive to acute haemorrhage (Patel *et al.*, 1996) and may also show old petechial haemorrhage

in infarcts (Keir, 2002) or in apparently unaffected tissue ('microbleeds) (Roob *et al.*, 1999). It adds an extra five minutes to the scanning time (Wardlaw, 2001).

The 'FLAIR' sequence

The FLAIR (fluid attenuated inversion recovery) sequence suppresses the signal from CSF, so lesions near the brain surface stand out more clearly from CSF in adjacent ventricles or sulci. FLAIR appears to detect ischaemic abnormalities better than T2-weighted images (Lansberg *et al.*, 2000a; Oppenheim *et al.*, 2000a), and shows small cortical and periventricular infarcts well. However, it may miss lesions in the posterior fossa, cannot distinguish between acute and subacute infarcts, and may be oversensitive (particularly for asymptomatic white matter lesions) (DeLaPaz & Mohr, 1998; Wardlaw, 2001).

Magnetic resonance angiography

Magnetic resonance angiography (MRA) is an attractive alternative to digital subtraction angiography (DSA), as it is non-invasive, and when combined with structural MRI provides more information than DSA alone (Ketonen & Berg, 1997). The principles underlying MRA techniques are complex. In general, arteries are imaged using time of flight techniques (whilst veins are imaged with the phase contrast technique). MRA can be used to demonstrate extracranial carotid stenosis, intracranial stenosis of the vessels at the base of the brain, and venous sinus thrombosis (Lee, 1998). Of greatest potential in acute stroke is the sequence that examines the cerebral vessels. Demonstration of an occluded major cerebral vessel confirms the diagnosis, and could help to select treatment (Schellinger *et al.*, 2001).

When compared with DSA, MRA has accuracy of 80-90% for detection of stenoses of the circle of Willis (Lee, 1998).

Important limitations of the MRA technique are (1) lower resolution than conventional DSA – the resolution becomes progressively worse as the vessel lumen size decreases, so vessels smaller than the second segment of the anterior, middle and posterior cerebral artery will not be seen reliably (Beauchamp, Jr. *et al.*, 1999); (2) sensitivity to patient movement, and (3) slow flow or turbulent flow causes loss of signal, which results in overestimation of the degree of stenosis or failure to visualise a vessel (Lee, 1998).

6.4.3 The clinical utility of structural MR

Structural imaging may point to an unusual cause of ischaemic stroke

MRI is recommended for young patients with ischaemic stroke (Brown, 2001), or older patients without clear risk factors for vascular disease (Warlow, 2001). In these situations, an unusual (i.e. non-atheromatous) cause of stroke becomes much more likely. Many of the rare causes of stroke can be readily identified with MR imaging (see **Table 6.4**); additional sequences may be performed at the same time (such as non-invasive angiography), and MR may be able to localise the site of the lesion better than CT (which may be important).

Is structural MR better than CT in detecting ischaemic stroke lesions?

Like CT, MR may remain normal after cerebral infarction. Kertesz and co-workers (1987) found that the MR was normal in 16/87 patients (18%) imaged within one week of stroke, and Alberts et al (1992) identified seven patients over a

two year period with normal scans. The cases were a mix of small and large vessel disease, brainstem and hemispheric location. It is highly likely that even more patients with true stroke and normal MR were missed, as the result of the scan strongly influences the final clinical diagnosis of stroke.

There have been several studies that compared the visibility of lesions on structural MR imaging with CT. Kertesz et al (1987) (*time to scanning*, t<72hrs, *sample size*, n=39) found that the MR was positive in 74%, whilst the CT was positive in 44%. For those scanned after 48 hours, CT and MR performed equally. Bryan et al (1991) (t<24hrs, n=31) found a visible infarct in 82% of patients on MR, and 58% on CT. Mean time to CT was eight hours, and mean time to MR was 12 hours. Mohr et al (1995) (t<6hrs, n=80) found that CT and MR were equal in their ability to demonstrate infarcts, although CT correlated better with outcome. CT was usually performed first, and median time to second scan was 72 minutes (range eight minutes to 11 hours). In the latter two studies there was bias against CT, as MR was performed later, and was thus more likely to show an abnormality.

For the detection of lacunar infarcts, studies have shown that MR was positive in 74-98%, compared with a positive imaging rate of 15-58% with CT (Salgado *et al.*, 1986; Rothrock *et al.*, 1987; Brown *et al.*, 1988; Arboix *et al.*, 1990b). Overall, it would seem that MR is better at identifying lacunar and brainstem lesions, but CT may be as good at showing early changes in cortical strokes (Wardlaw, 2001).

How does MR compare with CT for the detection of haemorrhage?

The complex pattern of changes seen on MR contrasts with the much more obvious hyperdensity seen immediately on CT. Despite the fact that until recently,

the main indication for brain imaging in stroke was to rule out haemorrhage, there have been few reports of direct comparisons between CT and MR in detection of acute haemorrhage. Schellinger et al's (1999) series of nine patients underwent MR on average two hours after CT. All cases of ICH were 'unambiguously identified' on MR; however the same clinician who interpreted the initial CT scan also interpreted the MR several hours later (the degree of blinding – if any – was unclear). Patel et al's (1996) six patients were evaluated within six hours of ICH. The haematoma on MR was 'easily identified when compared with the baseline CT'. Mohr et al's (1995) study – the only blinded study – recruited five acute haematomas, which were identified equally well by both imaging techniques. The paucity of data seems rather extraordinary given the importance of differentiating between haemorrhage and infarct (Tong *et al.*, 1999).

6.5 The promise of advanced imaging techniques for hyperacute cerebral ischaemia

Advancements in MR technology over the last decade have brought new imaging sequences that hold great promise for acute ischaemic stroke. The following sections deal with 'advanced' MR: diffusion-weighted (DWI) and perfusion imaging (PI). *[Functional MR and MR spectroscopy will not be considered in this thesis].*

6.5.1 Technical details of diffusion and perfusion imaging

Diffusion-weighted imaging (DWI)

The DWI sequence detects the random movements of water molecule protons. Water molecules can diffuse freely in the extracellular space and into cells,

although the degree of movement depends on the immediate environment (Fisher *et al.*, 1992; Beaulieu & Moseley, 1999). Natural barriers limit free diffusion of water molecules in different directions, giving rise to *anisotropic* diffusion. For example, water diffuses readily down and up white matter tracts, but diffusion perpendicular to the fibre is restricted by its myelin sheath (Baird & Warach, 1998).

Diffusion weighted images are obtained by adding two strong, rapidly switched gradient pulses to the standard T2-weighted spin echo sequence. Regions of fast diffusion (e.g. CSF) appear darker than normal brain tissue because movement of water results in signal loss (Baird & Warach, 1998). The rate of diffusion can be quantified, and is expressed as the apparent diffusion coefficient (ADC). Where diffusion is free, the ADC will be high; where diffusion is restricted, the ADC will be low.

A major early problem with DWI was that image acquisition was slow, and images were very sensitive to movement artefact. The new method of echoplanar imaging (EPI) has allowed ultrafast acquisition of DWI images, thus less sensitivity to movement and shorter scanning time. However, EPI is limited by air/bone edge susceptibility artefact causing image distortion in the posterior fossa, base of skull and frontal lobes (Baird & Warach, 1998).

DWI in ischaemia

In ischaemic brain tissue, inadequate supply of glucose and oxygen eventually results in failure of the cell's membrane pumps, leading to influx of sodium and water into the cell (**see Chapter 2**). Water passes from the interstitial (extracellular) space, where it can diffuse freely, to the intracellular space, where it is trapped (Beauchamp, Jr. *et al.*, 1999). It is generally accepted that high intensity

signal on DWI (and low ADC) is a reflection of early cytotoxic oedema due to failure of the membrane pump (see **Figure 6.10**) (Fisher *et al.*, 1992; Albers, 1998; Baird & Warach, 1998; Provenzale & Sorensen, 1999; Beauchamp, Jr. *et al.*, 1999; Beaulieu & Moseley, 1999).

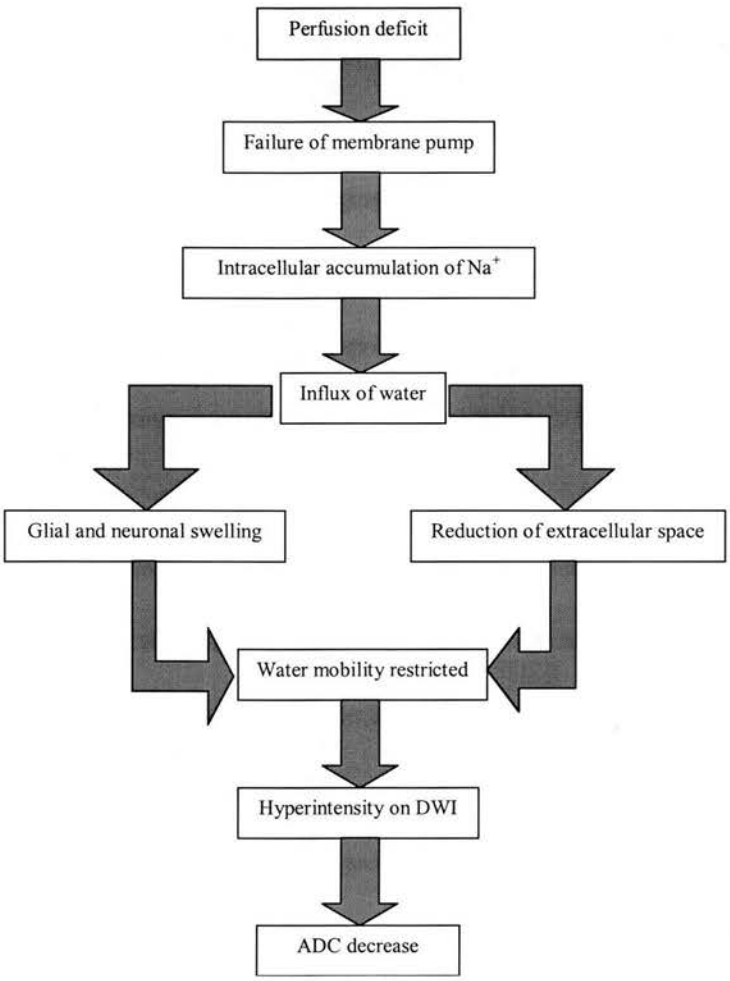


Figure 6.10 Chain of events thought to result in an observable lesion on DWI
Adapted from Beaulieu & Moseley (1999)

The ischaemic lesion appears hyperintense (white) on DWI (see **figure 6.11**), in contrast to the more subtle changes seen on CT. DWI is capable of detecting cerebral ischaemia very early: within minutes of arterial occlusion in animal models

(Moseley *et al.*, 1990), within the first few hours in human stroke (Warach *et al.*, 1995).

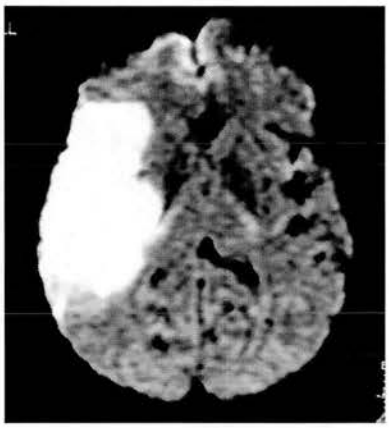


Figure 6.11 DWI appearance of acute ischaemia

A 42 year old man with a left hemiparesis (TACS). DWI scan at 24 hours showed extensive signal alteration in the right middle and anterior cerebral artery territories. The patient died 80 hours after onset due to 'malignant' middle cerebral artery infarction.

Both animal models and human studies have demonstrated a time course of the ADC following stroke. ADC values decrease after stroke onset, then normalise (after one to two days in rodent models, but longer in humans), before becoming high in the chronic phase (Baird & Warach, 1998). A decrease in ADC always precedes the development of infarction, but it is unclear whether decreased ADC values imply that the tissue is irreversibly bound for infarction. There is no consensus on the threshold of cerebral perfusion that results in a diffusion abnormality: some believe it is as low as 15-20ml/100g brain tissue/min (DeLaPaz & Mohr, 1998), whilst others believe it could be 30-40 m/100g brain tissue/min (Latchaw, 1999; Yuh *et al.*, 1999). Animal studies suggest that DWI lesions can recover, but this appears to be uncommon in humans (Baird & Warach, 1998; Provenzale & Sorensen, 1999).

Perfusion imaging (PI)

Magnetic resonance perfusion imaging (PI) measures the passage of blood through the brain's vascular network (Petrella & Provenzale, 2000). PI evaluates blood volume, blood transit times and blood flow as relative measures. The most popular method of PI is dynamic contrast bolus tracking. Gadolinium is given by rapid intravenous injection, and serial scans performed every one to two seconds for one to two minutes measure the concentration of gadolinium as it passes through the brain (Baird & Warach, 1998; Petrella & Provenzale, 2000). Gadolinium induces a strong local magnetic field change in the perfused area, hence there is a loss of signal intensity on T2 images. When the contrast leaves the area, the signal intensity returns to normal (Fisher *et al.*, 1992). The change in signal intensity is approximately proportional to the amount of gadolinium and hence 'flow'. By using the theory of tracer kinetics, signal-time course data can be converted to concentration-time course data. Tracer (i.e. gadolinium) concentration curves can then be analysed to determine various haemodynamic parameters.

The best measure of perfusion

There is as yet no consensus for the optimal method of measuring abnormal perfusion. Cerebral blood volume (CBV) is the easiest to measure, as the amount of signal loss is proportional to blood volume (Baird & Warach, 1998). However, studies have demonstrated that CBV can be decreased in the area of interest (Rother *et al.*, 1996), both increased and decreased (Kim *et al.*, 1999), or increased (Beauchamp, Jr. *et al.*, 1999). The distribution of reduced CBV in an ischaemic lesion may be heterogeneous (Wu *et al.*, 1998).

Relative time-to-peak maps (TTP, i.e. the time from injection of contrast until the highest concentration of contrast agent) are also easily calculated. Because of its simplicity, many investigators have favoured this method (Tong *et al.*, 1998; Thijs *et al.*, 2001). However, TTP maps can be non-specific because delayed arrival time may be due to vessel occlusion, or due to slow or indirect flow (Beauchamp, Jr. *et al.*, 1999).

Further calculations require an internal reference or 'arterial input function' and are more difficult. Mean transit time (MTT) is the average time it takes blood to pass through a given region of brain tissue. From this, cerebral blood flow (CBF) can be calculated according to the central volume principle (CBF=CBV/MTT) (DeLaPaz & Mohr, 1998; Beaulieu & Moseley, 1999; Petrella & Provenzale, 2000). MTT and CBF appear to be most widely used, and are favoured by our laboratory. After vessel occlusion, CBF maps will show hypointensity whilst the MTT map will show hyperintensity in the ischaemic area (see **Figure 6.12**).

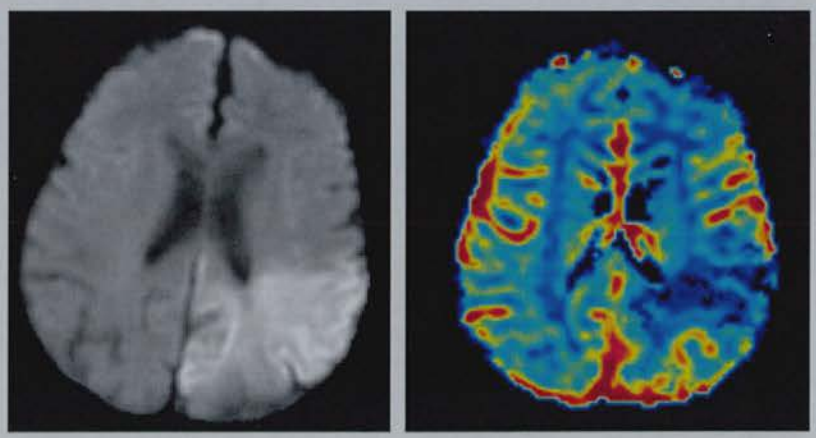


Figure 6.12 PI lesion

The DWI scan on the left shows a large left MCA hyperintensity, and the CBV map on the right shows a matched perfusion lesion (reduced cerebral blood volume is blue). Determination of any 'mismatch' requires superimposing the PI and DWI scans (in the mind's eye).

Limitations of PI

The main clinical limitations of PI are: (1) the requirement for intravenous access with a large bore catheter; (2) the need to give contrast (complete safety of gadolinium in acute stroke has not been established (Wardlaw, 2001)); (3) susceptibility artefacts, and (4) the extensive amount of postprocessing required (Baird & Warach, 1998; Petrella & Provenzale, 2000).

It should also be noted that as the complexity of the processing methods increase, the results become less reliable (Latchaw, 1999; Calamante *et al.*, 2002). The PI maps generated are *relative* to another area of brain (which in itself may not be normal), although many attempts are being made to make them absolute (Beauchamp, Jr. *et al.*, 1999; Petrella & Provenzale, 2000).

DWI-PI 'mismatch'

Many clinicians believe that combining PI with DWI may define 'tissue-at-risk', which could be rescued with appropriate treatment (Prichard & Grossman, 1999; Fisher & Albers, 1999; Beaulieu & Moseley, 1999). This stems from the observation that the initial perfusion deficit can be much larger than the initial DWI lesion (so-called 'mismatch', see **Figure 6.12**). With time, the DWI lesion increases in size to match the initial perfusion deficit (Fisher & Albers, 1999) (although others believe that initial perfusion deficit overestimates the final infarct area (Beauchamp, Jr. *et al.*, 1999;Baird & Warach, 1998; Latchaw, 1999). The PI/DWI mismatch theory is based on two major assumptions: (1) that the DWI lesion represents irreversibly ischaemic tissue (Prichard & Grossman, 1999), and (2) the perfusion lesion represents salvageable brain tissue – the ischaemic penumbra (Baird & Warach, 1998; Beaulieu & Moseley, 1999).

Four patterns of diffusion-perfusion abnormalities have been described: (1) perfusion volume > DWI volume, suggesting the presence of a penumbra; (2) perfusion volume = DWI volume, which suggests that there is no penumbra – but the lesion will not enlarge; (3) perfusion volume < DWI volume, suggesting reperfusion has occurred, and (4) normal perfusion with abnormal DWI, which also suggests reperfusion has occurred (Baird & Warach, 1998). These concepts are yet to be established as true.

6.5.2 The usefulness of advanced imaging for the stroke clinician

There has been tremendous enthusiasm expressed for advanced MR. Many experts argue passionately for it (Prichard & Grossman, 1999; Hacke & Warach, 2000), but others are not so convinced (Powers & Zivin, 1998; Yuh *et al.*, 1999; Powers, 2000). In the following sections, I will review the large number of clinical studies of DWI, PI and their combination.

Methodological flaws of many imaging studies

Powers (2000) pointed out that there was insufficient good quality evidence to support the use of DWI in the routine care of patients with acute ischaemic stroke. A recent systematic highlighted the problems common to many studies of advanced imaging (Keir & Wardlaw, 2000). These included small sample size, absence of blinding, inadequate information about inclusions /exclusions /failures /tolerability, comparing different imaging techniques performed at different time points (invariably favouring the newer technique), and retrospective study design. Often the imaging was performed in non-consecutive series of patients who were different to everyday practice (*selection* and *referral bias*), and the results of the MR study

were included among criteria to establish the final diagnosis, or outcome event (*incorporation bias*) (Powers, 2000; Keir & Wardlaw, 2000). *Publication bias* is another problem, as the current enthusiasm of expert referees may lead to negative or disappointing MR studies being rejected. Thus, studies of the usefulness of advanced imaging need to be interpreted with caution.

Are advanced imaging techniques a diagnostic aid?

DWI compared with structural MR

Most studies report that DWI has very high sensitivity, specificity and accuracy for the diagnosis of ischaemia, and is superior to standard structural MR (Hacke & Warach, 2000; Keir & Wardlaw, 2000). For example, Lansberg et al (2000a) (*time to scanning*, t<48hrs, *sample size*, n=49) showed that 46 patients (94%) had a positive DWI, whilst 34 (71%) had a lesion on T2. FLAIR may be just as sensitive: Oppenheim et al (2000a) (t<48 hrs, n=59) found DWI positive in 56 (95%), and FLAIR positive in 58 (98%)patients.

DWI compared with CT

There have been fewer studies of DWI in comparison with CT (Keir & Wardlaw, 2000). Typically, DWI identified an acute lesion in all patients (100% sensitivity), but sensitivity of CT varied from less than 33% (Sorensen *et al.*, 1996; Gonzalez *et al.*, 1999), to around 50% (Urbach *et al.*, 2000; Lansberg *et al.*, 2000b) to as high as 75% (Barber *et al.*, 1999a; Fiebach *et al.*, 2001). In all studies the CT was performed first, and the MR done 60 to 150 minutes later. The one dissenting study so far – in which the MR was still two hours after the CT – suggested that a

careful, systematic review of the CT (using the ASPECTS score) was as useful as DWI (Barber *et al.*, 2001c).

DWI is probably superior to CT and conventional MR in detecting acute infarcts (see **Figure 6.13**). Several studies showed that identification of DWI lesions was more reliable (Urbach *et al.*, 2000; Fiebach *et al.*, 2001), and that the image interpreter felt lesions were more conspicuous with DWI and so had greater confidence in reporting (Lansberg *et al.*, 2000a). Is this clinically useful? Albers et al (2000a) found that DWI provided "potentially clinically relevant findings" in up to 76% of patients, whilst it was only 10% of cases in another series (Lutsep *et al.*, 1997). The usefulness is likely to be strongly influenced by casemix.

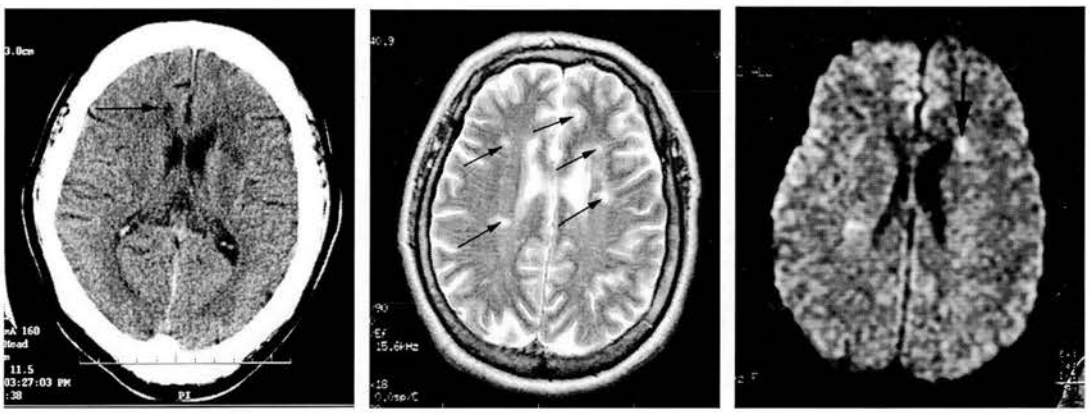


Figure 6.13 The DWI scan shows the relevant lesion

A 46 year old man, with a previous stroke causing right sided sensory disturbance, developed further right sided symptoms. CT (left) showed several low densities consistent with old lacunar infarcts (one marked by arrow). T2 image showed many more lesions in the white matter (arrows). DWI scan (right) showed a high attenuation lesion (arrow), suggesting this to be the infarct responsible for the recent clinical event.

Clinical situations in which DWI is particularly helpful

DWI appears to be superior to structural MR and CT for the imaging of lacunar infarcts, particularly when imaged close to symptom onset and when the lesion is in the brainstem (**Figure 6.13**) (Noguchi *et al.*, 1998; Singer *et al.*, 1998;

Schonewille *et al.*, 1999). DWI readily distinguishes recent lesions from old, which may be helpful in clinical management (Singer *et al.*, 1998; Fitzek *et al.*, 1998; Altieri *et al.*, 1999). In 16% of patients with a clinical lacunar syndrome, DWI showed multiple lesions suggesting the possibility of an embolic source (Ay *et al.*, 1999a). The finding of acute multiple brain infarcts (which is only possible with DWI) in any clinical presentation suggests the possibility an unusual mechanism or a proximal embolic source (Altieri *et al.*, 1999; Roh *et al.*, 2000; Baird *et al.*, 2000a).

Perfusion imaging

Few studies have looked at PI as a diagnostic aid (most have been technical in nature, or have focussed on DWI-PI mismatch) (Keir & Wardlaw, 2000). Perfusion abnormalities precede the development of DWI lesions (Baird & Warach, 1998), and occur within minutes of stroke onset (Fisher & Albers, 1999), so PI maps may be abnormal even before DWI shows a lesion. Sunshine et al (2001) ($t<6$ hours, $n=62$) found that seven patients had no lesion on DWI, yet had an abnormality on mean transit time (MTT) maps. In a further nine patients, the MTT lesion was the best evidence of disease distribution (the DWI showing a smaller lesion). Several other studies, all of small sample size, have shown that the volume of the lesion seen on PI correlates strongly with initial neurological deficit (Barber *et al.*, 1998; Neumann-Haefelin *et al.*, 1999; Beaulieu *et al.*, 1999).

However, studies have also shown that perfusion imaging might be normal in 10-20% of patients with acute stroke, even when scanned within six or seven hours of onset (Rother *et al.*, 1996; Beaulieu *et al.*, 1999; Kim *et al.*, 1999).

Can advanced imaging predict outcome?

DWI lesion volume

Many studies have demonstrated that early DWI lesion volume is correlated with outcome [e.g., Beaulieu et al (1999) (*time to scanning,* t<7hrs, *sample size,* n=21), Tong et al (1998)(t<6.5hrs, n=10), and Barber et al (1998)(t<24hrs, n=18)]. Lovblad et al (1997)(t<24hrs, n=50) showed that the correlation was less robust for lesions smaller than 5mL. van Everdingen et al (1998)(t<60hrs, n=42) found that lesion volume greater than 22mL was associated with a significantly worse outcome on univariate analysis. Thijs et al (2000)(t<48hrs, n=63) performed a logistic regression analysis which showed that DWI lesion volume was an independent predictor of outcome, but patients with no DWI lesion were excluded.

A recent study by Baird et al (2001)(t<48hrs, n=66) proposed a prognostic model for the prediction of outcome after stroke that incorporated the initial DWI lesion volume (as well as time to scanning and the NIHSS score). DWI lesion volume greater than 14.1mL was the radiological determinant of poor outcome. The many methodological flaws within the study seriously limits its potential clinical use (Hand *et al.*, 2001; Counsell *et al.*, 2001).

Schellinger et al (2001)(t<6hrs, n=51), in the largest prospective study of patients scanned within six hours, demonstrated weak correlation between baseline DWI lesion volume and stroke severity, and only moderate correlation between baseline lesion volume and outcome. There was strong correlation between day five DWI lesion volume and outcome, leading the authors to conclude that the early scan reflected a 'dynamic' infarct whose fate had not been decided. Studies that examined patients later than six hours (i.e. the vast majority) showed infarcts whose

fate had already been sealed, hence the observed correlation with outcome in many earlier studies.

Perfusion Imaging

There are many conflicting studies. Some investigators found a weak correlation between PI lesion volume and outcome (Beaulieu *et al.*, 1999)(t<7hrs, n=21)(Barber *et al.*, 1998)(t<24hrs, n=18)(Neumann-Haefelin *et al.*, 1999)(t<24hrs, n=20); others found a strong correlation (Tong *et al.*, 1998)(t<6.5hrs, n=10)(Karonen *et al.*, 1999)(t<24hrs, n=49)(Rohl *et al.*, 2001a)(t<6hrs, n=22).

There is also disagreement about the most accurate PI method. Several studies showed that abnormalities of cerebral blood volume (CBV) best correlated with final infarct size (Ueda *et al.*, 1999)(t<72 hrs, n=18),(Sorensen *et al.*, 1999)(t<12 hrs, n=23)(Karonen *et al.*, 2000)(t<24 hrs, n=49), although another study found rCBV unhelpful (Tong *et al.*, 1998). Parsons et al (2001)(t<6hrs, n=30) found that relative cerebral blood flow (CBF) lesion volume best correlated with outcome, and commented that it was not possible to rely on one single measure of PI – maps of relative CBV underestimated, and maps of relative mean transit time (MTT) overestimated tissue at risk. Yet Thijs et al (2001) were unable to replicate these findings.

DWI/PI mismatch

Although the mismatch theory is logical and attractive, it remains controversial Schellinger et al (2001). Central to the theory is the belief that the DWI lesion seen acutely represents the ischaemic core (tissue irreversibly destined for infarction). In support of this, many studies report that the DWI lesion increases or remains the same in all patients (e.g., Schlaug et al (1999) (t<24hrs, n=25),

Karonen et al (2000) (t<24hrs, n=49)). Conversely, some studies found that the final infarct volume was actually smaller than the initial or maximum DWI lesion; in 9% (Sorensen *et al.*, 1996), 40% (Neumann-Haefelin *et al.*, 1999), 55% (Baird *et al.*, 1997), and 86% of patients (Schwamm *et al.*, 1998). It seems unlikely, therefore, that the DWI lesion reliably represents tissue destined for infarction in every patient.

Most believe that the ischaemic penumbra is represented by the area of perfusion abnormality unaccompanied by DWI abnormality (i.e. PI>DWI). In the absence of treatment, where PI>DWI, the expected behaviour of the infarct on follow-up imaging is to grow to near the size of the PI lesion. This occurred in 100% of patients in some studies (Sorensen *et al.*, 1999; Karonen *et al.*, 2000), but was as few as 63% (Grandin *et al.*, 2001) or 56% (Neumann-Haefelin *et al.*, 1999).

Schlaug et al (1999) attempted to define the penumbra by measuring ADC and CBF values in the core and the mismatch. Similar figures were obtained by Rohl et al (2001b) (who further divided the penumbra into areas destined for infarction and return to normal state). A simpler method was proposed by Neumann-Haefelin et al (1999), who noted that a relative TTP delay of more than six seconds was associated with lesion growth, but stated that "large parts of the PWI-DWI mismatch are not 'at risk' on haemodynamic grounds."

Most studies have shown that the presence of a mismatch correlates with poor outcome (Barber *et al.*, 1998; Karonen *et al.*, 1999). Many studies have used infarct volume as a measure of outcome, but it has often been measured too early (e.g. day four, when swelling is at its peak (Oppenheim *et al.*, 2001) or at one week, when fogging can be a problem (Karonen *et al.*, 2000)), or there has been failure to account for tissue distortion when assessing change in lesion size.

Magnetic resonance angiography (MRA) and mismatch

Studies that combined MRA with PI and DWI showed that mismatch was associated with major vessel occlusion (Rordorf *et al.*, 1998; Jansen *et al.*, 1999; Barber *et al.*, 1999b; Schellinger *et al.*, 2001; Staroselskaya *et al.*, 2001). However, mismatch was also seen in patients without vessel occlusion (Staroselskaya *et al.*, 2001), and in only 70% of those with an occluded vessel in one study (Rordorf *et al.*, 1998). Schellinger et al (2001) found a weak correlation between initial lesion volume and outcome, and no correlation between the mismatch ratio and outcome; vessel occlusion was the key prognostic indicator. The key question is whether PI and DWI *adds* anything beyond the MRA (or arguably simpler methods of vascular assessment such as transcranial doppler ultrasound, or CT-angiography).

False positives and negatives of DWI

False negative DWI

In contrast to what most believe, DWI can provide false-negative information (Yuh *et al.*, 1999). There have been case reports of patients with negative DWI when performed in the hyperacute phase who progress to complete stroke (Lefkowitz *et al.*, 1999). Several retrospective reviews found negative DWI in 17/772 (2%) (Ay *et al.*, 1999b), 8/139 (6%) (Oppenheim *et al.*, 2000b), 7/62 (11%) scanned within six hours of onset (Sunshine *et al.*, 2001), and 18/151 (12%) patients (Lovblad *et al.*, 1998). False negative DWI was more common in brainstem strokes, very small lesions, and those imaged early.

False positive DWI

Conditions that mimic stroke may result in a hyperintense DWI lesion. False positive DWI has been reported in partial status epilepticus (Lansberg *et al.*, 1999), hypoglycaemia (Hasegawa *et al.*, 1996), cerebral venous thrombosis (Doege *et al.*, 2001) and transient global amnesia (Strupp *et al.*, 1998). As there has not been a study that has prospectively evaluated patients presenting with brain attack, the DWI findings of other non-stroke conditions are simply not known (Keir & Wardlaw, 2000).

Transient ischaemic attacks

Ideally, imaging should tell the clinician whether symptoms are likely to resolve (i.e., the patient will have a TIA). This is not possible with CT (Koudstaal *et al.*, 1992). Ueda et al (1999), Kidwell et al (1999) and Engelter et al (1999) have demonstrated that patients with TIA can have an abnormal DWI. The latter two studies were prospective, and most patients' symptoms had resolved at time of scanning. Nonetheless, up to 48% of patients demonstrated typical infarct lesions on DWI (Kidwell *et al.*, 1999), particularly if symptoms were of longer duration.

6.5.3 Practical issues/difficulties of imaging

Patients must remain motionless in a confined and noisy environment for up to 40 minutes to obtain good MR images. This can be a challenge for some stroke patients. Although often recommended MR as the ideal radiological examination (Prichard &Grossman, 1999), there is relatively little attention given to the practicalities of MR imaging of the acute stroke patient. This section will address the issue of *feasibility* of MR imaging for brain attack.

MR safety

Contraindications to scanning

There are important hazards to MR scanning that need to be considered in every patient. The presence of aneurysm clips, cardiac pacemakers, intravascular wires, shrapnel or intraocular foreign bodies are absolute contraindications to scanning, as the magnetic field may cause displacement or malfunction of the object (Moseley, 1988). Dental prostheses containing metal need to be removed. Radiofrequency waves can heat body tissues, which may cause symptoms in those with large metallic prostheses such as hip replacements. How best to determine whether an aphasic or confused patient could have an intraocular metallic foreign body has been completely omitted from these prior enthusiastic studies. The bottom line is that one might have to x-ray all aphasic patients, so further delaying time to treatment (and increasing the risk of scanning).

Patient monitoring

Reliable and accurate monitoring is an essential component of the safe examination of unwell patients (Peden *et al.*, 1992). However, once within the scanner, the patient is inaccessible to direct observation and monitoring (Moseley, 1988). Therefore, indirect monitoring (ECG, and pulse oximetry) is required. Careful attention to lead placement is required to avoid burns (due to current induction by radiofrequency waves in the monitoring leads) (Peden *et al.*, 1992). Monitors can generate noise that results in image degradation (Jorgensen *et al.*, 1994). In addition, the MR can interfere with the function of the monitor. Asymptomatic T wave and ST segment changes on ECG (particularly leads I, II, V_1 and V_2) are commonly seen. Pulsing of gradients may appear as spikes on the ECG

monitor large enough to produce an artificially elevated heart rate (Peden *et al.*, 1992). The pulse oximeter is the most difficult monitor to use within a magnetic field. The signal is often degraded because of induced currents in the cable, and poor signal/noise ratios (Peden *et al.*, 1992).

Medical emergencies

Life-threatening emergencies are a challenge. It is impossible to manage cardiopulmonary resuscitation in the scanner. The patient must immediately be removed from the bore and out of the magnetic field – resuscitation trolleys and equipment cannot be brought into the scanner (Moseley, 1988; Peden *et al.*, 1992).

Claustrophobia

An American study of ambulant outpatients found that four percent were too distressed to complete the procedure (Flaherty & Hoskinson, 1989). Patients reported a variety of anxiety symptoms, which they attributed to the physical conditions of the scanner (rather than fear of what the MR might discover). Other studies reported frequencies of around one percent (Avrahami, 1990; Dantendorfer *et al.*, 1991; Sarji *et al.*, 1998). A Malaysian study suggested that claustrophobia was more common in the educated or those from a higher socio-economic group (Sarji *et al.*, 1998).

There is little doubt that the procedure is uncomfortable, and at times, distressing for patients (Smith, 1990; Sheldon, 1996). Perhaps the best description of the actual experience of an MR examination came from a GP who wrote in the 'Personal view' section of the BMJ:

> "The bed glided slowly into the scanner, like a pizza into an oven, foreshadowing the imagery that has haunted me since. Despite earplugs, the knocking sounds were overwhelming.

> Time seemed endless. The roof of the tunnel was so close to my nose that I could not move... The cheerful image of the pizza oven soon metamorphosed into Auschwitz gas chambers." (Rosenthal, 1996)

Other colourful reports from medically qualified colleagues have likened MR scanning to "burial at sea" (personal communication, R. Tallis) and "being in a coffin on a train" (personal communication, A. Walker).

Stroke patient considerations

During MR scanning, particularly where many prolonged sequences are performed, the patient is required to lie motionless on his/her back. It is important for the success of the scan that clear instructions are provided to (and understood by) the patient (Moseley, 1988; Smith, 1990; Sheldon, 1996). There are certain features of stroke patients that may place them at increased risk from MR, and/or reduce the quality of the scan.

Impaired conscious state

This reduces the ability to explain the procedure to the patient and may increase the patient's risk of aspiration. The International Stroke Trial (IST) (International Stroke Trial Collaborative Group, 1997) recruited 19,435 hospitalised patients with a clinical diagnosis of acute ischaemic stroke within 48 hours of onset. Overall, 23% of patients had a reduced conscious state at randomisation, but amongst patients randomised within six hours, the frequency was 31%. When patients with intracerebral haemorrhage are included in the cohort, the figure is higher: 41% of patients (and 62% of those with ICH) in the Stroke Data Bank had a reduced Glasgow Coma Scale (GCS) (Foulkes *et al.*, 1988). Community-based stroke studies

show similar figures – 50% in the Perth Community Stroke Study had GCS below 15 (Hankey *et al.*, 2000).

Acute confusion (delirium)

Safety could be threatened by patient confusion, as it may not be clear that there are contraindications to scanning, and explanation of the procedure may be difficult. Confusion is common in stroke. Delirium may be the sole presenting symptom of acute (often right hemispheric) stroke (Brust & Caplan, 2001). Agitated hyperactive states may be seen after a variety of lesions (in both hemispheres) that involve the limbic system (Brust & Caplan, 2001). 48% of patients were acutely confused on admission, or developed an acute confusional state during the first week, in a prospective study of 150 stroke patients with a focal neurological deficit (Gustafson *et al.*, 1991). The major predictors of confusion were older age, pre-stroke dementia, previous episodes of confusion, or treatment with drugs possessing anticholinergic effects.

Aphasia

Aphasia also interferes with the ability to explain, and understand, a complex procedure such as MR. In the Stroke Data Bank, 31% of patients with cerebral infarction or ICH had abnormal language (Foulkes *et al.*, 1988). In the IST, aphasia was observed in 45% of patients overall, and 54% of patients randomised within six hours. The recovery from aphasia is often dramatic, and may occur surprisingly quickly (Kertesz, 2001), so it is possible that studies which examine patients days after onset have underestimated the frequency and severity of aphasia at the time of presentation.

Aspiration

Dysphagia and aspiration are significant complications of a variety of stroke syndromes, and predispose to chest infection and dehydration. Presumably, lying patients flat for an MR would increase the risk of aspiration (as sitting upright whilst eating seems to reduce the risk of aspiration (Horner *et al.*, 1988)). Several studies have shown that the problem of aspiration is common after stroke. Barer (1989) found dysphagia in 29% of acute stroke patients (within 48 hours of onset), particularly those who were drowsy or had a severe neurological deficit. In two recent prospective studies, bedside clinical assessment identified dysphagia in 51%, and videofluoroscopy identified aspiration in 22% of patients. Dysphagia was associated with chest infections, and poor outcome after stroke (Smithard *et al.*, 1996; Mann *et al.*, 1999).

Oxygen desaturation

Rowat and colleagues (2000) found that stroke patients have a small but significant difference in resting oxygen saturation when compared with elderly hospitalised patients and young healthy controls (and up to 25% had episodes where the saturation dropped to less than 90%). In a further study, Rowat et al (2001) demonstrated that positioning influenced the saturation – episodes of hypoxia were seen in 10% of patients when lying flat. MR, with its long scanning times, may place patients at risk of hypoxia.

How many stroke patients can be scanned?

It is instructive to search the many published studies for details of inclusions and exclusions and failed scans to determine whether MR is feasible for most

patients with acute stroke. Unfortunately, this is not revealing. A systematic review of 84 studies of advanced MR in human stroke (up to Dec 1999) revealed that only 6/47 studies of DWI gave details of patient inclusions and exclusions, and nine gave details of the number (and reasons for) inadequate scans (Keir & Wardlaw, 2000). None of the 84 studies provided details of patient tolerability of MR.

Highly selected patients

Most studies of advanced imaging techniques recruit small numbers of patients – a median of 34 patients for studies of DWI alone, 21 for DWI and PI (Keir & Wardlaw, 2000). It would appear that these patients are highly selected, and may not be representative of 'typical' acute stroke patients. For example, Baird et al's (2000b) study of the correlation between outcome and DWI /PI lesion volume included 18 patients from a potential 254, and a later study included only 66 patients out of a possible 347 scanned over a five year period (Baird *et al.*, 2001). A study of the 'feasibility and practicality of MR imaging' (Schellinger *et al.*, 2000) recruited 64 patients within 12 hrs of symptom onset over 2 years. During this time, the authors estimated that 1200 patients were seen per year (i.e. <3% were scanned). Exclusion criteria included age over 85, symptoms too mild to warrant aggressive intervention, or obvious CT changes (which meant that the authors did not feel MR was appropriate). Selection bias such as this limits the generalisability of many studies reported to date.

MR failures

The failure rate of MR is crucial to determine how widely applicable the investigation could be, but is not widely reported. It is likely that patients with poor quality scans were excluded from analysis in many studies (Keir & Wardlaw, 2000).

One study reported that 5/47 (11%) could not be scanned (van Everdingen *et al.*, 1998), and another excluded 11/57 (19%) because the images obtained were unsatisfactory (Karonen *et al.*, 2001). Both studies specified that they selected only patients who they felt were stable enough to undergo imaging safely. Despite this, patients were uncooperative or medically unstable.

Failure rates for recurrent scans are more frequently reported. For example, Beaulieu et al (1999) completed the full scanning protocol in 13 of 21 patients, and Parsons et al (2000) in 12 of 19 patients. Perhaps it is more difficult to recruit patients to research studies, which may have a longer protocol, than imaging for clinical purposes only. However, it is clear that MR scanning is difficult for many patients, and impossible in a proportion. There has been substantial selection bias in the studies reported, which has probably led to over-optimism about the applicability of MR imaging.

6.6 Conclusion to Section I: Aims of Sections II and III

In **section I,** I have proposed brain attack as a specific term to describe the patient who presents with symptoms of focal cerebral dysfunction within 24 hours of onset. Current understanding of the ischaemic penumbra has driven our approach to treating the patient as early as possible, and is the scientific rationale for the term. The history of stroke medicine suggests that complex or redundant terminology may be detrimental to patient care; however, brain attack fulfils a clinical need, is simple and is now clearly defined.

A systematic review demonstrated that the bedside (clinical) diagnosis of brain attack could be inaccurate. Conditions that mimic stroke are varied, and many

are rarely observed in non-specialist practice. There has been little research into the clinical clues that can help the clinician distinguish between stroke and mimic. In addition, evidence from the International Stroke Trial suggests that the clinical features of stroke patients who are assessed in the first few hours may be different to the 'average' patient.

Brain imaging is an essential part of patient assessment. At the very least, a scan is required to determine the pathological type of stroke. Evidence is emerging that CT may be able to positively diagnose ischaemia within hours of onset, but the signs seen are subtle, and current reliability is poor. MR has great potential to expand our understanding of the pathophysiology of ischaemia, and may be helpful for diagnosis and management. However, MR is not widely available, is impossible in some patients, and substantial biases in the literature may have given an over-optimistic impression of its value.

In the next sections I will present the results of several prospective studies that aimed to identify the best elements of clinical assessment and brain imaging for the diagnosis and management of patients with brain attack.

***Section II**: Clinical assessment of brain attack*

Issues in the clinical assessment that I hope to address include:

- Can an observational study avoid bias and produce good quality data?
- What are the conditions that mimic stroke and how frequently do they occur?
- How accurate (i.e. sensitivity and specificity, not just positive predictive value) is the bedside diagnosis compared with the gold standard?

- What clinical features can distinguish between stroke and mimic? Are these features independently predictive of the diagnosis? Could a simple, streamlined model assist the non-specialist?
- What elements of the clinical assessment are most reliable?

***Section III**: Imaging to improve diagnosis and management of brain attack*

Imaging issues that I hope to address include:

- What are the limitations of CT in the assessment of brain attack?
- How feasible and safe is MR in acute stroke patients?
- Can a methodologically sound study produce useful data?
- What is the added value of MR and should it replace CT? In particular,
  - How well does MR identify mimics and haemorrhages?
  - How accurately does MR diagnose ischaemia in a diverse sample of patients?
  - In what specific clinical situations should advanced MR be used?
  - Does the initial MR predict outcome, and could it guide treatment?

Table 6.1 CT signs of early infarction - why the confusion?

- hemispheric sulcal effacement
- loss of the insular ribbon
- obscuration of the lentiform nucleus
- midline shift
- mass effect
- loss of the grey-white matter junction
- attenuated cortico-medullary contrast
- 'early infarction'
- hyperdense middle cerebral artery
- effacement of the cortex
- hypodensity:
  - parenchymal hypodensity
  - hypodensity in <50%, 50-90%, >90% of the middle cerebral artery territory
  - hypodensity in <33%, >33% of the middle cerebral artery territory
- early infarct oedema (*does this mean swelling or low density?*)
- cortical hypodensity
- local swelling

A list of some of the names for signs of early infarction cited in the literature. Most of these signs actually describe one of two basic processes – loss of tissue density and tissue swelling. The subject is thus further confused by the use of multiple poorly defined terms.

Table 6.2 Standard MR images

MR image	Pulse sequence	Characteristics
T1-weighted image	Short TR, short TE	Fat has high signal, CSF low signal
T2-weighted image	Long TR, long TE	CSF has high signal, fat low signal
'Proton density' or intermediate-weighted image	Long TR, short TE	CSF has low signal (both T1 and T2 properties are minimised)

TR – repetition time for radiofrequency pulses
TE – time taken for a spin echo to return
CSF – cerebrospinal fluid

Table 6.3 Changes on structural MR imaging following an ischaemic stroke

	MR parameter		
Time	**T1-weighted images**	**T2-weighted images**	**Other**
0-3 hrs	Normal	Normal	Absent flow void in affected artery
3-6 hrs	Subtle swelling of structures	Normal	FLAIR may identify infarcts at ~ 4 hours
6-12 hrs	Swelling of structures	Increased signal	Proton density may still be normal
12-24 hrs	Low signal	Increased signal	
1-7 days	Low signal	Increased signal	Swelling surrounding the infarct
2-3 wks	May show increased signal (fogging)	May show reduction in signal (fogging)	Contrast enhancement occurs
>4 wks	Low signal	High signal	Ex-vacuo dilatation of ipsilateral ventricle; Wallerian degeneration in brainstem

FLAIR – fluid attenuated inversion recovery sequence (suppresses CSF signal)

Adapted from (Ketonen and Berg, 1997; DeLaPaz and Mohr, 1998; Yuh et al., 1999; Wardlaw, 2001).

Table 6.4 MR can assist in the diagnosis of rare causes of stroke

	MR appearances	
'Rare' cause	**Specific sequence**	**Notes**
Venous infarct	MR venogram	Readily demonstrates sinus thrombosis
	Structural	Infarct does not correspond to known vascular territory, and is often haemorrhagic
Dissection	Neck MRI	May display mural haematoma
	Neck MRA	Demonstrates the distribution of the pathology ('rat's tail' stenosis)
Mitochondrial Cytopathy (MELAS)	Structural	Cortical and subcortical ischaemic lesions commonly in the occipital regions but not confined to PCA territory
CADASIL	Structural	Focal, diffuse and confluent lesions in periventricular white matter, basal ganglia and pons. Cortical lesions are exceptional.
Intravascular lymphoma	Contrast-enhanced	Meningeal enhancement may be seen, marked subcortical lesions with evidence of haemorrhage as well as infarction
Cerebral vasculitis (of any form)	Contrast-enhanced	Lesions affect grey and white matter, not confined to vascular territory, meningeal enhancement may be seen (particularly in sarcoidosis)
Moyamoya disease	MRA	Demonstrates collateral vessels and absence of flow in major vessels
	Structural	Demonstrates basal ganglia collateral vessels
Cardiac embolism	Structural	Multiple cortical infarcts in various territories suggests a cardiac source (although the diagnosis is made by clinical examination and echocardiography)

MELAS – mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
PCA – posterior cerebral artery
CADASIL – cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Based on (Farrugia et al., 1997; Barnett et al., 1998; Warlow, 2001; Brown, 2001)

SECTION II

CLINICAL ASSESSMENT OF BRAIN ATTACK:

THE SCIENTIFIC BASIS OF 'THE ART'

Chapter 7 : The Brain Attack study

7.1 Introduction

In this chapter, I will describe the *Brain Attack* study, an observational study of a cohort of consecutive patients admitted to the Western General Hospital with brain attack. The intention of the project was to enhance understanding of the diagnostic process, and to produce tools which may aid the clinical (or bedside) diagnosis and lead to its improvement. The patients who presented within the first few hours of symptom onset will be described in more detail in **Chapter 8**. The results of brain imaging, and their impact on the diagnostic process, will be described in **Section III**.

7.2 Aims

The specific aims of the Brain Attack study were:

(1) To determine the conditions that caused brain attack

(2) To determine if the clinician could distinguish (at the bedside) between stroke and mimic

(3) To examine the accuracy of the bedside diagnosis of the cause of brain attack.

(4) To explore the reasons for disagreement between the clinical diagnosis and the final diagnosis.

7.3 Methods

7.3.1 Study design – methodological issues

The brain attack study was an observational study of a cohort of patients with brain attack. As discussed in **Chapter 4.3.2**, observational studies of the accuracy of the clinical (or bedside) diagnosis of stroke are prone to bias – and seven indicators of quality were proposed (see **Table 4.1**). In the brain attack study, I attempted to avoid bias by the following measures:

- Prospective study design
- Consecutive patient sample
- Avoiding restrictive exclusions
- The initial clinical assessment was made by the stroke research fellow before the results of investigations were known
- The final diagnosis was based on the consensus opinion of a panel of experts, who were aware of the clinical data, investigation results and short-term patient follow-up
- The panel meetings were convened at least one week after admission
- It was anticipated that most of the patient sample would have a brain scan

7.3.2 Inclusion criteria

Defining 'brain attack'

The sole entry criterion was that the patient was admitted to hospital with a brain attack. I defined a brain attack as:

"Apparently focal brain dysfunction of apparently abrupt onset"

The word *apparently* was chosen to prevent a rigid interpretation of the key terms *focal brain dysfunction* and *abrupt onset*. *Focal brain dysfunction* could be a symptom or a sign. The aim was to assess as many patients as possible, rather than restrict numbers to patients who could provide a good account of their symptoms (which would not reflect clinical reality).

Patients are often sent in to hospital, or admitted to the ward, with a diagnosis of "?Stroke", which may be the principal diagnosis, or one of a long list of differential diagnoses. Unless these patients had symptoms of a brain attack, they were not included in the study. For example, a patient with reduced mobility and difficulty coping at home – a common "?stroke" referral – was not considered a brain attack. This ensured that patients were selected on the basis of clear, pre-specified criteria, rather than depending on the referring clinician's skill (or lack thereof). In turn, this could make the results of the study applicable to other centres.

There were no other exclusion or inclusion criteria; in particular, the patient did not need to have a neurological deficit when first seen, there were no age limits, and a patient could be included more than once (if he/she represented with a further brain attack). In this thesis, subarachnoid haemorrhage was not considered to be a brain attack or a stroke and will not be discussed further.

Time limits

I did not set time limits for patient recruitment, although I tried to see them as soon as possible. Although the *concept* of 'brain attack' applies best to patients presenting within hours of symptom onset, around half present to the Western General Hospital later than six hours (Johnston *et al.*, 1999). By taking all patients, I

hoped to study the full spectrum of stroke and its mimics, and determine if time was a factor in the ease of diagnosis.

7.3.3 Case ascertainment

Source of patients

There were five potential areas to which eligible patients could be admitted.

(1) Acute Receiving Unit (ARU)

Most patients with brain attack are admitted to the Western General Hospital through the ARU. This department assesses patients with acute emergencies that are not trauma (e.g. myocardial infarcts). Patients can be referred to ARU by their General Practitioner (GP) or by ambulance (if the GP practice the patient is registered with is in the northern zone of Edinburgh). The main emergency department that accepts all patients (trauma, self-presentation, and GP referrals from the southern zone of Edinburgh) is located at the Edinburgh Royal Infirmary.

(2) Acute Stroke Unit

After assessment by ARU medical and nursing staff, a patient with brain attack could be admitted directly to the 10-bed Acute Stroke Unit (later enlarged to 16 beds at the end of patient recruitment) during working hours. One of two stroke consultants (Drs Dennis or Lindley) reviewed each new admission during daily ward rounds.

(3) Acute Medical Assessment Unit (ward 26)

If outwith working hours, or if no beds were available on the stroke unit, patients were admitted to ward 26. Patients were then transferred to the acute stroke unit after review by a stroke research fellow or stroke consultant.

(4) Department of Clinical Neurosciences (DCN)

The Western General Hospital is the site of Edinburgh's regional neuroscience service (DCN). Patients could be admitted directly to DCN, thus bypassing ARU. Typically, these were patients who presented to another hospital and were found to have had an intracerebral haemorrhage (admitted to neurosurgery), or were young stroke patients (admitted under neurology).

(5) Other medical/surgical specialty units

Patients known to another specialty could be admitted directly to their parent unit (e.g. a patient with known malignancy may be referred by the GP directly to oncology), or could have a brain attack whilst in hospital for another reason.

Identification of study patients

Direct referral

Multiple overlapping sources were used to ensure that all patients with brain attack were identified. ARU medical and nursing staff were encouraged to refer any potential patients upon their arrival. We carried a hospital bleep, placed posters in ARU, and maintained daily contact with medical and nursing staff to remind them of the project. Referrals were aided by the fact that (1) there was no NHS stroke registrar, and (2) we were able to assess the patient, take bloods, order brain imaging and arrange a bed, thus providing a strong incentive to the NHS ARU staff to refer

all possibly eligible patients. Consequently, during working hours, we saw most patients with brain attack.

Patients admitted outwith working hours

Patients admitted on weekends or outwith working hours were identified the following working day by inspection of the ARU admission register each morning. The ARU admission register contained a brief description of the patient's complaint (e.g. left arm weakness). We retrieved the filed medical notes for patients of interest – all those with a description that suggested brain attack, and all non-specific descriptions ('off legs', 'confused', 'unwell', 'decreased mobility' etc). The stroke research fellow read through the medical notes searching for features suggesting a brain attack. Doubts about the suitability of the patient were resolved by discussion at the time (but in general we aimed to see as many patients as possible). Patients identified in this manner were then assessed on the ward.

Overlapping sources

The admission registers of the Acute Medical Assessment Unit and the Acute Stroke Unit were also inspected daily to ensure that no patients were missed. Medical staff from other wards were encouraged to refer patients to the stroke research fellows. The stroke consultants (Drs Dennis and Lindley) notified us of any patients referred directly to them. One stroke research fellow attended the morning DCN x-ray meeting (during which all brain imaging from the previous day is reviewed), thus covering direct admissions to DCN.

7.3.4 Stroke research fellows

Four research fellows participated in this study. The majority of assessments were to be performed by the author (PJH) and Dr J Kwan (who was recruiting patients for his own study – data collected were shared). Dr S Keir assessed patients in the early part, and Dr B Lamont assessed patients in the latter part of the study.

When this study commenced, PJH and BL were fully trained neurologists undertaking sub-specialty training in stroke medicine. PJH trained in Australia and UK, BL trained in Belgium. JK and SLK were UK trainees in general internal medicine / care of the elderly, who had both performed stroke research for two years. JK was five years post registration, SLK was nine years post registration.

7.3.5 Patient assessment and data collection

Bedside clinical assessment of the patient with brain attack

The stroke research fellow performed a detailed patient assessment, and completed an acute assessment data form (see **Appendix 2**). The important elements of the bedside clinical assessment were:

Past medical history – included standard vascular risk factors, prior stroke or TIA, and risk factors I suspected would increase the likelihood of a stroke mimic (cognitive impairment, migraine, epilepsy, malignancy and psychological disturbance).

History of the present event – included the nature of the neurological symptoms, and any accompanying symptoms (such as loss of consciousness, or vomiting, which increase the likelihood of haemorrhage). There was particular emphasis on timing. I wanted to determine how often the exact time of onset was

known (and why it was not known). I wanted to validate a popular clinical rule of stroke diagnosis [that if the patient cannot recall exactly what he/she was doing at the time symptoms came on, then the cause is unlikely to be vascular (Warlow *et al.*, 1987)]. I reasoned that patients were more likely to have a mimic if they had been unwell in the week before symptom onset.

General examination – this assessed vascular risk factors (atrial fibrillation, cervical bruits), as well as signs in other systems. I assessed conscious level with the Glasgow Coma Scale (GCS) and the Reaction Level Scale (Starmark *et al.*, 1988) (see **Appendix 3**). Two scales were used as the verbal component of the GCS may be difficult to determine in the presence of aphasia (Johnstone *et al.*, 1993; Prasad & Menon, 1998). In patients who were alert and not aphasic, I assessed for acute confusion by testing orientation and attention (days of the week backwards), as suggested by Hodges (1994).

Neurological examination – included the National Institutes of Health Stroke Scale (NIHSS, see **Appendix 2**, pp6-7) and additional elements of the neurological examination not covered by the NIHSS (e.g. plantar response). The NIHSS was downloaded from the Internet Stroke Centre (*http://www.strokecenter.org/trials/scales/*) and modified to fit onto two sides of paper.

Diagnostic formulation – the examiner made a bedside diagnosis before assessing the patient (the 'end of bed assessment'), after taking the history, and at the end of the clinical assessment. The examiner assigned the Oxfordshire Community Stroke Project (OCSP) sub-classification at the end of the assessment (after Bamford et al (1991), see **Appendix 3**). I also collected information about tests that could bias the examiner, and details that could suggest a non-stroke diagnosis (e.g. if the signs

did not conform to vascular territory, or if there was discrepancy between symptoms and signs).

Difficulty in obtaining the history – the source of the history, any corroborating sources, and inconsistencies between sources was noted, as I felt these factors could result in an incorrect bedside diagnosis.

Form design and modification

The data collection form was designed to record the data obtained by the bedside clinical assessment. The forms were discussed at a research group seminar, and then piloted for several weeks before the study commenced. Further form modifications were required approximately one month into the study (see results).

7.3.6 The final diagnosis

Determining a gold standard for the diagnosis of stroke is difficult (D'Olhaberriague *et al.*, 1996). Whilst autopsy would be ideal, only 20% of patients actually die from the acute effects of a stroke, and it is increasingly difficult to obtain consent for autopsy (post Alder Hey scandal). Computerised tomography (CT) brain scans can be performed in almost all stroke patients, but are normal in around 50% of definite strokes (Hand & Wardlaw, 2001). Magnetic resonance (MR) brain scans cannot be used in all patients with stroke.

In the brain attack study, a panel of stroke experts determined the gold standard diagnosis by consensus. The research fellow gave the panel the clinical details, anonymised so that the clinician could not be influenced by any memory they might have of caring for that patient. Then the brain imaging was reviewed, and results of any further relevant investigations were discussed (all anonymised). If

there was still no consensus, the patient's identity was revealed so that the panel could receive detail of the patient's progress in hospital, and corroboration of the clinical details by the stroke consultant who had seen the patient.

'Expert panel' meetings

The panel met weekly to discuss the cases (see **Figure 7.1**). A minimum number of panel members was arbitrarily set at two consultant geriatricians (Drs Lindley, Dennis or Mead), one consultant neurologist (Professors Sandercock and Warlow), one consultant neuroradiologist (Professor Wardlaw), and two research fellows (PJH, JK, BL, SLK, Dr Sudlow). It was important to have several clinicians present as the final diagnosis was determined by consensus.

Figure 7.1 Some of the experts at a panel meeting
Meetings were held every Wednesday afternoon, and proved to be both educational and entertaining. From left to right: PJH, Dr C Sudlow, Prof. C Warlow, Dr M Dennis, Dr R Lindley, Dr S Keir. Photographed by JK.

The panel was asked to make a diagnosis after the history, then the examination, then the imaging, and then a final diagnosis (when all clinical details and investigation results were known). The brain imaging findings were recorded on

a standard form (**Appendix 4**). The diagnoses, plus any detail on the subtype of stroke (e.g., lacunar, striatocapsular or lobar haemorrhage), were recorded on the final diagnosis form (**Appendix 5**).

Definitions for the panel diagnoses

A *definite non-stroke* was diagnosed when the clinical details did not suggest a vascular aetiology, and another convincing explanation for the symptoms was discovered (often requiring supportive investigations, e.g. a brain tumour). A *definite stroke* was diagnosed when the history and examination were considered to be completely typical of a stroke; often imaging revealed an infarct or haemorrhage, but this was not essential. A *probable stroke* was defined as clinical features consistent with a vascular aetiology, with no better alternative explanation. A *possible stroke* was defined as clinical features that could be consistent with a vascular cause. An alternative explanation for the clinical syndrome may have been present, and may have been more likely than stroke, but there was no definite proof of a non-stroke. A *definite transient ischaemic attack* was defined as an appropriate clinical syndrome with full resolution of symptoms within 24 hours. A *possible transient ischaemic attack* was a less convincing clinical syndrome that resolved within 24 hours, with no definite proof of another cause for the patient's symptoms.

These diagnostic categories were somewhat arbitrary, and probably differed between clinicians. However, consistency was achieved by maintaining a similar number and type of clinician at each meeting, and by resolving differences by discussion so that a consensus was obtained.

7.3.7 Sample size

An approximate sample size for this study was determined by several factors. The systematic review of stroke mimics (**Chapter 4.2**) suggested that a mimic rate of around 20% could be anticipated. The confidence intervals (CI) for a 20% mimic rate are determined by the number of patients seen. If 100 patients are seen, the 95% CI ranges from 12.7% to 29.2% mimic rate; if 300 patients are seen, the 95% CI is 15.5–24.5%, and if 400 patients are seen, the 95% CI is 16.1-23.9%.

There are approximately 250 admissions to the acute stroke unit per year (personal communication, Dr Martin Dennis). I aimed to recruit patients into the brain attack study for 12-18 months, thus 300 patients was judged to be a practical number. [This number would also be suitable for logistic regression analyses, which will be discussed in **Chapter 10**.]

7.3.8 Ethics and consent

The chairman of the local ethics committee of the Western General Hospital approved the study. Where possible, consent to participate in the study was obtained from the patient or a close relative. Where obtaining consent was impossible (i.e. a small number of patients who were confused or unconscious), the patient was seen and the data obtained was handled in accordance with the Scottish Data Protection Act (2000).

7.3.9 Data management

Data collected and recorded by the research fellow at the bedside were entered into a database (designed and developed in-house by Neurosciences Trials

Unit Senior Programmer, Ms Vera Soosay). Every entry was double-checked to minimise inaccuracies. Any errors identified were remedied by referring to the original paper data forms, hospital case notes, or discussion with the relevant research fellow. Changes to the data were made prior to analysis.

Once patient recruitment and data checking were complete, the data were anonymised and transferred to a Microsoft Excel spreadsheet (version 97 SR-2, ©Microsoft Corporation 1997). The original paper files (with no patient identifiable details on the cover) were kept in locked, fireproof cabinets.

7.3.10 Statistical analyses

'Patient-episodes' and 'patients'

The same patient could be recruited into the study several times. Each hospital admission was defined as an episode (i.e. the episode commenced when the patient was admitted, and ended when the patient was discharged). Multiple presentations by the same patient has implications for the analysis of the data. In the results, I refer to 'patient episodes' as the recruiting event or brain attack, and 'patients' as the true number of patients. I restricted analysis of demographic data and past medical history to the number of patients, as these items are constant (whilst the features of the event that led to recruitment – history of the complaint, examination findings – are unique, no matter how many times that patient presents).

'Collapsing' the final diagnostic categories

The six final diagnostic categories were dichotomised to allow easier analysis of the data, and to ensure adequate numbers in each category. However, it was not

possible at the panel meetings to be definitive about every event, which made dichotomising difficult. The major difficulties were (a) what to do with *possible* events, and (b) how to treat transient ischaemic attacks (TIA).

Definition of 'thrombolysis-eligible' brain attack

A clinically sensible solution was to define the 'target' population as brain attacks that would be 'thrombolysis-eligible'. I have used this term purely to denote the level of diagnostic certainty that a clinician would require before considering treating a patient with thrombolysis. Only if the clinician were sure that the diagnosis was definite or probable stroke would a risky treatment then be contemplated. In this study, definite or probable strokes were considered 'thrombolysis-eligible.'

Naturally, all other conditions would have to be favourable (timing, severity of deficit etc) for that patient to actually receive treatment; but the starting point in the decision process is that the clinician is reasonably certain that the diagnosis is stroke. In the present study, it is used to denote the diagnostic certainty, thus a patient labelled as 'thrombolysis-eligible' may not be once other factors were considered.

The clinician would wish to avoid thrombolysis for brain attacks due to a non-stroke, or possible strokes. This group, therefore, constituted the "mimic" group. I treated patients with a final diagnosis of TIA as if they were strokes (i.e. definite TIA became "thrombolysis-eligible", possible TIA became "mimic"). Patients with a definite TIA would presumably be 'thrombolysis-eligible' if they presented early enough and were still symptomatic.

The other possible way of analysing the data was to dichotomise the groups into definite non-stroke and all other stroke. This may be acceptable if the purpose of separating the two groups was to provide a relatively safe intervention (such as admission to a stroke unit, or scanning within 24 hours). However, thrombolysis can be hazardous, so one would only wish to treat patients one was reasonably certain had a stroke. As an underlying aim of this research was to increase the proportion of patients receiving thrombolysis, I elected to divide patients into 'thrombolysis-eligible brain attacks' and 'stroke mimics'.

Statistical packages

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997), SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999), Review Manager (version 4.1, ©Wintertree Software Inc. 1997) and Confidence Interval Analysis (version 1.0, ©Martin J Gardner and British Medical Journal, 1989) statistical programs.

Statistical tests

To determine if the data were normally distributed, histograms were plotted and inspected visually, and the Kolmogorov-Smirnov test of normality was performed. If normally distributed, the continuous data were presented using the mean, standard error of the mean, and the range. If the distribution was not normal, then data were presented as median and interquartile range. Standard parametric and non-parametric tests of significance were performed on the data (as appropriate). The odds ratio (OR) [with 95% confidence intervals (95% CI)] was calculated for

dichotomised data. More detailed statistical methods will be discussed in the relevant sections.

7.4 Results

Patient recruitment commenced on 24/7/00, and was completed on 30/4/01. During this time, there was a break in recruitment from 14/11/00 – 7/1/01 (for conferences and holidays). Total duration of patient recruitment was 33 weeks (7½ months). During the study period, there were 350 presentations of brain attack by 336 patients. Eight patients presented twice, and three patients presented three times.

7.4.1 General characteristics

General Description

The general characteristics of the patient-episodes are detailed in **Table 7.1**. 321/350 (92%) entered hospital through ARU, and a small number had in-hospital brain attacks (n=14, 4%) or were admitted directly to another ward (n=15, 4%). The median time of admission was 4.7 hours, with 187 patient-episodes (57%) admitted within six hours of onset (see **Figure 7.2**). 209 (62%) of ARU admissions were in working hours, yet the median time between symptom onset and evaluation by the research fellow was 25.8 hours. Only 56 patient-episodes were assessed by the research fellow within six hours of symptom onset (see **Figure 7.3**). 213 (61%) patient-episodes of brain attack were initially admitted to a general ward (many were later transferred to the acute stroke unit). 52% of patient episodes were evaluated by the author.

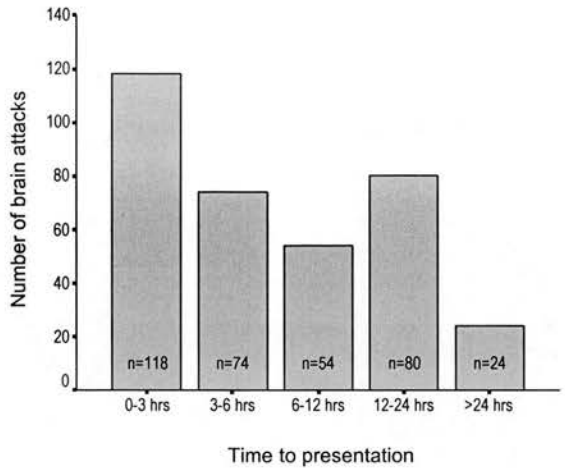


Figure 7.2 Time to presentation at hospital in the brain attack study (n=330)
15 episodes were inpatient brain attacks, details of onset unknown in four, details of ARU arrival unknown in one.

Table 7.2 shows the demographic details of the *patients* recruited into the brain attack study (n=336). I used the data from the first presentation for the 11 patients recruited more than once. 297/336 (88%) of patients had one or more vascular risk factor. 129/323 (40%) of patients had a previous brain attack, and in 69/129 (53%) symptoms had completely resolved before the current admission. Despite this, only 7% of patients were unable to walk independently prior to admission. A small number of patients had a proposed risk factor (migraine, epilepsy, malignancy, and psychological disturbance) for stroke mimic.

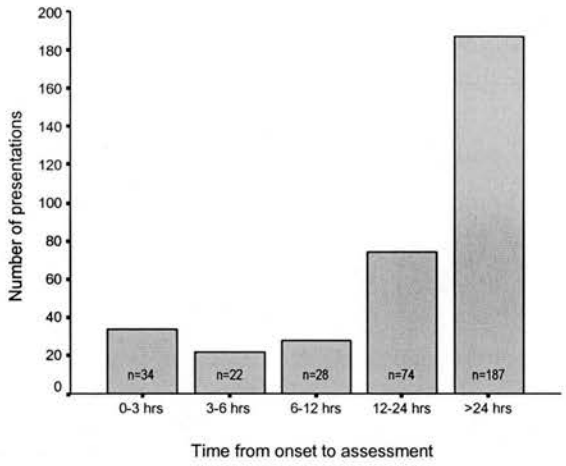


Figure 7.3 Time from onset to assessment by the stroke research fellow
Onset details unknown for four patients

For all patient-episodes of brain attack (see **Table 7.3**), an exact onset of symptoms could be determined in 247/350 (71%) patients. Almost 1/3 first noticed symptoms on waking from sleep. 112 (32%) presentations had blood pressure greater than 150/90 mmHg, and 72 (21%) were found to be in atrial fibrillation on admission. When examined by the stroke research fellow, 92/256 (36%) were confused (either because of errors in orientation or attention), but 236/350 (67%) were documented to have a normal GCS. 47/350 (13%) presentations had no neurological signs at the time of examination by the stroke research fellow.

There were a small number of patients in whom presence or absence of each variable was unknown. These were patients who were confused, or aphasic and other reliable sources of history were unavailable.

At the time of assessment by the research fellow, results of investigations were available in 287/350 (82%) patient-episodes [blood sugar level alone (n=87), ECG alone (n=33) both tests (n=166), or the MSU result (n=1)]. These were tests

performed immediately in ARU by nursing staff as part of their 'suspected stroke' protocol.

I did not record whether the research fellow was aware of the brain imaging result, as I anticipated that almost all patients would be seen either before scanning, or before a report was available. I estimate that fewer than 15 patients were assessed in knowledge of the brain imaging. The proportion of the sample that underwent brain imaging was 302/350 (86%), and two additional patients had imaging of the spine, which was diagnostic. [The imaging findings, and reasons patients were not scanned, will be discussed in **Chapter 11**].

Expert panel meetings were held at a median of 20 days after admission (interquartile range (IQR): 14 – 43 days), with a median seven doctors present at each meeting (IQR: 6 – 8 doctors).

Data form modifications

Three revisions were made to the initial data collection form, with the last revision made on 30/8/00. Approximately 40 patients were enrolled prior to the final alteration to the data form. The major changes were:

- Additional diagnostic categories (expanded to include definite, probable and possible stroke and non-stroke).
- An approximate time and date of onset (when exact time could not be determined).
- Clarification of whether there were any focal neurological symptoms, and which side they affected.
- Describing the neurological signs for both sides of the body (I had hoped to keep this simple by referring only to the symptomatic side, however

this proved unworkable as some patients had bilateral signs, or old signs on the unaffected side).

- Clarification of whether there were no signs present at the time of examination

The data form was densely packed and initially not easy to use. For the first 75 or so patients, several questions were continually unanswered due to poor form layout (e.g., 'Can patient or relative recall time of onset?'; 'Does the patient have an overwhelming comorbid condition (making assessment difficult)?'; 'If so, can the patient be engaged (follow your face)?'). However, these data were easily extracted from other sources. Two questions were discarded: (1) 'Evolution to maximal deficit took:' was left blank 113 times and given a time of zero minutes 167 times, reflecting the difficulty in answering this question. I asked the research fellow to record the number of minutes it took to reach maximal deficit, but in retrospect if would have been simpler to use categories (e.g. 'maximal at onset', 'evolved over minutes' and so on). (2) 'Visuospatial dysfunction' had too many alternatives, and was confusing and unreliable (the NIHSS 'neglect' section was used instead).

7.4.2 What conditions cause brain attack?

350 presentations with brain attack were studied. The final diagnoses, as determined by the expert panel, for the 350 brain attacks are detailed in **Table 7.4**. In **Figure 7.4**, the six diagnostic categories were collapsed into vascular, non-vascular and uncertain causes. The majority of brain attacks were almost certainly due to a vascular cause (n=237 definite, probable stroke and definite TIA).

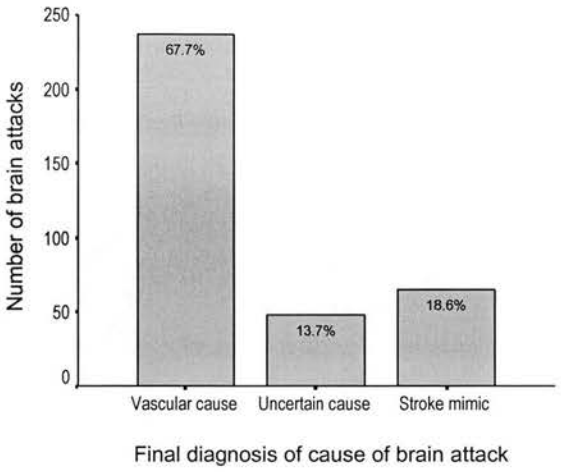


Figure 7.4 Final diagnosis of the causes of brain attack

Definite non-strokes

A definite non-stroke accounted for 65 brain attacks (18.6%) in 61 patients (see **Table 7.5**). The most common mimic was seizure (n=13); 7/13 patients had known epilepsy, whilst 2/13 had prior stroke and 2/13 had known dementia. 10 patients were found to have a space-occupying lesion: seven primary brain tumours (glioblastoma multiforme in five patients, meningioma in two); two patients with cerebral metastases, and one patient with a subdural haematoma. Eight brain attacks were due to sepsis, with chest infection the most common site (n=4). 2/8 patients had a prior history of stroke, and 2/8 were known to have dementia. Toxic/metabolic disturbance accounted for eight brain attacks, 4/8 due to hypoglycaemia, 1/8 due to hyperglycaemia. There were three presentations with acute facial nerve palsy, and one presentation with sciatic nerve palsy. Three brain attacks were labelled as acute confusional state as there was no more definitive diagnosis. In two of these patients, there was a clear history of dementia, and in the remaining patient, dementia was suspected but had not been formally confirmed. The spinal cord lesions were metastatic cord compression (n=2), and infection resulting in deterioration of cervical

myelopathy. The five miscellaneous causes were Parkinsonian syndrome (n=1), migrainous aura (n=1), subarachnoid haemorrhage (n=1), transient global amnesia (n=1) and dementia (n=1). Overall, 20/61 (32.7%) patients with a mimic had suffered an earlier stroke (with symptoms completely resolved in 11/20), and 12/61 (19.7%) were known to have cognitive impairment.

'Stroke mimics'

There were 48 presentations of brain attack where the expert panel could not determine the definitive cause of the symptoms. As these patients may have had a stroke, they were labelled as possible stroke (or TIA). However, in all but four episodes, there was an alternate, plausible non-stroke diagnosis. If these patient-episodes are combined with the definite non-strokes, there were 109/350 (31.1%) brain attacks that were probably NOT due to a vascular cause. The combined list of stroke mimics is detailed in **Table 7.6**. The major difference between this table and **Table 7.5** is the seven patients with vestibular dysfunction – the expert panel were unable to make a definitive diagnosis of a non-vascular aetiology in any of these patients.

Overall, there were 109 presentations with brain attack by 106 patients whose current medical problem was not cerebrovascular disease. 44/106 patients (41.5%) had suffered an earlier stroke (with symptoms completely resolved in 19/44), and 27/106 patients (25.5%) were known to have cognitive impairment. 62/109 (56.9%) mimics were neurological conditions, and in a further 20 mimics (syncope, confusional state, dementia), neurological conditions were amongst the differential diagnoses.

7.4.3 Can the clinician distinguish between stroke and mimic at the bedside?

In this section, the aim was to determine the clinical features that could allow the clinician to distinguish between a 'thrombolysis-eligible' brain attack and a mimic at the bedside. The category of 'thrombolysis-eligible' brain attack made the assumption that all other conditions – timing, severity, absence of contraindications, etc. – were favourable. The possible stroke events with no alternate, plausible non-stroke diagnosis were included in the 'thrombolysis-eligible' group.

General features

There were 241 presentations with a thrombolysis-eligible brain attack from 237 patients, and 109 presentations with a stroke mimic from 106 patients. Seven patients had at least one thrombolysis-eligible brain attack *and* a stroke mimic. I have compared the characteristics of the two groups to identify factors/variables that might help distinguish them on first assessment. In the following sections I present the results of the univariate analyses (multivariate logistic regression will be discussed in **Chapter 10**).

The two groups had similar age, gender, and time from onset to presentation (see **Table 7.6**). Each research fellow examined a similar proportion of patients in each group. The main differences related to stroke severity. Patients with thrombolysis-eligible brain attacks had a higher NIHSS score ($p<0.01$, Mann-Whitney U), and were more likely to present with signs that could be classified by the OCSP classification [particularly total anterior circulation syndrome (TACS) or lacunar syndrome (LACS)] ($p<0.01$, Mann-Whitney U). Fewer patient-episodes of

stroke mimic received a brain scan (72/109, 66%) than thrombolysis-eligible brain attacks (232/241, 96%, $p<0.01$, Mann-Whitney U).

History items

The history component of the clinical assessment was divided into past history and history of the presenting complaint. For past history, patients' details were included only once (n=343 patients). Three items reached significance ($p<0.05$) (see **Figure 7.5**): known cognitive impairment favoured a mimic (Odds Ratio (OR) 0.4, 95% confidence intervals (95% CI) 0.2-0.7); ischaemic heart disease (OR 1.8, 95% CI 1.0-3.1) and peripheral vascular disease (OR 3.5, 95% CI 1.2-10.3) favoured a thrombolysis-eligible brain attack. Confidence intervals for peripheral vascular disease were wide, reflecting its low frequency (only 29/218 (13%) thrombolysis-eligible events). The other vascular risk factors – hypertension, diabetes, smoking and atrial fibrillation – did not distinguish mimic from stroke. The conditions thought likely to predispose to a mimic – migraine, epilepsy, known malignancy and psychological disturbance – did not prove to be helpful (due to low frequency; there was a trend for these factors to favour a mimic). Similarly, there was a trend for previous stroke to favour the possibility that the current event was a mimic, but this did not reach significance (OR 0.6, 95%CI 0.4-1.0). Patients with walking difficulties before the event might be at higher risk of a stroke mimic (e.g., sepsis leading to further deterioration in gait may simulate a stroke), however this was observed infrequently (5.5% of strokes, 9.5% of mimics) and so was not a useful distinguishing factor.

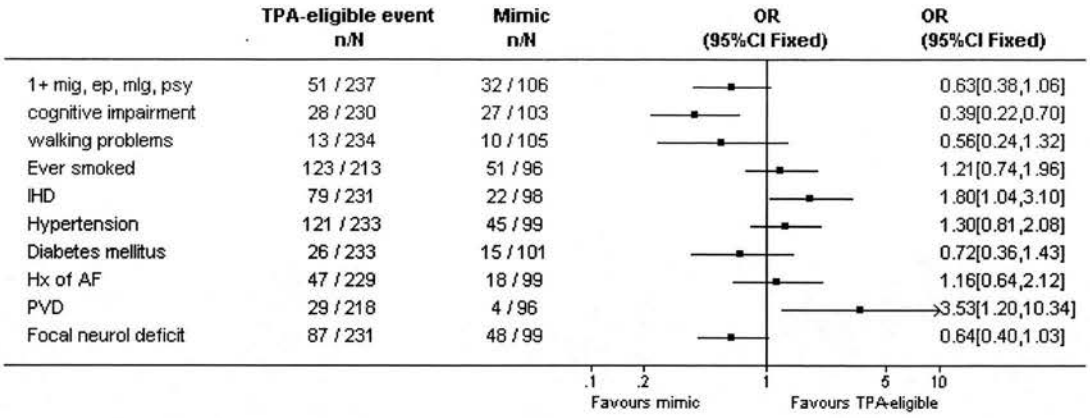


Figure 7.5 Past medical history: features that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

TPA-eligible - 'thrombolysis-eligible' assuming all other conditions were favourable
1+ mig, ep, mlg, psy - one or more of migraine, epilepsy, malignancy or psychological disturbance
IHD - ischaemic heart disease
Hx of AF - history of atrial fibrillation
PVD - peripheral vascular disease

Data for the history of the presenting complaint were available for all 350 brain attacks. I have broken this down into general or associated symptoms (**Figure 7.6**) and the specific neurological symptoms (**Figure 7.7**). General symptoms that favoured a 'thrombolysis-eligible' brain attack included (**Figure 7.6**): the patient complained of definite focal symptoms (OR 16.5, 95% CI 7.0-38.6); an exact time of onset could be determined (OR 2.5, 95% CI 1.6-4.1); the patient could recall exactly what he/she was doing at the time of onset (OR 2.2, 95% CI 1.4-3.6), and the patient was well in the week before symptom onset (OR 2.5, 95% CI 1.6-4.0). General symptoms that favoured a mimic were: loss of consciousness (OR 0.3, 95% CI 0.2-0.5); seizure (OR 0.3, 95% CI 0.1-0.6), and still being able to walk after symptom onset (OR 0.5, 95% CI 0.3-0.8). Headache proved to be more common in those with a stroke (78/216, 36%) than those with a mimic (22/95, 23%), and actually favoured the diagnosis of stroke (OR 1.9, 95% CI 1.1-3.3).

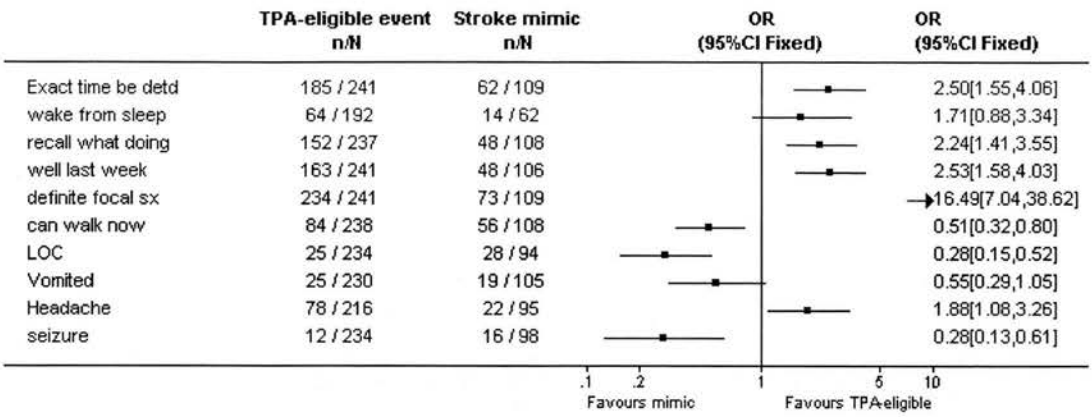


Figure 7.6 History of the presenting complaint: features that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

TPA-eligible - 'thrombolysis-eligible' assuming all other conditions were favourable
detd - determined
sx – symptoms
LOC – loss of consciousness

Focal neurological symptoms favoured a thrombolysis-eligible event (**figure 7.7**). In particular, visual loss, loss of speech/language, abnormal facial sensation, arm weakness and/or abnormal sensation, hand weakness and/or abnormal sensation, and leg weakness and/or abnormal sensation were all significant ($p<0.05$). A mimic was strongly suggested if the symptoms could not be lateralised to one side of the body (OR 0.18, 95% CI 0.11-0.30).

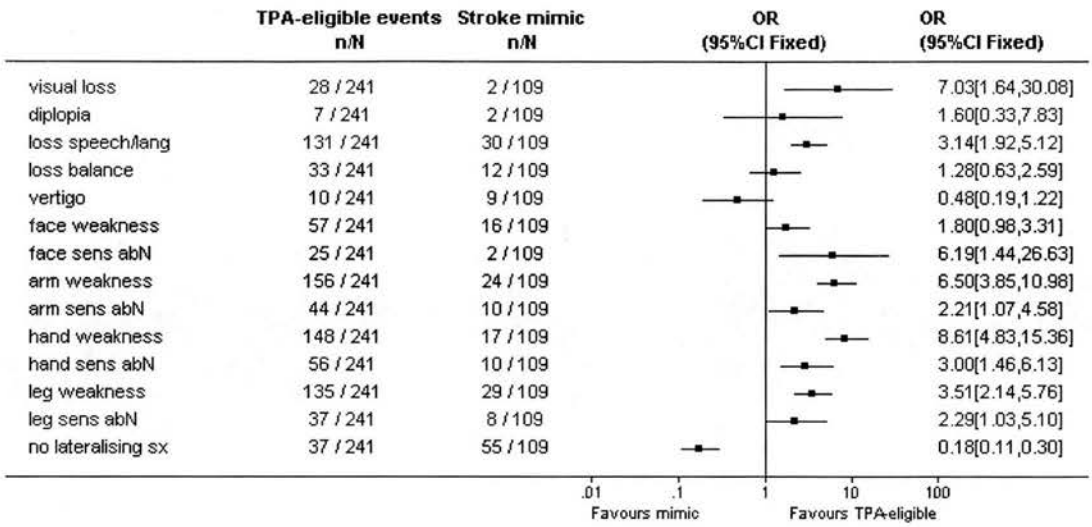


Figure 7.7 Focal neurological symptoms: features that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

Note – scale 0.01 – 100 (ten times larger than other figures)
TPA-eligible - 'thrombolysis-eligible' assuming all other conditions were favourable
Sens abN – sensory abnormality
sx – symptoms

Examination items

General examination findings were available for all 350 patient episodes (see **Figure 7.8**). The finding of hypertension (systolic blood pressure greater than 150 mmHg, or diastolic blood pressure greater than 90 mmHg) was associated with stroke (OR 1.7, 95% CI 1.1-2.7 and OR 2.0, 95% CI 1.2-3.2, respectively), as was valvular heart disease (OR 2.7, 95% CI 1.2-5.9), although this was observed infrequently. Abnormal physical findings in other systems (OR 0.5, 95% CI 0.3-0.8) or confusion (OR 0.5, 95% CI 0.3-0.8) favoured a mimic.

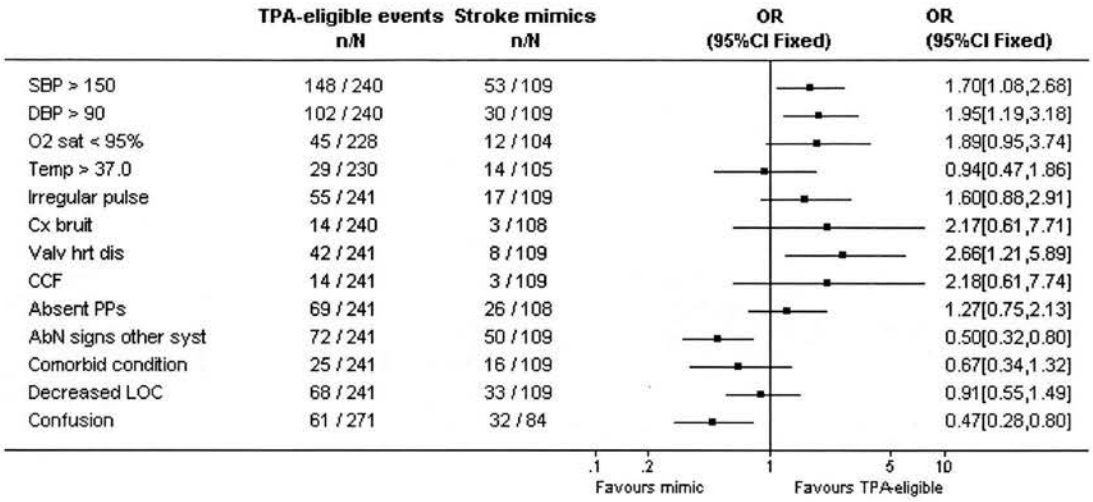


Figure 7.8 General examination: features that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

TPA-eligible - 'thrombolysis-eligible'
SBP – systolic blood pressure; DBP – diastolic blood pressure; O2 sat – oxygen saturation
Cx bruit – cervical bruit
Valv hrt dis – valvular heart disease
CCF – congestive cardiac failure
Absent PPs – absent peripheral pulses
AbN signs other syst – abnormal signs in other (non-neurological or vascular) systems
Decreased LOC – decreased level of consciousness

On neurological examination (see **Figure 7.9**), impaired comprehension, oculomotor cranial nerve palsy, nystagmus, lower limb ataxia and reflex asymmetry were not statistically significant distinguishing factors. All other neurological signs strongly suggested a thrombolysis-eligible brain attack. The most common findings were arm weakness (162/237, 68%), hand weakness (158/237, 67%), abnormal verbal output (146/241, 61%) and leg weakness (128/238, 54%). A unilateral extensor plantar response was a common finding (117/235, 50%) and a useful sign suggesting a thrombolysis-eligible stroke (OR 2.6, 95% CI 1.6-4.3). Even uncommon findings such as visual inattention (39/223, 17%) or eye deviation (23/239, 10%), proved to be useful discriminators as they were rarely seen in the mimics (4/101, 4% and 1/109, 1%, respectively).

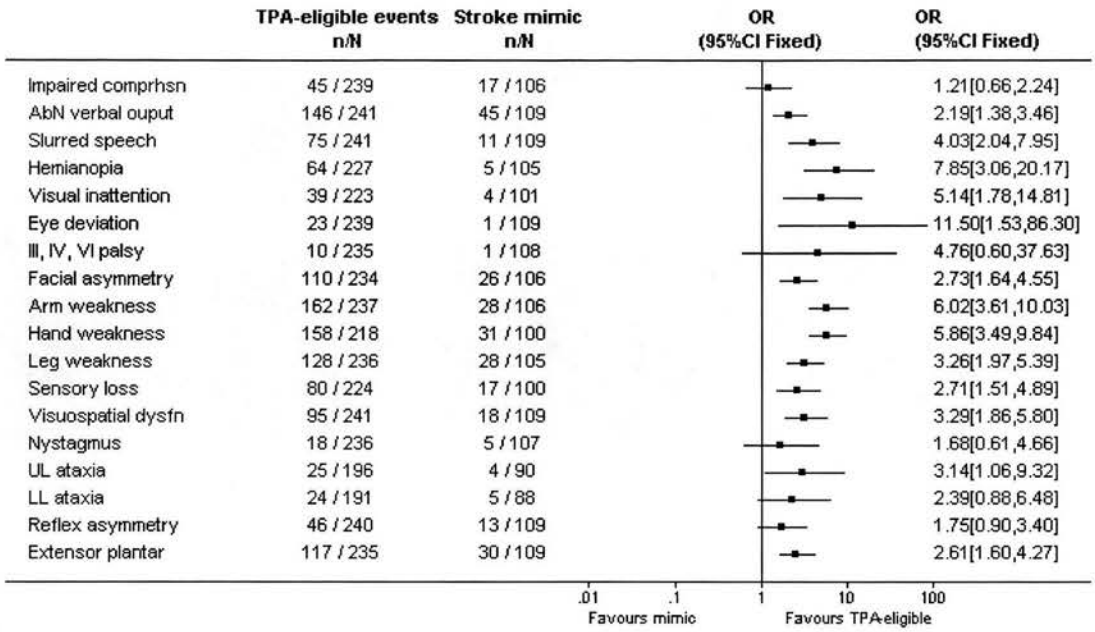


Figure 7.9 Neurological signs that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

Note – scale 0.01 – 100 (ten times larger than other figures)
TPA-eligible - 'thrombolysis-eligible'
AbN verbal output – abnormal verbal output
III, IV, VI palsy – oculomotor, trochlear or abducens cranial nerve palsy
dysfn – dysfunction
UL – upper limb, LL – lower limb

Diagnostic Formulation

Strong pointers towards a mimic were the absence of neurological signs (OR 0.04, 95% CI 0.01-0.10) and the inability to lateralise the signs (OR 0.3, 95% CI 0.1-0.6) (see **Figure 7.10**). When the signs could be lateralised to the right or left side of the brain, a stroke was more likely. The research fellow was asked to record whether the signs were consistent with the symptoms, and whether the neurological signs conformed to a known vascular territory. A negative response to either question strongly favoured a mimic (OR 0.2, 95% CI 0.1-0.5, and OR 0.1, 95% CI 0.05-0.2, respectively). A thrombolysis-eligible brain attack was highly likely when the research fellow classified the clinical syndrome as lacunar or total anterior

circulation syndrome (OR 7.1, 95% CI 2.2-23.5, and OR 3.9, 95% CI 1.5-10.1, respectively). Mimics were more likely if the clinical classification could not be determined (OR 0.2, 95% CI 0.1-0.4).

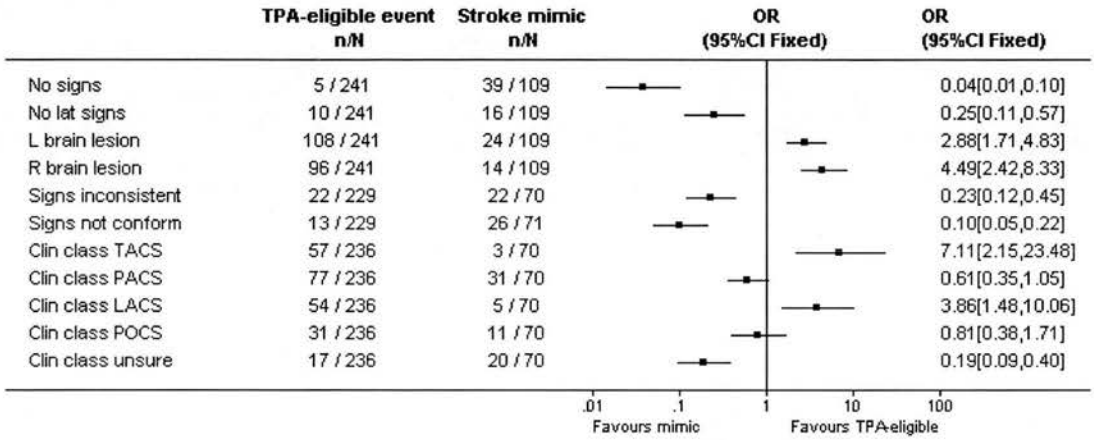


Figure 7.10 Diagnostic formulation: features that distinguished 'thrombolysis-eligible' brain attack from stroke mimic

Note – scale 0.01 – 100
TPA-eligible - 'thrombolysis-eligible'
No lat signs – no lateralising signs
L – left, R – right
Signs inconsistent – with the symptoms reported in the history
Signs not conform – to known vascular territory
Clin class – OCSP clinical classification

7.4.4 The accuracy of the clinical diagnosis of brain attack

The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy and likelihood ratio (LR) for the *bedside clinical diagnosis* was determined by comparing it to the final consensus panel diagnosis (the gold standard) (see **Table 7.8** for description of terminology). Up to five bedside diagnoses could be given to each patient: the general practitioner (GP) diagnosis, ARU staff member (nurse or doctor) diagnosis, 'end of bed' diagnosis by stroke research fellow, research fellow diagnosis after the history, and stroke research fellow's final bedside diagnosis (see below). In this section, I have again divided the

final diagnosis into 'thrombolysis-eligible' brain attacks (n=241) and stroke mimics (n=109).

The initial referral

General Practitioner

GPs referred 239/350 patient-episodes (97 brain attacks presented directly via ambulance and 14 occurred in hospital). No specific diagnosis was provided in 24 GP referral letters. GPs thus made 215 diagnoses: 16 were non-stroke and 199 stroke. Of the 24 events with no GP diagnosis, 12 turned out to be mimics; and of the 97 events with no GP letter, 32 events (33%) were mimics. The raw data (in 2x2 tables) are provided in **Appendix 6**, and the summary data in **Table 7.9**. Whilst sensitivity of the GP diagnosis of stroke was excellent (95.4%), specificity was poor (14.5%); overall, the GP diagnosis of stroke increased the likelihood of stroke by only a small amount (likelihood ratio 1.12).

Acute Receiving Unit

The Acute Receiving Unit (ARU) was the entry point to the hospital for 321 brain attacks (there were 14 inpatient events, and 15 events admitted directly to other wards). The ARU diagnosis was 'stroke' (n=244), 'non-stroke' (n=46) or 'unsure' (n=31). I have grouped the non-stroke and unsure categories together, as a patient in either category would not be a suitable candidate for thrombolysis. The diagnoses of ARU staff had higher specificity, better positive predictive value, better negative predictive value, and greater accuracy than the GPs' diagnoses (**Table 7.9**). The likelihood ratio was 1.71. A medical senior house officer provided a diagnosis for 271/321 (84%) events, and a nurse provided a diagnosis for 50/321 (16%) events.

The accuracy (i.e. total number of correct diagnoses / all diagnoses made, see **Table 7.8**) of the medical staff was 205/271 (75.6%), and 36/50 (72.0%) for the nursing staff.

The research fellow's assessment

'End of bed assessment'

At the beginning of the assessment, the stroke research fellow was asked to record his/her 'end of bed assessment', which was based on a brief clinical history (from the ARU medic or nurse) and inspection of the patient. 278/350 (79%) end of bed diagnoses were stroke, 31/350 (9%) were non-stroke, and 41/350 (12%) were unsure. I grouped unsure diagnoses with non-strokes in these analyses. The accuracy of the stroke research fellow's end of bed assessment was almost identical to the ARU staff (see **Table 7.9**). Accuracy did not differ significantly depending on the clinician – PJH assessed 181 events, accuracy 77.3%, JK assessed 136 patients, accuracy 73.5% (confidence intervals for difference in proportions overlap).

Diagnosis after taking the history

It is often claimed that the clinical diagnosis is based predominantly on the history (Warlow, 1991). By asking the clinician to record his/her diagnosis after taking the history (but before performing a physical examination), I hoped to explore the relative impact of the history and examination on the diagnostic process. There was a modest improvement in overall accuracy (80.0% after history, compared with 75.1% for end of bed assessment, p=0.15, χ^2), however the likelihood ratio was only 1.94 (**Table 7.9**).

Research fellow's final bedside diagnosis

At the completion of the clinical assessment, the research fellow recorded his/her final diagnosis based on all the available clinical data. The diagnoses were definite stroke (n=151), probable stroke (n=74), possible stroke (n=68), and non-stroke (n=57). These were collapsed into 'thrombolysis-eligible' brain attacks (definite and probable stroke, n=225), and stroke mimics (possible stroke and non-stroke, n=125). The accuracy of the research fellow was 84.6%, and both specificity and sensitivity were greater than 80% (**Table 7.9**, see **Appendix 6** for raw data in 2x2 tables). The likelihood ratio was 4.9. Assuming a prevalence of stroke of around 70% (the pre-test probability in unselected patients with brain attack), a LR of 5 raises the possibility of stroke to 95% after the bedside assessment (Sackett *et al.*, 1985b).

The difference in accuracy between the research fellow's end of bed assessment and the research fellow's final diagnosis was significant (9.4% difference, 95% CI 3.5 – 15.3%, $p<0.01$, χ^2). The accuracy of each clinician also increased after the full clinical assessment (77.3% to 86.7% for PJH, 73.5% to 81.6% for JK).

7.4.5 Reasons for disagreement between research fellow bedside diagnosis and the gold standard diagnosis

This section explores the reasons for an inaccurate bedside diagnosis. I compared the stroke research fellow's final bedside diagnosis (the bedside diagnosis) with the gold standard expert panel diagnosis (made in knowledge of the brain

imaging and early progress), and divided patients into those with a correct bedside diagnosis, and those with an incorrect bedside diagnosis.

There were 296 correct bedside diagnoses: 90 were mimic and 206 were 'thrombolysis-eligible' brain attack. 54 incorrect bedside diagnoses were made by the research fellows: 35 (65%) events initially diagnosed as mimic received a panel diagnosis of thrombolysis-eligible stroke, and 19 (35%) events diagnosed as stroke received a final diagnosis of mimic. The 19 mimics initially diagnosed as stroke were space occupying lesion (n=5), sepsis (n=4), vestibular disturbance (n=3), seizure (n=2), functional (n=1), migraine (n=1), toxic/metabolic (n=1), dementia (n=1), and syncope (n=1).

The general features of patient-episodes, divided into correct and incorrect bedside diagnosis, are detailed in **Table 7.10**. The two groups were similar in age, gender, research fellow examiner, and baseline stroke severity. The main difference was that incorrect bedside diagnoses were more frequent in patients who presented after six hours: 61% of incorrect diagnoses were made in patients who presented after six hours, compared with 41% of correct diagnoses (p=0.01, χ^2 test for trend). Patients with an incorrect bedside diagnosis were seen by the research fellow later than patients with a correct bedside diagnosis (p=0.03, Mann-Whitney U).

History items

The only significant variable was that patients who re-presented (i.e. had been recruited into the study earlier) were more likely to be given an incorrect diagnosis (OR 3.3, 95% CI 1.1 – 10.1) (see **Figure 7.11**). Inability to obtain the history from the patient or a relative, absence of a second source of history, and inconsistencies in the details provided by different sources (all postulated to cause difficulties bedside

diagnosis) did not reach significance. There were trends for vertigo or past history of stroke (particularly with incomplete recovery) to increase the likelihood of an incorrect bedside diagnosis, but these were not significance (probably due to low numbers).

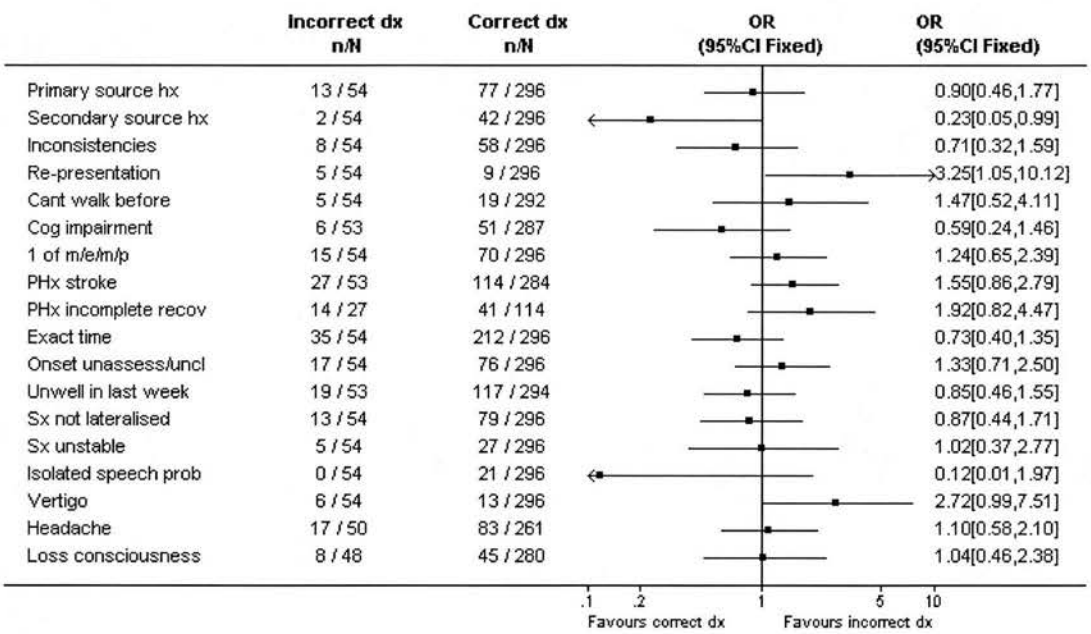


Figure 7.11 History items that favoured an incorrect bedside diagnosis

Dx – diagnosis
Primary source hx – primary source of history was not patient or relative
Secondary source hx – no secondary source of history available
Cog impairment – cognitive impairment
1 of m/e/m/p – one of migraine, epilepsy, malignancy or psychological disorder
PHx – past history; Sx –symptoms

Examination items

Factors such as altered level of consciousness, confusion, aphasia, or the presence of a comorbid condition that made examination difficult, did not significantly increase the likelihood of an incorrect bedside diagnosis (see **Figure 7.12**). Patients with right hemisphere cortical lesions may exhibit anosognosia (Ghika-Schmid & Bogousslavsky, 2001), which might result in difficulties with the

bedside diagnosis. However, in our series, right hemispheric events did not predict an incorrect diagnosis.

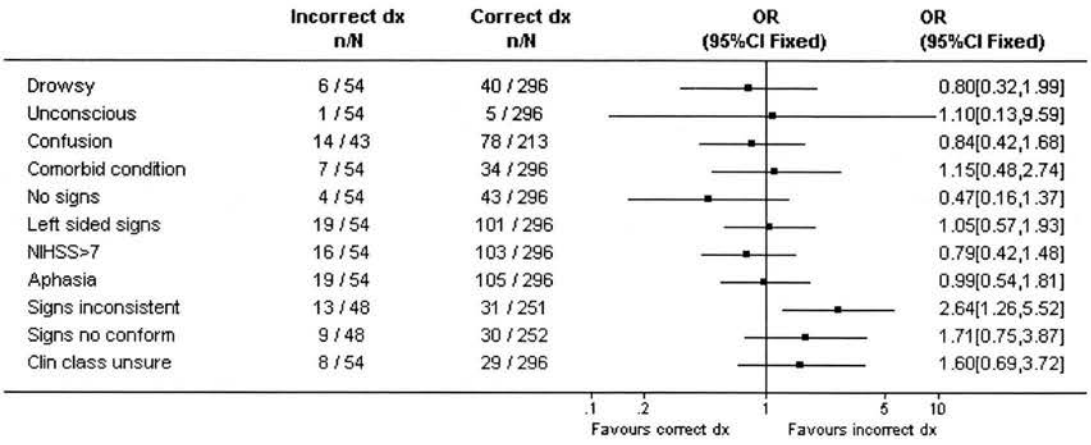


Figure 7.12 Examination and diagnostic formulation items that favoured an incorrect bedside diagnosis

Dx – diagnosis
No signs – no neurological signs
Signs inconsistent – neurological signs inconsistent with the symptoms
Signs no conform – neurological signs did not conform to known vascular territory
Clin class unsure – OCSP clinical classification could not be determined

I anticipated that an incorrect bedside diagnosis would be likely if the neurological signs were inconsistent with the symptoms, or if the neurological signs did not conform to known vascular territory. This proved to be the case for signs that were inconsistent with the symptoms (OR 2.6, 95% CI 1.3 – 5.5). However, there were differences in the way these questions were answered by the research fellows. For examiner PJH, signs were consistent in 115/136 (85%) of correct diagnoses and 9/19 (47%) of incorrect diagnoses ($p<0.01$, χ^2); and signs conformed to vascular territory in 113/136 (83%) of correct diagnoses and 14/19 (74%) of incorrect diagnoses ($p=0.497$, χ^2). For examiner JK, signs were consistent in 86/94 (91%) of correct diagnoses and 21/24 (88%) of incorrect diagnoses ($p=0.836$, χ^2); and signs conformed to vascular territory in 88/95 (93%) of correct diagnoses and 20/24 (83%)

of incorrect diagnoses (p=0.312, χ^2). Thus, 'signs consistent with symptoms' was useful in predicting an incorrect diagnosis for one examiner but not the other.

7.5 Discussion

7.5.1 Stroke mimics

Frequencies

Of 350 presentations, a definite non-stroke accounted for 65 (18.6%), and a probable non-stroke accounted for 44 (12.6%). In my systematic review of the accuracy of the clinical diagnosis of stroke, the overall frequency of mimics was 18.1% (see **Figure 4.1** [Note that the measure of accuracy used was the positive predictive value; the frequency of mimics is 1 – positive predictive value]). For studies based in the hospital (rather than the community), mimics were a much smaller proportion of admissions (11.2%). The present study identified a frequency of 31.1%, although if only definite mimics are counted, the figure is 18.6%.

Why was the frequency higher in the present study?

In the Brain Attack study, I specifically aimed to identify all non-strokes in a consecutive sample of patients. Many of the hospital-based studies that reported low frequency of mimics [e.g. 1.2% for O'Brien et al (1987b), and 5.0% for Besson et al (1996a)] were much more selective. Community-based studies were less selective, and consequently the misdiagnosis rate was higher; but these studies are less relevant to the hospital-based stroke physician. The study of Libman et al (1995b), although retrospective, similarly aimed to identify all patients presenting with "sudden onset

of a focal deficit" to a general hospital. 78/411 (19%) patients were found to have mimics – an almost identical figure to the definite mimics of the present study.

Causes

The four leading causes of mimic were seizure (21% of mimics), sepsis (13%), toxic / metabolic disturbance (11%), and space occupying lesion (9%). The mimics identified, and their frequencies, were similar to earlier studies (see **Figure 4.2**). I did not use the category 'sequelae of old stroke' as this is a non-specific term, and we were able to determine a precise cause in almost all cases. Nonetheless, 41.5% of mimics in this study had suffered a previous stroke. In both the present study, and the review of 25 earlier studies, there was a long list of infrequently observed stroke mimics – conditions such as transient global amnesia, meningitis, multiple sclerosis (presenting acutely), spinal cord lesions, and so on.

Implications

The present study probably provides typical figures for doctors working in a typical general hospital. Around 30% of patients presenting with brain attack will have a stroke mimic. Some mimics will be definitively diagnosed (by brain imaging or other laboratory tests), but many cannot be diagnosed with certainty. In the present study, they were labelled as 'possible stroke'. Patients with possible stroke would not be candidates for thrombolysis or other risky treatments.

82/109 (75%) mimics in the present study could be classed as a neurological disorder. This highlights the need for neurologists – or stroke physicians with adequate neurological training – to be involved in the assessment of patients with

brain attack, as has been argued by others since the 1950s (Rankin, 1957b; Bratina *et al.*, 1995; Hachinski, 1996; Horowitz, 1998).

7.5.2 Transient ischaemic attacks

In the present study, the final diagnosis was TIA in 48/350 events (14%), similar to the frequency identified by other studies (e.g., 10% (Allder *et al.*, 1999a) to 18% (Kolominsky-Rabas *et al.*, 1998b)). I simply treated those with a definite TIA (n=35) as thrombolysis-eligible brain attacks, and those with possible TIA (n=13) as mimics. It is not possible to distinguish, in the first few hours, those likely to recover spontaneously (TIAs) from those who will not (strokes). Thus, patients with a TIA who present early enough and are still symptomatic may receive unnecessary treatment. Ideally, one would avoid treating patients with thrombolysis if there were a reliable method of determining if their symptoms would resolve within 24 hours. Unfortunately, numbers were too small in the present study to explore this issue further.

7.5.3 Diagnostic certainty

In the present study, the expert panel had great difficulty in arriving at a definitive diagnosis for all patients (e.g. the patient with vestibular disturbance and a normal brain scan). This reflects clinical reality: the diagnosis is not always clear-cut, and a gold-standard for the diagnosis of stroke is lacking (D'Olhaberriague *et al.*, 1996). Our category of possible stroke contained patients who could not be classed as definite non-stroke, but a non-stroke explanation for their symptoms may actually have been more likely than stroke. As this thesis is directed towards acute interventions such as thrombolysis, which carries significant risks, I treated possible

strokes as mimics. However, possible strokes may be treated differently in other management scenarios (e.g. treating with aspirin).

The simple observation of the difficulty in arriving at a final consensus diagnosis is not widely reported. Only four of 25 earlier studies identified possible stroke as a category, yet the frequency ranged from 4% to 28% (von Arbin *et al.*, 1981; Ellekjaer *et al.*, 1997a; Horn *et al.*, 1997b; The members of the Lille Stroke Program, 1997c). When some class up to one quarter of patients as uncertain, how were the majority of studies able to be so definite? Absence of a possible category makes interpretation of a study's results difficult, and limits their extrapolation to other clinical settings.

7.5.4 Features that distinguish between stroke and mimic

Despite the importance of the clinical assessment, there have been few studies that specifically examined how clinical assessment might be improved. The largest previous study, by Libman and colleagues (1995b), identified six significant clinical predictors on univariate analyses. Female gender, abnormal visual fields, diastolic blood pressure > 90mmHg and atrial fibrillation increased the odds of stroke; and normal eye movements and abnormal admission neurological examination increased the odds of a mimic (Libman *et al.*, 1995b). In the present study, we also found that diastolic blood pressure > 90mmHg and abnormal visual fields predicted stroke, but we did not find that female gender, atrial fibrillation or normal eye movements were significant predictors. We found that an abnormal neurological examination actually predicted a stroke (rather than a mimic)

Several studies provided clinical pointers to distinguish stroke from mimic, but did not systematically evaluate the clinical assessment. Ferro et al (1998a) suggested that a mimic was more likely if the patient had no vascular risk factors; but this was not confirmed by the present study (odds ratio for absence of vascular risk factors to predict a mimic 1.7, 95% CI 0.8–3.3, p=0.20, χ^2). Allen (1983a) provided clinical features that distinguished mass lesions from vascular lesions. The significant features were that the symptoms had evolved over more than 24 hours, and in a stuttering manner. Similarly, Weisberg & Nice (1977), in an early study on the usefulness of CT in stroke, found that the temporal evolution of the deficit was crucial in differentiating vascular from non-vascular aetiology. Unfortunately, in the present study, these details could not be adequately established. However, an exact time of onset, the patient being able to recall exactly what he/she was doing at symptom onset, and being well in the last week were all strongly predictive of ('thrombolysis-eligible') stroke, and all point to an abrupt onset.

Implications

Table 7.11 lists the significant clinical factors that helped to distinguish between stroke and mimic at the bedside. As patients with previous stroke were at risk of both stroke and mimic, few elements of the past history can be relied on, although cognitive impairment increases the likelihood of a mimic. A history of an exact onset of symptoms, and no health problems in the last week suggest a stroke, whilst seizures or loss of consciousness suggest a mimic. Focal neurological symptoms, and almost any focal neurological signs (with five exceptions, see **Table 7.11**) suggest stroke, but absence of either, and the findings of confusion or abnormalities in another body system suggest a mimic. If the features can be

classified into an OCSP category, a stroke is likely, but if the signs are unclassifiable, or do not conform to known vascular territory (or to the symptoms), suspect a mimic.

These data could be used to develop clinical algorithms to assist the non-specialist. This, in turn, could increase clinician's confidence in the diagnosis of brain attack, and improve the speed of assessment and referral for brain imaging, a major current barrier to the implementation of time-sensitive treatments (Johnston *et al.*, 1999).

7.5.5 The bedside diagnosis

Accuracy

The accuracy of the bedside diagnosis increased progressively as the experience of the assessor increased (see **Table 7.12**). The general practitioner's diagnosis was least accurate overall, although the most sensitive. High sensitivity suggests GPs are good at diagnosing stroke. A more clinically useful measure, for a hospital doctor faced with a GP diagnosis of stroke, is the positive predictive value (PPV), or the chance of a positive diagnosis being correct. For the present study, the general practitioner PPV was 73%. This was similar to other studies that examined GP accuracy [e.g. 85% for the patients referred to the stroke clinic in the study of Ferro et al (1998a); 69% for the study of Horn et al (1997b; 2001)]. The GP's positive assessment of stroke may be helpful, but is not satisfactory for difficult management decisions.

Importance of the elements of the clinical assessment

In the present study, the research fellows achieved the greatest accuracy, reinforcing the finding of Norris & Hachinski (1982) that clinical skill improves accuracy. However, we found that a quick, 'end of bed' assessment by an experienced stroke research fellow was no more accurate than the assessment of the ARU staff. Similarly, the research fellow's diagnosis after taking a history was less accurate than at the completion of the history and examination. Our findings suggest that the clinical assessment is a package, and all the individual components are required for it to function optimally. Our findings would also suggest that there is little point in having an experienced stroke expert stationed at the door of the emergency department to 'triage' potential stroke patients for fast-tracking (by asking a few brief questions).

Disagreements

I attempted to discover the features that made the diagnosis difficult in certain patients. As the number of incorrect diagnoses was small, the present study lacked power. Others (Allen, 1983a; Sandercock *et al.*, 1985a) found that an inadequate history predicted an incorrect diagnosis, but in the present study the source of the history (whether direct from patient/relative or indirect from notes/ambulance sheet/GP referral letter) was not a significant factor.

Only three significant factors were identified: re-presentation, late (>6 hours) presentation, and signs inconsistent with symptoms suggested an incorrect bedside diagnosis (see **Table 7.13**). The implications of time to presentation will be discussed further in **Chapter 8**. An important cause of disagreement was when the clinical symptoms did not correlate with the signs. However, the variation in the

way this question was answered by the two examiners suggested that it had not been fully understood. The question was part of the diagnostic formulation, a section of data collection left open to the free thought processes of the clinician. For this to be a useful factor in clinical practice, further training would be necessary.

7.5.6 Limitations of the study

There were several limitations to the present study. I shall discuss how these may have impacted on the results obtained in the following sections.

Were cases missed?

I attempted to recruit all patients with brain attack who were admitted to the Western General Hospital during the study period. It is possible that the definition of brain attack was too restrictive. von Arbin et al (1980) used a similar definition to select patients for entry to a stroke unit ("patients with acute onset of focal neurological deficit...without trauma to the head"). Of 1865 patients who did not fulfil entry criteria for the stroke unit, only 24 had a stroke (a 1.3% false negative rate). Thus, it is probably unlikely that I missed many true strokes by using the definition of brain attack (although I may not have seen all of the patients considered by the referring doctor to have a possible stroke).

Despite using multiple overlapping sources of case ascertainment, it is possible that suitable patients were missed. This was true of direct admissions to the Department of Clinical Neurosciences, which were difficult to monitor. Many of these patients were transferred from another hospital for neurosurgical evacuation of an intracerebral haematoma. These patients did not present de-novo to the Western

General Hospital, and could not be assessed without knowing the results of important investigations.

During August 2000, I monitored the number of patients we were unable to see. There were three patients missed (and 56 patients recruited): one was a brief admission to neurology unit with transient global amnesia, the other two were admitted with symptoms due to malignancy. I judged this to be an acceptable rate.

Was the spectrum of patients recruited 'typical'?

The patients recruited were consecutive, unselected admissions to the Western General Hospital (WGH). The broad description of the cohort seems similar to other published studies (International Stroke Trial Collaborative Group, 1997), although older than patients in the Lausanne Stroke Registry (Bogousslavsky *et al.*, 1988) and Stroke Data Bank (Foulkes *et al.*, 1988). This age difference is very important, as stroke can be difficult to diagnose when patients are frail or have co-morbidity. The age difference can be explained by the WGH stroke unit offering an 'all-age' service with active involvement of geriatricians.

Our patients had milder strokes than patients recruited to trials of thrombolysis (The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group, 1995; Hacke *et al.*, 1998). The admission policy of the stroke unit is to accept all patients, no matter how severe. The vast majority of admissions come through the Acute Receiving Unit, referred in by GP or by ambulance. Due to the complexity of the zoning arrangements for the Edinburgh area, it is possible that some of the severe patients were taken to the Royal Infirmary (particularly if there were any trauma). This may explain the milder composition of our cohort. However, more severe strokes are probably easier to diagnose clinically.

Was the bedside assessment performed blind to results of brain imaging?

It was anticipated that all patients would be seen prior to brain imaging (and no provisions were made for collection of this data). However, some patients had already been scanned (particularly weekend patients) when seen by the research fellow. The best available estimate is that fewer than 15 patients (4%) were assessed when the scan result was available, and this is not likely to have caused significant bias.

Problems with the gold standard diagnosis

Panel composition

Inevitably, the members of the panel were unable to attend every meeting. As decisions were made by consensus, and certain members of the team were more likely to dominate the meeting than others, the consistency of the diagnoses varied. If the neuroradiologist was absent, clinicians had to interpret the scans themselves, which may have diminished certainty.

There were several sources of additional bias. The history and examination at the expert team meetings were provided by the research fellow who had seen the patient. To allow errors to be avoided, if there was any uncertainty or dispute about the history/examination, the name of the patient was revealed and the responsible clinician invited to clarify the details. In attempting to reduce one source of bias, another bias was introduced.

Definitions

The definitions provided were loose. Subtle interpretations changed from week to week (e.g., a 'probable' stroke became a 'definite' stroke when the panel

was 90% sure, but other times it was when 95% sure). The diagnoses applied were more rigid than 'real life', which particularly impacted on the possible stroke category. Even when the responsible clinician told us that the patient was treated as (and behaved as) a non-stroke, unless there was laboratory or convincing clinical evidence of an alternate diagnosis, the patient was diagnosed as a possible stroke.

Was it appropriate to split the diagnostic categories as I did, or was this just a post-hoc analysis?

The large group of possible strokes presented a difficulty for data analysis. Eligible patients should not be excluded from analysis, as this creates potentially strong biases (Piantadosi, 1997). It seemed clinically sensible to group those with a plausible alternative non-stroke diagnosis with the definite non-strokes, as these patients are unlikely to be given thrombolysis. This was chosen as my primary analysis because it was clinically relevant. Restricting the analysis to definite non-strokes (n=65) compared with any stroke (n=285) produced broadly similar results. I elected not to present both data sets to maintain clarity for the reader.

Were there any confounding factors?

The main sources of possible confounding in this study were:

- Differences in training and experience between examiners
- Improvements in clinical skills with time (i.e. our training in stroke medicine)
- Inability to obtain key data in some situations (e.g. aphasic patient with no relative)

- Patients were assessed by the research fellow later than they presented (median delay from presentation to assessment was 17 hours), and may have fluctuated in this time. It would have been ideal to see patients immediately on presentation, but this was not possible. This issue will be considered further in **Chapter 8**.

Was the sample size adequate?

For the purposes of determining a reasonably precise point estimate of the frequency of stroke mimics, and calculating odds ratios for clinical factors that distinguish between stroke an mimic, the sample size was adequate. However, there were relatively few situations in which there was disagreement between the clinical and final diagnoses, so for these analyses confidence intervals were wide (and a type II error could not be excluded).

7.6 Summary

- Although the present study has many limitations, the results add substantial knowledge to a field of limited and variable quality studies
- In the thrombolysis era, a detailed clinical assessment needs to be performed quickly and with confidence
- These results provide, for the first time, numerical scientific data to support the 'art' of the clinical assessment of patients with brain attack.
- The value of the clinical assessment is cumulative: 'end of bed' accuracy is improved by taking a history, which is improved by performing an examination.

- Around 30% of brain attacks are due to stroke mimics, and 75% of these mimics are neurological disorders. Adequate training in neurology is certainly required, and this study provides evidence that UK neurologists should become more involved in acute stroke services.
- Important 'rule in' laws for the diagnosis of stroke include: definite time of onset, definite focal neurological symptoms and signs, a classifiable clinical syndrome
- Cautionary features that suggest a mimic include: dementia, confusion, absence of focal neurological symptoms or signs, when the features 'don't make sense'
- Much of what I have shown would be familiar to the experienced clinician. Placing numerical values ('weights') on the diagnostic discriminating ability of each feature means it can be taught to junior doctors to help them gain experience and skill

Recommendations for further research

- The clinical factors suggested in this chapter should be tested for reliability, and validated on an external, prospectively recruited dataset
- Clinical methods to distinguish TIA from stroke in the first few hours are needed

Table 7.1 General characteristics of patient recruitment in Brain Attack study

Feature	Number (%)
Age (n=336 patients):	
Median (IQR)	76.3 years (66.5–82.9)
Mean (standard deviation)	73.5 years (13.4)
Range	17.4 years – 98.7 years
Gender (n=336 patients):	
Male	163 (48.5%)
Female	173 (51.5%)
Referred to research team by (n=350 episodes):	
ARU	321 episodes (92%)
Other ward	15 episodes (4%)
Inpatient brain attacks	14 episodes (4%)
Source of referral to research team (n=350 episodes):	
Doctor	299 (85%)
Nurse	51 (15%)
Median time from symptom onset to presentation (n=330 episodes) (IQR):*	4.7 hours (2.0-13.7)
Time of ARU admission (n=335 episodes):†	
9.00am – 5.00pm	209 episodes (62%)
5.01pm – Midnight	90 episodes (27%)
Midnight – 8.59am	36 episodes (11%)
Median time from symptom onset to evaluation (n=345 episodes) (IQR):‡	25.8 hours (12.5-50.5)
Median Delay between presentation to hospital and evaluation by research team (n=330 episodes) (IQR):*	17.0 hours (1.3-25.7)
Admission destination (n=350 episodes):	
Stroke unit	126 (36%)
General ward	213 (61%)
Neuroscience unit	11 (3%)
Examiner (n=350 episodes):	
PJH	181 (52%)
JK	136 (39%)
BL	25 (7%)
SLK	8 (2%)

IQR – interquartile range

** - 14 episodes were inpatient brain attacks, in 5 episodes the time of onset was unknown, in one episode the time of arrival in ARU was unknown*

† - 14 inpatient brain attacks, 1 brain attack with unknown time of arrival in ARU

‡ - time of onset could not be determined in 5 episodes of brain attack

Table 7.2 Baseline demographic data of patients in brain attack study (n=336)

Feature	n/total known (%)*
Patient could walk independently before admission:	309 / 332 (93%)
Vascular risk factors:	
Hypertension	159 / 325 (49%)
Ischaemic heart disease	100 / 322 (31%)
Smoker (past or present)	172 / 326 (53%)
Atrial fibrillation	62 / 321 (19%)
Diabetes mellitus	40 / 327 (12%)
Peripheral vascular disease	33 / 307 (11%)
Past history of stroke or TIA	129 / 323 (40%)
(Proposed) risk factors for stroke mimic:	
Cognitive impairment	54 / 326 (17%)
Known history of migraine	16 / 336 (5%)
Known history of epilepsy	12 / 336 (4%)
Known malignancy	33 / 336 (10%)
Psychological disturbance†	28 / 336 (8%)

** - In a small number of patients, the presence or absence of an individual feature could not be determined. Thus the denominator excludes those patients in whom the feature was unknown*

† - one or more episodes of psychological disturbance severe enough to warrant medication

Table 7.3 Presenting features and examination findings of all patient-episodes (n=350)

Feature	n/total known (%)*
Presenting event:	
Exact time of onset	247 / 350 (71%)
Woke from sleep with symptoms	78 / 253 (31%)
Patient was well in last week	211 / 347 (61%)
Focal neurological symptoms	307 / 350 (88%)
Loss of consciousness	53 / 328 (16%)
Vomited	44 / 335 (13%)
Headache	100 / 311 (32%)
Patient could walk after symptom onset:	140 / 346 (40%)
Examination findings:	
BP≥ 150/90	112 / 349 (32%)
Irregular pulse	72 / 350 (21%)
GCS = 15	236 / 350 (67%)
Confusion†	92 / 256 (36%)
No neurological signs	47 / 350 (13%)

** - In a small number of patients, the presence or absence of an individual feature could not be determined. Thus the denominator excludes those patients in whom the feature was unknown*

† - made one or more errors on tests for confusion (orientation and attention, see Appendix 2). Note the denominator was smaller than for GCS

Table 7.4 Final diagnosis in the brain attack study (n=350)

Category	Number	(%)	*95% Confidence Intervals*
Definite stroke	186	(53%)	*48%–58%*
Probable stroke	34	(10%)	*7%–13%*
Definite TIA	17	(5%)	*3%–8%*
Possible stroke	35	(10%)	*7%–13%*
Possible TIA	13	(4%)	*2%–6%*
Stroke mimic	65	(19%)	*15%–23%*

Table 7.5 Definite non-strokes in the brain attack study

Condition	Number	(%)*	*95% Confidence Intervals**
Seizure	13	(3.7%)	*2.0% – 6.3%*
Space occupying lesion	10	(2.9%)	*1.4% – 5.2%*
Sepsis	8	(2.3%)	*1.0% – 4.5%*
Syncope/presyncope	8	(2.3%)	*1.0% – 4.5%*
Toxic/metabolic	8	(2.3%)	*1.0% – 4.5%*
Acute mononeuropathy	4	(1.1%)	*0.3% – 2.9%*
Acute confusional state	3	(0.9%)	*0.2% – 2.5%*
Functional (medically unexplained)	3	(0.9%)	*0.2% – 2.5%*
Spinal cord lesion	3	(0.9%)	*0.2% – 2.5%*
Other causes	5	(1.4%)	*0.5% – 3.3%*
Total	**65**	**(18.6%)**	***14.5% – 22.6%***

* - *expressed as the proportion of all patient episodes in the brain attack study (n=350)*

Table 7.6 All stroke mimics (definite non-stroke and possible stroke with a plausible alternative explanation for symptoms) (n=109)*

Condition	Number	(%)†
Seizure	23	(21.1%)
Sepsis	14	(12.8%)
Toxic / metabolic	12	(11.0%)
Space occupying lesion	10	(9.2%)
Syncope / presyncope	10	(9.2%)
Acute confusional state	7	(6.4%)
Vestibular dysfunction	7	(6.4%)
Acute mononeuropathy	6	(5.5%)
Functional/medically unexplained symptoms	6	(5.5%)
Dementia	4	(3.7%)
Migraine	4	(3.7%)
Spinal cord lesion	3	(2.8%)
Other‡	3	(2.8%)
Total	**109**	**(100%)**

** this includes the 65 brain attacks definitely due to a mimic, and the 44 brain attacks labelled as possible stroke/TIA in which there was a highly plausible alternate diagnosis. There were four presentations diagnosed as possible stroke/TIA with no plausible alternate diagnosis (these patient-episodes have not been included).*

† expressed as a proportion of the 109 mimics

‡ includes subarachnoid haemorrhage, transient global amnesia and Parkinsonian syndrome

Table 7.7 General features of 'thrombolysis-eligible' brain attacks and stroke mimics

Feature	'Thrombolysis-eligible' brain attacks *n=241 episodes n=237 patients*		Stroke mimics *n=109 episodes n=106 patients*		P-value*
Median age (years)†	76.27		76.95		*.568*
Male gender†	118	(49.8%)	48	(45.3%)	*.441*
Median time from onset to presentation (hours):	4.47		4.67		*.586*
Number presenting:‡					*.916*
0-6 hours	129	(53.5%)	60	(55.0%)	
6-12 hours	38	(15.8%)	13	(11.9%)	
>12 hours	63	(26.1%)	33	(30.3%)	
Examiner:					*.791*
PJH	124	(51.5%)	57	(52.3%)	
JK	93	(38.6%)	43	(39.4%)	
NIHSS:					*<.001*
Mean	8.56		4.65		
Median	5.0		3.0		
Clinical classification:§					*<.001*
TACS	57	(23.7%)	3	(2.8%)	
PACS	77	(32.0%)	31	(28.4%)	
LACS	54	(22.4%)	5	(4.6%)	
POCS	31	(12.9%)	11	(10.1%)	
Unsure/No signs	22	(9.2%)	59	(54.1%)	
Number with brain imaging	232	(96.3%)	72	(66.1%)	*<.001*

** - p value determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables).*
† - refers to the number of patients
‡ - incomplete numbers, as inpatient strokes were not included
§ - OCSP clinical classification. TACS: total anterior circulation syndrome, PACS: partial anterior circulation syndrome, LACS: lacunar syndrome, POCS: posterior circulation syndrome

Table 7.8 Assessing the performance of a diagnostic test

	Gold Standard	
Diagnostic test	Disease present	Disease absent
Positive	a	b
Negative	c	d

Feature	Question addressed	Formula
Sensitivity	How well the test diagnoses those with the condition	a / (a+c)
Specificity	How well the test excludes those without the condition	d / (b+d)
Positive predictive value (PPV)	If the test is positive, how likely is it that the patient has the condition?	a / (a+b)
Negative predictive value (NPV)	If the test is negative, how likely is it that the patient does not have the condition?	d / (c+d)
Accuracy	The proportion of all diagnoses that are correct	(a+d) / (a+b+c+d)
Likelihood ratio (LR) (of a positive test)	The ratio of the proportion with a true positive diagnosis to the proportion with a false positive diagnosis	Sensitivity / (1-specificity)

Adapted from (Ebrahim & Harwood, 1999a; Greenhalgh, 2000)

Table 7.9 Accuracy of the bedside diagnosis, subdivided by clinician

	Diagnosis by:				
Feature	**GP** *(95% CI)*	**ARU** *(95% CI)*	**Research Fellow - 'End of bed'** *(95% CI)*	**Research Fellow - After history** *(95% CI)*	**Research Fellow - Final** *(95% CI)*
Sensitivity	95.4% *(91-98)*	88.0% *(83-92)*	89.6% *(85-93)*	92.5% *(89-95)*	85.5% *(81-89)*
Specificity	14.5% *(8-25)*	48.6% *(39-58)*	43.1% *(34-53)*	52.3% *(43-89)*	82.6% *(74-89)*
PPV	73.4% *(67-79)*	77.9% *(72-83)*	77.9% *(72-82)*	81.1% *(76-85)*	91.6% *(87-95)*
NPV	56.3% *(33-77)*	66.2% *(55-76)*	65.3% *(54-75)*	76.0% *(65-84)*	72.0% *(64-79)*
Accuracy	72.1% *(66-78)*	75.1% *(70-80)*	75.1% *(70-79)*	80.0% *(76-84)*	84.6% *(80-88)*
LR	1.12 *(1.0-1.2)*	1.71 *(1.4-2.1)*	1.58 *(1.3-1.9)*	1.94 *(1.6-2.4)*	4.90 *(3.3-7.4)*

Table 7.10 General features of patients with incorrect and correct bedside diagnosis by the research fellow

Feature	Incorrect diagnosis *n=54 episodes, n=49 patients*		Correct diagnosis *n=296 episodes, n=287 patients*		P-value*
Median age (years)†	73.79		76.38		*.270*
Male gender†	22	(44.9%)	141	(49.1%)	*.584*
Median time from onset to presentation (hours):	6.50		4.27		*.064*
Number presenting:‡					*.014*
0-6 hours	20	(37.0%)	169	(55.0%)	
6-12 hours	11	(20.4%)	40	(11.9%)	
>12 hours	20	(37.0%)	76	(30.3%)	
Median time from onset to assessment by research fellow (hours):	30.58		25.12		*.028*
Examiner:					*.316*
PJH	24	(44.4%)	157	(53.0%)	
JK	25	(46.3%)	111	(37.5%)	
NIHSS:					*.296*
Mean	6.06		7.58		
Median	4.0		4.0		
Clinical classification:§					*.234*
TACS	5	(9.3%)	55	(18.6%)	
PACS	20	(37.0%)	88	(29.7%)	
LACS	6	(11.1%)	53	(17.9%)	
POCS	9	(16.7%)	33	(11.1%)	
Unsure/No signs	14	(25.9%)	67	(22.6%)	

** - p value determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables)*
† - refers to the number of patients
‡ - incomplete numbers, as inpatient strokes were not included
§ - OCSP clinical classification (Bamford et al., 1991). TACS – total anterior circulation syndrome, PACS – partial anterior circulation syndrome, LACS – lacunar syndrome, POCS – posterior circulation syndrome

Table 7.11 Summary features that distinguish between stroke and mimic

	Likely stroke if:	**Likely mimic if:**
Past medical history	- Peripheral vascular disease	- Cognitive impairment
History of presenting complaint	- Any focal neurological symptoms	- No lateralising symptoms
	- Exact time of onset	- Loss of consciousness
	- Well in the last week	- Seizure
Examination	- Hypertension	- Confusion
	- Valvular heart disease	- Signs in other systems
	- Any neurological sign*	- No neurological signs
Diagnostic formulation	- Lateralised to right/left brain	- Signs not consistent with symptoms
	- TACS	- Signs did not conform to vascular territory
	- LACS	- Can't determine side of brain
		- Signs unclassifiable

** any sign except: (1)impaired comprehension; (2) III, IV, VI cranial nerve palsy; (3) nystagmus;(4) lower limb ataxia, and (5) reflex asymmetry*

Table 7.12 Summary accuracy of the clinical diagnosis of brain attack

	Accuracy*	**(%)**	***95% CI***
GP diagnosis	154 / 215	(72.1%)	*65.7 – 77.7%*
ARU diagnosis	241 / 321	(75.1%)	*70.1 – 79.5%*
Research fellow - 'End of bed' diagnosis	263 / 350	(75.1%)	*70.4 – 79.4%*
Research fellow after history	280 / 350	(80.0%)	*75.5 – 83.9%*
Research fellow final clinical diagnosis	296 / 350	(84.6%)	*80.4 – 88.0%*

** Accuracy = all correct diagnoses / total number diagnoses*

Table 7.13 Summary of factors that resulted in an incorrect clinical diagnosis

	Incorrect diagnosis likely if:
History	
	- Re-presentation
	- Later presentation (>6 hours)
Examination	
	- Signs inconsistent with symptoms

Chapter 8 : The hyperacute brain attack

8.1 Introduction

The following chapter describes a sub-study of the Brain Attack study. The features of patients who presented to hospital within six hours of symptom onset – 'hyperacute' brain attack – will be presented. These patients are the subject of a separate chapter because: patients who arrive at hospital within three hours (and up to six in clinical trials) are currently eligible for stroke treatments such as thrombolysis; I have shown that patients assessed within six hours in the International Stroke Trial were different to those assessed later, and I wanted to discover if the findings of the last chapter – determined by analysis of all patients with brain attack – are relevant to those presenting very early.

8.2 Aims

The present study will focus on patients recruited into the Brain Attack study within six hours of onset to address the following aims.

(1) Are the clinical features of patients who present with brain attack in the first few hours different to those who present later?

(2) Are the key clinical features of a 'thrombolysis-eligible' brain attack the same in patients who present earlier compared to later?

(3) Is the clinical diagnosis more difficult in the first few hours?

(4) How often can an exact time of onset be determined, and what are the reasons for difficulty in the hyperacute phase?

(5) Can clinical tools, such as the OCSP classification and the NIHSS score, help distinguish between mimic and stroke?

8.3 Methods

This is a sub-study of the patients recruited into the brain attack study within six hours of symptom onset. Patient eligibility criteria, case ascertainment, data collection forms, final diagnosis, and data management were all identical to the main study, and are described in detail in **Chapter 7.2**. In this section, I will highlight the methods that were of relevance to the present analyses.

8.3.1 Patients

Inclusion criteria

Patients with brain attack who presented within six hours of symptom onset were studied. A six hour time limit was chosen because the Cochrane systematic review of thrombolysis for acute ischaemic stroke suggests that treatment is promising when given within six hours of onset (Wardlaw *et al.*, 2001a).

Symptom onset was defined as the time that symptoms were first noted, even if the patient woke from sleep with symptoms. Presentation was defined as the time the patient arrived in acute receiving unit (ARU), or the time of evaluation by the research team for those patients who had a brain attack whilst in hospital. Where precise timing details were unknown, we estimated a time of onset from all available sources (GP letter, ambulance note, friend or relative).

Clinical assessment

The key components of the clinical assessment for the present chapter were the National Institutes of Health Stroke Scale (NIHSS) and the Oxfordshire Community Stroke Project (OCSP) classification. The NIHSS score (see **Appendix 2**) provides a global description of the patient's neurological deficit, and has been shown to correlate with outcome (Muir *et al.*, 1996; Adams, Jr. *et al.*, 1999). Two examiners (PJH & BL) had been officially certified as competent to administer the NIHSS prior to the study commencing. JK and PJH successfully completed the re-certification program during the study.

The OCSP classification (see **Appendix 3**) groups patients into one of four categories that define the site and size of the stroke, and gives an indication of likely outcome (Bamford *et al.*, 1991). This classification applies to the patient's deficit at its greatest. Where appropriate, the research fellow incorporated information about the maximal deficit (obtained from the history) to determine the classification if there had been a delay between presentation and assessment. There is no official training program for the OCSP classification.

8.3.2 Statistics

Brain attacks were divided into those presenting within six hours, and those presenting after six hours from symptom onset, for most of the analyses. Continuous data (age, NIHSS, times) were not normally distributed, and were presented as median (with interquartile range). Standard non-parametric tests of statistical significance were performed. Categorical data were analysed by chi-squared (or similar) tests, with presentation of a p-value or an odds ratio (with 95% confidence

intervals [95% CI]). Significance was assumed when $p<0.05$ or the 95% CI did not cross one. For clarity, I have rounded the p-value to two decimal places in the text.

The clinical features of brain attack in the hyperacute phase

In **Chapter 5**, I demonstrated that there were important differences in the clinical features of patients recruited within the first few hours to the International Stroke Trial (IST). In the present study, I wished to determine if the findings from the IST, an international multicentre trial, could be reproduced in a single Scottish hospital. Similar analyses and data presentation styles were used to facilitate comparisons between the present study and **Chapter 5**.

The key clinical features of a thrombolysis-eligible brain attack

The two primary diagnostic categories that were used in the Brain Attack study were also used in the present chapter. 'Thrombolysis-eligible' brain attack refers to a definite or probable stroke (and assumes that all other conditions necessary for thrombolysis were favourable), and mimic refers to a definite non-stroke or possible stroke with a plausible alternative explanation. The rationale behind this division is detailed in **Chapter 7.3.10**.

In the previous chapter, it was shown that several clinical features could be used to distinguish a thrombolysis-eligible brain attack from a mimic (see **Table 7.11**). I tested whether these features were present in 'thrombolysis-eligible' brain attacks recruited within six hours. I compared the frequencies of the key items of history, examination and diagnostic formulation for thrombolysis-eligible brain attacks that presented within and after six hours. I limited the analysis to features that identify thrombolysis-eligible brain attacks (rather than mimics), as I felt it was

more useful in a clinical setting to be able to make a positive diagnosis of stroke. I also limited the analysis to the predictive features that were reasonably frequent (arbitrarily defined as around 50%) to minimise the possibility of spurious associations.

Is the clinical diagnosis more difficult in the first few hours?

I determined the frequency and nature of mimics that presented in the first few hours. I used accuracy and positive predictive value (PPV) to ascertain if diagnostic accuracy was affected by early presentation. I determined if disagreements between the clinical diagnosis and final diagnosis were more common in those presenting within six hours.

Exact time of symptom onset

The decision to treat a patient with thrombolysis (or randomise the patient into a trial of thrombolysis) is critically dependent on knowing the exact time of symptom onset. As this is such an important factor, I wanted to explore how often the time of onset could not be determined, and why. Brain attacks that presented within six hours were divided into those with an exact time of onset and those with an estimated time of onset. The clinical features of each group were compared for significant differences.

The OCSP and NIHSS in brain attack

Both the OCSP classification and the NIHSS severity score are widely used in the assessment of stroke patients. I aimed to determine if either scale could usefully distinguish a mimic from a stroke. The NIHSS was arbitrarily divided into five categories (on the basis of the author's clinical experience): NIHSS = 0, NIHSS

1-4, NIHSS 5-10, and NIHSS > 10. The OCSP divides into four categories, with an additional category for those who could not be classified ('unsure'). The proportions of stroke and mimic in each category were determined. Analysis was limited to brain attacks that presented in the hyperacute phase.

8.4 Results

8.4.1 The clinical features of patients who presented within the first few hours of symptom onset.

Patient recruitment

192/350 patient-episodes presented to hospital within six hours (55%). The research fellow saw three in-hospital brain attacks within six hours of onset. The exact time of onset could not be determined for six events (although the day of symptom onset was known – all presented greater than six hours). The histogram of time to presentation (within six hours) is provided in **Figure 8.1**, and the histogram of time to assessment by the research fellow is provided in **Figure 8.2**.

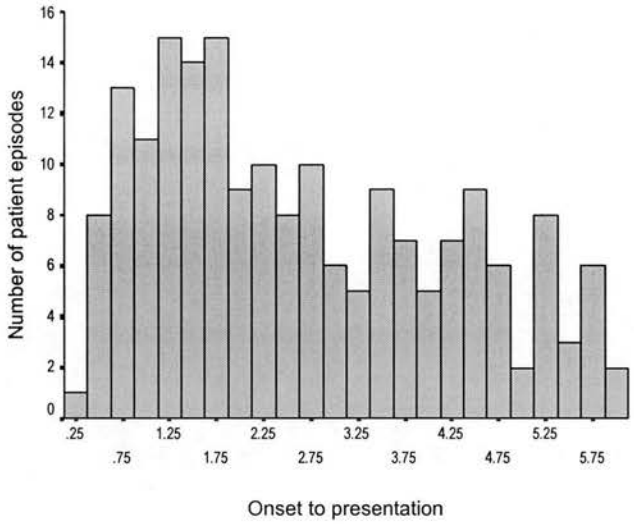


Figure 8.1 Histogram of time to presentation (hours) for patients with hyperacute brain attack (189 patient-episodes)

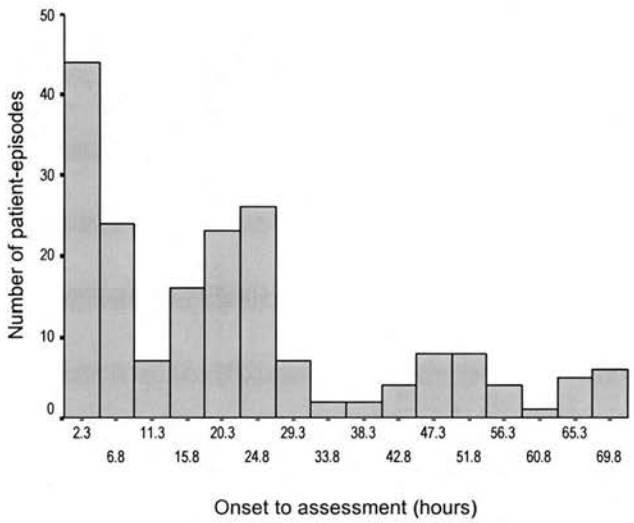


Figure 8.2 Histogram of time to assessment (hours) by research fellow for patients with hyperacute brain attack (192 patient-episodes)

Note different scale on x-axis

The general features of patients who presented within six hours are compared with those who presented after six hours in **Table 8.1.** For early presenters, the median time from onset to presentation (at ARU) was 2.33 hours, whilst the median time from onset to evaluation by a research fellow was 19.75 hours. Around a third

of early presenters were seen by the research fellow within three hours of arrival at ARU (as were late presenters).

Clinical features

The clinical characteristics of the patients who presented in the hyperacute phase are detailed in **Table 8.2** (set out identically to the table describing the features of patients randomised into the International Stroke Trial within six hours [**Section I, Table 5.1**]). Compared with patients who presented later, patients who presented within six hours were more likely: to be aged 80 and over (42% within six hours vs. 28% after six hours, p=0.02); to have altered conscious level (29% vs. 16%, p<0.01); to have signs of cortical involvement (61% vs. 43%, p<0.01), or to have a clinical syndrome of total anterior circulation involvement (TACS). Patients who presented early were less likely, when compared with patients who presented later, to be asleep at symptom onset (23% vs. 43%, p<0.01), have a lacunar clinical syndrome (13% vs. 22%, p<0.01), or to have a clinical syndrome of brainstem involvement (8% vs. 17%, p<0.01).

Many of the baseline clinical features associated with patients who presented early were a reflection of greater stroke severity. In the present study, the NIHSS was used to characterise the patients' clinical deficits and thus stroke severity. The median NIHSS (and interquartile range) for brain attacks that presented in each of five time intervals is shown in **Figure 8.2**. There was a weak but significant inverse correlation between NIHSS and time (correlation coefficient, r_S –0.16, p<0.01. Spearman's).

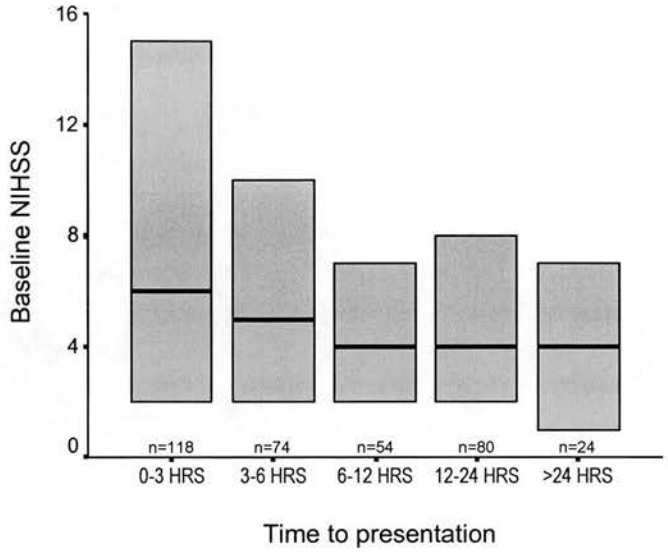


Figure 8.3 Baseline severity (measured as NIHSS) in all patients recruited to the brain attack study

The shaded box represents the interquartile range, and the horizontal bar represents the median for each time category.

Final diagnosis

There was no significant difference in the frequency of mimics observed in the two time intervals (**Table 8.3**). However, brain attacks that were later diagnosed as definite transient ischaemic attacks (TIAs) were more frequent in the first six hours (7.3% vs. 1.9%, p=0.02, Fisher's exact). Intracerebral haemorrhage accounted for 10.8% of patients who presented within six hours, and 3.6% of patients who presented after six hours (p=0.04, Fisher's exact). As there were fewer haemorrhages, TIAs and possible strokes in the late group, a confirmed infarct was the final diagnosis in 91% (compared with 78% of the early group, p=0.01, χ^2).

Patients assessed within six hours

The research fellow assessed 56/192 (29%) patients within six hours of onset. 46 of these patients arrived at hospital between 8am and 5pm. The clinical features

of patients assessed within six hours are compared with patients who were assessed later (but still presented within six hours) in **Table 8.4**. 'Static' items of the history and examination (e.g. atrial fibrillation or whether patient woke from sleep with deficit) were not significantly different between the two groups. However, items that may change over time (e.g. conscious level or NIHSS) showed significant differences between the groups: patients admitted and assessed within six hours showed greater stroke severity than those admitted within six hours but not assessed till later. There was no significant overall difference in OCSP classification, but a trend for more TACS to be observed in patients assessed within six hours.

8.4.2 Are the key distinguishing clinical features for thrombolysis-eligible brain attack the same in patients who present earlier?

130 thrombolysis-eligible brain attacks (from 126 patients) presented within six hours, and 111 thrombolysis-eligible brain attacks (from 111 patients) presented after six hours. In the present analysis, a history of arm, hand or leg weakness, and signs of abnormal verbal output, facial asymmetry, sensory loss, extensor plantar, or arm, hand or leg weakness were compared. Peripheral vascular disease and valvular heart disease were not used in this analysis as their frequency was less than 50%.

History items

There was no major difference between early and later stroke events in any of the history items except one: exact time of onset (see **Figure 8.4**). This factor was more frequent in the thrombolysis-eligible brain attacks presenting within than after six hours (OR for presentation within six hours 2.2, 95% CI 1.2 – 4.0).

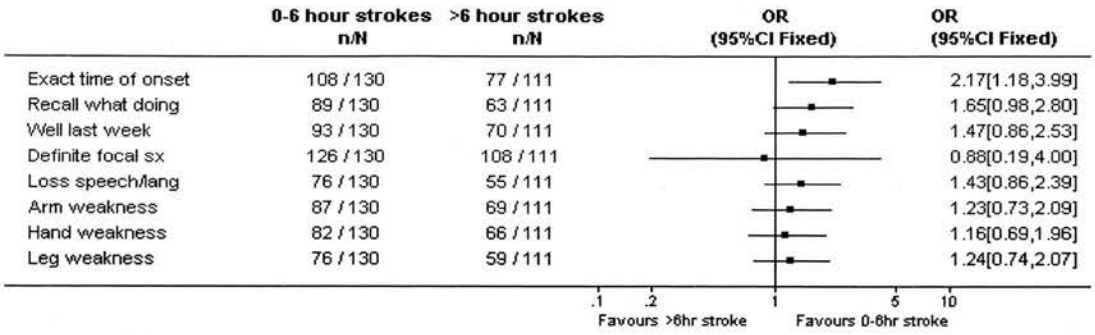


Figure 8.4 Were the history items that can help diagnose a thrombolysis-eligible stroke valid in the hyperacute patient?

OR=1 indicates that the clinical factor was equally useful in predicting a stroke (whether the patient presented within or later than six hours)

Examination items

There were no significant differences in the neurological examination of the patients with a thrombolysis-eligible brain attack who presented within six hours when compared with those who presented later (see **Figure 8.5**).

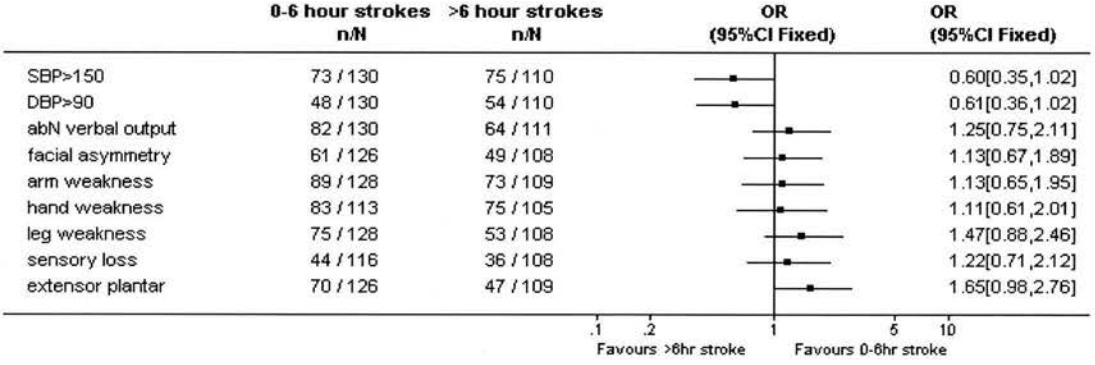


Figure 8.5 Were the examination items that can help diagnose a thrombolysis-eligible stroke valid in the hyperacute patient?

OR=1 indicates that the clinical factor was equally useful in predicting a stroke
SBP – systolic blood pressure, DBP – diastolic blood pressure, AbN – abnormal

Diagnostic formulation

Patients with signs that were classified as a total anterior circulation syndrome (TACS) were more likely to present early (OR 2.6, 95% CI 1.3 – 5.3) (see **Figure 8.6**). Patients whose signs could be lateralised to the left or right side of the brain were also more likely to present early (OR 2.4, 95% CI 1.3 – 4.5). Patients

with signs classed as a lacunar syndrome (LACS) were more likely to present later (OR 0.4, 95% CI 0.2 – 0.8).

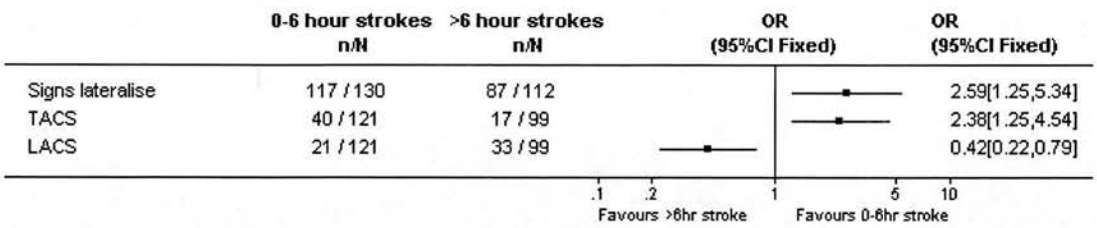


Figure 8.6 Items of the diagnostic formulation that can assist in the diagnosis of a thrombolysis-eligible stroke: are they valid in the hyperacute patient?

OR=1 indicates that the clinical factor was equally useful in predicting a stroke (whether the patient presented within or later than six hours)
Signs lateralise to left or right side of brain; TACS – total anterior circulation syndrome; LACS – lacunar syndrome

8.4.3 Is the clinical diagnosis more difficult in the first few hours?

Are the mimics different in the first few hours?

Mimics accounted for slightly more brain attacks that presented within six hours than brain attacks that presented later (32.3% vs. 29.7%, p not significant, χ^2). The nature of the mimics that present within and after six hours is provided in **Table 8.5**. The commonest condition overall, seizure, was most frequently observed within six hours, but was the fourth leading cause beyond six hours (p=0.04, Fisher's exact). Syncope/presyncope was the second most common mimic within six hours, but was rarely observed beyond six hours (p=0.03, Fisher's exact). There was an overall trend for conditions with an abrupt onset (such as acute mononeuropathy or functional symptoms) to be more frequent early on, whilst conditions in which the onset is often gradual (sepsis, toxic or metabolic disturbance, space occupying lesion, confusional state) were more frequent in those who presented after six hours.

Is diagnostic accuracy worse?

In **Table 8.6** I have tabulated two measures of overall diagnostic accuracy (accuracy [all correct diagnoses / total number of diagnoses]; and positive predictive value [PPV, correct diagnosis of stroke / correct and incorrect stroke diagnoses]) for the patients presenting within six hours, and compared these results to patients presenting after six hours.

For the general practitioners and ARU staff, there were no significant differences in accuracy or PPV for events that presented earlier. There was a trend towards *improved* overall diagnostic accuracy for the research fellow's final bedside diagnosis of brain attacks that presented within six hours (accuracy 89.6%, PPV 95.1%). This was significant for the measure of correct diagnoses / total diagnoses (accuracy), but not for the PPV.

Exploring reasons for improved diagnostic accuracy early

Was the trend of better diagnostic accuracy for patients seen early after symptom onset due to the act of being assessed promptly, or due to the nature of the brain attacks? The research fellows saw 99 patients within three hours of their arrival in ARU (irrespective of time from onset of symptoms). I therefore compared accuracy and PPV for the patients assessed within 3 hours, and compared this to the results for patients assessed after six hours, to determine if the act of assessing the patient promptly was important. Accuracy was 85/99 (85.9%) for the patients seen within three hours of arrival in ARU, and 192/227 (84.6%) for patients seen after six hours ($p=0.90$, χ^2). PPV was 69/72 (95.8%) for the patients seen within three hours of arrival in ARU, and 123/138 (89.1%) for patients seen after six hours ($p=0.17$, χ^2).

Overall diagnostic accuracy (for the research fellow) was no different for patients assessed promptly or patients seen later (regardless of time to presentation).

The patients who presented within six hours and were assessed within six hours (n=56) had features suggesting more severe strokes than patients who presented within six hours but were assessed later (n=136). I compared accuracy and PPV in these two groups to determine the impact of the timing of the research fellow's assessment. Accuracy was 51/56 (91.1%) for patients assessed within six hours of onset, and 121/136 (89.0%) for patients who presented within six hours but were assessed later ($p=0.86$, χ^2). PPV was 42/43 (97.7%) and 74/79 (93.7%) respectively ($p=0.59$, χ^2). Once again, the actual timing of the assessment was less important than the time of presentation, suggesting that the improved diagnostic accuracy was due to the more severe nature of the patients who presented early.

Are disagreements more frequent in patients presenting within 6 hours?

There were 20 incorrect diagnoses of events that presented within six hours (37.0% of all incorrect diagnoses, yet events that presented within six hours constituted 54.9% of all patient-episodes). Compared with patients presenting later, clinical disagreements for patients presenting within six hours were more likely when the signs were inconsistent with the symptoms ($p<0.01$, χ^2). There was a non-significant trend for disagreements to be more common when patients re-presented, there was a past history of stroke, or the clinical classification was a partial anterior circulation syndrome (PACS) (see **Table 8.7**).

8.4.4 How often could an exact time of onset be determined, and what were the reasons for difficulty in the hyperacute phase?

In the brain attack study, 192 events presented to hospital within six hours of onset. An exact time of onset could be determined confidently in 115 events (60%). 35 patients (18%) first noticed their symptoms or deficit on waking from sleep. For these patients, the median time from when they were last known to be normal to the time they woke with symptoms was 8.25 hours (interquartile range 5.00 – 10.88 hours, time last known to be normal could not be determined for two patients). If one defined onset as the last time the patient was known to be normal (as randomised trials of thrombolysis have done), then only 3/35 patients who woke from sleep with a brain attack presented to ARU within six hours.

Where the research fellow could not determine an exact time of onset, an approximate time was estimated (from all available data sources). A comparison between those in whom time of onset was estimated and those in whom exact time of onset was known is presented in **Table 8.8**. When compared to patients with a known time of onset, those *without* an exact time of onset were more likely to have known cognitive impairment (34% vs. 15%, p=0.02, χ^2), be confused on examination (70% vs 36%, p=0.01, χ^2), to have aphasia (55% vs. 37%, p=0.04, χ^2), or to receive a final diagnosis of mimic (48% vs. 33%, p=0.02, χ^2). Where the patient or relative was not the primary source of history, the time of symptom onset had to be estimated more frequently. Overall stroke severity did not differ between the groups (median NIHSS 4.5 for exact onset, 7.5 for estimated onset, p=0.58, Mann-Whitney U). A right sided brain lesion was not more frequently observed in those without an exact time of onset.

8.4.5 *Can the NIHSS severity score distinguish mimic from stroke?*

Figure 8.7 shows that the proportion of mimics was greatest when the NIHSS was zero. When brain attacks were divided into NIHSS zero and NIHSS one or more, mimics accounted for 61 % of NIHSS=0, and 27% of NIHSS>0 ($p<0.01$, χ^2). However, even at high NIHSS scores, there was still a considerable proportion of mimics. When brain attacks were divided into NIHSS 0-10 and NIHSS>10, mimics accounted for 39% of NIHSS 0-10, and 19% of NIHSS>10 ($p<0.01$, χ^2).

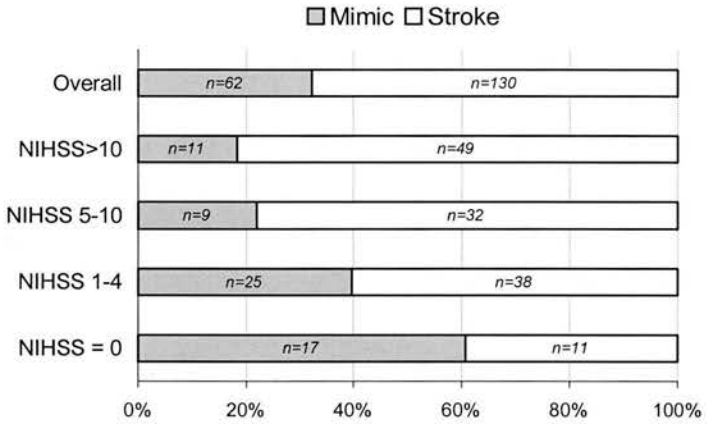


Figure 8.7 The value of the NIHSS score to distinguish between mimic and stroke in brain attacks that presented within six hours (n=192)

The OCSP classification was better able to distinguish between stroke and mimic (see **Figure 8.8**). All those classified as total anterior circulation syndrome (TACS) had a thrombolysis-eligible stroke, as did 88% of those classified as a lacunar syndrome (LACS). Neither partial anterior circulation syndrome (PACS) nor posterior circulation syndrome (POCS) classification was able to differentiate stroke from mimic, and over half of those who could not be classified had a mimic. When brain attacks were divided into those that could be assigned an OCSP classification

and those that could not, mimics accounted for 5% of classified patients and 56% of unclassified ($p<0.01$, χ^2).

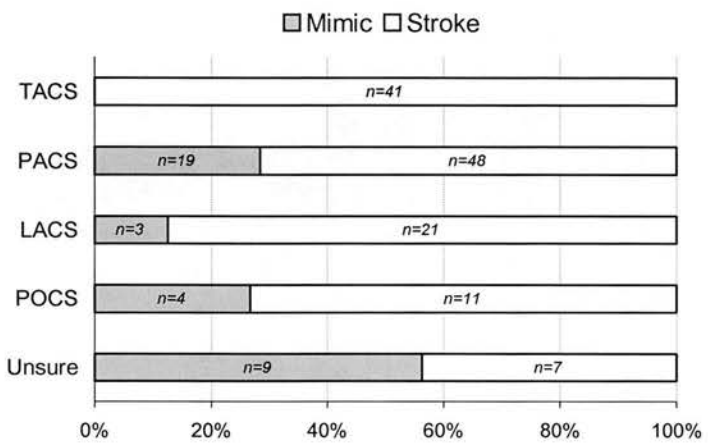


Figure 8.8 The value of the OCSP classification to distinguish between mimic and stroke in brain attacks that presented within six hours

n=162, excludes 29 patients with no signs when examined

8.5 Discussion

8.5.1 Limitations of the present study

The limitations that were identified for the general Brain Attack study (**Chapter 7.5**) also apply to the present sub-study of patients who presented within the first six hours. Specific limitations will be addressed below.

The delay between presentation and evaluation

This was a major confounding factor. It would have been desirable for the research fellow to see the majority of patients immediately after presentation. This did not occur, for the following reasons:

- Over 1/3 of admissions were between 5pm and 9am; and weekend or holiday admissions were seen on the next working day (which comprised a further 2/7 to 1/3 of admissions)
- Referrals within the hospital, although complete, were often received late (as the perceived view was that all the stroke team had to offer was 'rehab')
- There was reluctance by ARU staff to refer possible strokes or clear non-strokes (possibly a hangover effect from previous clinical trials and observational studies at this hospital where only definite strokes were recruited). Although we identified and saw most of these patients, it was usually the next day

Impact of the delay to assessment

The majority of patients who presented within six hours were actually assessed the following day. This may have had no impact on 'static' items of the history and examination (e.g. past history, whether patient woke from sleep with symptoms etc), which remain stable irrespective of the time of assessment. Some items of the assessment can change considerably (e.g. conscious level, NIHSS), and it must be remembered that the assessment was performed much later than the patient was admitted.

I compared clinical features of the 56 patients who presented within six hours and were assessed within six hours with the 136 patients who were assessed later (see **Table 8.4**). All severity parameters were greater in the patients assessed within six hours, which suggests that: (1) the patients assessed within six hours were particularly severe – and not representative of all the patients who presented within

six hours; and/or (2) stroke severity is milder when assessed the following day. The static items of history and examination were not significantly different between the two groups, and even the OCSP classification appeared reasonably stable (allowing for the possibility that more TACS were assessed earlier).

It is unlikely that the delay between patient presentation and evaluation by the research fellow resulted in major bias. The distribution of delay from presentation to assessment was identical for patients who presented within six hours of onset and patients who presented later (i.e. about 30% were assessed promptly, the rest were assessed the next day, see **Table 8.1**). Although stroke severity measures were probably underestimates of true severity at presentation, both groups were equally affected – differences between groups are probably valid.

Was the cut-off time of six hours appropriate?

Six hours was chosen as the cut-off time because evidence suggests that this is the extent of the critical therapeutic time window for thrombolysis. Patients who present to hospital within six hours may be eligible for thrombolysis (intravenous or intra-arterial, as part of a trial or open-label) provided they fulfil other criteria for treatment. However, the time from patient presentation to actual treatment ('door to needle' time) can be as low as 45 minutes (Grond *et al.*, 1998) to as high as 90 minutes (Albers *et al.*, 2000b). The National Institute of Neurological Disorders and Stroke (NINDS) recommended that the door to needle time be less than sixty minutes (Marler *et al.*, 1997). Thus, the actual cut-off time for patient presentation may need to be reduced to five hours to allow for brain imaging and patient consent. If so, then the figures provided in the present study may be an overestimate.

Stroke research fellow training

The clinical data were obtained by four research fellows with probably greater than average previous exposure to stroke medicine and/or neurology. Three of four research fellows had undergone specific training in the use of the NIHSS. All received training in the OCSP classification (and other aspects of clinical assessment) at the weekly team meetings. This level of training and supervision may make generalisation of the results difficult; however it is likely that the data obtained were accurate.

8.5.2 Implications of the study

The clinical features of patients who present with brain attack in the first few hours differ to those who present later

The present study has demonstrated that patients who present to hospital within six hours have more severe strokes. These findings support the analysis of the International Stroke Trial (IST), presented in **Chapter 5**. Although on a much smaller scale than the IST, this study makes an important contribution. This is because the cohort was unselected, and patients with mimics, TIAs or intracerebral haemorrhages were all recruited. All three conditions were seen more frequently in patients presenting within six hours. Patients who present to hospital with a *brain attack* comprise a heterogeneous group of serious medical conditions and not all will have a cerebral infarct (which seems to be the starting point of so many other studies).

The present study has implications for acute treatments, such as thrombolysis. Thrombolysis has rarely been tested in the older population (Wardlaw *et al.*, 2001a),

yet more patients aged 80 and over presented early in the present study (and in the IST). Previous studies did not find that older patients presented earlier than young patients (Harper *et al.*, 1992; Jorgensen *et al.*, 1996). There is still much to be learnt about the interplay between stroke severity, time, and the risks and benefits of treatment (Lindley, 2001). Many of the clinical factors identified in this analysis, and the IST analysis, may be important determinants of the success of thrombolysis – but more data, ideally from large randomised trials, are required.

The key distinguishing clinical features for thrombolysis-eligible brain attacks are similar regardless of time from symptom onset

In an earlier chapter, several clinical predictors that could positively identify a thrombolysis-eligible brain attack were identified. As the clinical features of patients presenting within six hours are different, it was reasonable to consider whether the clinical predictors would still be of use in 'hyperacute brain attack'. Overall, there were no major unexpected differences, suggesting that the clinical predictors can be safely used in patients presenting within hours of symptom onset.

The clinical diagnosis appears to be no more difficult in the first few hours than later

The general feeling of stroke clinicians, supported by some evidence [e.g. (Allder *et al.*, 1999a), the IST analysis], is that stroke is more difficult to diagnose in the first few hours. There has been almost no research into this issue. The present study, and the earlier study of Ferro et al (1998a), found that the clinical diagnosis was no more difficult in patients who present within six hours. In fact, there was a trend for hospital-based doctors to have *greater* diagnostic accuracy when assessing

patients in the first few hours after symptom onset. This may well be due to the effect of severity: patients with more severe strokes present to hospital earlier, and the diagnosis is more obvious.

An exact time of onset is often unavailable

Time of symptom onset is a critical issue for thrombolysis. Barber et al (2001a) found that uncertain time of onset resulted in 33% of patients being excluded from thrombolytic therapy. Most of these patients awoke with symptoms. Many earlier studies have noted that time of onset is often difficult to obtain. In retrospective studies, exact onset time may be missing from the case notes in around 30% of patients (Smith *et al.*, 1998b; Kothari *et al.*, 1999). Some prospective studies excluded those with unknown exact time of onset (Jorgensen *et al.*, 1996), whilst in others, the proportion without an exact time ranged from 21% (Streifler *et al.*, 1998) to 45% (Salisbury *et al.*, 1998). A recent retrospective review of 'the stroke patient who woke up' found that 27% of patients woke from sleep with the deficit (Fink *et al.*, 2002). Although there were no statistically significant differences in clinical features, those who woke from sleep were more likely to have a lacunar stroke, compared with those with onset whilst awake.

In the present study, an exact time of onset could not be determined in 22%, and a further 17% awoke from sleep with symptoms too late to be eligible for thrombolysis. The clinical features of patients with unknown onset did not differ greatly from those with known time of onset. I wondered if right cortical lesions resulting in anosognosia or neglect could explain part of the difficulty in determining time from onset. However, right sided brain lesions were not over-represented in the

patients without an exact time of onset. Instead, factors such as aphasia, confusion and dementia explained the difficulty in determining time of onset.

The implications of these findings are clear: almost 40% of patients who present within six hours of onset are ineligible for treatment with thrombolysis. It is difficult to see how clinical methods to improve the determination of onset time could possibly overcome the difficulties of aphasia, confusion, and absence of a reliable second source of history. Perhaps imaging will hold the key to discovering whether patients with unclear time of onset, or waking from sleep with symptoms, may be eligible for thrombolysis (Barber *et al.*, 2001a). This shall be considered further in **Chapter 14**.

The NIHSS score and OCSP classification may help discriminate between stroke and mimic

The NIHSS was developed for use in clinical trials and has become part of the routine assessment for many clinicians (Lyden & Hantson, 1998). The baseline NIHSS strongly predicts outcome after stroke (Adams, Jr. *et al.*, 1999). Although not intended to discriminate between stroke and mimic, I wondered if this might be possible. Most patients with a baseline NIHSS of zero were mimics, and most with a severe brain attack (NIHSS>10) were strokes. However, at all NIHSS scores, mimics constituted a small proportion. The NIHSS measures severity, but cannot distinguish old lesions from new, which may explain why almost 20% of mimics had a NIHSS score of greater than 10. Additionally, patients with dementia could score up to 5 points without any focal neurological deficit, because of difficulty with naming objects, naming the month and stating their age, or following commands.

The advantage of the OCSP classification [compared with other systems, such as the 'TOAST' subtype (Adams, Jr. *et al.*, 1993; Madden *et al.*, 1995)] is that it does not depend on investigations, so may be applied at the bedside. The OCSP predicts site and size of cerebral infarction on CT (Wardlaw *et al.*, 1996), as well as outcome (Bamford *et al.*, 1991). In the present study, an OCSP classification could not be made in 10% of brain attacks, and over half of these patients proved to be mimics. 100% of patients classified as total anterior circulation syndrome and 88% classed as lacunar syndrome proved to be strokes. Thus, the OCSP can be useful in discriminating between stroke and mimic, but only when the diagnosis is lacunar or total anterior circulation syndrome (approximately 1 in 3 patients).

8.6 Summary

- This study has limitations, but the results are in general agreement with those of the IST analysis, which demonstrated that patients who were assessed earlier were different to those assessed later.
- Patients with brain attacks who present to hospital early are older, the strokes are more severe, TIAs or intracerebral haemorrhages are more likely, and the nature of the mimics differs.
- Despite the differences, patients who present earlier are no more difficult to diagnose than those who present later – probably because severe strokes are easier to diagnose.
- Patients who present within six hours are potentially eligible for thrombolysis, but many will not qualify, as the time of onset cannot be confidently established clinically.

- Rules for the clinician: be wary of stroke mimics if the NIHSS is low, and if it is difficult to classify the neurological deficit into an OCSP category.

Recommendations for further research

- The OCSP classification needs to be tested for reliability in the hyperacute phase
- Further research on patients assessed very early is required to validate the suggestion that the diagnosis is easier in the hyperacute phase
- We need to evaluate imaging (or other) methods to determine if patients with unknown time of onset may be treatable with thrombolysis.

Table 8.1 General characteristics of patient recruitment

Feature	Patient presenting: Within 6 hours	After 6 hours	*P**
Median age (n=336 patients):	76.33 years	76.24 years	*.625*
Median time from symptom onset to presentation:†	2.33 hours	18.25 hours	*<.001*
Time of ARU admission:‡			
9.00am – 5.00pm	111 (58.7%)	95 (65.1%)	
5.01pm – 12.00am	53 (28.0%)	40 (27.4%)	
12.01am – 8.59am	25 (13.3%)	11 (7.5%)	
Median time from symptom onset to evaluation by research fellow:§	19.75 hours	40.00 hours	*<.001*
Delay between presentation and evaluation by research fellow: †			*.696*
0 – 3 hrs	58 (31%)	41 (29%)	
3 – 6 hrs	3 (2%)	1 (1%)	
> 6 hrs	128 (68%)	99 (70%)	
Referred to research team by:			*.018*
ARU	182 (95%)	139 (88%)	
Other ward	7 (3.5%)	8 (5%)	
Inpatient brain attacks	3 (1.5%)	11 (7%)	
Examiner:			*.472*
PJH	102 (53%)	79 (50%)	
JK	74 (39%)	62 (39%)	
Other	16 (8%)	17 (11%)	

** P value determined by Mann Whitney U test for continuous variables, and χ^2 test for categorical variables*

† n=330 episodes: 14 were inpatient brain attacks, in 5 the time of onset was unknown, and in one episode the time of arrival in ARU was unknown

‡ n=335 episodes: 14 inpatient brain attacks, 1 brain attack with unknown time of arrival in ARU

§ n=345 episodes: time of onset could not be determined in 5 brain attacks

Table 8.2 Clinical features at baseline in brain attack study, subdivided by time

	Features among patients presenting:				
Clinical Feature	**0-6 hours**	**(%)**	**>6 hours**	**(%)**	***P****
Male	82 / 181	**(45.3)**	81 /155	**(52.3)**	*.124*
Age 80 and over	76 / 181	**(42.0)**	44 / 155	**(28.4)**	*.015*
Asleep at onset	35 / 152	**(23.0)**	43 / 101	**(42.6)**	*.001*
Reduced consciousness	56 / 192	**(29.2)**	25 / 158	**(15.8)**	*.003*
Systolic BP>185	31 / 192	**(16.1)**	20 / 158	**(12.7)**	*.370*
In Atrial Fibrillation	38 / 192	**(19.8)**	34 / 158	**(21.5)**	*.691*
Cortical Signs:					
Aphasia	79 / 192	**(41.1)**	45 / 158	**(28.5)**	*.014*
Neglect	74 / 192	**(38.4)**	39 / 158	**(24.7)**	*.006*
Hemianopia	62 / 192	**(32.3)**	37 / 158	**(23.4)**	*.067*
Any cortical sign	117 / 192	**(60.9)**	68 / 158	**(43.0)**	*.001*
Stroke Subtype:†					
TACS	40 / 146	**(20.8)**	20 / 123	**(12.7)**	*.043*
PACS	67 / 146	**(34.9)**	41 / 123	**(25.9)**	*.071*
LACS	24 / 146	**(12.5)**	35 / 123	**(22.2)**	*.016*
POCS	15 / 146	**(7.8)**	27 / 123	**(17.1)**	*.008*

** P value determined by χ^2 test*
† Stroke subtype could not be determined in 81 patients

Table 8.3 Final diagnosis in brain attack study subdivided by time

	Diagnosis among patients presenting:				
Final diagnosis	**0-6 hours**	**(%)**	**>6 hours**	**(%)**	***P****
Mimic	62 / 192	**(32.3)**	47 / 158	**(29.7)**	*.609*
Possible stroke	1 / 192	**(0.5)**	3 / 158	**(1.9)**	*.283*
TIA	14 / 192	**(7.3)**	3 / 158	**(1.9)**	*.019*
Definite & probable stroke	115 / 192	**(59.9)**	105 / 158	**(66.5)**	*.206*
ICH	14 / 130	**(10.8)**	4 / 111	**(3.6)**	*.036*
Infarct	101 / 130	**(77.7)**	101 / 111	**(91.0)**	*.009*

** P value determined by χ^2 test and Fisher's exact test (where numbers were small)*
† mimic defined as all definite non-strokes and possible strokes with a plausible non-stroke explanation

Table 8.4 A comparison of clinical features in those who presented and were seen by the research fellow within six hours of onset, and those who presented within six hours but were seen by the research fellow later

	Patients who presented within six hours, but were assessed by the research fellow:				
Clinical Feature	**0-6 hours**	*(%)*	**>6 hours**	*(%)*	***P****
Asleep at onset	13 / 50	*(26.0)*	22 / 102	*(21.6)*	*.542*
Reduced consciousness	22 / 56	*(39.3)*	34 / 136	*(25.0)*	*.048*
Median Systolic BP	155 mmHg		152 mmHg		*.098*
In Atrial Fibrillation	9 / 56	*(16.1)*	29 / 136	*(21.3)*	*.406*
Cortical Signs:					
Aphasia	26 / 56	*(46.4)*	53 / 136	*(39.0)*	*.340*
Neglect	32 / 56	*(57.1)*	42 / 158	*(30.9)*	*.001*
Hemianopia	23 / 56	*(41.1)*	39 / 136	*(28.7)*	*.095*
Any cortical sign	40 / 56	*(71.4)*	77 / 136	*(56.6)*	*.056*
Median NIHSS	8.0		4.0		*.005*
Stroke Subtype:†					*.083*
TACS	17 / 50	*(34.0)*	23 / 126	*(18.3)*	
PACS	18 / 50	*(36.0)*	49 / 126	*(38.9)*	
LACS	8 / 50	*(16.0)*	16 / 126	*(12.7)*	
POCS	4 / 50	*(8.0)*	11 / 126	*(8.7)*	

** P value determined by χ^2 test and Mann-Whitney U test*
† Stroke subtype could not be determined in 16 patients

Table 8.5 Causes of mimics subdivided by time

Condition*	Mimics presenting: Within 6 hrs (%)	*After 6 hrs (%)*	P†
1. Seizure	18 *(29.0%)*	5 *(10.6%)*	.035
2. Sepsis	6 *(9.7%)*	8 *(17.0%)*	.276
3. Toxic / metabolic	6 *(9.7%)*	6 *(12.8%)*	.568
4. Space occupying lesion	3 *(4.8%)*	7 *(14.9%)*	.088
5. Syncope / presyncope	9 *(14.5%)*	1 *(2.1%)*	.027
6. Acute confusional state	3 *(4.8%)*	4 *(8.5%)*	.470
7. Vestibular dysfunction	3 *(4.8%)*	4 *(8.5%)*	.470
8. Acute mononeuropathy	4 *(6.5%)*	2 *(4.3%)*	.659
9. Functional/medically unexplained symptoms	4 *(6.5%)*	2 *(4.3%)*	.659
10. Dementia	2 *(3.2%)*	2 *(4.3%)*	.793
11. Migraine	2 *(3.2%)*	2 *(4.3%)*	.793
12. Spinal cord lesion	- *(0%)*	3 *(6.4%)*	.077
13. Other	2 *(3.2%)*	1 *(2.1%)*	.784

** Conditions have been ranked according to their percentage overall (*see **Table 7.5**)*
† significance determined by Fisher's exact test

Table 8.6 The accuracy of the bedside diagnosis of brain attack in the first six hours

	Patients presenting: 0-6 hours (%)	After 6 hours (%)	*P**
GP diagnosis:			
Accuracy†	74 / 108 (68.5%)	81 / 108 (75.0%)	*.364*
Positive predictive value‡	70 / 97 (72.2%)	76 / 112 (67.9%)	*.599*
ARU diagnosis			
Accuracy	141 / 182 (77.5%)	100 / 139 (71.9%)	*.315*
Positive predictive value	111 / 141 (78.7%)	79 / 103 (76.7%)	*.826*
Research fellow final bedside diagnosis			
Accuracy	172 / 192 (89.6%)	124 / 158 (78.5%)	*.007*
Positive predictive value	116 / 122 (95.1%)	90 / 103 (87.4%)	*.067*

** P value determined by χ^2 test*
† Accuracy = all correct diagnoses / total number diagnoses
‡ Positive predictive value = correct diagnosis of stroke / all diagnoses of stroke

Table 8.7 Features of patients who presented within the first six hours incorrectly diagnosed by the research fellow (compared with patients who presented later than six hours)

	Incorrect diagnosis:				
Feature	**Within 6 hrs (*n=20*)**		**After 6 hrs (*n=34*)**		**P***
Median age (years)†	68.12		76.11		*.450*
Male gender†	9 / 17	(52.9%)	13 / 32	(40.6%)	*.409*
Number of representations:	3 / 20	(15.0%)	2 / 34	(5.9%)	*.316*
Past history of stroke†	11 / 17	(64.7%)	12 / 31	(38.7%)	*.155*
Known cognitive impairment†	2 / 18	(11.1%)	3 / 30	(10.0%)	*.895*
Confused on examination	5 / 13	(38.5%)	9 / 30	(30.0%)	*.603*
Signs inconsistent with symptoms	9 / 17	(52.9%)	4 / 31	(12.9%)	*.005*
NIHSS:					*.570*
Mean	7.85		5.00		
Median	4.0		4.0		
Clinical classification:‡					
TACS	2	(10.0%)	3	(8.8%)	*.619*
PACS	10	(50.0%)	10	(29.4%)	*.111*
LACS	2	(10.0%)	4	(11.8%)	*.609*
POCS	1	(5.0%)	8	(23.5%)	*.078*
Unsure/No signs	5	(25.0%)	9	(26.5%)	*.920*
Final diagnosis:					*.541*
Stroke	14 / 20	(70.0%)	21 / 34	(61.8%)	
Mimic	6 / 20	(30.0%)	13 / 34	(38.2%)	

** - p value determined by χ^2 test, and Fisher's exact test (for categorical variables), and Mann-Whitney U test (for continuous variables)*
† - denominator refers to the number of patients (not events)
‡ - OCSP clinical classification. TACS – total anterior circulation syndrome, PACS – partial anterior circulation syndrome, LACS – lacunar synrome, POCS – posterior circulation syndrome

Table 8.8 Brain attacks that presented within six hours – a comparison between those with estimated and known time of onset

Feature	Time of symptom onset: Estimated (*n=42*)		Known (*n=150*)		P*
Examiner:					*.425*
PJH	19	(45.2%)	83	(55.3%)	
JK	18	(42.9%)	56	(37.3%)	
Other	5	(11.9%)	11	(7.3%)	
Median age†	77.55		76.33		*.415*
Male gender†	18 / 40	(45.0%)	64 / 141	(45.4%)	*.965*
History details:					
No patient/relative as primary source of history	23 / 42	(54.8%)	29 / 150	(19.3%)	*<.001*
No patient/relative as secondary source history	13 / 23	(56.5%)	20 / 29	(69.0%)	*.525*
Inconsistencies in history	8 / 42	(19.0%)	33 / 150	(22.0%)	*.842*
Symptoms affected L body	9 / 30	(30.0%)	53 / 131	(40.4%)	*.393*
Past history of stroke†	20 / 37	(54.1%)	57 / 137	(41.6%)	*.244*
Known cognitive impairment†	13 / 38	(34.2%)	21 / 140	(15.0%)	*.015*
Examination findings:					
Confused	14 / 20	(70.0%)	38 / 105	(36.2%)	*.010*
Altered conscious state	16 / 42	(38.1%)	40 / 150	(26.7%)	*.150*
Aphasia	23 / 42	(54.8%)	56 / 150	(37.3%)	*.042*
Neglect	14 / 42	(33.3%)	60 / 150	(40.0%)	*.433*
Signs affect L body	8 / 30	(26.7%)	53 /131	(40.5%)	*.232*
Diagnostic formulation:					
R brain affected	7 / 21	(33.3%)	43 / 101	(42.6%)	*.589*
Cortex involved	24 / 42	(57.1%)	83 / 150	(55.3%)	*.974*
Final diagnosis:					*.016*
Stroke	22 / 42	(52.4%)	101 / 150	(67.3%)	
Mimic	20 / 42	(47.6%)	49 / 150	(32.7%)	
Incorrect clinical diagnosis	3 / 42	(7.1%)	17 / 150	(11.3%)	*.461*

** - p value determined by χ^2 test, and Fisher's exact test (for categorical variables), and Mann-Whitney U test (for continuous variables)*
† - denominator refers to the number of patients (not events)

Chapter 9 : Interrater study of the clinical assessment

9.1 Introduction

> "The need for reproducible, reliable clinical measurement goes beyond the requirement for powerful diagnostic, prognostic, and treatment data."(Sackett *et al.*, 1985c)

Reliability (*precision*) is the assessment of agreement between different observers. It complements accuracy (*validity*), as there is no point in determining criteria that make a diagnosis with 100% accuracy if these criteria are unreliable. The following chapter describes an inter-rater reliability study of the clinical assessment of patients with brain attack. Real patients (rather than vignettes, or videotaped observations) were examined in a routine manner by several observers with varied levels of experience. The results are presented using the kappa statistic (κ), a measure of agreement that takes account of chance.

9.2 Aims

This study had two primary aims:

(1) To determine the reliability of the clinical assessment of patients with brain attack.

(2) To explore if modifiable external factors (such as experience, time, or confidence) could explain clinical disagreements.

9.3 Methods

9.3.1 Design

Setting

The study was based in an urban teaching hospital with an acute stroke unit and an academic interest in stroke medicine. Patients presenting with symptoms of brain attack were studied prospectively. The time between assessments was kept to a minimum to reduce the effect that fluctuations in patient state could have on reliability.

Procedure

We aimed to recruit consecutive patients with brain attack to the interrater study. Identification of patients was exactly the same as described for the Brain Attack study. This study ran parallel with the Brain Attack study, so patients were recruited into both studies. Allocation of examining pairs to patients was determined by a random list (see below).

Once identified, a patient was assessed by the first examiner. Immediately after this, the second examiner assessed the patient. Observers were given no specific instructions as to how to elicit or score the assessment. Examiners were permitted to read the one-page acute receiving unit (ARU) admission summary, but were not able to inspect the rest of the patient's notes (the ARU sheet is kept loosely and separately). Each examiner independently recorded his/her findings on a standard data form (see **Appendix 7**) at the end of the assessment. On completion, the examiner's data form was placed in a sealed envelope and collected by Ms J

Haisma (a senior medical student who co-ordinated the study during a four-month research elective). Discussions about the patient were only permitted once both envelopes were sealed and collected.

Achieving balance in randomising pairs

To maintain an even number of pairings and an equal number of times that each observer was the first or second examiner, a randomised and counterbalanced list was generated [using random number tables, (Neave, 1978)]. The available examining pair was allocated to each patient in the order of the list. Allocation was performed by JH, who was unaware of any patient details.

9.3.2 Patient recruitment

Patient eligibility and case ascertainment for the reliability study was as outlined in the brain attack study (**Section II, Chapter 9**). Every patient (or relative) agreed to enter the study. Consent was obtained by the first examiner at the time that the patient was invited to enter the brain attack study. The study had ethics committee approval.

9.3.3 Observers

Three of four observers who performed the clinical assessments were medically qualified physicians. PJH was in his ninth, JK was in his sixth, and BL was in his fifth post-graduate year. BL had five years, and PJH four years of neurology training; JK had no formal training in neurology. BL and PJH trained overseas (English was not the primary language of BL). All were undergoing further training in stroke medicine.

The other examiner, JH, was in her fourth year of medical school in the Netherlands. She was not proficient in neurological examination, or the assessment of stroke patients. For the four weeks before the study commenced, she read standard stroke and neurology examination textbooks, and received practical demonstrations in examination and history taking when she accompanied PJH to see patients.

9.3.4 Data collection

The data collection forms were designed to be brief, so that a clinical assessment took 15 to 20 minutes. A long second assessment risked causing fatigue to the patient. The key items from the brain attack data form (considered to be most important in making a clinical diagnosis of stroke) were selected. The data form (see **Appendix 7**) was divided into four areas: vascular risk factors, history of the presenting complaint, examination (including neurological examination), and diagnostic formulation (including the Oxfordshire Community Stroke Project (OCSP) classification). Brief instructions were provided (primarily to aid the medical student). An 'unknown' category was accepted, as there was confusion amongst observers as to how to score items when information could not be elicited from patients (e.g. due to aphasia).

An important component of the brain attack study, the National Institute of Health Stroke Scale (NIHSS), was not assessed in the present study. This was to keep the training of the medical student to a minimum, and because several other studies have assessed the reliability of the NIHSS (Goldstein *et al.*, 1989; Brott *et al.*, 1989a; Lyden *et al.*, 1994; Dewey *et al.*, 1999). The three medically qualified

examiners had completed the NIHSS training videotapes and were familiar with the scale.

9.3.5 *Data processing*

The data were entered onto a Microsoft Excel spreadsheet (version 97 SR-2, ©Microsoft Corporation 1997). All data were double-checked to ensure accuracy. Corrections were made before the analysis: omitted answers or typographical errors were corrected by referring to the Brain Attack data form where this was available. Analyses were performed in SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999), and confidence intervals for kappa values were calculated using Confidence Interval Analysis (version 2.0.0, ©Trevor Bryant, 2000)

9.3.6 *Statistical analysis*

The kappa statistic

There are several ways to measure interobserver variability. The simplest is the percentage of cases in which both observers agree on the presence or absence of the item studied. This measure gives a misleadingly good impression of agreement, as it does not account for agreement that is expected by chance (Rothwell, 2000). The present study used Cohen's kappa statistic (κ), a measure of the extent to which agreement is greater than expected by chance alone (Cohen, 1960) (see **Figure 9.1**). When the obtained agreement equals chance agreement, $\kappa = 0$. Greater than chance agreement leads to positive κ values, to a maximum of +1.00, which indicates perfect agreement between observers. Less than chance agreement leads to negative κ values, to a minimum of –1.00 (perfect disagreement).

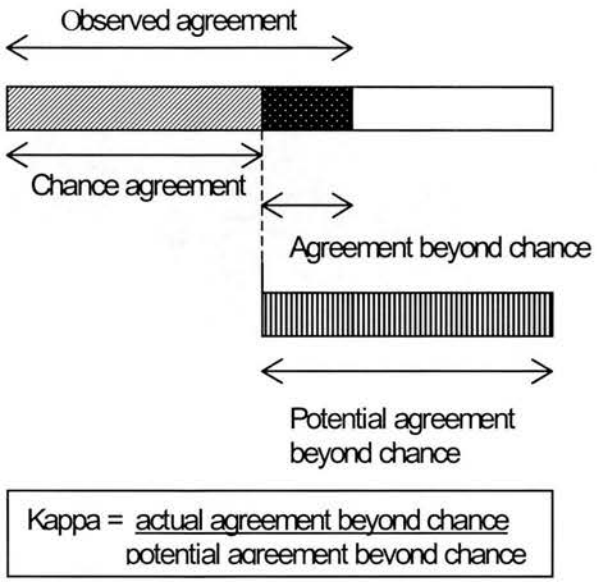


Figure 9.1 The kappa statistic
Adapted from Sackett et al (1985c)

κ values between 0 and +1.00 are generally interpreted as suggesting agreement that ranges from poor to excellent (see **Table 9.1**) (Brennan & Silman, 1992). The κ statistic was developed for categorical, unranked data (e.g., yes/no, present/absent), but has since been extended for observations with more than two categories (e.g., yes/no/maybe) or ranked categories (e.g., 0-33%, 33-66%, 66-100%). To adjust for the different levels of agreement that can occur when mulitple categories are used, the κ statistic can be weighted (Cohen, 1968). I have not used weighted κ in this analysis, as it is arbitrary, may not reflect clinical practice, and often prevents meaningful comparisons between studies (Maclure & Willett, 1987; Al Shahi *et al.*, 2002).

Subgroup analyses

This study aimed to assess the influence of several variables on the reliability of the clinical assessment. Therefore, further analyses were performed on the poorly performing items (identified by fair or moderate κ values). Pre-specified subgroups included:

- *Observer experience*: around half of the patients were assessed by a medical student-physician pair, and the remainder were assessed by a physician-physician pair (of similar experience), thus enabling an assessment of the impact of experience on the assessment.
- *Time from onset of symptoms to presentation*: half of the patients studied presented to hospital within six hours, and were assessed sooner than the remainder of the patients who presented after six hours from symptom onset. This allowed an assessment of the impact of time on the reliability of the clinical assessment.
- *Confidence of the examiners*: each examiner was asked to rate his/her confidence for the three components of the clinical assessment (history, examination, and diagnostic formulation). A highly confident pair was defined as where both examiners stated that they were highly confident; a low confidence pair was defined as where one or both examiners stated that their confidence was low. Comparing the two categories allowed the impact of confidence to be assessed.

In addition, the impact on the reliability of the 'unknown' category was analysed by re-classifying the data in a clearly specified manner. Results of subgroup analyses were tabulated for qualitative comparisons. Significance tests

were not available, as they have limited validity when applied to the κ statistic (Cohen, 1960; Maclure & Willett, 1987), and may prevent real differences between groups from being recognised (personal communication, Dr S.Lewis, statistician).

9.4 Results

9.4.1 General features

The reliability study began recruiting patients on 9 February 2001, and completed recruitment on 30 April 2001. 98 patients were seen (see **Table 9.2**). The age, gender distribution, and time from onset to presentation were similar to the brain attack study, although patients were seen slightly later (median 25.3 hours). 55% of patients presented to hospital within six hours of symptom onset (but only 11 patients were assessed within six hours of onset).

The median time from commencement of the first examination to commencement of the second was 0.9 hours. The median time taken for completion of the clinical assessment was 20 minutes, thus around 30 minutes elapsed between evaluations. The research fellows performed an equal number of assessments as first and second examiner, and an even number of pairings were achieved (except that the author and JH saw more patients).

Difficulties in patient recruitment

Although we aimed to recruit consecutive patients with brain attack, this was not possible. During the study period of time, 125 consecutive presentations with brain attack were recruited into the Brain Attack study. Thus, 98/125 (78%) of all brain attacks entered the reliability study. Patients were not recruited to the

reliability study due to lack of consent (e.g. absent relative, or refusal) in a small number of patients, and unavailability of an examination pair in the majority of patients. It proved too difficult to have four clinicians available at all times of the day to participate in the study. Consequently, most patients were identified and seen the following morning – hence the median time between onset and assessment was 25 hours.

Difficulties encountered in data collection

During the course of the study, the data forms changed several times. Extra questions were added: e.g., the presence of diabetes (somehow initially missed as a vascular risk factor!), the time that the patient was last normal, whether the patient could walk. Some questions were unintentionally left blank

One observer (BL) stated that an exact time of symptom onset could be determined, but was unable to provide the time (instead providing the date and an approximate time such as 'morning'). This occurred for five patients (four physician-physician pairings, one student-physician pairing).

9.4.2 Reliability of the clinical assessment

Vascular risk factors

The summary kappa values are provided in **Table 9.3**, and the raw data are available in **Appendix 8**. There was substantial agreement for the presence of the vascular risk factors ischaemic heart disease (κ: 0.64) and diabetes mellitus (κ: 0.65), and whether the patient was a current smoker (κ: 0.69). Agreement was moderate for all other items.

History of the presenting complaint

Table 9.4 shows that there was substantial agreement for whether an exact time of onset could be determined (κ: 0.63). Good agreement was obtained for many of the focal neurological symptoms, and the presence of headache. Agreement was only fair for whether the patient could recall what he/she was doing at the time of onset (κ: 0.37), and if the patient was well in the last week (κ: 0.40).

There was consensus that an exact time of onset could be determined for 46 patients, and both examiners provided the exact date and time for 42 patients. There was complete agreement for date and time (hour and minute) in 19/42 (45%), agreement for date and hour in 11/42 (26%), agreement for date only in 9/42 (21%), and complete disagreement for date and time in 3/42 (7%). The median difference in onset times for the 23 patients where there was disagreement was 30 minutes (interquartile range 10 – 90 minutes). There were 34 patients in whom there was agreement that it was *not* possible to determine time of onset.

In three patients where there was no consensus for date or time of onset, the dispute arose over whether symptoms were first noted on waking, or the night before. In these patients, symptoms had fluctuated, and the examiners could not determine whether symptoms had resolved completely before the patient went to bed. None of these patients presented within the time window for thrombolysis.

Examination findings

Many items achieved good or better kappa values, including perfect agreement for patients who were unconscious (κ: 1.00) (see **Table 9.5**). Neglect was less reliable than other items of the neurological examination, with 'other forms of neglect' achieving a fair rating (κ: 0.34). There was poor agreement for determining

if signs affected both sides of the body (κ: 0.19). Inspection of the raw data (**Appendix 8)** shows that both examiners agreed that the signs were bilateral in one patient, and *not* bilateral for 90 patients. Hence, the crude agreement was 91/98 (93%).

Diagnostic formulation

The reliability of the diagnostic formulation was generally good (**Table 9.6**). The initial classification – stroke or non-stroke – achieved κ 0.77, and localisation to the left or right side of the brain was extremely good (κ: 0.90 and κ: 0.81, respectively). Agreement for brainstem localisation was moderate (κ: 0.40), but – as with bilateral signs – crude agreement was 70/75 (93%).

There was moderate reliability for the OCSP classification (overall κ: 0.58). There was consensus between observers for total anterior circulation syndrome (TACS) 13 times, partial anterior circulation syndrome (PACS) 20 times, lacunar syndrome (LACS) 13 times, and posterior circulation syndrome (POCS) seven times (70% of all OCSP classifications were in agreement). Individual κ values were good for POCS (0.70), TACS (0.64) and LACS (0.64), but only moderate for PACS (0.43). The disagreements were most frequently between TACS and PACS, and LACS and PACS.

9.4.3 Exploring reasons for poor reliability

Selection of items for further analysis

Some items achieved only fair agreement, and several important components of the history or examination achieved modest agreement. I have selected some of

these items for further analysis, to determine if the reliability depends – in part – on another factor (such as experience, or time). Variables selected were: peripheral vascular disease and past history of a focal neurological deficit (moderate agreement); patient could recall what he/she was doing at the time of onset, and patient was well in the week before symptom onset (fair agreement only); items from the neurological examination with moderate agreement, and the OCSP classification.

The impact of experience

A pair of physicians saw 45 patients, and a medical student-physician pairing saw 48 patients. **Table 9.7** demonstrates that the kappa was higher for the doctor-doctor pairing across almost all components of the clinical assessment. The difference was generally greatest for the neurological examination (e.g., κ for visual neglect was 0.23 for student-doctor and 0.64 for doctor-doctor), and the OCSP classification (κ 0.38 and 0.70, respectively); and least for the items of history (e.g., κ for whether the patient was well in the last week was 0.37 and 0.44, respectively).

The impact of time

In the present study, 54 patients presented within six hours of symptom onset. The median time of assessment was 21.3 hours (interquartile range 11.9 – 29.8 hours). 44 patients presented after six hours from onset, including four patients in whom an onset time was unknown. Median time of assessment in the later presenting group was 31.8 hours (interquartile range 25.0 – 56.2 hours). There was a trend for the reliability of the clinical assessment to be better when patients who presented in the first six hours were evaluated (see **Table 9.8**). However, this did not hold true for the assessment of facial weakness, which was moderately reliable in the

hyperacute patients, but attained good agreement later on (κ 0.42 to 0.62, respectively). The agreement for visuo-spatial dysfunction was modest to fair no matter when patients were assessed.

Was clinician's confidence important?

Examiners recorded their level of confidence for the history, examination, and diagnostic formulation. 47 pairs of examiners both reported high confidence for the items of history. **Table 9.9** shows that the kappa values were impressive for past history of focal neurological deficit (κ 0.71) and whether the patient woke from sleep with the deficit (κ 0.80) when both examiners were confident about the history gathered. Yet agreement was only fair – and no different to that of the low confidence pairs – for whether the patient could recall what he/she was doing at the time of symptom onset (κ 0.26), and whether the patient was well in the last week (κ 0.33).

60 pairs of examiners both reported high confidence for the examination, and there was greater agreement for neurological signs in this group (e.g., κ 0.67 for face weakness, compared with κ 0.31 for the same sign when one or both examiners were not confident). The agreement for confusion and other forms of neglect (i.e., not visual or sensory neglect) actually improved when confidence was low. For the 42 pairs who were confident about the final diagnosis, the OCSP classification achieved good agreement (κ 0.68).

How to deal with the 'unknowns'

The 'unknown' category represented a difficulty for statistical analysis, as a greater number of categories inevitably results in a lower κ (Brennan & Silman,

1992). We wanted to distinguish between whether an item was truly absent, or unanswerable, hence we allowed the unknown category. But it could be argued that if something is unknown it is of little clinical value – in the setting of thrombolysis, decisions need to be made swiftly, so unknown items cannot be used to make a decision. Hence, an alternative approach would be to class an item as absent unless it was definitely known to be present.

To determine if some of the poor reliability was due to the extra category, the data were re-analysed with unknown re-classified to no. The results are provided in **Table 9.10**. There was no observable trend: some items improved (e.g. for 'patient can recall what he/she was doing at time of onset', κ improved from 0.37 to 0.55), some remained the same, and some deteriorated (e.g. for visual neglect, κ went from 0.41 to 0.13).

9.5 Discussion

9.5.1 Importance of the present study

The history and examination form the cornerstone of neurological diagnosis (Goldstein & Matchar, 1994). Many studies of the reliability of the clinical assessment of stroke have now been reported (Tomasello *et al.*, 1982; Shinar *et al.*, 1985; Gelmers *et al.*, 1988; Gordon *et al.*, 1993; Lindley *et al.*, 1993; Dewey *et al.*, 2001), particularly studies of the NIHSS (Goldstein *et al.*, 1989; Brott *et al.*, 1989a; Lyden *et al.*, 1994; Dewey *et al.*, 1999). The present study adds important additional information, for five main reasons. Firstly, real patients were used as subjects. This is a clinically realistic method of assessment, arguably more so than clinical vignettes (Gordon *et al.*, 1993), or videotaped observations (Lyden *et al.*, 1994). It has been

suggested that the latter are more suited to studies of the acute phase of stroke, where patient's signs may change rapidly (D'Olhaberriague *et al.*, 1996). This is a valid point, but we were able to minimise patient fluctuations by examining patients on average 30 minutes apart [much sooner than other studies, e.g. (Shinar *et al.*, 1985; Lindley *et al.*, 1993)]. In addition, the ability to score reliably an item that is demonstrated on video does not imply that the clinician will achieve similar reliability when directly examining the patient.

Secondly, this was the largest study to date. A broad spectrum of patients was studied – some had stroke mimics, many were old, and some were confused or aphasic. Unlike studies in which stable stroke patients were used, and the observers were thus expecting to find neurological symptoms or signs (Shinar *et al.*, 1985; Gelmers *et al.*, 1988; Brott *et al.*, 1989a; Lindley *et al.*, 1993; Dewey *et al.*, 1999), the present study selected patients who presented with the undifferentiated clinical syndrome of brain attack. This minimised bias.

Thirdly, a wide range of observers participated in this study. Clinical experience differed, and the first language of two observers was not English. Previous studies used highly trained stroke neurologists (Shinar *et al.*, 1985; Gelmers *et al.*, 1988), or the signs were demonstrated to the less experienced members of the team by a stroke neurologist (Brott *et al.*, 1989a). Two studies by the same clinicians (Dewey *et al.*, 1999; Dewey *et al.*, 2001) compared trained research nurses to a neurologist.

Fourthly, items of history were tested. Just two other studies tested the history (Tomasello *et al.*, 1982; Shinar *et al.*, 1985), although one study only reported the crude index of agreement (Tomasello *et al.*, 1982).

These strengths – which aim to replicate real-life, hence provide a realistic impression of reliability – might be expected to diminish agreement. The final strength of the study is that we attempted to explore some of the reasons for clinical disagreements, which has not previously been performed in the field of stroke.

9.5.2 Comparison with other studies

History

The two earlier studies reported generally disappointing reliability for the neurological history [it is not possible to directly compare the findings of Tomasello et al (1982)]. **Table 9.11** shows that in Shinar et al's (1985) study, kappa values were poor to fair for the four items of history that could be compared directly. In the present study, agreement was much better (despite – or perhaps because of – the difference in observers' experience in the two studies).

Neurological examination

Our results are in broad agreement with the other studies (**Table 9.11**), and reinforce the general finding of moderate to good reliability for the component parts of the NIHSS. Like Lindley et al (1993), we found that confusion was an unreliable sign. Unlike Shinar et al (1985), we found that hand weakness was reliable.

Diagnostic formulation

The reliability of the clinical diagnosis of stroke has not been tested before (Goldstein & Matchar, 1994). Reassuringly, we found that this achieved good agreement. In common with Lindley et al (1993) and Dewey et al (2001), we found that the OCSP classification overall was moderately reliable (κ 0.58, 0.54 and 0.42-

0.58, respectively). The categories of POCS, LACS and TACS achieved better reliability than PACS, and we also observed an improvement in κ when an experienced pair of observers was compared to a pair containing an inexperienced observer.

9.5.3 Limitations of the study

There are some limitations of the present study. Although we aimed to see patients as promptly as possible, the median time from symptom onset to evaluation by the first observer was rather long (25 hours). The patient sample was not consecutive, and we were unable to allocate examining pairs in the exact order listed in the random number sheet. Despite this, there was no systematic bias in patient exclusion or allocation.

Examiners were able to see patients within 30 minutes of each other, thereby limiting changes in patient state, but even within this short time, important fluctuations did occur (in at least three patients). Despite an examination time of 15 to 20 minutes, when patients were examined closely together, fatigue was a problem (two patients refused to allow a second assessment). These difficulties would have reduced agreement between examiners.

9.5.4 Limitations of the kappa statistic

The κ statistic, although widely used, has been criticised (Maclure & Willett, 1987; Brennan & Silman, 1992; Byrt *et al.*, 1993). When there are more than two categories (e.g., the four OCSP subtypes), the opportunities for disagreement increase, and the κ value decreases (Brennan & Silman, 1992) (e.g. the overall κ for the OCSP classification was lower than the individual categories). In this situation,

use of the intraclass correlation coefficient may be preferable (Maclure & Willett, 1987).

κ is affected in complex ways by the prevalence of abnormality amongst the subjects observed, and by observer bias. Very low (or high) prevalence results in high levels of expected agreement, and consequently the κ value is often low despite near perfect agreement (Brennan & Silman, 1992). This was seen in the present study for the items of whether signs affect both sides of the body, and whether the lesion was in the brainstem. Observer bias, in this sense a systematic difference between two observers in the way questions are answered, influences agreement. Bias was seen in the present study – one examiner consistently scored the onset as 'exactly known' when it was actually unknown (as the examiner was unable to provide the exact time). Bias is a form of disagreement with important practical implications, but it is not separately identified by κ. Statistical methods to adjust for bias and prevalence have been proposed (Byrt *et al.*, 1993), but have not become widely accepted.

It can be difficult to compare κ values between different studies, and within studies. A significance test for a κ value can be calculated, but this merely states the likelihood that the result did not arise by chance – and chance has already been eliminated from the value, making a p-value trivial in comparison to the actual κ (Cohen, 1960). Finally, although formulae are available to compare two independent κ values (Cohen, 1960), these have not become standard, so it is difficult to quantify differences between κ.

9.5.5 Implications of the study

The present study found that certain components of the clinical assessment achieved good or better reliability (summarised in **Table 9.12**). As these items proved reliable when assessed by inexperienced students, doctors with a primary language other than English, and in a broad range of (often difficult) patients, it can be concluded that these items are reliable in everyday clinical practice. Little additional training beyond medical qualification would be required to ensure competence with such items. The present study also found that certain components of the assessment had poor reliability, and performance was not improved under any of the conditions tested. These questions and signs, despite any possible validity, are probably useless in clinical practice (**Table 9.12**).

Our results have important implications for training. The reliability of a substantial proportion of the clinical assessment could probably be improved. We observed that increased clinical experience in our examiners led to better reliability in our study, particularly for the examination. However, it would be wrong to simply target the neurological examination for additional training, as reliability depends on knowing the patient's history (allowing hypotheses to be tested) (Vogel, 1992; Hansen *et al.*, 1994). A reasonable strategy would be to provide less experienced observers with detailed rules or guidelines for the interpretation of the information obtained. Such guidelines have been demonstrated to improve reliability for the diagnosis of transient ischaemic attack (Koudstaal *et al.*, 1989) and the NIHSS (Lyden *et al.*, 1994). This may improve the confidence of examiners, which was shown in the present study to be crucial to achieving good reliability.

We observed that reliability was no worse for patients who presented within six hours, and were examined earlier, than for patients who presented after six hours. However, most patients admitted within six hours were actually assessed at around 24 hours after symptoms onset; only 11 patients presented and were assessed within six hours, too few to draw meaningful conclusions about the reliability of the assessment of the 'hyperacute' patient.

The determination of time of symptom onset has crucial implications for acute stroke. Although good agreement was reached that an exact time of onset could be determined, in fewer than 50% of patients did the examiners actually agree on the precise time. Whether the patient woke from sleep with the deficit, or whether symptoms had improved since onset, achieved only modest agreement. At present, the only factor shown to be significant in determining eligibility for thrombolysis is time from symptom onset, yet our evidence suggests that this can not be determined reliably.

9.6 Summary

- This study has identified the reliable parts of the clinical assessment of patients with brain attack
- Many of the items with only moderate agreement could probably be improved with training
- Confidence improves reliability

Recommendations for further research:

- We need more studies of patients who present within six hours of symptom onset
- We need to explore ways of improving reliability of time of onset – or alternate strategies to determine eligibility for thrombolysis.

Table 9.1 Interpretation of the kappa statistic

Kappa value	Strength of agreement
< 0.20	Poor
0.21 – 0.40	Fair
0.41 – 0.60	Moderate
0.61 – 0.80	Good or substantial
0.81 – 1.00	Very good

After Brennan and Silman (1992)

Table 9.2 General features of patients recruited into the reliability study (n=98)

Feature	Number	*(% / IQR*)*
Median age (IQR*):	78.6 years	*(69.3-85.7)*
Male gender:	44 / 98	*(45%)*
Final diagnosis of mimic	24 / 98	*(24%)*
Known cognitive impairment/confusion on examination	39 / 98	*(40%)*
Aphasia	37 / 98	*(38%)*
Median time from symptom onset to presentation (IQR):†	4.8 hours	*(1.9-13.3)*
Median delay between presentation to hospital and evaluation by research team (IQR):†	25.3 hours	*(16.3-49.7)*
Median time between commencement of first and second assessment (IQR):	0.9 hours	*(0.5-1.9)*
First examiner:		
PJH	27 / 98	*(28%)*
JK	23 / 98	*(24%)*
BL	22 / 98	*(22%)*
JH‡	26 / 98	*(27%)*
Second examiner:		
PJH	26 / 98	*(27%)*
JK	24 / 98	*(25%)*
BL	21 / 98	*(21%)*
JH‡	27 / 98	*(28%)*
Pairings:		
PJH-JK	17 / 98	*(17%)*
PJH-BL	14 / 98	*(14%)*
PJH-JH‡	22 / 98	*(22%)*
JK-BL	14 / 98	*(14%)*
JK-JH‡	16 / 98	*(16%)*
BL-JH‡	15 / 98	*(15%)*

** IQR – interquartile range*
† time of onset details were unknown in 4 patients, and there were 3 inpatient brain attacks (hence time of presentation to ARU not appropriate).
‡ JH was the medical student

Table 9.3 Reliability of the assessment of vascular risk factors

Item	Kappa value	*95% Confidence Intervals*
Hypertension	0.47	*0.32 – 0.62*
Smoker within 12 months	0.69	*0.55 – 0.83*
Ischaemic heart disease	0.64	*0.50 – 0.78*
Atrial fibrillation	0.54	*0.38 – 0.70*
Peripheral vascular disease	0.44	*0.27 – 0.62*
Diabetes mellitus	0.65	*0.45 – 0.84*
Past history of a focal neurological deficit	0.51	*0.36 – 0.66*

Table 9.4 Reliability of the assessment of the history of the presenting complaint

Item	Kappa value	*95% Confidence Intervals*
An exact time of onset can be determined	0.63	*0.47 – 0.78*
The patient woke from sleep with deficit	0.55	*0.40 – 0.69*
The patient can recall what he/she was doing at time of onset	0.37	*0.20 – 0.53*
Improvement since onset	0.54	*0.39 – 0.68*
Symptoms are now stable	0.59	*0.42 – 0.77*
Patient well in the week before onset	0.40	*0.24 – 0.57*
A definite history of focal neurological deficit	0.59	*0.42 – 0.75*
Hemianopia/quadrantanopia	0.63	*0.47 – 0.79*
Loss of speech/language	0.64	*0.50 – 0.77*
Loss of sensation	0.62	*0.48 – 0.76*
Loss of power	0.59	*0.44 – 0.75*
Headache	0.65	*0.51 – 0.79*
The symptoms affect the:		
Left side	0.62	*0.48 – 0.76*
Right side	0.56	*0.42 – 0.71*
Both sides	0.43	*0.23 – 0.63*

Table 9.5 Reliability of the physical examination

Item	Kappa value	*95% Confidence Intervals*
The patient is alert	0.70	*0.52 – 0.89*
The patient is drowsy	0.74	*0.53 – 0.94*
The patient is unconscious	1.00	*1.00 – 1.00*
The patient is confused	0.45	*0.28 – 0.62*
Arm weakness	0.65	*0.49 – 0.80*
Hand weakness	0.72	*0.59 – 0.86*
Face weakness	0.50	*0.34 – 0.67*
Leg weakness	0.57	*0.41 – 0.73*
The patient could walk	0.62	*0.47 – 0.76*
Visual loss	0.46	*0.28 – 0.64*
Dysarthria	0.41	*0.25 – 0.58*
Dysphasia	0.66	*0.51 – 0.80*
Sensory disturbance	0.49	*0.34 – 0.65*
Visual neglect	0.41	*0.25 – 0.58*
Sensory neglect	0.59	*0.45 – 0.73*
Other form of neglect	0.34	*0.16 – 0.51*
The signs affect the:		
Left side	0.74	*0.61 – 0.88*
Right side	0.69	*0.54 – 0.83*
Both sides	0.19	*-0.40 – 0.77*

Table 9.6 Reliability of the diagnostic formulation

Item	Kappa value	*95% Confidence Intervals*
The patient has had a stroke	0.77	*0.60 – 0.93*
The lesion affects the:		
Left side of the brain	0.90	*0.79 – 1.00*
Right side of the brain	0.81	*0.68 – 0.94*
Brainstem	0.41	*-0.09 – 0.91*
OCSP classification:		
TACS	0.64	*0.43 – 0.85*
PACS	0.43	*0.22 – 0.64*
LACS	0.64	*0.43 – 0.85*
POCS	0.70	*0.45 – 0.85*
Overall	0.58	*0.43 – 0.72*

Table 9.7 The impact of experience on the reliability of the clinical assessment

	Kappa value for pairing:	
Item	**Student-Doctor**	**Doctor-Doctor**
Vascular risk factors		
Peripheral vascular disease	0.38	0.53
Past history of focal deficit	0.46	0.59
History of presenting complaint		
Patient woke from sleep with the deficit	0.55	0.53
Patient can recall what he/she was doing at time of onset	0.33	0.40
Patient was well in the last week	0.37	0.44
Examination		
The patient is confused	0.38	0.53
Face weakness	0.41	0.61
Visual loss	0.35	0.60
Dysarthria	0.40	0.41
Visual neglect	0.23	0.64
Other form of neglect	0.33	0.33
Diagnostic formulation		
OCSP classification	0.38	0.70

Table 9.8 The impact of time to presentation on the reliability of the clinical assessment

	Kappa value for patients presenting:	
Item	**Within 6 hours**	**After 6 hours**
Vascular risk factors		
Peripheral vascular disease	0.46	0.42
Past history of focal deficit	0.56	0.44
History of presenting complaint		
Patient woke from sleep with the deficit	0.59	0.50
Patient can recall what he/she was doing at time of onset	0.45	0.26
Patient was well in the last week	0.46	0.34
Examination		
The patient is confused	0.52	0.30
Face weakness	0.42	0.62
Visual loss	0.55	0.32
Dysarthria	0.47	0.32
Visual neglect	0.40	0.41
Other form of neglect	0.36	0.30
Diagnostic formulation		
OCSP classification	0.58	0.54

Table 9.9 Impact of the examiners' level of confidence on the reliability of the clinical assessment

	Kappa value when confidence was:	
Item	**High**	**Low**
History items	*n=47 pairs*	*n=48 pairs*
Peripheral vascular disease	0.51	0.27
Past history of focal deficit	0.71	0.32
Patient woke from sleep with the deficit	0.80	0.31
Patient can recall what he/she was doing at onset	0.26	0.24
Patient was well in the last week	0.33	0.36
Examination items	*n=60 pairs*	*n=36 pairs*
The patient is confused	0.41	0.44
Face weakness	0.67	0.31
Visual loss	0.52	0.35
Dysarthria	0.45	0.36
Visual neglect	0.49	0.24
Other form of neglect	0.24	0.45
Diagnostic formulation	*n=42 pairs*	*n=52 pairs*
OCSP classification	0.68	0.45

Table 9.10 The impact of re-classifying 'unknown' items on the reliability of the clinical assessment

Item	Kappa value: 'Unknown' becomes 'no'	Kappa value: Original results
Vascular risk factors		
Peripheral vascular disease	0.31	0.44
Past history of focal deficit	0.51	0.51
History of presenting complaint		
Patient woke from sleep with the deficit	0.59	0.55
Patient can recall what he/she was doing at onset	0.55	0.37
Patient was well in the last week	0.40	0.40
Definite history of focal neurological deficit	0.62	0.59
Examination		
The patient is confused	0.40	0.45
Visual loss	0.46	0.46
Sensory disturbance	0.45	0.49
Visual neglect	0.13	0.41
Sensory neglect	0.59	0.59
Other form of neglect	0.21	0.34

Table 9.11 Reliability of the clinical assessment – the present study compared with earlier studies (where a kappa was provided)

Kappa values	Present study (n=98)	Shinar (n=17)	Lindley (n=85)	Dewey* (n=31)	Gelmers (n=12)	Brott* (n=24)	Goldstein* (n=20)
History items							
Previous stroke	0.51	0.31	-	-	-	-	-
Deficit on waking	0.55	0.11	-	-	-	-	-
Focal deficit at onset	0.59	0.15	-	-	-	-	-
Headache	0.65	0.36	-	-	-	-	-
Examination items							
Conscious level	0.70-1.00	0.38	0.60	0.58	0	0.42	0.50
Confusion	0.45	-	0.21	-	0.19	-	-
Face weakness	0.50	0.51-0.66†	0.63	0.79	0.13	0.46	0.22
Arm weakness	0.65	-	0.77	0.85-0.82†	0.91-0.46†	0.79	0.77
Hand weakness	0.72	0.58-0.49†	0.68	-	-	-	-
Leg weakness	0.57	-	0.64	0.84-0.53†	0.64-0.40†	0.81	0.78
Visual fields	0.46	0.40	0.39	0.62	0.16	0.89	0.57
Dysarthria	0.41	0.53	0.51	0.56	-	0.44	0.32
Dysphasia	0.66	0.54	0.70	0.60	0.76	0.61	0.79
Sensory disturbance	0.49	-	-	0.73	0.27	0.63	0.50
Neglect	0.59	-	0.44	0.77	-	0.54	0.61

** these were studies of the NIHSS, in which the κ for individual components was provided. Dewey's study used a weighted κ. Three different κ values were reported (depending on the examining pair). I have taken the κ for the neurologist-neurologist pair. Brott's study assessed patients twice; I have used the κ for the initial assessment.*

† first κ refers to the right limb, second κ refers to the left limb

Table 9.12 Summary of the reliability of the clinical assessment

		Item of the assessment
Reliable:	*History*	• Smoker
		• Ischaemic heart disease
		• Diabetes
		• An exact time of onset could be determined*
		• Any focal neurological symptoms
		• Headache
	Examination	• Conscious state
		• Arm weakness
		• Hand weakness
		• Dysphasia
		• Side of signs
	Diagnostic formulation	• Stroke or mimic
		• Side of brain lesion
Could be improved:	*History*	• Other vascular risk factors
		• Patient woke from sleep with deficit
		• Improvement since onset
	Examination	• Facial weakness
		• Leg weakness
		• Visual loss
		• Visual inattention
		• Sensory disturbance
	Diagnostic formulation	• OCSP classification
Unreliable:	*History*	• Patient can recall what he/she was doing at time of onset
		• Patient was well in the last week
	Examination	• Confusion
		• Neglect (other than sensory & visual)
		• Dysarthria

** Although κ was good, less than 50% of patients had the **same** time recorded*

Chapter 10 : A predictive model to distinguish stroke from non-stroke using clinical features

10.1 Introduction

This chapter will attempt to draw together the findings of earlier chapters to discover if certain clinical features *independently* predict the diagnosis, and whether these could be put to clinical use in a simple tool. I will use the multivariable statistical technique of logistic regression to develop a tool to assist in the diagnosis. Careful attention to the basic methodological principles of model building – which shall be covered in some detail – is critical to ensuring that potentially useful models are generated.

10.2 Aims

(1) To use multivariable logistic regression to determine which clinical factors *independently* predict the diagnosis of stroke (or mimic)

(2) To develop predictive models, using clinical data available at the bedside, to distinguish between stroke and mimic in patients presenting with brain attack

(3) To develop simple clinical guidelines to assist the less experienced clinician in the assessment of patients with brain attack

10.3 Methods

10.3.1 Predictive models: ensuring methodological quality

I chose to develop predictive models using logistic regression for two reasons. Firstly, there is considerable 'in-house' experience of prognostic modelling using multiple logistic regression analysis (Counsell & Dennis, 2001), and therefore clinical and statistical support were available. Secondly, this is an accepted and valid method of distilling a vast amount of data into something smaller and clinically useful (Braitman & Davidoff, 1996; Laupacis *et al.*, 1997). Many authors have proposed methodological standards for predictive modelling using logistic regression, which I have summarised in **Table 10.1**. I have attempted to conform to these standards wherever possible.

10.3.2 Patient selection

Inception cohort

The inception cohort was assembled from patients who entered the brain attack study. As described in **Chapter 7**, consecutive patients who presented with symptoms of brain attack – apparently focal neurological dysfunction of apparently abrupt onset – were recruited to the study. A standard clinical assessment was performed by one of four stroke research fellows, and the data obtained were entered onto a standard data form.

In the brain attack study, there were 350 presentations by 336 patients. By convention, the entry point for predictive modelling is defined as the time that the patient first entered the study (so I excluded the 14 recurrent events).

Referral pattern

This was described in detail in **Chapter 7**, but the essential points are that the study was situated in a medium-sized urban teaching hospital with an acute stroke unit and an academic interest in stroke medicine (although not a tertiary referral centre for stroke). The hospital has an Acute Receiving Unit (ARU), which receives all medical emergencies from the north of Edinburgh. Patients were referred directly to the research fellows by ARU staff. ARU and ward admission registers were inspected daily, and potentially eligible patients were assessed to achieve full case ascertainment.

10.3.3 Definition of outcome events

The aim of the model was to predict the diagnosis in patients presenting with symptoms of brain attack. The outcome event was the final diagnosis as determined by the expert panel. Logistic regression works best when the outcome variable is a binary event (e.g. stroke or not) (Laupacis *et al.*, 1997), so the six diagnostic categories were dichotomised. 'Thrombolysis-eligible' strokes (meaning that, if all else were favourable, the clinician would be prepared to consider thrombolysis for that patient) were patients with a definite or probable stroke or transient ischaemic attack (TIA). Mimics were patients with a definite non-stroke or a plausible alternative diagnosis for a clinical syndrome thought to be a possible stroke.

The issue of TIAs deserves clarification. I included patients with TIA, although they are often excluded from prognostic models [e.g. Baird et al (2001)]. This was because: (1) it would be inconsistent (and not clinically sensible) to exclude patients after they had already entered the study, and (2) patients who have

symptoms of brain attack are 'thrombolysis-eligible'. At present there is no reliable way to determine those whose symptoms will persist (i.e. stroke), and those whose symptoms will resolve by 24 hours (i.e. TIA).

'Outcome' (i.e. the final diagnosis) was assessed blind to the prediction of the model. The panel was unaware of the variables that were used to generate the model (although it is plausible that they used some of the variables to make their decisions). The two categories for logistic regression analysis were pre-specified, transparent, and clinically sensible.

10.3.4 Selection of variables

Data reduction

The number of variables used in multiple logistic regression analysis must be carefully controlled to produce reliable models (Concato *et al.*, 1993; Harrell, Jr. *et al.*, 1996). Too many variables entered into a model can result in overfitting of the model to the dataset (Concato *et al.*, 1993), which severely limits its generalisability. The critical factor is not just the absolute number of variables entered into the model, but rather the ratio of the number of outcome events to the number of variables entered [the events per variable (EPV)]. Empirical research has shown that an EPV of 10 or more, for the less frequent outcome event, is required to avoid producing unreliable models (Peduzzi *et al.*, 1996). For example, in a study of 100 patients, in which 70 have a stroke and 30 a mimic, the maximum number of variables that should be entered (to produce a reliable model) is three.

In the brain attack study, 135 individual items of data (variables) were collected for each patient (see data collection form, **Appendix 2**). Thus considerable

data reduction was required before performing the statistical analyses. The methods used to eliminate variables should be clinically sensible and not based on univariate comparisons between single variables and the outcome of interest, as this can give rise to spurious associations (Harrell, Jr. *et al.*, 1996). I therefore used several criteria that were independent of the outcome to eliminate variables. These were:

(1) variables with too much missing data (arbitrarily defined as missing in more than 30 patients, or lower if the event rate was low) as this suggested they were not easy to collect;

(2) variables in which the event rate was low (defined as less than 30);

(3) variables in which the reliability was moderate or poor (as defined by the kappa obtained in the reliability study, **Chapter 9**);

(4) variables that I considered to be clinically irrelevant, and

(5) variables that duplicated others.

I was also able to combine several variables to create composite variables. Where possible, data were dichotomised to make the models as simple as possible (Harrell, Jr. *et al.*, 1996).

Data quality – what to do with 'unknowns'

Variables in which there was a large amount of missing data were discarded. However, it would have introduced major bias to discard *patients* in whom data was unassessable (Norris *et al.*, 2000). The strategy used to deal with missing data was that if an item were 'unassessable', it was assumed to be absent. For example, if the presence or absence of a vascular risk factor could not be determined at the bedside, then the clinician would have to assume that it was absent; likewise, when examining a patient, if sensation could not be tested (because the patient was unconscious), then

the clinician would assume that there was no impairment. This is a conservative approach that places value on items that are definitely known to be present, and – for diagnostic purposes – reflects clinical reality.

10.3.5 Generation of the models

Sample size

The sample size needs to be adequate to ensure statistical validity. For logistic regression analyses, the key issue is not the overall sample size, but the number of outcome events (of the least common event) (Concato *et al.*, 1993). The problem of overfitting can be minimised by conforming to the 10 EPV rule (discussed above). An additional problem is that of underfitting, where there are too few outcome events which reduces the power of the model to detect important associations such that important variables are omitted erroneously [equivalent to a type II error (Concato *et al.*, 1993)]. Before this study commenced, it was estimated that a sample size of 300 – 400, which would include about 100 mimics, would allow a simple model to be developed using 10 variables.

Statistical techniques

As the outcome event was binary (stroke or mimic), forward stepwise multiple logistic regression was used to develop the predictive model. In this method the computer identifies the predictor variable that has the strongest association with the outcome, and enters it first (Counsell & Dennis, 2001). The variables not included in the model are then re-analysed, and the one that explains the largest amount of remaining variability is entered next. This process occurs until all of the

predictor variables associated with the outcome have been included in the model (those remaining are not significantly associated with the outcome). In addition, after each new variable has been added to the model, the variables already in the model are re-examined to see if they still have a significant association with the outcome – if not they are removed from the model.

Multiple regression can give rise to spurious results if all variables are simply entered into the model. This is because variables that are highly correlated with each other may cancel each other out so that neither appears to be a significant predictor of outcome – this is called collinearity (Concato *et al.*, 1993). Collinearity can be minimised by choosing only the most clinically relevant (among similar) variables for inclusion in the model (Concato *et al.*, 1993), and by using stepwise regression methods (Counsell & Dennis, 2001).

Translating the predictive model into a clinically useful tool

The intended audience for the predictive model

I envisaged three possible audiences:

(1) A stroke or neurology registrar who may need to make the final decision on thrombolysis for a patient. This clinician would be capable of performing a thorough history and examination, and be familiar with the OCSP classification and NIHSS. A model aimed at this clinician could include some complex tasks.

(2) An emergency room doctor who needs to decide whether to fast-track the patient to CT, to call in someone more senior (possibly out-of-hours), or get a bed ready on the stroke ward. This clinician would be expected to

be able to perform a limited neurological examination, and a model would have to be simple to be useful.

(3) An ambulance paramedic or triage nurse in ARU who needs to identify a possible stroke that should be seen promptly by someone with more experience. A model would need to be very simple and brief.

What should the model achieve?

In each situation, the needs for a predictive tool will vary. In the first scenario, the neurology or stroke doctor must make a decision that entails major risk to the patient. The clinician would want to be very sure that the diagnosis was stroke; I have arbitrarily defined an acceptable positive predictive value (PPV) of 95% (i.e. 19 out of every 20 predictions of stroke will actually have a stroke).

In the second situation, the risks of an incorrect diagnosis are less – the patient has an urgent scan (which costs money) and a senior colleague is called in unnecessarily. Here, it would be acceptable to lower the threshold to increase the number of true strokes identified, at the expense of an increased false positive rate. A reasonable PPV would be 85% (an arbitrary decision).

In the third situation, the risks to the patient of an incorrect initial diagnosis of stroke are almost negligible, but the risk of a missing a true stroke becomes important. Here, an ideal model should identify all potential stroke patients, at the expense of low specificity. A PPV of 75% would be acceptable.

I therefore developed a different model for each of the above scenarios. It was necessary to define the variables for inclusion in each model according to the circumstances, and to test the performance of the model according to the arbitrary criteria established above.

Statistical package

All analyses were performed in SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999). The outcome of interest was defined as stroke (coded as one, with mimic coded as zero), all but two predictor variables were dichotomous (with a positive response coded as one, negative response coded as zero). The models were developed using forward stepwise selection, with entry criteria defined as $p<0.05$ and removal criteria defined as $p>0.10$ for the significance level of the likelihood-ratio test. Where required, 95% confidence intervals for the odds ratios were calculated.

10.3.6 Evaluation of the model

The computer-produced model comes complete with its own set of statistics that measure the 'goodness of fit' of the model to the dataset (these vary according to each computer package, as there is no consensus among statisticians about which index is most appropriate (Concato *et al.*, 1993)). These include the Hosmer and Lemeshow test, which provides a χ^2 statistic and significance test, and a model summary with a calculated r-square statistic that measures the proportion of the variation explained by the model. However, these mathematical estimates do not necessarily provide an indication of how accurate the model's predictions are likely to be (Concato *et al.*, 1993; Hall & Round, 1994).

There are several approaches to assessing the performance or accuracy of a predictive model (Altman & Royston, 2000). It should be remembered that although the outcome event is either present or absent (in binary terms, one or zero), the model provides a predicted probability of the outcome event occurring, which lies between the extremes of zero and one. Thus, one may compare observed and predicted

outcomes for groups of patients (calibration) or individuals (accuracy scores). The model should be able to distinguish between patients who do or do not experience the outcome event (discrimination). It is also important to compare a model's performance with clinicians' informal judgement, if it is to be used in clinical practice (Counsell & Dennis, 2001).

Calibration

Calibration refers to the degree of bias of model predictions for groups of patients, and can be estimated by plotting calibration curves (Diamond, 1992; Harrell, Jr. *et al.*, 1996). To derive the curves, I ordered the dataset by ascending predictions of outcome and then divided it into 10 equal groups (where possible, depending on the data). For each group, I plotted the mean observed outcome against the mean predicted outcome. A model is well calibrated if, within each decile, the proportion of patients predicted to have an event and the proportion observed to have done so is the same (i.e. the calibration curve follows a 45° line).

Discrimination

Discrimination is the ability of the model to differentiate between patients who do and do not experience the outcome, and was measured using the area under the receiver operating characteristic (ROC) curve. This method compares random pairs of patients, one with the outcome event (i.e. stroke) and one without (i.e. mimic), to determine if a higher probability is assigned to the patient with stroke than to the one with a mimic (Hanley & McNeil, 1982; Swets, 1988; Justice *et al.*, 1999). The area under the curve (AUC) ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination); the value can be interpreted as the 'percentage correct': for example,

when the value is 0.82, this means that the model correctly predicts the outcome 82% of the time (Swets, 1988). I constructed ROC curves and calculated the area under the curve for each model using the data obtained from each logistic regression analysis.

Comparison with clinical judgement

The accuracy of the models' predictions was compared with the research fellow's final clinical diagnosis and end of bed assessment, the ARU referral diagnosis and the general practitioner's diagnosis. The sensitivity and specificity for each clinical diagnosis were determined in **Chapter 7**. The single point representing sensitivity by 1-specificity for each clinical diagnosis was plotted on the appropriate ROC curve, and compared with the model's curve. If the clinical diagnosis lay to the left of the curve, the clinical diagnosis was more accurate; if the clinical diagnosis lay to the right of the curve, it was less accurate.

10.4 Results

10.4.1 Baseline characteristics

Three hundred and thirty-six patients were included in the present study, which included the initial presentation of consecutive patients who presented with symptoms of brain attack. After the expert panel meeting, the final diagnosis was determined to be a 'thrombolysis-eligible' stroke (hereafter referred to as stroke) in 234 patients, and a mimic in 102 patients. Following the 10 EPV rule (Peduzzi *et al.*, 1996), this meant that predictive models were allowed a maximum of 10 variables.

Selection of variables

Initial reduction

The process of reducing variables proved to be challenging. Variables were initially excluded according to the methods outlined (see **Table 10.2**). Data such as side of the lesion, and time-related information (such as were the symptoms getting worse) were excluded, and where clinically relevant, composite variables were created from related items of data (see **Table 10.3**). The OCSP category was simplified to whether a classification was possible (on clinical grounds). Unknown or unassessable responses, which ranged from one (peripheral vascular disease) to 22 (sensory disturbance), were altered as described in the methods section.

This left 36 variables, still too many to produce a reliable model. However, all seemed clinically plausible explanatory variables. At this point, I examined the univariate analyses to assist me to reduce the variables even further. I was able to eliminate age, gender, past history of stroke, and presence of migraine, epilepsy, malignancy or psychological disturbance as none were significant predictors of the final diagnosis. I excluded vascular risk factors, because as a group they did not significantly predict diagnosis. Individually, certain conditions were strong predictors (e.g. peripheral vascular disease), but occurred infrequently.

The three models

I was left with 16 variables. Further refinement of variable selection depended on the intended audience for the model. For nurses and emergency department doctors, I created models with few variables, as I considered that these clinicians would not be capable of collecting every item of information (e.g. the OCSP classification). However, for the stroke/neurology registrar, I created complex

models with more variables as I considered that the stroke/neurology registrar ought to be able to determine the answer to all questions.

I verified my own impressions by conducting an informal poll of five emergency nurses, five medical senior house officers in the Acute Receiving Unit, three stroke registrars (two with a neurology background, one with a general medical background) and two stroke consultants. I asked each person to indicate whether he/she thought a clinician in his/her category would be capable of determining the response to 16 clinical variables. The consensus of all responses is provided in **Table 10.4**, and the results were used to inform each model.

Model aimed at a stroke or neurology registrar. The variables chosen represented one more than the maximal number allowed (11) (see **Table 10.5**). I was able to remove the individual elements of the neurological examination, replacing these with the NIHSS. I arbitrarily divided NIHSS into four categories, as the relationship between NIHSS and diagnosis was not linear (with NIHSS = 0 as the reference group).

Model aimed at an emergency department doctor. For this model, I removed the NIHSS and OCSP variables, and used the individual components of the neurological examination (see **Table 10.6**). I removed 'known cognitive impairment' as I assumed this might not always be possible to collect immediately by a junior doctor.

Model aimed at nursing staff or paramedics. For this model, I simplified the variables even further, so that only a few key items need be collected (see **Table 10.7**). I added in the variable of 'abnormal verbal output' as this did not require the

operator to discrimination between aphasia and dysarthria, merely to decide whether verbal output was completely normal.

Description of clinical features

The patients for this model have been described in detail in **Chapter 7**. The frequencies of the variables used for the analyses are detailed in **Tables 10.5 – 10.7**.

10.4.2 Generation of the models

Model aimed at a stroke or neurology registrar

This was the most complex model. It included several composite variables that accounted for a vast amount of the physical examination: abnormal vascular findings included measurement of blood pressure and pulse, auscultation of the heart and palpation for peripheral pulses, and abnormal signs in other systems included an assessment of the respiratory, abdominal locomotor and skin systems. The NIHSS score summarises the neurological examination, and the ability to sub-classify the patient's signs into one of four OCSP categories requires skill and knowledge.

Eight factors were demonstrated to independently predict the diagnosis (see **Table 10.8**). A definite history of focal neurological symptoms, an exact onset of symptoms, and *absence* of cognitive impairment (NB the odds ratio was less than one, which predicted a mimic if cognitive impairment was present) predicted a stroke. Abnormal vascular findings, *absence* of abnormalities in other systems and increasing NIHSS score (particularly greater than 10) on examination predicted a diagnosis of stroke. In the diagnostic formulation a stroke was favoured when an

OCSP classification was possible and the signs could be lateralised to one side of the brain.

Model aimed at an emergency department doctor

The simpler model aimed at doctors with little additional training in stroke medicine consisted of five factors, all of which suggested a diagnosis of stroke (see **Table 10.9**). In the history, a definite history of focal neurological symptoms, and an exact onset were independently predictive. Arm weakness, abnormal vascular findings and the ability to determine the side of the brain that was affected predicted a stroke. Neither aphasia nor abnormal verbal output was independently predictive.

Model aimed at nursing staff or paramedics.

The simplest model, designed for nurses or paramedics, contained four items (see **Table 10.10**). A diagnosis of stroke was predicted if there was a definite history of focal neurological symptoms, an exact onset could be determined, there was demonstrable arm weakness and verbal output was abnormal.

10.4.3 Evaluation of the models

Once generated, the key questions were how well did the models perform, and was there any penalty for simplicity? The logistic regression program in SPSS generated statistics that provide an overall assessment of performance. These have been provided for the three models in **Table 10.11**. The Hosmer and Lemeshow test is a goodness-of-fit test that the model adequately fits the data. When the significance is low (<0.05), the model does not fit the data. The model summary attempts to provide a measure of the proportion of variation that is explained by the

model (equivalent to the r-square statistic in linear regression). The smaller the deviance, and the greater the pseudo r-square values, the better the fit.

All models adequately fitted the dataset (Hosmer and Lemeshow test significance >0.05). As the models became simpler there was a reduction in goodness-of-fit and accuracy. The stroke registrar model had a pseudo r-square of 0.51 and correctly classified 83% of cases, whilst the nurse/paramedic model had a pseudo r-square of 0.39 and classified 79% of cases correctly.

Calibration

The calibration curves for the three models are provided in **Figure 10.1**. These show that the predictive models were well calibrated, with the point estimates close to the diagonal line, and the 95% confidence intervals overlapping the line.

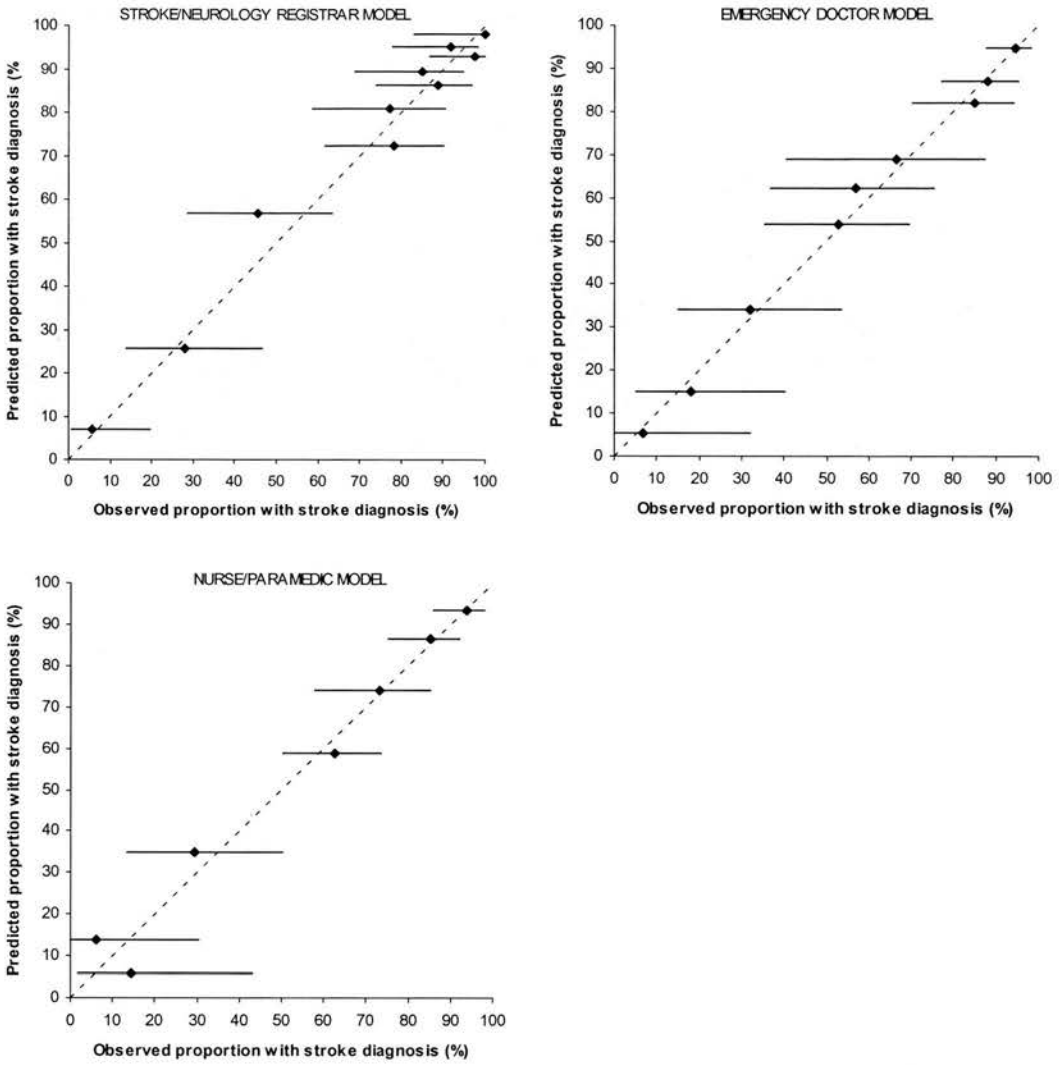


Figure 10.1 Calibration curves for the three models

Upper left – stroke/neurology registrar model; upper right – emergency doctor model; lower left – nurse/paramedic model. The dotted 45° line represents perfect calibration

Discrimination

The ROC curves for the three models are provided in **Figures 10.2**. The stroke/neurology registrar model had the greatest area under the curve (AUC 0.87, 95% CI 0.83 – 0.91), suggesting that it predicted much better than chance. Both the emergency department doctor model (AUC 0.85, 95%CI 0.80 – 0.90) and the nurse/paramedic model (AUC 0.82, 95% CI 0.77 – 0.87) also predicted better than

chance, although not as well as well as the more complex stroke registrar model (statistical tests for the difference in area under the ROC curves were unavailable).

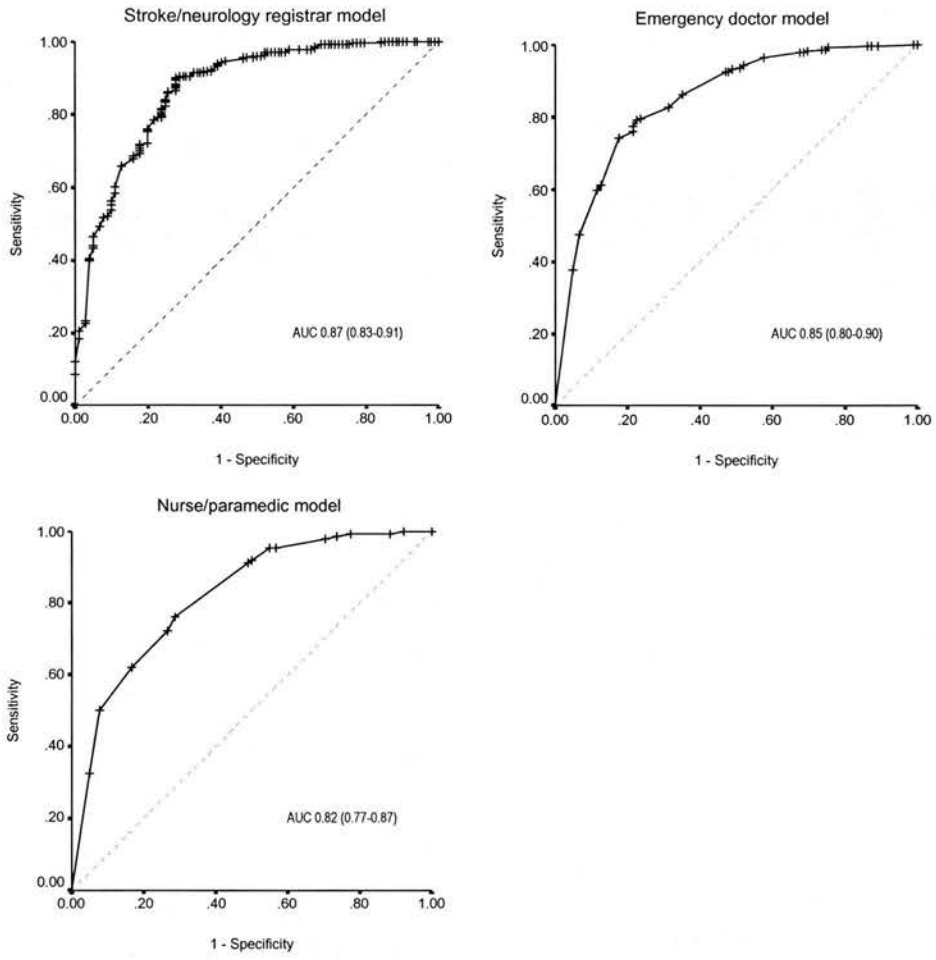


Figure 10.2 ROC curves for the three models

Upper left – stroke/neurology registrar model; upper right – emergency doctor model; lower left – nurse/paramedic model. The dotted line marks area under the curve of 0.5 (no discrimination). AUC: area under the curve (with 95% confidence intervals)

10.4.4 Could the models be used clinically?

The apparent usefulness of a model depends on more factors than its goodness of fit, calibration and discrimination. An important factor is how often the model can predict that an outcome is either very likely or very unlikely (i.e. the majority of its probabilities lie closer to one or zero, rather than around the middle) (Weir *et al.*, 2001). As can be seen in **Table 10.12**, over ¾ of the predictions of the

stroke registrar model were in the very likely/unlikely range. 90% of those who had a stroke had predicted probabilities greater than 0.75. The nurse or paramedic model proved less helpful, with 43% of predictions between 0.25 and 0.75.

Each model's performance according to defined criteria

Model aimed at the stroke or neurology registrar

I envisaged that the stroke or neurology registrar might be the last clinician separating the patient from a needle containing thrombolysis. The utmost importance is that treatment is given to patients likely to benefit, and withheld from mimics. I previously argued that a positive predictive value (PPV) of 95% would be necessary for a model in this situation.

To achieve a PPV of 95%, the model aimed at a stroke or neurology registrar selected patients with a probability of stroke of 0.90 or more. 106/336 patients were identified as being strokes, of which 101 were actually strokes and 5 were mimics. The sensitivity was 43%, but specificity was 95%, and the likelihood ratio (LR) for the model using this cut-off was 8.8 (95% CI 3.7 – 21.0).

Model aimed at the emergency department doctor

The emergency department doctor is unlikely to be expert in the nuances of the neurological examination, so the model needed to be simpler. The costs of an incorrect diagnosis are less, but it would still be important to be accurate. I arbitrarily defined a PPV of 85% as desirable.

To achieve this PPV, the model designed for the emergency physician selected patients with a probability of stroke of 0.62 or more. This identified 238/336 patients as strokes, of which 202 were actually strokes and 36 were mimics.

In this scenario, the model's sensitivity was 86% and specificity was 65%. The LR at a cut-off of 0.62 was 2.5 (95% CI 1.9 – 3.2).

Could this simpler model work as well for the stroke or neurology registrar? Using a probability cut-off of greater than 0.90 to achieve a 95% PPV, the simpler model identified 93/336 patients as strokes, of which 88 were strokes and 5 were mimics. The LR was 7.7 (95% CI 3.2 – 18.3), sensitivity 38%, and specificity 95%.

Model aimed at the emergency nurse or paramedic

Here the nurse or paramedic should identify as many strokes as possible. Using a cut-off of greater than 0.10 probability identified 232/234 strokes, but also 90/102 mimics. A cut-off of 0.30 identified 229 strokes and 72 mimics, and a higher cut-off of 0.4 identified 223 strokes and 58 mimics. One could argue about the ideal cut-off, but if one chose a probability of 0.30, the model had a sensitivity of 98%, specificity of 29%, and PPV of 76%. The LR was only 1.4 (95% CI 1.2 – 1.6).

At the other end of the spectrum, imposing a cut-off for this model of greater than 0.90 identified 81 patients, 76 strokes and 5 mimics. This very simple model of 4 variables achieved a LR of 6.6 (95% CI 2.8 – 15.9), a PPV of 94%, sensitivity 33% and specificity of 95%.

Comparison of model's predictive ability versus clinician's assessment

A comparison of the model's performance with clinical judgement was obtained by plotting the sensitivity and 1-specificity for each clinician (this provides a 'snap-shot' of accuracy) on the respective ROC curve. There were insufficient data to allow a comparison of nursing staff or paramedics to the model designed for this setting. The results for general practitioners (sensitivity 95%, specificity 15%) and

acute receiving unit doctors (sensitivity 88%, specificity 49%) were plotted on the ROC curve for the model designed for use by emergency department doctors with little additional training (**Figure 10.3**). In both cases, the model performed better than clinical judgement (the point for each clinician was closer to 0.5).

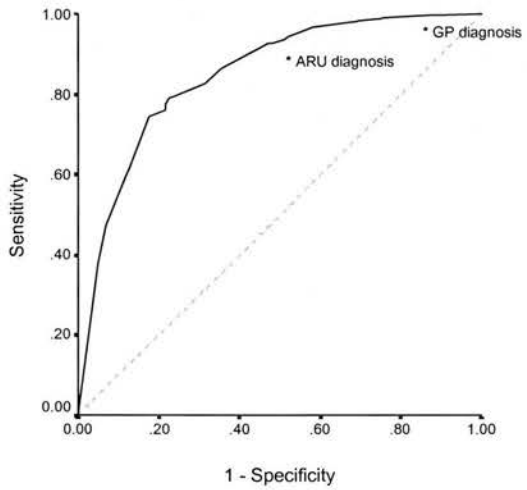


Figure 10.3 Accuracy of general practitioner and acute receiving unit doctor compared with the model designed for use by an emergency department doctor
When the points are to the right of the curve, the model is more accurate

I compared the stroke research fellow's end-of-bed assessment and final clinical diagnosis against the model designed for use by a stroke or neurology registrar (**Figure 10.4**). The model performed better than the end-of-bed assessment (sensitivity 90%, specificity 43%), but not as well as the final clinical diagnosis (made after a detailed history and examination, sensitivity 86%, specificity 83%). The accuracy after the research fellow had taken a history (sensitivity 93%, specificity 52%) also plotted to the right of the ROC curve for the model (not pictured).

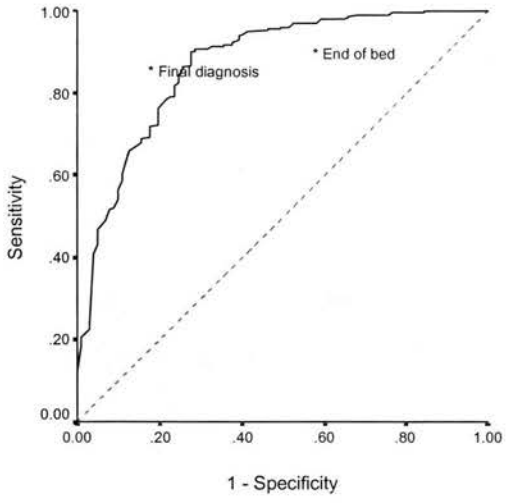


Figure 10.4 Accuracy of research fellow's end-of-bed assessment and final clinical diagnosis compared with the model designed for use by a stroke or neurology registrar
When the points are to the right of the curve, the model is more accurate

10.5 Discussion

10.5.1 Strengths of the present study

The study followed rigorous methodological criteria to ensure quality (Peduzzi *et al.*, 1996; Harrell, Jr. *et al.*, 1996; Braitman & Davidoff, 1996; Laupacis *et al.*, 1997). The patient sample was well defined, the entry criteria were simple and clinically relevant, and there were no restrictions. The data were collected prospectively. Sample size was adequate to allow 10 variables to be entered into each model without risking overfitting; variable selection was driven by clinical common sense (in particular choosing variables with demonstrated good reliability). Finally, the models were evaluated using several different robust methods.

Three models of varying complexity were produced, intended for three different clinical scenarios. Accuracy was demonstrated for all models, and they performed adequately in their intended clinical situation. The simplest model, aimed

at nurses or paramedics, consisted of four variables, yet performed almost as well as the more complicated models. The model designed for the emergency physician, with limited in-depth knowledge of stroke medicine or neurology, contained just five variables. This model was shown to be more accurate than clinical judgement by ARU senior house officers.

The model designed for the stroke or neurology registrar contained eight variables. Two of these variables required a reasonable degree of diagnostic skill, but not in excess of skills expected of trainees in stroke medicine (personal communication Dr M Dennis). As anticipated, this complex model was the most accurate overall. It was reassuring to see that the variables included in each model showed a logical hierarchy – with each more complex model adding to the variables of the earlier model.

This study was unique. To my knowledge, only three multivariable models of the acute diagnosis of stroke have been reported (Allen, 1983a; Libman *et al.*, 1995b; Mielke & Hennerici, 2001). None were adequate. One study was only available in abstract form (Mielke & Hennerici, 2001). The multivariable model reported by Allen (1983a) used discriminant function analysis to identify independently predictive factors that could separate haemorrhage from infarct. Libman and colleagues (1995b) entered 12 variables into a logistic regression model (there were 78 mimics in this study) and identified decreased level of consciousness as independently predictive of a mimic, and a history of angina as predictive of a stroke. In the present study, vascular risk factors were not significant on univariate analysis, and reduced consciousness was not significantly associated with diagnosis

in the multivariable models (probably because other markers of severity were more powerful predictors).

It is surprising that there has been little interest in the clinical diagnosis of stroke. In contrast, there have been many studies that have attempted to determine prognosis after stroke (Counsell & Dennis, 2001). A consistent finding is that the prediction of outcome is largely affected by factors that reflect initial stroke severity – implying that late survival and functional improvement may only be achieved by reducing the initial severity of stroke (Ebrahim & Harwood, 1999b). Thrombolysis is the most promising treatment available to reduce the initial severity of ischaemic stroke (Wardlaw *et al.*, 2001a). Simple bedside clinical tools to aid the diagnosis could improve accuracy, confidence and speed of the initial assessment, thus increasing the number of patients who might receive thrombolysis.

10.5.2 Limitations

Limitations of models in general

Prognostic models are frequently published but rarely used to inform clinical decisions (Wyatt & Altman, 1995). Although logistic regression is widely available (and easy to perform), researchers need to understand the methodology behind the statistical technique to ensure good quality, clinically useful models are produced (Concato *et al.*, 1993; Wyatt & Altman, 1995; Laupacis *et al.*, 1997; Counsell & Dennis, 2001; Bagley *et al.*, 2001). A recent systematic review of prognostic models for acute stroke (Counsell & Dennis, 2001) documented poor quality in most of the identified studies. None of 83 models met all quality criteria. Small sample sizes were a particular problem (only 28/83 studies met or exceeded the 10 EPV rule).

Cut-offs for variables were often chosen to fit the data, rather than make clinical sense [e.g. a recent prognostic model used DWI lesion volume of 14.1ml as the key cut-off (Baird *et al.*, 2001)]. Yet models can be useful if they are methodologically sound, clinically credible and simple to perform (Wyatt & Altman, 1995; Ebrahim & Harwood, 1999c).

An alternate method of analysis that could have been used instead of logistic regression is recursive partitioning analysis (Cook & Goldman, 1984). This technique builds a tree in which the patient populations are split into smaller and smaller categories based on response to each variable [and was recently used to create the 'Canadian CT head rule for patients with minor head injury' (Stiell *et al.*, 2001)]. It has appeal because of its similarity with the way clinicians make decisions (Cook & Goldman, 1984; Marshall, 2001). However it has been criticised as an extreme form of 'data dredging' in which the model fits perfectly with the training dataset but lacks any generalisability and clinical sense (Marshall, 2001) [additionally, it requires complex software and expertise that were unavailable to me].

Limitations of this study

There are limitations of this study. I entered 11 variables, one more than was recommended, because I was unable to sensibly eliminate a further variable. The sample size was relatively small, so it is possible that the models may have missed important associations due to lack of power. The patient sample was probably older and milder than other reported hospital cohorts (although our sample may be more realistic than other highly selected series). It could be argued that the simplification of the final diagnosis from seven into two binary categories was arbitrary, but I

attempted to keep the classification clinically relevant (and the simplification occurred before any analyses were performed). Internal validation of the models is notoriously unreliable; even though the models were all highly accurate, this does not imply that the models can be generalised to other cohorts of patients (Braitman & Davidoff, 1996) (and suggests that they may be overfitted to the dataset).

The recommended method to avoid these problems is to validate predictive models on an unrelated, external dataset (Harrell, Jr. *et al.*, 1996; Laupacis *et al.*, 1997; Justice *et al.*, 1999). I considered doing this using three independent datasets that were available to me (the Lothian Stroke Register, the International Stroke Trial, and the Oxfordshire Community Stroke Project). Unfortunately, all were unsuitable, as they contained almost no details of patients with mimics. As the inception point for most observational studies and stroke registers is when stroke is diagnosed, I suspect that future external validation of my models will require a specific, prospective study. Until then, the models I have generated cannot be considered ready for clinical use (Sackett *et al.*, 1985d; Laupacis *et al.*, 1997).

10.5.3 Implications of the study

Clinical guidelines

Using multivariable statistical techniques, I have demonstrated that there are several clinical factors that independently predict the likely diagnosis of patients presenting with brain attack. Some items carry greater weight than others, and some predict that a mimic is more likely than a stroke. I have summarised these factors into a clinical guideline for the diagnosis of brain attack (**Table 10.13**).

Guidelines such as these, which have been rigorously developed, provide an 'evidence base' for the clinical methods that a senior stroke physician uses in the assessment of the patient with brain attack. It is clear that a good proportion of patients (in many cases the majority) present to hospital promptly; however, few receive promising treatments such as thrombolysis within the narrow therapeutic time window. The delay that a patient experiences is often waiting for clinical assessment and brain imaging. Our focus must now turn to methods of accelerating the patient's passage from the emergency department door to the acute stroke unit, via the CT or MRI scanner.

Education and training of junior staff

The first clinicians that a patient with brain attack is likely to encounter in hospital are nurses and junior doctors. Patients with acute neurological conditions can be daunting for an inexperienced clinician. It may be difficult for a junior doctor to arrange an urgent brain scan or consultation with a senior doctor when he/she is lacking in confidence. With better knowledge of the key features that reliably distinguish stroke from mimic, a junior doctor's assessment can be brief but more focussed and assured.

The results of the present study have important implications for senior doctors in how they train junior staff. The key items of the history have been highlighted. The important components of the physical examination should be tailored to the needs of the junior doctor. I believe that both the NIHSS and OCSP classification are of great benefit in the assessment of patients with brain attack, and should be taught to trainees in stroke or neurology.

Further work is necessary

Whilst the logistic regression analysis has identified independent variables that predict the diagnosis, there is still much work required before the models could be put to clinical use. It would not be worthwhile attempting to create a clinical tool without first validating the existing model on an external dataset. Assuming this, it is clear that a predictive model must be simple to be attractive to clinicians (who dislike complex, mathematical prediction rules that require a calculator (Ebrahim & Harwood, 1999c), or having to carefully measure the volume of a lesion seen on brain imaging). The clinical tool could be developed as a simple checklist, with a tick or cross to be entered against each variable, and a minimum number of ticks to diagnose stroke. For example, the nurse/paramedic model might require two or three questions to be ticked to satisfy criteria for a diagnosis of stroke.

An alternative would be to take advantage of the relative weightings of each variable (its coefficient in the logistic regression model) to construct a simple score. Extending the above example, the coefficients for arm weakness and focal neurological symptoms are around two, the coefficient for an exact time of onset is near one, and for the sake of simplicity, the coefficient for abnormal verbal output could be rounded up to one. Thus, there are a total of six points possible, and a diagnosis of stroke might require four or more points. Obviously the complexity of such a system would increase with more variables in the model, and mathematical calculations would be required to determine the appropriate number of points/questions to use as a cut-off for the tool. Whether it would ever be used – or just quickly forgotten (Wyatt & Altman, 1995) – is another matter.

10.6 Summary

- I have used rigorous methods to develop a clinically sensible predictive model to differentiate stroke from mimic at the bedside
- Three items of history, three items of examination, and two items of diagnostic formulation are the key clinical factors that can aid bedside diagnosis
- I have developed several models, ranging from very simple to complex. These appear to have good accuracy, and could potentially be of benefit to less experienced junior staff (and their patients). The simple items could easily be taught to junior staff. Including all the complex items of examination and assessment does not greatly increase accuracy, which is acceptable for most situations
- Clinical algorithms may improve junior doctors' confidence and hence accelerate the patient's progress through emergency department to the acute stroke unit (via the scanner)

Recommendations for further research:

- External validation of these models is required before they can be used in practice or developed further
- More studies are required on the reliability of the clinical assessment (particularly those factors not examined in our reliability study, and using nurses or paramedics)

Table 10.1 Minimum methodological requirements for studies using predictive models

• An inception cohort was assembled with patients identified at a uniform point, and adequately described
• The referral pattern was adequately described
• The outcome event was clearly defined, clinically important, and assessed blind to any predictions of outcome made by the model
• Predictive variables were clinically sensible and collected prospectively
• The statistical technique used to determine which predictive variables were independent was clearly stated
• Appropriate measures, in particular sufficient events per variable, were taken to avoid overfitting of the model to the dataset.
• The model was validated (internally and externally)

Adapted from (Sackett et al., 1985d; Concato et al., 1993; Wyatt & Altman, 1995; Harrell, Jr. et al., 1996; Braitman & Davidoff, 1996; Laupacis et al., 1997)

Table 10.2 Variables excluded from brain attack training dataset

Variable	Reason (number where appropriate)
1. Primary referral source	Uncertain relevance
2. Who made the referral	Uncertain relevance
3. The referring diagnosis	Uncertain relevance
4. GP diagnosis	Uncertain relevance
5. Diagnosis before assessment	Not appropriate
6. Diagnosis after history	Not appropriate
7. Diagnosis after examination	Not appropriate
8. Primary source of history	Uncertain relevance
9. Secondary source of history	Uncertain relevance
10. Had previous focal deficit resolved before symptoms onset?	Too much missing data (205)
11. Nature of previous deficit	Too many alternatives make data analysis difficult
12. Patient woke from sleep with deficit	Too much missing data (94)
13. Patient can recall what he/she was doing at time of onset	Poor reliability
14. Symptoms were stable at assessment	Uncertain relevance
15. Evolution to maximal deficit	Too much missing data (105)
16. Are the symptoms getting worse?	Poor reliability
17. Was patient well in last week	Poor reliability
18. Symptom side	Uncertain relevance
19. Other symptoms	Text field only
20. Lost consciousness	Too much missing data (20) with a low event rate (50)
21. Vomited	Too much missing data (15) with a low event rate (43)
22. Headache	Too much missing data (35)
23. Seizure	Too much missing data (16) with a low event rate (26)
24. Pulse	Uncertain relevance
25. Diastolic BP	Poor reliability – may not be as reliable as Systolic BP
26. Temperature	Uncertain relevance
27. Oxygen saturation	Not always available at the bedside
28. Cervical bruits	Uncertain relevance

Variable	Reason (number where appropriate)
29. Cardiac failure	Too few events (16)
30. Co-morbid condition	Uncertain relevance (Field was intended to explore difficulties in making diagnosis)
31. Glasgow coma score	May be unreliable in presence of aphasia/dysarthria
32. Presence of confusion	Poor reliability
33. Visual inattention	Too much missing data (25) with a low event rate (42)
34. Eye deviation	Too few events (24)
35. Nystagmus	Too few events (23)
36. 3rd, 4th. 6th cranial nerve palsies	Too few events (10)
37. Hand weakness	Too much missing data (30)
38. Dysarthria	Poor reliability
39. Cerebellar signs	Poor reliability
40. Reflex asymmetry	Poor reliability
41. Plantar response	Moderate or poor reliability
42. Any important tests available	Not appropriate
43. Did the patient fulfil FAST criteria?	Not appropriate
44. No lateralisable signs	Too few events (26), and some redundancy

Table 10.3 Composite variables

Composite variable	Components
• Inconsistencies	Inconsistency in time of onset, evolution of symptoms, presence or absence of major symptoms
• One of migraine, epilepsy, malignancy or psychological disturbance	Low frequency of individual items
• One or more vascular risk factor	Hypertension, smoking (past or present), ischaemic heart disease, diabetes, atrial fibrillation, peripheral vascular disease (intermittent claudication/prior surgery)
• Brainstem symptoms	Visual loss, diplopia, vertigo, loss of balance, other brainstem symptoms
• Motor symptoms	Loss of power or function of the face, arm, hand or leg
• Sensory symptoms	Loss of feeling or altered sensation of the face, arm, hand, or leg
• Abnormal vascular findings	Systolic blood pressure > 150 mmHg, clinical atrial fibrillation, valvular heart disease or absent peripheral pulses
• One or more abnormalities in other systems	Abnormal signs of the respiratory, abdominal or other (e.g., skin) systems
• Neurological signs	Sign recorded for each side was reduced to presence or absence of appropriate sign (e.g., from left hemianopia and normal right visual field to 'hemianopia')
• Aphasia	Used NIHSS question 11
• Face weakness	Used NIHSS question 4
• Neglect	Used NIHSS question 13

Table 10.4 Capabilities of the different clinicians who diagnose stroke

Clinical variable	Stroke / neurology registrar	Emergency department doctor	Emergency nurse / paramedic
History items			
1. Known cognitive impairment	✓	X	X
2. Exact time of onset could be determined	✓	✓	✓
3. Definite history of focal neurological symptoms	✓	✓	✓
4. Motor symptoms	✓	✓	✓
Examination items			
5. One or more abnormal vascular findings	✓	✓	X
6. One or more abnormalities in other systems	✓	X	X
7. Normal level of consciousness	✓	✓	✓
8. No neurological signs	✓	✓	X
9. Aphasia	✓	✓	X
10. Abnormal verbal output	✓	✓	✓
11. Arm weakness	✓	✓	✓
12. Leg weakness	✓	✓	✓
13. NIHSS	✓	X	X
Diagnostic formulation			
14. Signs lateralise to left or right side of brain	✓	✓	X
15. Neurological deficits consistent with symptoms	✓	?	X
16. An OCSP classification was possible	✓	X	X

Table 10.5 Variables included in the stroke/neurology registrar dataset, and characteristics of the patients

Clinical variable	Stroke	(%)	Mimic	(%)	Total	(%)
History items						
1. Known cognitive impairment	27	*(12)*	27	*(27)*	54	*(16)*
2. Exact time of onset could be determined	179	*(77)*	57	*(56)*	236	*(70)*
3. Definite history of focal neurological symptoms	227	*(97)*	69	*(68)*	296	*(88)*
4. Motor symptoms	177	*(76)*	42	*(41)*	219	*(65)*
Examination items						
5. One or more abnormal vascular findings	188	*(80)*	71	*(70)*	258	*(77)*
6. One or more abnormalities in other systems	71	*(30)*	48	*(47)*	119	*(35)*
7. Normal level of consciousness	167	*(71)*	73	*(72)*	240	*(71)*
8. NIHSS category:						
0	18	*(78)*	29	*(28)*	47	*(14)*
1-4	87	*(37)*	40	*(39)*	127	*(38)*
5-10	59	*(25)*	17	*(17)*	76	*(23)*
>10	70	*(30)*	16	*(16)*	86	*(26)*
Diagnostic formulation						
9. Signs lateralise to left or right side of brain	196	*(84)*	39	*(38)*	235	*(70)*
10. Neurological deficits consistent with symptoms	202	*(86)*	61	*(60)*	263	*(78)*
An OCSP classification could be made	212	*(91)*	45	*(44)*	257	*(77)*

Table 10.6 Variables included in the emergency department doctor dataset, and characteristics of the patients

Clinical variable	Stroke	(%)	Mimic	(%)	Total	(%)
History items						
1. Exact time of onset could be determined	179	*(77)*	57	*(56)*	236	*(70)*
2. Definite history of focal neurological symptoms	227	*(97)*	69	*(68)*	296	*(88)*
3. Motor symptoms	177	*(76)*	42	*(41)*	219	*(65)*
Examination items						
4. One or more abnormal vascular findings	188	*(80)*	71	*(70)*	258	*(77)*
5. Normal level of consciousness	167	*(71)*	73	*(72)*	240	*(71)*
6. No neurological signs	12	*(5)*	33	*(32)*	45	*(13)*
7. Aphasia	88	*(38)*	33	*(32)*	121	*(36)*
8. Arm weakness	158	*(68)*	25	*(25)*	183	*(55)*
9. Leg weakness	125	*(53)*	25	*(25)*	150	*(45)*
Diagnostic formulation						
10. Signs lateralise to left or right side of brain	196	*(84)*	39	*(38)*	235	*(70)*
11. Neurological deficits consistent with symptoms	202	*(86)*	61	*(60)*	263	*(78)*

Table 10.7 Variables included in the nurse or paramedic dataset, and characteristics of the patients

Clinical variable	Stroke	(%)	Mimic	(%)	Total	(%)
History items						
1. Exact time of onset could be determined	179	*(77)*	57	*(56)*	236	*(70)*
2. Definite history of focal neurological symptoms	227	*(97)*	69	*(68)*	296	*(88)*
3. Motor symptoms	177	*(76)*	42	*(41)*	219	*(65)*
Examination items						
4. Normal level of consciousness	167	*(71)*	73	*(72)*	240	*(71)*
5. Abnormal verbal output	143	*(61)*	41	*(40)*	121	*(36)*
6. Arm weakness	158	*(68)*	25	*(25)*	183	*(55)*
7. Leg weakness	125	*(53)*	25	*(25)*	150	*(45)*

Table 10.8 Logistic regression model for stroke/neurology registrars to predict the diagnosis of brain attack

Variable	Coefficient	Odds Ratio	95% C.I.	
			Lower	*Upper*
1. Constant	-3.324	0.036		
2. Known cognitive impairment	-1.118	0.327	*0.140*	*0.763*
3. An exact onset could be determined	0.952	2.590	*1.303*	*5.151*
4. Definite history of focal neurological **symptoms**	1.975	7.207	*2.482*	*20.927*
5. Any abnormal vascular findings*	0.934	2.544	*1.277*	*5.068*
6. Abnormal findings in any other system†	-0.824	0.439	*0.227*	*0.847*
7. NIHSS = 0‡				
NIHSS 1-4	0.651	1.917	*0.702*	*5.230*
NIHSS 5-10	1.145	3.144	*1.025*	*9.645*
NIHSS >10	1.979	7.233	*2.176*	*24.047*
8. The signs could be lateralised to the left or right side of the brain	0.707	2.027	*0.921*	*4.462*
9. OCSP classification was possible	1.627	5.090	*2.421*	*10.701*

The model gives a predicted probability of stroke (ranging from 0 – 1. The mathematical equation uses the coefficient for each variable plus the constant to calculate the probability.
** systolic blood pressure > 150 mmHg, atrial fibrillation, valvular heart disease, and/or absent peripheral pulses*
† respiratory, abdominal or other abnormal signs
‡NIHSS=0 was entered as the reference group (therefore it does not have a coefficient)

Table 10.9 Logistic regression model for emergency department doctors to predict the diagnosis of brain attack

Variable	Coefficient	Odds Ratio	95% C.I.	
			Lower	*Upper*
1. Constant	-3.830	0.022		
2. An exact onset could be determined	1.006	2.736	*1.466*	*5.105*
3. Definite history of focal neurological symptoms	2.179	8.838	*3.310*	*23.596*
4. Any abnormal vascular findings*	0.984	2.676	*1.390*	*5.151*
5. Arm weakness	1.384	3.989	*2.104*	*7.564*
6. The signs could be lateralised to the left or right side of the brain	1.159	3.187	*1.680*	*6.044*

The model gives a predicted probability of stroke (ranging from 0 – 1. The mathematical equation uses the coefficient for each variable plus the constant to calculate the probability.
** systolic blood pressure > 150 mmHg, atrial fibrillation, valvular heart disease, and/or absent peripheral pulses*

Table 10.10 Logistic regression model for nurses or paramedics to predict the diagnosis of brain attack

Variable	Coefficient	Odds Ratio	95% C.I.	
			Lower	*Upper*
1. Constant	-3.080	0.062		
2. An exact onset could be determined	1.047	2.670	*1.475*	*4.832*
3. Definite history of focal neurological **symptoms**	2.483	11.471	*4.540*	*28.986*
4. Abnormal verbal output	0.595	1.814	*1.006*	*3.269*
5. Arm weakness	1.637	6.066	*3.387*	*10.863*

The model gives a predicted probability of stroke (ranging from 0 – 1. The mathematical equation uses the coefficient for each variable plus the constant to calculate the probability.

Table 10.11 Overall performance and goodness-of-fit of the three models

	Hosmer and Lemeshow test			Model summary		
Model	**χ^2**	**df**	**Significance**	**Deviance***	**Pseudo r-square†**	**% correct classifications**
Stroke registrar	5.12	8	.746	262.5	.509	83.3
Emergency doctor	2.14	6	.907	287.2	.440	80.7
Paramedic/nurse	2.72	5	.743	304.4	.389	79.2

** estimated by –2 log-likelihood (smaller numbers are better)*
† estimated by the Nagelkerke R square statistic (ranges from 0 to 1)

Table 10.12 Predictions in the very likely (or unlikely) range

	Predicted probabilities (number of patients)					
Model	**Below 0.25***	*(%)*	**Above 0.75†**	*(%)*	**Total**	*(%)*
Stroke registrar	51	*(15.2)*	210	*(62.5)*	261	*(77.7)*
Emergency doctor	37	*(11.0)*	192	*(57.1)*	229	*(68.2)*
Nurse/paramedic	30	*(8.9)*	162	*(48.2)*	192	*(57.1)*

**there were 102 mimics in total*
† there were 234 strokes in total

Table 10.13 Proposed clinical guidelines for the diagnosis of brain attack

Clinical Item	**Importance***	**Suggests the likely diagnosis is:**
History		
• Definite history of focal neurological symptoms	★★	*STROKE*
• An exact onset of symptoms can be determined	★	*STROKE*
• Known cognitive impairment	★	*MIMIC*
Examination		
• Any abnormal vascular findings	★	*STROKE*
• Any abnormal findings in other systems	★	*MIMIC*
• *Either*		
NIHSS 1-4	★	*STROKE*
NIHSS 5-10	★	*STROKE*
NIHSS >10	★★	*STROKE*
• *Or*		
Arm weakness	★★	*STROKE*
Diagnostic formulation		
• Signs can be lateralised to the right/left brain	★	*STROKE*
• Signs can be placed in an OCSP category	★★	*STROKE*

** number of stars indicate relative importance of each item*

SECTION III

CAN IMAGING IMPROVE THE DIAGNOSIS AND MANAGEMENT OF BRAIN ATTACK?

Chapter 11 : The impact of routine brain imaging in patients with brain attack

11.1 Introduction

This chapter explores the results of routine brain imaging in the series of patients with brain attack, whose clinical features have been described in **Section II** of this thesis. Here I will integrate the clinical features, imaging findings and the final diagnosis. The emphasis is on imaging that was performed as part of routine clinical care ('advanced' magnetic resonance imaging will be considered in later chapters). Where relevant, brief case histories and scans will be provided to illustrate some of the difficulties in diagnosis.

11.2 Aims

(1) To describe the results of routine brain imaging in patients with brain attack

(2) To assess the influence of routine imaging on the final diagnosis, and in particular, if imaging helped to resolve clinical uncertainties

(3) To define the limitations of routine brain imaging

(4) To determine the sensitivity and specificity of routine brain imaging for the detection of an acute stroke lesion

11.3 Methods

11.3.1 Definition of 'routine brain imaging'

'Routine brain imaging' refers to that which was performed as part of normal clinical care of the patient with brain attack. For most, this was an unenhanced computed tomogram (CT) of the brain. Some patients had magnetic resonance imaging of the brain (with or without CT). A routine MR brain scan consisted of structural imaging only (diffusion-weighted and perfusion imaging were not performed).

The Western General Hospital has an additional MR scan devoted to research. During the latter part of the present study, some patients underwent advanced MR imaging in the research scanner – with or without CT – as part of an imaging study (to be presented in later chapters). I have used the results of the structural imaging in patients who only had MR, and just the CT results in patients who had both CT and MR, in the present study.

'Routine' also implied that the timing of the scan was unaffected by any research requirements. For most patients, the research fellow provided written advice to the referring team, but the decision to act on this advice, and the urgency of any action, was left to the referring team. However, the research fellow could arrange urgent scanning for patients that were assessed in the acute receiving unit (ARU) at the time of admission if clinically indicated.

11.3.2 Patients

Consecutive patients who presented to the Western General Hospital with 'brain attack' (*apparently focal brain dysfunction of apparently abrupt onset*) were recruited. The clinician made a **bedside** diagnosis (which in almost all cases was made blind to the imaging results) of non-stroke or definite, probable or possible stroke. No definitions for the distinction between definite, probable, and possible were provided. Full details of the methodology of the brain attack study are provided in **Chapter 7**.

11.3.3 Scan interpretation

All brain scans received a routine formal report from one of four consultant neuroradiologists. The scans were retrieved for later review at the expert panel meetings (see **Figure 11.1**). The study neuroradiologist (Professor J.M.Wardlaw) has a sub-specialty interest in the imaging of stroke, and given that she was often aware of additional clinical information, and could therefore give a more informed interpretation of the scan, her opinion prevailed if there was a clash with the official report. When JMW was absent from the meeting, the clinicians still inspected the scans, but the routine formal report was considered final.

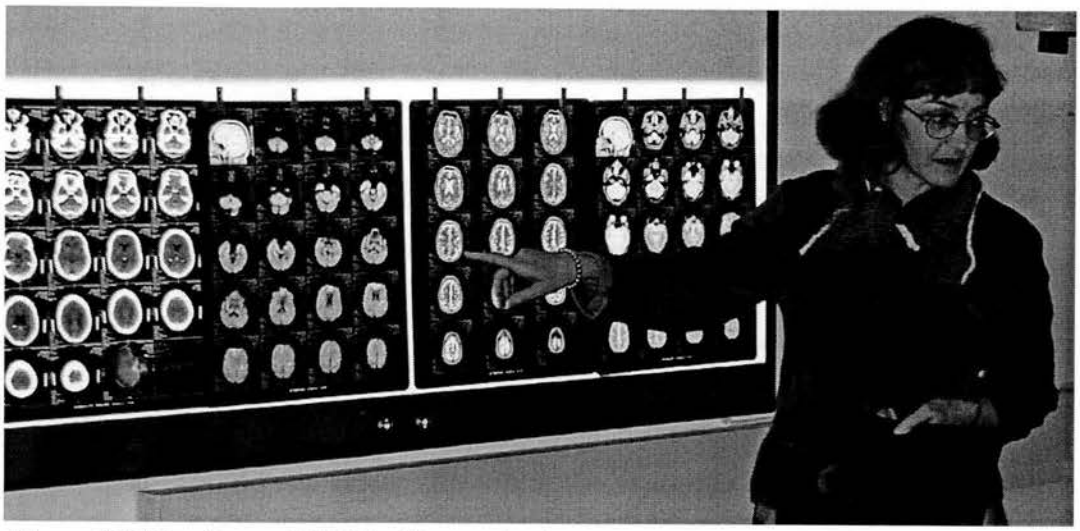


Figure 11.1 Professor J.M. Wardlaw reviewing scans at an expert panel meeting

At the expert panel meetings, scan findings were recorded on a data form (see **Appendix 4**), and were summarised into one of four categories, then recorded on the final diagnosis data sheet (see **Appendix 5**). Scans were categorised as (i) a relevant acute stroke lesion – which could be infarct or haemorrhage, (ii) no relevant lesion – the scan could be normal, or show irrelevant abnormalities such as periventricular lucencies or atrophy, (iii) old stroke pathology, or (iv) a relevant non-stroke lesion. Signs of infarction on CT brain imaging were established infarcts, defined as a wedge-shaped or rounded hypodensity within recognised vascular territory, or early ischaemic changes, defined as a loss of tissue density and/or swelling. The abnormality had to be appropriate to the symptoms to be classed as relevant. If several lesions were present, the lesion that explained the patient's presentation took precedence (i.e. if there were both old stroke lesions and an acute infarct, the scan was classed as showing acute stroke pathology).

Infarcts were further classified according to the anatomical site of the lesion (but not the size). Haemorrhages were classified according to likely aetiology based on location and appearance of the lesion.

11.3.4 Final diagnosis

The **final consensus** diagnosis was made by a panel of experts, as described in **Chapter 7.3** (see also **Figure 7.1**). The expert panel met after the patient had been discharged. The panel's final consensus diagnosis was based on an independent review of all available clinical and investigational data. Patients were classed as definite stroke, probable stroke, possible stroke, definite transient ischaemic attack (TIA), possible TIA or definite non-stroke (as before, see **Chapter 7.3**). A relevant stroke lesion on brain imaging was not required for a definite stroke diagnosis.

11.3.5 Statistics

The imaging results were described in patients with brain attack. Patients were further divided into groups based on the brain scan result, and clinical features were compared. I used the OCSP classification and NIHSS score as descriptors of the severity of the stroke syndrome.

The value of the brain scan to resolve bedside uncertainty was assessed, by comparing the certainty of the final consensus diagnosis – made in knowledge of the brain imaging results – with the initial bedside diagnosis. Patients were divided into bedside diagnosis of definite, probable, possible stroke and non-stroke. The final consensus diagnosis was simplified by incorporating definite TIA with definite stroke, and possible TIA with possible stroke.

Accuracy parameters for the detection of a stroke lesion by brain imaging were determined against the final consensus diagnosis (which was dichotomised to 'thrombolysis-eligible stroke' or mimic, using the same definitions as earlier chapters). I calculated point estimates (with 95% confidence intervals) for the sensitivity, specificity, positive predictive value and likelihood ratio, and compared these with the research fellow's bedside diagnosis. Differences in observed proportions were calculated (and statistical significance assumed if the 95% confidence intervals for the difference did not cross zero).

As the data were not Normally distributed, non-parametric tests were used to assess for significant relationships (χ^2 or Fisher's exact tests for categorical data, Mann-Whitney U test for continuous data).

Statistical packages

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997), Confidence Interval Analysis (version 2.0.0, ©Trevor Bryant 2000) and SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999).

11.4 Results

11.4.1 General characteristics

350 patient-episodes of brain attack were recruited into the study. 299 (85%) episodes received a brain scan as part of routine clinical care. The 51 patient-episodes that were not scanned shall be discussed separately (see below).

The nature of the brain scan

275/299 (92%) patients had a CT, and 24/299 (8%) had a MR brain scan. 33 patients received both CT and MR, and 23 patients received a second CT scan (as part of routine care), but only the results from the first CT scan will be reported in the present study. Contrast was given for the CT brain scan on 21 occasions, but it provided no additional diagnostic information.

Scan reports

The study neuroradiologist (JMW) was present at the meeting and provided a 'dynamic' opinion (i.e. she received a more informed clinical history, and the clinicians could ask questions) for 150/299 (50.2%) scans.

Timing of the scan

The time from presentation to scanning is shown in **Figure 11.2**. 107/299 (35.8%) patient-episodes were scanned on the same day as admission, and 238/299 (79.6%) were scanned within the first 48 hours of admission. Of the 24 patients whose brain imaging was MRI, 17 (70.8%) were scanned on the same day as presentation (reflecting their participation in a research study). Precise details of who arranged the scan, and whether it was performed urgently, were unavailable. During the study period, 99 patients were seen within three hours of presentation to ARU (though not all would have been scanned urgently).

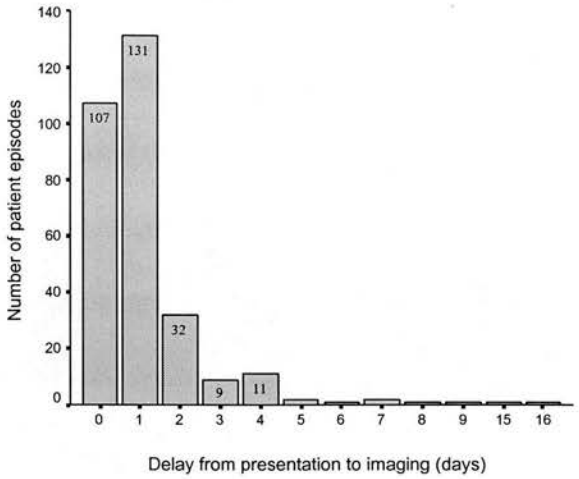


Figure 11.2 Delay from presentation to brain imaging in the brain attack study *(n=299 episodes)*

Clinical features of patients who were scanned

The general features of the 287 patients (299 patient-episodes) who were scanned are detailed in **Table 11.1**. The median age was 76 years, and the median time from symptom onset to presentation was five hours (although most were not seen by the research team until a day later). The final diagnosis was a definite or probable vascular event in 76% of events.

The specific clinical features of patients are provided in **Table 11.2**. A definite history of focal neurological symptoms was present in 91%, motor symptoms in 66% and normal conscious level in 71%. The median NIHSS was 5.0, 19% had a total anterior circulation syndrome, and 17% could not be assigned an OCSP classification. Almost 60% of patients who received a brain scan had a past history of a focal neurological deficit. Of these 105 patients, symptoms had completely resolved in 60 (57%, with details unknown for a further eight patients).

11.4.2 The patients who were not scanned

49 patients – 51 (15%) patient-episodes of brain attack – did not receive a brain scan during the hospital admission. Two patients had diagnostic imaging of the spine (rather than the brain).

Clinical features of patients not scanned

Patients not scanned were older than those scanned (median age 80 years vs. 76 years, p=0.01, Mann-Whitney U, see **Table 11.1**). **Table 11.2** shows that patients not scanned in hospital were more likely to have cognitive impairment (29% vs 14% in those scanned, $p<0.01$, χ^2), less likely to have speech problems (28% vs 49% in those scanned, $p<0.01$, χ^2), and had a lower NIHSS score (median 2.0 vs 5.0 in those scanned, p=0.01, Mann-Whitney U). In addition, 61% of those who were not scanned could not be assigned an OCSP classification, compared with 17% of those who were scanned ($p<0.01$, χ^2).

55% of patients not scanned received a final diagnosis of definite non-stroke. 14 patients (27%) were diagnosed as possible stroke, there were three (6%) definite TIAs and two (4%) probable strokes. Four patients (8%) were diagnosed as definite stroke but did not receive a scan, as follows:

- PH018, an 86 year old, developed profound right-sided weakness at 6am. On examination at 8.30am, the patient was deeply unconscious with fixed and dilated pupils (NIHSS 37). He died at 12.10pm that day.
- PH107 presented in a similar but less dramatic fashion. On examination two hours after symptom onset she was drowsy, had a right hemiplegia (with head and eye deviation to the left), and NIHSS 30. The patient died later that day.

- PH096 was aged 98 and previously dependent on family for basic care. She presented with aphasia and right hemiparesis, NIHSS 26, and was not expected to live (but did, and was later transferred to a nursing home).
- PH030 presented with left-sided weakness and poor co-ordination. On examination he had an ataxic hemiparesis pattern of lacunar deficit (NIHSS 3). Symptoms rapidly resolved (within three days).

Causes of stroke mimic

There were 109 mimics recruited into the brain attack study. 67/109 (61.5%) received a brain scan, and 42 (39.5%) were not scanned. The causes of stroke mimic, subdivided by whether the patient had a brain scan, are provided in **Figure 11.3**. Some conditions did not require a brain scan: 100% of patients with a cord lesion; 90% of those with syncope, and 75% of those with dementia were not scanned in the present study. Conversely, all of those with space occupying lesions and functional disorders, 86% of those with vestibular disorders, and even 2/3 of those with migraine or mononeuropathy were scanned. In the absence of brain imaging, the final consensus diagnosis of a stroke mimic was determined by the clinical features, ancillary investigations (such as urine microscopy and culture) and progress in hospital.

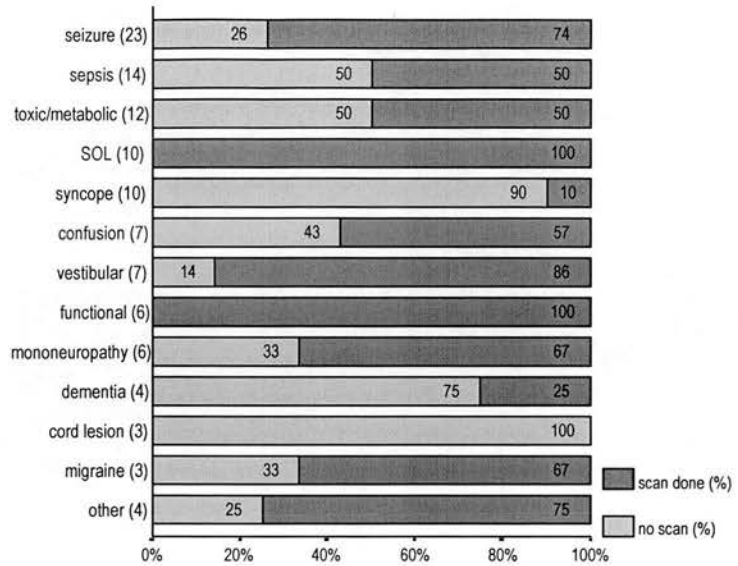


Figure 11.3 Causes of stroke mimics (n=109), subdivided by whether the patient was scanned

Stroke mimicking condition listed in order of frequency (number of episodes in parentheses). Light grey bar represents the proportion without a brain scan, dark grey bar represents the proportion with a brain scan (number in each bar is the percentage).

11.4.3 Scan results in patients with brain attack

A brain scan was performed in 299 patient-episodes. The scan showed a relevant acute stroke lesion in 127/299 (42.5%), a non-stroke lesion in 11/299 (3.7%), previous stroke pathology in 56/299 (18.7%), and no relevant pathology in 105 (35.1%) patient-episodes (see **Figure 11.4**).

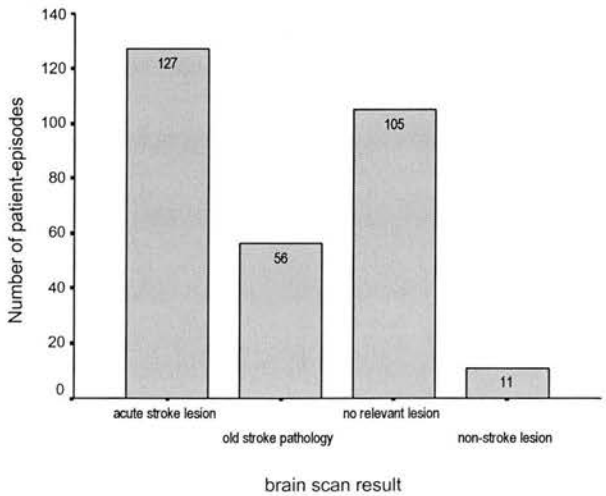


Figure 11.4 Results of routine brain scans in the brain attack study (n=299)

A key factor in the interpretation of the scan may be the time after symptom onset that brain imaging was performed. I have plotted histograms of the approximate time from onset of symptoms to scanning (measured in days, as I did not have the exact time of scanning available), subdivided by scan result, in **Figure 11.5**. Overall, 97/299 scans were performed within 24 hours of symptom onset (230/299 patients were admitted within 24 hours of onset). For scans that showed: an acute stroke lesion, the median time from symptom onset to imaging was 1.1 days (interquartile range [IQR] 0.2-2.0 days); no relevant pathology, 1.2 days (IQR 0.5-2.2 days); old stroke pathology, 1.3 days (IQR 0.5-3.5 days), and non-stroke lesion (n=11), median time was 1.8 days (IQR 1.2-5.6 days).

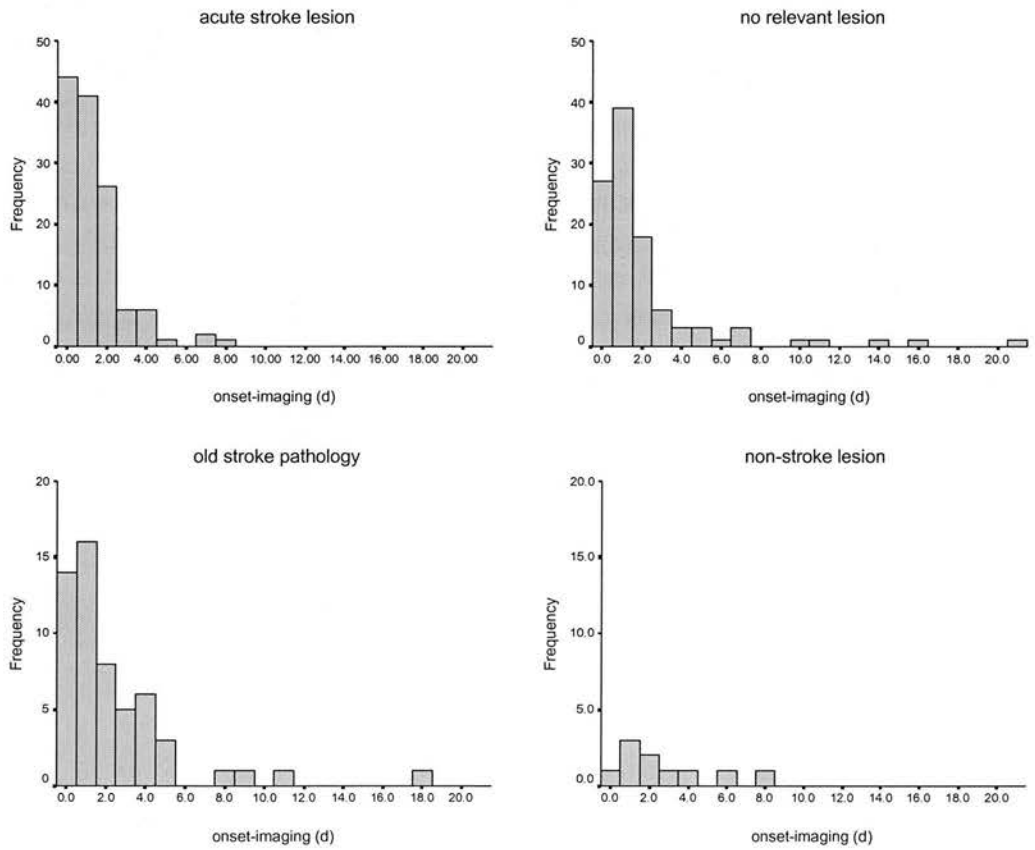


Figure 11.5 Histograms of approximate time from onset of symptoms to scanning, subdivided by scan result

In the following four sections I shall discuss the findings of the brain scans, grouping patients by their scan result (acute stroke lesion, no relevant pathology, old stroke pathology, non-stroke lesion). The clinical features of the patients, and their final consensus diagnosis will be presented, to provide a clear description of the nature of the brain imaging results in patients with brain attack.

Acute stroke lesion

An acute stroke lesion was seen in 127 patients who received a brain scan. **Table 11.3** shows that patients who had a relevant stroke lesion on CT had greater stroke severity (measured by NIHSS and OCSP) than patients with other scan findings. Only 5 patients had an NIHSS of zero, indicating no or very mild deficit (e.g. a 'cortical hand'). A large proportion (37%) of patients with an acute stroke lesion was scanned within 24 hours of onset of symptoms.

Infarcts

The scan showed an acute infarct in 108/127 (85%) of patients. Of the 42 patients with an infarct who were scanned within 24 hours of symptom onset, early ischaemic changes were seen in 25 (60%) of these patients. Early ischaemic changes were seen in two of 35 patients scanned 24-48 hours after onset, and in none of the 31 patients scanned after 48 hours from symptom onset.

The likelihood of seeing an infarct depended on stroke severity. **Figure 11.6** shows that 41% of those with an infarct had an NIHSS score greater than 10. Similarly, those classed as TACS made up 35% of patients with an infarct (**Figure 11.7**). Of all patient-episodes that were scanned (n=299), a relevant stroke lesion was observed in 57/81 (70%) of those with NIHSS > 10 (13 of 57 were bleeds), and

47/57 (83%) of those classed as TACS (9 of 47 were bleeds). At the other end of the severity spectrum, a relevant stroke lesion was observed in 7/34 (21%) of those with NIHSS = 0, and 23/57 (40%) of those classed as LACS (see **Tables 11.4 & 11.5**).

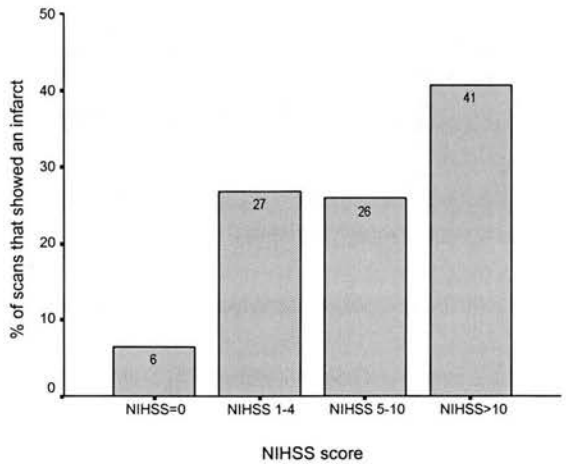


Figure 11.6 Higher NIHSS scores were associated with a greater proportion of infarcts seen on brain imaging

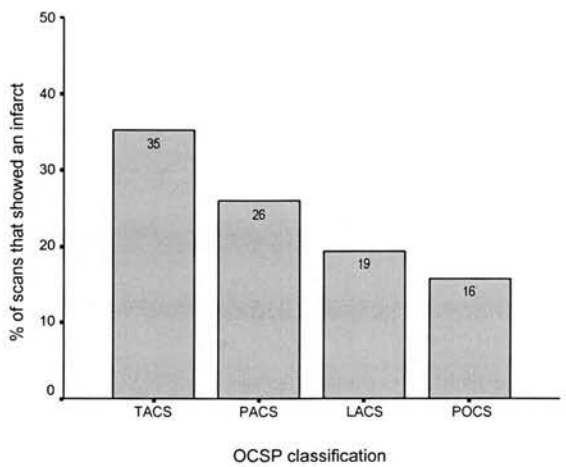


Figure 11.7 The OCSP classification also influenced the likelihood of seeing an infarct on brain imaging

The OCSP classification and the ***site*** *of the infarct*

Details of the site of the infarct were tabulated against the research fellow's clinical classification for the 108 patients with a relevant ischaemic lesion on imaging (see **Table 11.6**). The site of the infarct was divided into broad anatomical

territories (middle [MCA], anterior [ACA] and posterior [PCA] cerebral artery territory, borderzone, striatocapsular, lacunar and brain stem location). Overall, the clinical classification matched the infarct location in 88/108 (81%) patients. 33/38 (87%) patients classed as a TACS had an MCA infarct, and one patient had a striatocapsular infarct; 18/21 (86%) classed as a LACS had a lacunar infarct; 23/28 (82%) patients classed as PACS had MCA, ACA, borderzone or striatocapsular infarcts, and 13/17 (76%) patients classed as POCS had either a brainstem or PCA infarct. PCA infarcts caused difficulty in clinical classification (only 7/15 correctly classified as POCS); and striatocapsular infarcts produced a variety of clinical syndromes – 3/5 were PACS, with one TACS and one LACS.

Haemorrhages

The scan revealed haemorrhage in 19 patients (15%). Compared to patients with infarcts (108, 85%), those with bleeds were more likely to have reduced level of consciousness (63.2% vs 35.2%) or a total anterior circulation syndrome (47.4% vs 35.2%, $p<0.05$ for both, χ^2). There was a non-significant trend for patients with haemorrhage to present to hospital earlier (median 3.0 hours vs 4.2 hours), and have a higher NIHSS (median 12 vs 7 for patients with an infarct). Scan features indicated that the likely underlying mechanism for the haemorrhage was amyloid angiopathy in 12 patients, and hypertension in 6 (in the remaining patient, it was unclear whether the bleeding was into an infarct or a primary intracerebral haemorrhage).

The final consensus diagnosis in patients with an acute stroke lesion

122/127 (96.0%) patients with an acute stroke lesion received a final diagnosis of stroke. There were five patients whose CT scan showed a relevant infarct, yet the final consensus diagnosis was not stroke, as follows:

- PH113 presented at 0.63 hours after symptom onset. When assessed by the research fellow (at 7 hours), the signs suggested a TACS (NIHSS 11), but symptoms fully resolved by 24 hours, thus the final diagnosis was TIA.
- PH165 presented at 3.5 hours with speech loss and right arm weakness, but when examined several days later symptoms had resolved. CT showed a left middle cerebral artery territory infarct. Final diagnosis was TIA.
- PH129 presented at 8.25 hours with left sided face, arm and leg motor and sensory disturbance, but symptoms resolved fully – final diagnosis was TIA.
- PH184 presented with aphasia and right arm and leg weakness (exact onset unclear), but fully resolved within a day of admission, thus diagnosed as TIA.
- PH234, a 66 year old man, was found lying on the floor in the late afternoon. He was last seen by his wife four hours earlier (and had been drinking alcohol with friends in the intervening time). On arrival at ARU, he was drowsy and smelt of alcohol. There was dysphasia and a moderate right hemiparesis. He was fast-tracked to scanning as a potential candidate for thrombolysis, but whilst under observation his

deficit improved, and by the following morning he had returned to normal. The bedside diagnosis was alcohol intoxication, but the CT showed clear early ischaemic changes in the left middle cerebral artery territory (**figure 11.8**). Thus the final consensus diagnosis was possible TIA.

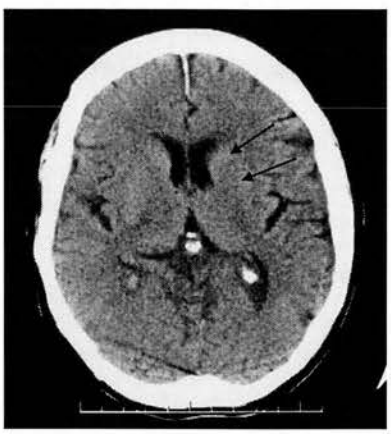


Figure 11.8 A patient with early ischaemic changes on CT suggesting an infarct, but a final clinical diagnosis of possible TIA

CT brain performed 5 hours 22 minutes after symptom onset demonstrates early ischaemic changes with loss of grey-white definition around the basal ganglia (arrows).

No relevant lesion

There was no relevant lesion seen on the brain scan in 105 patients (35%). Patients without a relevant brain scan lesion had milder stroke severity than patients with a brain scan lesion (see **Table 11.3**). Median NIHSS was three, and 20 patients (19%) had NIHSS = 0 (when compared with all other scan categories, the difference in NIHSS score was significant, $p<0.01$, Mann-Whitney U).

Scan findings

The scan was completely normal in 54/105 (51.4%). In the remainder, there were abnormalities such as atrophy (34 scans, 32.4%), periventricular lucencies (21

scans, 20%) or an unrelated lesion (5 scans, 4.8%). The unrelated lesions included developmental cysts, basal ganglia calcification, basilar artery ectasia, and a pituitary tumour. The majority of patients had CT brain scans (n=275), but a few had MR scans (n=24). The imaging modality had no influence on the frequency of normal scans, although numbers were small (35.2% for CT, 33.3% for MR, p=0.85, χ^2).

The final consensus diagnosis in those with 'normal' scans

The consensus panel's final diagnosis was non-stroke for 20 patient-episodes (including six patients with seizure, three with sepsis, three with functional symptoms, two with Bell's palsy, and one each with confusion, hepatic encephalopathy, syncope, migraine, subarachnoid haemorrhage [diagnosed by angiogram] and transient global amnesia). The final diagnosis was stroke in 55/105 (52.4%) patients with no relevant lesion on brain imaging. Four patients were classified as TACS yet had normal scans, as follows:

- PH058, a 47 year man, presented at 45 minutes with aphasia, mild right sided weakness and right hemianopia. When seen at 1.3 hours, NIHSS was eight (low for a TACS). The CT was performed urgently, and was normal. Symptoms resolved completely within 24 hours, and the final diagnosis was definite TIA.
- PH198, a 99 year old woman, presented at 3.6 hours and was examined at 4.5 hours. There was a dense left hemiparesis, neglect and reduced consciousness (NIHSS 11). CT at 6 hours was normal (as was the MR, see **Figure 13.10**). Despite this, the final diagnosis was definite stroke.

- PH285 presented at 5.25 hours with a moderate left hemiparesis, neglect and visual loss (NIHSS was eight when seen at 5.5 hours). CT on the same day was normal. The final diagnosis was definite stroke.
- PH337 presented at 7.25 hours with weakness of the left arm, dowsiness and confusion. She was not examined until the following day, when there was a left hemianopia, moderate hemiparesis and neglect (NIHSS 11). A CT brain on the day of presentation was normal, as was a repeat scan several days later – when symptoms were still present (see **Figure 11.9**). The final diagnosis in this patient was probable stroke.

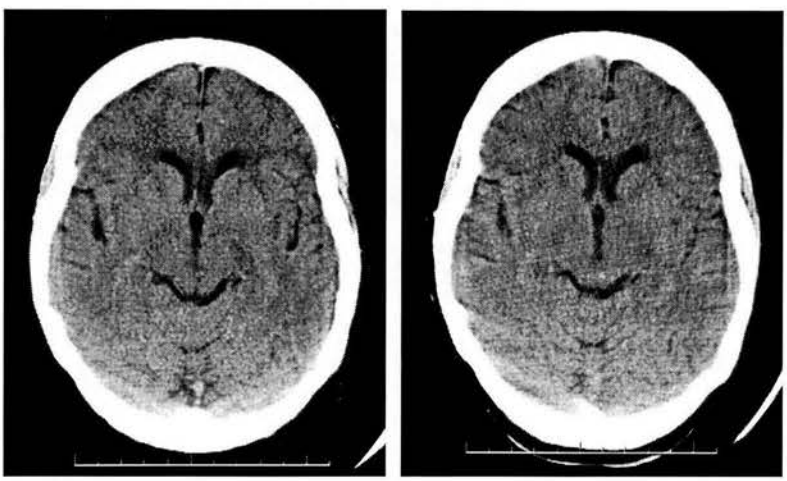


Figure 11.9 A patient with a total anterior circulation syndrome (TACS) with two normal CT scans

On the left is the normal CT brain that was performed on same day as symptom onset, and on the right is the repeat CT brain 12 weeks later (still normal)

Old stroke pathology

56 scans (18.7%) showed evidence of old stroke pathology as the only abnormality. 39/56 (71%) gave a history of a focal neurological deficit in the past. The clinical features of these patients were similar to patients whose scans showed no relevant pathology (**Table 11.3**). Median NIHSS was four – lower than patients

with an acute stroke or non-stroke lesion. Only four patients (7%) were classed as TACS.

Old stroke pathology was also observed in those with a relevant stroke lesion. 22/108 (20%) patients with an infarct had old lesion, as did 4/19 (21%) patients with a haemorrhage (all four had bleeds thought to be typical of amyloid angiopathy).

The final consensus diagnosis in those with old stroke pathology

36/56 (64%) patients with old stroke pathology as the only abnormality received a final consensus diagnosis of stroke. 7/56 (12.5%) were diagnosed as non-stroke. Three had seizures, two sepsis, one had acute confusion, and one had hypoglycaemia; all presented with focal neurological signs, so presumably the old stroke signs were 'unmasked' by these conditions.

Non-stroke lesion

11 scans (3.7%) demonstrated a relevant non-stroke lesion that accounted for the patient's presentation. These patients' clinical features resembled those of patients who were found to have an acute stroke lesion: the median NIHSS was six, all had neurological signs, with a large proportion (91%) suggesting cortical involvement (TACS or PACS classification). No lacunar syndromes were observed.

The final consensus diagnosis in patients with a non-stroke lesion

10 patients received a final diagnosis of non-stroke, and one patient was given a final diagnosis of probable stroke, as follows:

- Nine patients had brain tumours – six were glioblastoma multiforme, two were metastases, and one was a meningioma
- One patient had a large subdural haematoma

- One patient received a final diagnosis of probable stroke. PH084, a 55 year old woman, presented with headache, left sided weakness and parasthesiae that had started the previous night. Over the last year, she had experienced similar symptoms (which had been called migrainous hemiplegia). On examination, there was a mild left hemiparesis and sensory loss, and clear cerebellar findings on the left (NIHSS 6, OCSP classification POCS). The MR brain scan (**Figure 11.10**) showed a solitary high signal lesion on T2 in the right pons (but no other signs of demyelination). Cerebrospinal fluid was normal, oligoclonal bands were not detected, and visual evoked responses were normal. The thrombophilia screen was negative, but antinuclear antibodies were positive (1 in 640 titre, anticentromere pattern). The diagnosis was difficult in this patient, but the consensus panel opinion was probable stroke as there was insufficient evidence to diagnose demyelination.

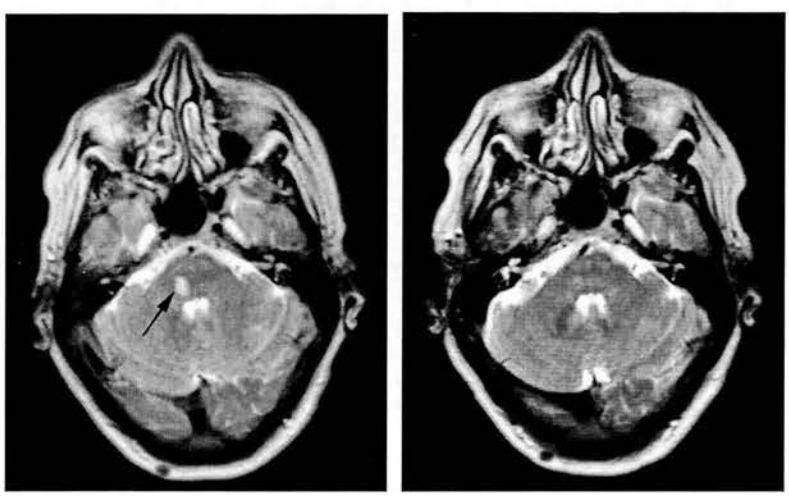


Figure 11.10 A patient with a solitary lesion in the pons on MR: what is the final diagnosis?

The T2 axial image through the pons (left) demonstrates a solitary high signal lesion (arrow), thought to be most consistent with demyelination. There were no other lesions. Scan 11 months later (right) shows almost complete disappearance of the lesion.

Overall, positive scans were seen in only 10/37 (27%) patients with a final consensus diagnosis of definite non-stroke.

11.4.4 The value of brain imaging to resolve bedside uncertainty

In this section, I will examine how brain imaging helped to resolve uncertainties in the bedside diagnosis of brain attack (in the 299 patient-episodes that had brain imaging). At the completion of the clinical assessment, the research fellow made a bedside diagnosis, which was blind to imaging results. The patient then had a brain scan, which showed either a relevant acute lesion (an infarct, haemorrhage or a non-stroke lesion) or no acute lesion (old stroke pathology, irrelevant pathology or completely normal scan). At a later time, an independent panel of experts recorded the final consensus diagnosis. Comparing the bedside diagnosis with the final consensus diagnosis provided an insight into the value of routine brain imaging.

Of the 299 patient-episodes that received a brain scan, the bedside diagnosis was definite stroke in 145 (48.5%), probable stroke in 71 (23.7%), possible stroke in 53 (17.7%) and non-stroke in 30 (10.0%). The relationship between bedside diagnosis and imaging findings is detailed in **Table 11.7**. The proportion of patients with any relevant lesion decreased as bedside certainty decreased (from 64% in those with a definite stroke to 19% of those with a possible stroke), and the proportion of patients with no relevant lesion increased (from 35% of patients with definite stroke to 81% patients with possible stroke). This trend was significant ($p<0.01$, χ^2 test for trend).

The final consensus diagnosis (grouped into four categories by combining TIA and stroke) has been tabulated against the clinical diagnosis in **Table 11.8**. Of

the 299 patient-episodes, the final consensus diagnosis was definite stroke in 196 (66%), probable stroke in 32 (11%), possible stroke in 34 (11%), and non-stroke in 37 (12%). Compared with the bedside diagnosis, it was therefore possible for the final consensus diagnosis to become more certain, remain the same, become less certain, or change completely (from stroke to non-stroke or vice versa). In the following sections, I shall describe the effect of the scan result on the certainty of the final consensus diagnosis, for each of the four bedside diagnostic categories.

I have divided the clinical diagnostic categories into whether a relevant lesion was seen (which may have been a stroke or non-stroke lesion), and determined the effect of the scan findings on the certainty of the final diagnosis in **Table 11.9**.

A bedside diagnosis of definite stroke

Table 11.9 shows that of the 145 patients thought to have a definite stroke after the bedside assessment, imaging influenced the final consensus diagnosis in nine patients (6%). In the other 136/145 (94%) patient-episodes, the certainty of the final diagnosis matched the bedside diagnosis. 45 patients had no lesion seen on imaging, but the final diagnosis remained definite stroke.

The impact of imaging on the final diagnosis was as follows:

- Two patients thought to have definite stroke after the bedside assessment had a malignant glioma on brain imaging, thus the diagnosis changed from definite stroke to non-stroke in two patients.
- The final diagnosis became less certain in six patients who had no relevant lesion on brain imaging
- The final diagnosis became less certain in one patient who had early ischaemic changes on CT (PH234, see **Figure 11.8**). This patient

improved rapidly over several hours, and was probably intoxicated. The finding of an abnormality on imaging reduced the panel's certainty that this event was a non-stroke.

A bedside diagnosis of probable stroke

Of the 71 patients with a bedside diagnosis of probable stroke, imaging influenced the final consensus diagnosis in 59/71 (83%). In 12/71 (17%) episodes, the final diagnosis matched the bedside diagnosis (see **Table 11.8 & 11.9**).

The impact of imaging for those with probable stroke after bedside assessment was as follows:

- Certainty increased in 46 patient-episodes. The scan showed a lesion in 24, but no lesion was seen in 22 patient-episodes.
- Certainty reduced in the nine patients with no relevant lesion seen on imaging.
- The diagnosis changed in four patients. Three had brain tumours seen on brain scan (glioma, metastases, and meningioma). One patient [PH282] had a normal scan. This patient presented with poor co-ordination on a background of flu-like symptoms, and had mild cerebellar signs on examination. He had prominent respiratory findings, and a chest x-ray was abnormal. The final diagnosis was chest infection.

A bedside diagnosis of possible stroke (the uncertain category)

Of the 53 patients with a bedside diagnosis of possible stroke, the least certain diagnosis, imaging influenced the final consensus diagnosis in 38/53 (72%)

of episodes. In 15/53 (28%), the final consensus diagnosis matched the bedside diagnosis (see **Table 11.8 & 11.9**). The impact of imaging was as follows:

- In 25 episodes the final diagnosis became more certain
- In 13 the final diagnosis changed from stroke to non-stroke
- When a lesion was seen on brain imaging, the final diagnosis always changed. However, absence of a lesion on imaging was less helpful, with 15 patients remaining in the same uncertain category.
- Overall, where the clinical diagnosis was uncertain, a lesion was seen on imaging in only 10/53 (19%) patients.

A bedside diagnosis of non-stroke

Of the 30 patients with a bedside diagnosis of non-stroke, imaging influenced the final consensus diagnosis in 12/30 (40%) of episodes. In 18/30 (60%), the final consensus diagnosis matched the bedside diagnosis (see **Table 11.8 & 11.9**). The impact of imaging was as follows:

- In two patients, the bedside diagnosis was changed to a definite stroke based on an abnormal scan. For example, PH076 presented with a subacute history of confusion, on a background of known dementia. The general practitioner thought he had visual inattention. On examination, the patient was drowsy, perseverated to commands, but there were no convincing focal signs. The clinical diagnosis was non-stroke, but the CT scan showed a left parietal haemorrhage (see **Figure 11.11**).
- In two patients, the bedside diagnosis was changed to a definite stroke based on clinical findings (the scan showed no acute lesion). For

example, PH260 presented following a seizure, and was found to have right-sided weakness and aphasia. There was a background of recurrent similar presentations following a left middle cerebral artery territory infarct one year earlier. The bedside diagnosis was seizure. Although the CT showed evidence of the old lesion, and no new pathology, the final diagnosis was definite stroke as her clinical course failed to improve.

- Three patients' final diagnosis was possible TIA, as the symptoms lasted less than 24 hours. Although the symptoms were non-specific, and the brain imaging was normal, there were no other investigation results to confirm the clinical diagnosis.
- Five patients with a bedside diagnosis of non-stroke were changed to a final diagnosis of possible stroke. Two of the presentations were with dizziness, one was seizure, one was drowsiness, and one was possibly functional. All eight patients had normal brain scans, but other investigations failed to confirm another cause for the presentation.

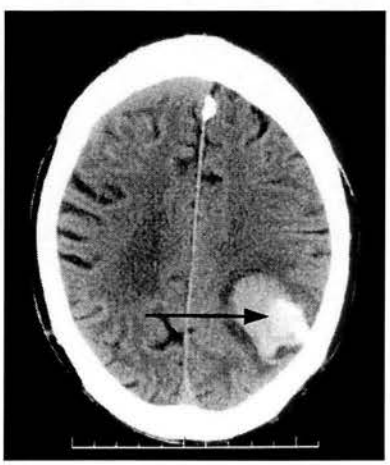


Figure 11.11 A patient with known dementia presented with an acute confusional state – the imaging changed the diagnosis

Arrow points to a subacute left parietal haematoma (probably secondary to cerebral amyloid angiopathy)

11.4.5 What is the accuracy of routine brain imaging?

The accuracy of brain imaging in this cohort of patients can be assessed by comparing imaging findings with the final consensus diagnosis. However, this has several major problems: the final diagnosis was based in part on the findings of the brain scan, and a normal brain scan may be seen in up to 50% of cerebral infarcts yet is still helpful (as it rules out haemorrhage). In the present study of 299 patient-episodes that were scanned, I dichotomised the scan findings to either a relevant stroke lesion or no relevant stroke lesion (which included a non-stroke lesion, old stroke pathology or normal scan). I dichotomised the diagnosis to 'thrombolysis-eligible' stroke (n=232) or mimic (n=67) to maintain consistency with earlier chapters.

Routine brain imaging showed a sensitivity of 54% (95% CI 48-61), specificity of 99% (95% CI 92-100) and likelihood ratio of 36 (95% CI 5-256) for the detection of a relevant stroke lesion (see **Table 11.10**). The accuracy (i.e. correctly showed a stroke lesion for stroke diagnoses, and no stroke lesion for mimics) was 64% (95% CI 59-69). Compared with the research fellow's bedside diagnosis, the specificity of imaging was significantly better (16% difference [95% CI 7-24]). However, sensitivity was significantly worse (31% difference [95% CI 23-39]), as was accuracy (20% difference [95% CI 14-27]).

11.5 Discussion

The diagnosis of brain attack can often be challenging, as highlighted by many of the clinical vignettes provided. Imaging identified a small proportion of non-strokes – only space occupying lesions (3% of the total), but these were equally distributed amongst the bedside definite strokes and less definite strokes. When present, a relevant lesion on imaging sealed the diagnosis of stroke (or changed the diagnosis completely) and was thus very useful.

The strengths of the present study are that it used an unselected cohort of patients, so that it reflected routine clinical management of patients with brain attack. This allowed a realistic assessment of the findings of imaging, and their impact on the diagnosis in this setting. Previous studies have often used highly selected patient samples to establish the value of imaging [such as excluding haemorrhage, e.g.(Al-Buhairi *et al.*, 1998), selecting middle cerebral artery infarcts, e.g. (Lev *et al.*, 1999) or thrombolysis recipients (Scott *et al.*, 1999)]. Even a study of 1,191 'unselected' patients referred for CT (Sotaniemi *et al.*, 1990) reported a mean age of 46 years for the patients scanned, suggesting considerable selection bias. The present study specifically recruited all patients with brain attack, including those with mimics and possible strokes, which has not been done in earlier studies.

Despite methodological difficulties in determining accuracy parameters, the present study found that routine scanning had a sensitivity of 54% for the detection of stroke lesions. This was very similar to other reports, such as 64% for Sotaniemi et al (1990), and 55% for Sandercock et al (1985a) (combining infarcts and haemorrhages). Other studies have demonstrated sensitivity for detection of ischaemic stroke ranging from 49% [in mild stroke and TIA (Koudstaal *et al.*, 1992)]

to 75% [for early ischaemic changes in thrombolysis recipients (Barber *et al.*, 2000)]. The present study was also able to calculate the specificity and likelihood ratio of imaging. Identification of a relevant stroke lesion helped to confirm that the clinical syndrome was a stroke; using Sackett et al's (1985b) nomogram for diagnostic tests, assuming a 70% pre-test probability of stroke, a positive CT scan increases the post-test probability to 99%.

11.5.1 Limitations of this study

Although this study aimed to reflect 'real life', there are some important caveats to our findings. Our cohort was older, and stroke severity milder, as we included all patients (including those with possible stroke, who tended to have milder symptoms). As the likelihood of observing a relevant lesion was related to severity, our findings may have underestimated the true value of scanning.

We are fortunate to have a friendly and efficient radiology service at our hospital, hence the proportion of scans performed within 48 hours [as per National Clinical Guidelines for Stroke (Intercollegiate Working Party for Stroke, 2002)] was higher than in other UK centres (Ebrahim & Redfern, 1999). Scan times may well have been influenced by the stroke research fellow's assessment.

All brain scans were interpreted by a neuroradiologist, and over half received a second opinion by a neuroradiologist with a special interest in stroke (who was not blind to the clinical details). The services of a neuroradiologist – let alone one with a particular expertise in the imaging of stroke – would not be available in many centres, and possibly provided us with an over-optimistic view of the value of scanning. For example, early ischaemic changes were identified in 24/41 patients

with infarcts who were scanned within 24 hours. A less expert radiologist may not have 'seen' these early changes, thus reducing the sensitivity of the early scan from 60% to 29%.

As noted earlier, it is difficult to determine the accuracy of brain imaging, as it plays a large part in determining the final diagnosis. To minimise this problem, I focussed on the value of imaging in resolving clinical or bedside uncertainty (rather than presenting the results of brain imaging for each final consensus diagnostic category). The accuracy figures presented, however, may be an overestimation due to the bias generated by using imaging to inform the gold standard diagnosis.

Finally, 51 patient-episodes of brain attack were not scanned. Usually this was for legitimate reasons – those with stroke died soon after admission, or symptoms resolved promptly; and brain imaging in many of those with a non-stroke condition would not have been helpful (e.g. spinal cord lesions, syncope). However, diagnostic certainty could have been improved if these patients were scanned.

11.5.2 Implications of the study

The role of clinical assessment

Brain imaging was very helpful when a lesion was present, but not so useful when no lesion was observed. In contrast, the stroke research fellow's bedside diagnosis achieved almost equivalent sensitivity and specificity, leading to better overall accuracy than brain imaging. It is a mistake to believe that better (and more) imaging would obviate the need for adequate training in clinical assessment.

Clinical certainty clearly influenced the likelihood of observing a relevant lesion on scan. When the clinician made a diagnosis of definite stroke, the scan was

four times more likely to show a relevant stroke lesion, and 1/3 as likely to show a non-stroke lesion than when the diagnosis was possible stroke. When the clinical diagnosis was certain, the final diagnosis rarely changed. However, when the clinician was unsure, imaging proved to be very helpful.

The OCSP classification and NIHSS severity score were both associated with scan findings. As the NIHSS increased (reflecting greater severity of signs), the scan was more likely to show a relevant stroke lesion. This is in agreement with others who have shown that NIHSS also correlates with the size of the infarct (Brott *et al.*, 1989b; Tomsick *et al.*, 1996; Johnston *et al.*, 2000). The OCSP classification was also associated with the presence of a relevant stroke lesion in all patients with brain attack. In addition, for those with infarcts, it was shown that the OCSP classification predicted the likely site of infarction. This finding is consistent with those of several larger studies (Al-Buhairi *et al.*, 1998; Mead *et al.*, 2000), which also demonstrated an association between lesion size and OCSP classification (not possible in the present study). Like Mead and colleagues (2000), we noted that the patient with a posterior cerebral artery or striatocapsular infarct posed particular difficulties for clinical classification.

There are limitations of routine imaging

This study has shown that imaging is extremely helpful, *when a lesion is present*. The problem was that quite often imaging did not show a lesion: 35% of patients with a final diagnosis of definite stroke, and 88% of those with probable stroke. When the bedside diagnosis was certain, absence of a lesion on imaging did not greatly affect the final diagnosis, but when the bedside diagnosis was uncertain –

precisely the time that imaging should help – no lesion was seen in 43/53 (81%) patients. Of these 43, the final diagnosis was definite or probable stroke in 15 (35%).

Bedside diagnosis was most difficult in patients with milder symptoms and signs. Although patients with milder severity have better prognosis (Bamford *et al.*, 1991; Adams, Jr. *et al.*, 1999), and are less likely to be considered for a risky treatment such as thrombolysis, a correct diagnosis is still very important. Issues such as driving, fitness for work or life insurance, and secondary prevention all depend on a correct diagnosis. Unfortunately, this limitation of the bedside diagnosis is also a weakness of routine imaging.

The usefulness of imaging is highly dependent on the skill of the radiologist. This was demonstrated in the present study by the high rate of early ischaemic changes noted in patients undergoing imaging within 24 hours of onset. Early ischaemic changes can be very difficult to detect (Hand & Wardlaw, 2001), and their reliability is poor (particularly when the image is viewed by a clinician or general radiologist) (Wardlaw *et al.*, 1999; Grotta *et al.*, 1999). As noted, most other stroke centres in the UK would be unlikely to have a neuroradiologist with expertise in stroke at its disposal. The results we have obtained probably represent the 'best-case scenario' for routine (CT) imaging.

How might advanced MR help?

Advanced MR imaging (i.e. diffusion- and perfusion-weighted imaging) could solve many of the problems of conventional scanning. As discussed in detail in **Chapter 6**, the advantages that MR appears to offer include:

- Positive identification of ischaemic lesions within minutes of symptom onset, with lesions appearing bright on diffusion-weighted imaging

- Better sensitivity for smaller lesions, and lesions in the posterior fossa
- The ability to discriminate new lesions from old, which is of particular benefit in patients with a past history of stroke who may present with a mimic such as seizure or metabolic disturbance that resembles a new ischaemic event
- Better reliability for lesion detection (thus less dependence on the skill of the operator)
- Better overall sensitivity thus greater use in predicting outcome and guiding management decisions in the acute phase

However, as discussed in **Chapter 6**, our knowledge of the usefulness of MR imaging is based on small studies of highly selected patients. Would advanced MR be of benefit in brain attack? The remainder of this thesis will explore the issue.

11.6 Summary

- Imaging is vitally important for the discrimination of haemorrhage from infarct in patients with stroke
- In patients with brain attack, routine imaging can identify a small number of stroke mimics (space-occupying lesions), but many patients with a mimic will have an essentially normal scan (and thus diagnosis depends on clinical skills)
- The likelihood of seeing a relevant abnormality on imaging is associated with the severity of clinical findings.
- Routine brain imaging is often normal, particularly in situations where the bedside diagnosis is uncertain, and where the clinical features are mild

- The operator dependence of CT imaging may have been underestimated

Recommendations for further research:

- Advanced MR imaging may solve many of the problems of CT imaging, and should be tested in an unselected brain attack cohort

Table 11.1 General features of patients in the brain attack study

Feature	Brain scan performed *n=299 episodes, n=287 patients*		No brain scan *n=51 episodes, n=49 patients*		*P**
Median age (IQR)†	75.92 yrs	(66.3-82.0)	80.30 yrs	(75.5-87.0)	*.014*
Male gender†	143	(49.8%)	20	(40.8%)	*.244*
Median time from onset to presentation (IQR):	5.0 hrs	(2.1-15.5)	3.75 hrs	(1.6-10.8)	*.686*
Number presenting within 6 hours:‡	158	(52.8%)	34	(66.7%)	*.067*
Median time from onset to examination (IQR):	25.5 hrs	(21.0-51.1)	26.0 hrs	(15.5-48.3)	*.195*
Final diagnosis of event:					*<.001*
Definite stroke	182	(60.9%)	4	(7.8%)	
Probable stroke	32	(10.7%)	2	(3.9%)	
Definite TIA	14	(4.7%)	3	(5.9%)	
Possible stroke/TIA	34	(11.4%)	14	(27.4%)	
Definite non-stroke	37	(12.4%)	28	(54.9%)	

* - *p value determined by Mann-Whitney U test or χ^2 test as appropriate*
† - *refers to the number of patients*
‡ - *incomplete numbers, as inpatient strokes were not included*

Table 11.2 Clinical features of patients in the brain attack study (subdivided by whether a brain scan was performed)

Feature	Brain scan performed *n=299 episodes, n=287 patients*		No brain scan *n=51 episodes, n=49 patients*		P*
History					
Past history of stroke†‡	105	(59.7%)	24	(42.6%)	*.092*
Cognitive impairment†‡	40	(14.4%)	14	(28.6%)	*.014*
Definite focal neurological deficit	271	(90.6%)	36	(70.6%)	*<.001*
Exact onset	213	(71.2%)	34	(66.7%)	*.508*
Motor symptoms	197	(65.9%)	28	(54.9%)	*.130*
Sensory symptoms	69	(23.1%)	9	(17.6%)	*.389*
Loss of speech	147	(49.2%)	14	(27.5%)	*.004*
Examination					
Normal conscious state	213	(71.2%)	36	(70.6%)	*.925*
Abnormalities in other systems	100	(33.4%)	22	(43.1%)	*.179*
Confusion‡	76	(35.5%)	16	(38.1%)	*.750*
Atrial fibrillation	65	(21.7%)	7	(13.7%)	*.191*
Median NIHSS (IQR)	5.0	(2.0-11.0)	2.0	(0.0-5.0)	*<.001*
Clinical classification:§					*<.001*
TACS	57	(19.1%)	3	(5.9%)	
PACS	93	(31.1%)	15	(29.4%)	
LACS	57	(19.1%)	2	(3.9%)	
POCS	42	(14.0%)	0	(0%)	
Unsure/No signs	50	(16.7%)	31	(60.8%)	

** - p value determined by Mann-Whitney U test or χ^2 test as appropriate*
† - refers to the number of patients
‡ - denominator incomplete as some items were unassessable
§ - OCSP clinical classification (Bamford et al., 1991). TACS: total anterior circulation syndrome, PACS: partial anterior circulation syndrome, LACS: lacunar syndrome, POCS: posterior circulation syndrome

Table 11.3 Features of patients, subdivided by scan result

	Acute stroke lesion	No relevant lesion	Old stroke pathology	Non-stroke lesion
Number	127	105	56	11
Number performed ≤ 24 hrs of onset	50 (39.4%)	31 (29.5%)	15 (26.8%)	1 (9.1%)
Median age of patients (IQR)	74.7 (66.4-85.2)	75.9 (62.3-81.3)	76.3 (70.7-82.6)	73.8 (67.1-77.0)
Median NIHSS (IQR):	8 (4-19)	3 (1-5.5)	4 (1-7.5)	6 (6-12)
NIHSS = 0	7 (5.5%)	20 (19.0%)	7 (12.5%)	0 (0%)
NIHSS 1-4	32 (25.2%)	50 (47.6%)	26 (46.4%)	1 (9.1%)
NIHSS 5-10	31 (24.4%)	21 (20.0%)	16 (28.6%)	7 (63.6%)
NIHSS >10	57 (44.9%)	14 (13.3%)	7 (12.5%)	3 (27.3%)
OCSP classification:				
TACS	47 (37.0%)	4 (3.8%)	4 (7.1%)	2 (18.2%)
PACS	32 (25.2%)	25 (23.8%)	29 (51.8%)	7 (63.6%)
LACS	23 (18.1%)	26 (24.8%)	8 (14.3%)	0 (0%)
POCS	17 (13.4%)	18 (17.1%)	6 (10.7%)	1 (9.1%)
Final diagnosis:				
Stroke (definite or probable)	122 (96.0%)	55 (52.4%)	36 (64.3%)	1 (9.1%)
TIA	4 (3.1%)	9 (8.6%)	1 (1.8%)	0 (0%)
Possible vascular event	1 (0.8%)	21 (20.0%)	12 (21.5%)	0 (0%)
Non-stroke	0 (0%)	20 (19.0%)	7 (12.5%)	10 (90.9%)

Table 11.4 Imaging findings in patients scanned, subdivided by NIHSS score (n=299)

		Imaging findings			
		Relevant lesion		No relevant lesion	
NIHSS group:	**n**	**Stroke lesion**	**Non-stroke lesion**	**Old stroke pathology**	**No relevant pathology**
NIHSS = 0	34	7 *(21%)*	0 *(0%)*	7 *(21%)*	20 *(59%)*
NIHSS 1-4	109	32 *(29%)*	1 *(0.9%)*	26 *(24%)*	50 *(46%)*
NIHSS 5-10	75	31 *(41%)*	7 *(9.3%)*	16 *(21.3%)*	21 *(28%)*
NIHSS >10	81	57 *(70%)*	3 *(3.7%)*	7 *(8.6%)*	14 *(17%)*

Note: $p<0.001$ for association between NIHSS and scan finding (Mann-Whitney U, using NIHSS as a continuous variable)

Table 11.5 Imaging findings in patients scanned, subdivided by OCSP classification (n=299)

		Imaging findings			
		Relevant lesion		No relevant lesion	
OCSP classification:	**n**	**Stroke lesion**	**Non-stroke lesion**	**Old stroke pathology**	**No relevant pathology**
TACS	57	47 *(83%)*	2 *(3.5%)*	4 *(7.0%)*	4 *(7.0%)*
PACS	93	32 *(34%)*	7 *(7.5%)*	29 *(31%)*	25 *(27%)*
LACS	57	23 *(40%)*	0 *(0%)*	8 *(14%)*	26 *(46%)*
POCS	42	17 *(41%)*	1 *(2.4%)*	6 *(14%)*	18 *(43%)*
Unsure	50	8 *(16%)*	1 *(2.0%)*	9 *(18%)*	32 *(64%)*

Note: $p<0.001$ for association between OCSP and scan finding (χ^2 test)

Table 11.6 Does the OCSP classification predict the site of the infarct? (n=108 patients with a relevant infarct)

	Clinical syndrome				
Infarcted territory	**TACS** (n=38)	**PACS** (n=28)	**LACS** (n=21)	**POCS** (n=17)	**Unsure** (n=4)
MCA territory	**33**	**16**	1	3	1
ACA territory		**1**			
PCA territory	3	4		**7**	1
Borderzone		**3**			
Striatocapsular	**1**	**3**	1		
Lacunar		1	**18**	1	
Brainstem	1		1	**6**	2

Numbers in bold indicate an appropriate clinical syndrome/infarct combination

Table 11.7 The bedside diagnosis of brain attack, and imaging findings for each category (n=299)

		Imaging findings			
		Relevant lesion		No relevant lesion	
Bedside diagnosis	**n**	**Stroke lesion**	**Non-stroke lesion**	**Old stroke pathology**	**No relevant pathology**
Definite stroke	145	92 *(63%)*	2 *(1.3%)*	13 *(9.0%)*	38 *(26%)*
Probable stroke	71	25 *(35%)*	3 *(4.2%)*	20 *(28%)*	24 *(34%)*
Possible stroke	53	8 *(15%)*	2 *(3.8%)*	14 *(26%)*	29 *(55%)*
Non-stroke	30	2 *(6.7%)*	4 *(1.3%)*	9 *(30%)*	15 *(50%)*

Table 11.8 The final consensus diagnosis versus the initial bedside diagnosis

	Final consensus diagnosis:				
Bedside diagnosis:	**Definite stroke/TIA**	**Probable stroke**	**Possible stroke/TIA**	**Non-stroke**	*Total*
Definite stroke	136	6	1	2	*145*
Probable stroke	46	12	9	4	*71*
Possible stroke	13	12	15	13	*53*
Non-stroke	2	2	8	18	*30*
Total	*196*	*32*	*34*	*37*	*299*

Table 11.9 How did the diagnosis change when there was a relevant lesion seen on imaging?(n=299)

		Final consensus diagnosis:			
Bedside diagnosis	**Lesion on imaging?**	**More certain**	**Remained same**	**Less certain**	**Changed category***
Definite stroke	*Yes (n=94)*	--	91 (97%)	1 (1%)	2 (2%)
(n=145)	*No (n=51)*	--	45 (88%)	6 (12%)	0 (0%)
Probable stroke	*Yes (n=28)*	24 (86%)	1 (4%)	0 (0%)	3 (11%)
(n=71)	*No (n=43)*	22 (51%)	11 (26%)	9 (21%)	1 (2%)
Possible stroke	*Yes (n=10)*	9 (90%)	0 (0%)	--	1 (10%)
(n=53)	*No (n=43)*	16 (37%)	15 (35%)	--	12 (28%)
Non-stroke	*Yes (n=6)*	--	4 (67%)	0 (0%)	2 (33%)
(n=30)	*No (n=24)*	--	14 (58%)	8 (33%)	2 (8%)

* *went from stroke to non-stroke or vice-versa*

Table 11.10 Accuracy of routine brain imaging for the detection of a relevant stroke lesion

	Bedside diagnosis		**Routine brain imaging**	
Feature		*(95% CI)*		*(95% CI)*
Sensitivity	86%	*(81-89)*	54%	*(48-61)*
Specificity	83%	*(74-89)*	99%	*(92-100)*
Positive predictive value	92%	*(87-95)*	99%	*(96-100)*
Negative predictive value	72%	*(64-79)*	38%	*(31-46)*
Accuracy	85%	*(80-88)*	64%	*(59-69)*
Likelihood ratio	4.9	*(3.3-7.4)*	36.4	*(5-256)*

NB Diagnosis dichotomised to 'thrombolysis-eligible' stroke or mimic

Chapter 12 : The feasibility of performing advanced MR brain imaging in patients with brain attack

12.1 Introduction

There are clear limitations to CT scanning, and many apparent benefits to MR scanning patients with brain attack. Some authorities now call for advanced MR to be the initial investigation of choice for acute stroke (Hacke & Warach, 2000), yet reading the many published reports of small, highly selected patient groups suggests that this may not be very practical. Is advanced MR the solution to all of our problems? To answer this question, one needs to assess the potential risks and the benefits in a cohort of patients that reflect real life. This chapter will examine the difficulties of scanning patients – the potential *risks*.

12.2 Aims

(1) To determine if it were possible to perform advanced MR as the initial imaging assessment of acute stroke in a broad patient group

(2) To determine if there were any potential problems with safety in MR scanning patients with acute stroke

12.3 Methods

12.3.1 Patients

Eligibility

Consecutive patients who presented to the Western General Hospital with brain attack were eligible for the present study. However, we were unable to scan all potential patients with brain attack, and had to impose two additional criteria. First, the research fellow must have assessed the patient within 24 hours of symptom onset (we wanted to concentrate on acute stroke). Second, the research fellow's clinical diagnosis must have been probable or definite stroke (as we wanted to focus on the patients with a high likelihood of acute stroke).

Initial assessment

We attempted to perform MR scanning as the initial brain imaging modality in all patients eligible for the study. If MR scanning was not possible, the reasons were recorded. A Brain Attack data form (see **Appendix 2**) was completed for eligible patients until the Brain Attack study closed in May 2001. Thereafter, patients who underwent MR scanning had a complete assessment (including brain attack data form), but patients who could not be scanned had a limited assessment (brain attack data forms were not filled out). This was because after May, one research fellow (PJH) performed all patient assessments.

12.3.2 Scanning

Patients were scanned at the Scottish Higher Education Funding Council Brain Imaging Research Centre, which is situated in the Department of Clinical

Neurosciences, Western General Hospital. The study had almost unrestricted access – during working hours – to the centre's 1.5 Tesla GE Signa Echoplanar MR scanner (see **Figure 12.1**). Patients must lie supine in the tunnel, with their heads enclosed in a coil (**Figure 12.2** shows the head coil, with the patient about to be taken into the 'tunnel'. Vision is possible through the small mirror).

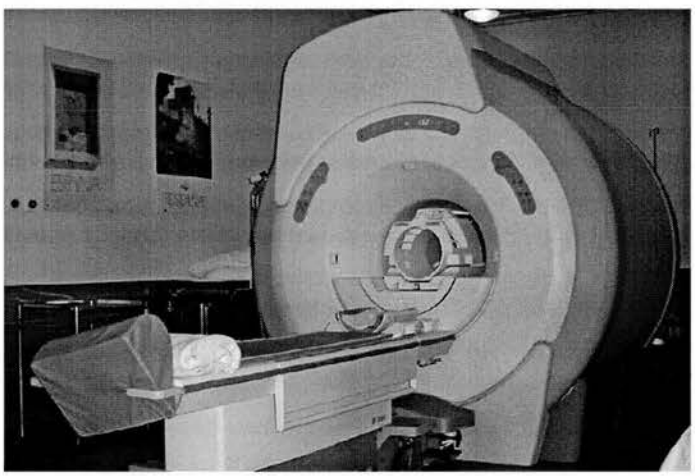


Figure 12.1 The research scanner at WGH

Scanning protocol

All patients received a scan sequence that consisted of: a gradient echo sequence (sensitive to old and fresh blood), diffusion-weighted imaging, perfusion imaging (using the dynamic bolus tracking method, which required rapid intravenous injection of 20ml gadolinium), and T2 axial images. This sequence took approximately 20 minutes. In addition, certain selected patients received magnetic resonance angiography of the Circle of Willis, and diffusion-tensor imaging. The longer sequence could take up to 40 minutes.

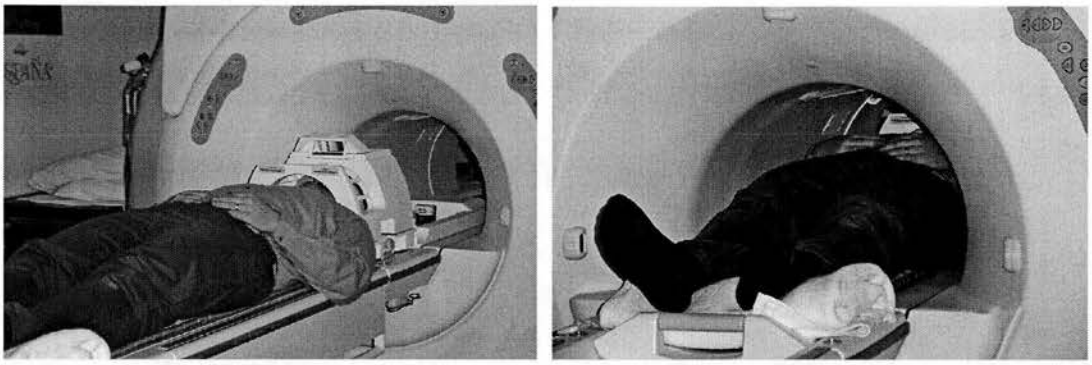


Figure 12.2 The MR head coil is a close fit (left), and observation of the 'patient' once in the scanner can be difficult. [The 'patient' is the author].

The rationale behind the sequences chosen, and the scan results, will be discussed in detail in the following two chapters.

Patient monitoring

To monitor for any potential safety problems, a member of the research team (PJH, AMR [Post-doctoral fellow] or JH [medical student]) was present with the patient in the scanner. A data form (see **Appendix 9**) was filled out for each patient. Prior to scanning, the observer made an overall assessment of the patient's risk of complications, noted whether x-ray of orbits were required (and why), and repeated the NIHSS if there had been a delay of greater than one hour since initially performed. During the scan, the patient's pulse and oxygen saturation were recorded every 5 minutes (we did not record blood pressure as this would require an automated cuff, which can be distressing to patients). The requirement for any form of intervention, and premature termination of the scan were also noted.

The pulse oximeter module of Odam Maglife (MR compatible) multi-modal monitoring device measured arterial oxygen saturation (SaO_2) non-invasively via a finger probe. This provided a continuous signal (from readings every 8 seconds) that was displayed in the scanner, so that motion or magnetic field artefact could be

recorded by the observer. Hypoxia was defined as a fall in SaO_2 to 90% or less, sustained for at least one minute.

Interventions were divided into three categories. Medical intervention might require administration of a drug, nursing intervention could include providing suction, oxygen or other nursing procedure, and reassurance had to include physical contact with the patient (not just verbal reassurance, which can be provided by the radiographers from outside the scanning room).

12.3.3 Ethics and consent

The chairman of the local ethics committee of the Western General Hospital approved the study. Where possible, consent to participate in the study was obtained from the patient. When obtaining consent from the patient was impossible, assent was obtained from a relative before the patient was scanned.

12.3.4 Statistics

Statistical analyses

The present study used key measures of stroke severity – the OCSP classification, and NIHSS score – and a limited number of other items of clinical assessment to compare different groups of patients. Data were analysed with standard descriptive statistics, using non-parametric tests, as data were not Normally distributed.

Statistical packages

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997) and SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999).

12.4 Results

Consecutive patient recruitment commenced on 9 Jan 2001 and completed on 3 Oct 2001. During the 34 week period, 138 presentations by 136 patients were recruited to the study. Two patients presented twice during the study period. *[N.B. The results of the MR scans will be presented in* ***Chapters 13 & 14****.]*

12.4.1 General Features

Table 12.1 shows the general features of all presentations included in the study (with the same features from the entire brain attack study cohort presented for comparison). Consistent with the eligibility criteria for the study, the delay between onset of symptoms and evaluation was considerably shorter in the present study. Thus, patients' symptoms were also more severe, and fewer had normal conscious level or NIHSS of zero (compared with overall figures for the brain attack study).

Patients were eligible for MR scanning if the clinician felt that acute stroke was the likely explanation for the brain attack. The final diagnosis was stroke or TIA in 89%, with a few additional patients diagnosed as non-stroke or possible stroke (**Table 12.1**).

12.4.2 Patients not scanned

Of 138 consecutive patients who were eligible for MR scanning during the study period, 53 (38%) could not be scanned. 27 entered the Brain Attack study, but 26 were seen after the Brain Attack study had stopped (thus details of this group were often incomplete). There were two patients who re-presented. Both were scanned on one occasion (but not the other).

Clinical features

The clinical features of patients who were not scanned are detailed in **Table 12.2**. Compared with those who were scanned, patients not scanned were significantly older (median age 77 years vs 74 years, p=0.03, Mann-Whitney U) and had signs of a more severe stroke (median NIHSS 11 vs 5, p=0.03, Mann-Whitney U). The oldest patient who could not be scanned was 97.0 years. Patients not scanned were also drowsy (57% vs 32%, p=0.01, χ^2) and less likely to have an exact time of onset of symptoms (64% vs 86%, p=0.01, χ^2).

Reasons eligible patients were not scanned

There were several major reasons for eligible patients not to be scanned (**Figure 12.3**). The most frequent cause was that the patient was medically unstable (15 patients, or 11.0% of the consecutive series of 138 patients). In 9/15, the patient was too confused to be able to lie down flat and comply with the MR scan. In the remainder, the patient's condition was too poor to justify the MR scan (e.g. Glasgow Coma Score of eight, acute pulmonary oedema with oxygen saturation of 60%). 10 patients (7.4% of the consecutive series) were not scanned as they presented after working hours, and by the morning (when I came to recruit them) symptoms had

resolved. Despite open access to the scanner, it was unavailable to scan nine patients. This was because of a scheduled service day for one patient, and presentation after 4pm in five patients (radiographers were not willing to take patients after 4pm).

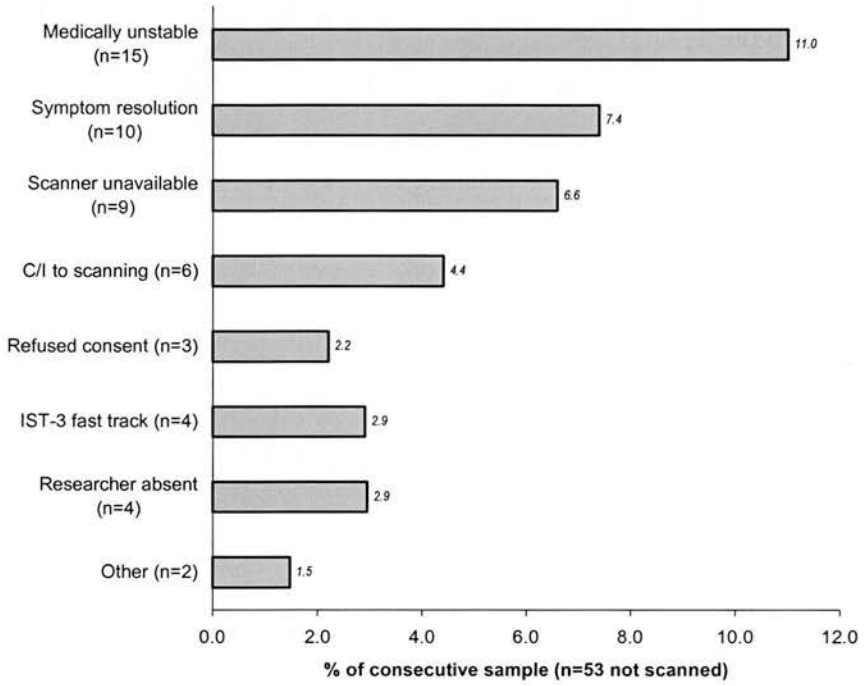


Figure 12.3 Reasons eligible patients were not scanned (see text for details)

Six patients had a contraindication to MR scanning – pacemaker in four, recent surgery (with metal abdominal sutures still present), and a prosthetic mitral valve (N.B. this is not a definite contraindication to MR scanning, and it was later established that this patient would have been safe to scan). Three patients refused consent for scanning on the grounds of claustrophobia. Four patients were fast-tracked to the CT scanner for thrombolysis (it would have been unethical to deny these patients the opportunity of thrombolysis, as the time to undertake MR would have placed them beyond the six hour time window of the third International Stroke

Trial). Four patients – a conservative estimate – were missed as the research fellow was away; and the 'other' category consisted of the patient who had already been scanned who re-presented, and another patient who was missed because the research fellow was too busy that day.

Patients who could not be scanned with MR underwent an unenhanced CT brain. All were able to tolerate the CT.

12.4.3 Patients scanned

Clinical features

The features of patients who were scanned are provided in **Table 12.2**. The research fellow evaluated 34/85 (40%) patients within six hours of onset. Over one third of patients awoke with symptoms (27/85). Patients who were scanned had milder strokes than those who could not be scanned: NIHSS scores were significantly lower, and there were fewer patients with an OCSP classification of TACS (14% vs 23%). The oldest patient scanned was 98.7 years.

Preliminary observations

Risk of complications

15/85 (18%) patients were judged to be at high risk of complications before scanning commenced. The features of these 'high risk' patients are detailed in **Table 12.3**. High risk patients had more severe neurological signs (median NIHSS 20 vs median NIHSS 4.0 for those at low risk, $p<0.01$, Mann-Whitney U); were more likely to be drowsy (60% vs 10%, $p<0.01$, χ^2), and all but three had other medical

issues – such as respiratory problems, recent surgery or poor hearing – that could potentially make scanning more difficult.

X-ray orbits

Departmental protocol required X-ray orbits to rule out metallic foreign body if the patient was unable to do so. 11 patients (13%) required orbit x-rays before MR scanning (four were aphasic, two had reduced level of consciousness, and five had prior exposure to metal). This caused a delay estimated at 20-30 minutes (precise details unavailable). All X-rays were normal.

Settling time

Patients required a settling time of 10 minutes (median, IQR 7-17 minutes) from when they entered the MR scanner until scanning actually commenced. During this time, the patient was given a detailed explanation of the procedure. There was no significant association between length of settling time and NIHSS score (Spearman rho test), presence of confusion (Mann-Whitney U), level of consciousness (Mann-Whitney U), or presence of aphasia (Mann-Whitney U).

12.4.4 Observations during scanning

Oxygen saturation

Monitoring

We attempted to monitor all 85 patients, but were successful in only 61 (72%). Failure to monitor was usually because the patient was unable to keep the finger probe in place (due to confusion, or aphasia), or the signal was weak or unreliable (due to irregular pulse, or poor tissue perfusion). A comparison of

relevant clinical features in those that could and could not be monitored is provided in **Table 12.4**. The only significant difference between the two groups was that those who could not be monitored had shorter duration scans, which was almost certainly a consequence of the inability to monitor them (rather than a cause). As can be seen, many features – such as age, NIHSS, frequency of confusion, reduced level of consciousness and atrial fibrillation – were slightly higher in the non-monitored patients. As numbers were small, differences were not significant.

Hypoxia

11/61 (18%) patients had at least one episode of hypoxia – SaO2 $\leq$ 90% for at least one minute – during MR scanning. The lowest recorded saturation was 74%. **Table 12.5** details the features of patients whose oxygen saturation was successfully monitored. Patients who had episodes of hypoxia were slightly older, but shared similar stroke severity to those without hypoxia. All patients had a similar oxygen saturation when measured in the acute receiving unit, but by the time the patient commenced MR scanning, the saturation had fallen to 94% in those who went on to experience episodes of hypoxia (non-significantly lower than those who did not develop hypoxia). The duration of scanning was longer for patients who experienced hypoxia (median 32 minutes vs median 25 minutes), which may have been an important factor. No observed associations were significant, due to the small numbers of patients involved.

Premature termination of scans

85 patients agreed to undergo MR scanning, but 17 (20%) could not complete the full scanning sequence. The most frequent reason for early termination was

patient claustrophobia (10 patients). Four scans were halted because the observer was concerned that the patient was medically unwell. The median duration of the scan for those who terminated prematurely was 23 minutes, whilst it was 25.5 minutes for those who completed the full sequence (p=0.07, Mann-Whitney U). In four patients, termination occurred very early (before any imaging data were obtained). Most patients could tolerate around 20 minutes in the MR scanner.

Where insufficient imaging data were obtained during the MR (four patients), an unenhanced CT brain scan was performed without difficulty.

Interventions required

Some form of intervention was required in 27 patients (32%). In most (21) this was physical reassurance (which varied from a brief pat to the patient desperately clinging onto the observer's hand for the entire sequence!), but in six patients nursing intervention was required (oxygen given to two patients, assistance with vomiting in four patients).

Table 12.6 shows that patients who required intervention during the scan (compared with those who did not) were more likely to have a severe stroke (median NIHSS 8 vs 4.5, $p<0.01$, Mann-Whitney U) or aphasia (44% vs 22%, $p=0.04$, χ^2). In addition, there were non-significant trends for those requiring intervention to be older, more confused or have reduced conscious state. Patients who required intervention were far more likely to terminate the scan prematurely (56% vs 3%, $p<0.01$, χ^2).

Was the preliminary prediction of high risk accurate?

Patients judged to be at high risk of complications (for whatever reasons) before scanning commenced proved to be less tolerant of scanning than those judged to be at low risk (see **Table 12.7**). High risk patients were significantly more likely to require intervention during the scan, and to terminate the scan prematurely than low risk patients ($p<0.01$ for both, Fisher's Exact). However, hypoxia was twice as frequent in the patients where there was no clinical suspicion of risk (not significant).

When compared with those who could be monitored, patients who could *not* be monitored were also more likely to require physical intervention (63% vs 20%, $p<0.01$, χ^2), and less likely to tolerate the full scanning sequence (scan completed in 58% non-monitored vs 89% monitored, $p<0.01$, Fisher's Exact).

12.5 Discussion

The biggest limitation of MR scanning, at least in this country, is its scarcity. Few stroke consultants (8%) have unrestricted access to MR, and most (85%) scan fewer than 10% of their stroke patients (Ebrahim & Redfern, 1999). The present study had unrestricted access to a state-of-the-art MR scanner during working hours, thus the results provide a realistic assessment of the number of acute stroke patients who could be scanned successfully, and the problems likely to be encountered.

Of 138 consecutive patients with acute stroke (symptoms less than 24 hours duration), we were able to start scanning in only 85 (62%). The major reason for the inability to scan patients was that they were medically unstable. When scanned, 'unwell' patients – those with major strokes, reduced conscious level, or co-existing medical problems – proved to be at greater risk for developing hypoxic episodes,

requiring intervention, or terminating the scan prematurely. Our scanned cohort, therefore, had strokes at the milder end of the spectrum.

Once in the scanner, the major problems we encountered were claustrophobia and the requirement for long scanning times. Claustrophobia was an issue in 9.4% (95% CI 5.6-15.5%) of our consecutive sample, a higher frequency than that reported in other patient groups undergoing MR (who were stable) (Flaherty & Hoskinson, 1989; Avrahami, 1990; Dantendorfer *et al.*, 1991; Sarji *et al.*, 1998). Inspection of **Figures 12.2 & 12.3** provides a graphic illustration of why claustrophobia can be a problem (as it was for the author on his first scan). The duration of the MR – 20 minutes in a confined, noisy environment – made it difficult to successfully image acutely unwell stroke patients who may be anxious, distressed, confused or unable to communicate. In contrast, the CT scan takes less than five minutes, is less confined and is quieter.

Monitoring patients undergoing MR was difficult. **Figure 12.3** shows that only the patient's legs are in direct view of the radiographers – patients could vomit, aspirate or even have a seizure undetected. By having a trained observer present in the room, we were able to detect that patients frequently became distressed and required physical reassurance. Less frequently, patients required nursing care, or developed hypoxia. Many patients – possibly the 'sickest' – could not have their saturations measured, because of poor peripheral perfusion, tachyarrhythmia, restlessness or confusion. The signal obtained from the toe was unusable in most of our patients, particularly the old (because of poor perfusion, weaker signal, or even very thick nails).

12.5.1 Comparison with other studies

How do our data compare with other studies? It is difficult to know. A systematic review of advanced MR imaging in stroke (Keir & Wardlaw, 2000) found that only 6/47 studies of diffusion-weighted imaging (DWI) gave details of patient inclusions and exclusions, and no studies of DWI or perfusion imaging provided details of patient tolerability. When numbers are provided, the impression obtained is that MR imaging is possible in only a handful of patients. Examples include a German study titled the 'feasibility and practicality of MR imaging' (Schellinger *et al.*, 2000) that recruited 64 patients within 12 hrs of symptom onset over 2 years. During this time, the authors estimated that 1200 patients were seen per year (i.e. <3% were scanned), yet claimed that MR was practical and feasible. Baird et al's (2001) prognostic model included only 66 patients out of a possible 347 scanned over a five year period (i.e. they scanned just over one patient per week for five years). The current trial of intravenous desmotoplase (a thrombolytic agent) aims to recruit patients within eight hours of onset, on the basis of MR abnormalities. As of February 2002, 30 patients had been enrolled, whilst 2,463 had been screened (personal communication, DIAS trial co-ordinators).

Of course it is difficult to directly compare these studies with the present one. The desmotoplase trial requires patients to have a perfusion-diffusion mismatch to be eligible for enrolment; so this (or the eight-hour time window) could be the reason for the low recruitment rate. Schellinger et al's study excluded patients aged over 85, and selected only those with a definite stroke. Baird et al's study was retrospective, and excluded patients with TIA and mimic. Almost certainly, many patients would have been excluded from these studies because their scans were of

insufficient quality. Overall, these studies suggest that scanning is possible in a few specially selected patients (without spelling out what these selection criteria are).

The present study demonstrated that MR imaging was possible and yielded usable results in 81/138 (59%) of a truly consecutive and prospective sample. These patients came direct from our Acute Receiving Unit to the MR scanner. Of course, it would be possible to sedate patients, but this would require considerable extra resources (more staff, anaesthetic equipment, etc) and would delay time to treatment. If patients who were not scanned due to medical problems, claustrophobia and the like could be anaesthetised, all but around 5% – those with absolute MR contraindications – could potentially be scanned.

12.5.2 Limitations of the study

The limitations of the present study are that complete clinical data were unavailable for 26/53 patients who were not scanned. For most of these patients (19), details were estimated from the patient's notes. The NIHSS was unavailable for 20 patients. This may have resulted in some inaccuracy of the data for patients not scanned.

We measured SaO_2 non-invasively by finger probe. It is possible that movement or magnetic field artefact affected measurements, although the observer was able to view the tracings on the monitor. To be certain that the changes we observed were due to acute stroke rather than another factor (e.g. ageing), it would have been ideal to recruit a series of age-matched controls. Unfortunately, this was beyond the scope of the present study, but is the subject of a current study by my

colleague Dr A.Rowat. Preliminary data suggest that hypoxia is infrequently observed in healthy older adults (personal communication, Dr A.Rowat).

It could be argued that our scanning protocol was part of a research project, and thus far longer than a 'clinical' protocol. As we discovered, patients tolerate shorter scanning sequences much better, so our long scanning time may have artificially increased the frequency of complications. Whilst it is certainly true that a more targeted scanning sequence (e.g. just DWI) would be quicker, the problem is deciding which sequence to use. For example, dropping perfusion means that the presence of a mismatch cannot be determined; dropping the gradient echo may make diagnosis of acute haemorrhage unreliable difficult, and dropping the T2 axial image makes it difficult to diagnose mimics such as acute demyelination. At this time, the ideal minimum sequence has not yet been established.

12.5.3 Implications of the study

Scanning acute stroke patients is a challenge

There is little doubt that MR scanning patients with acute stroke is challenging. One in three patients, who had generally mild strokes, required some form of intervention, and one in five patients could not complete the full scanning sequence. Patients are at risk of hypoxia, vomiting and aspiration, yet it is difficult to directly observe patients, and non-invasive monitoring may not work (in those at greatest risk of complications). Our experience would suggest that it is important to have a trained nurse (a sensible doctor would also suffice!) present in the scanner with the patient.

Is MR scanning dangerous in stroke patients?

This study provides insufficient data to state that MR scanning is dangerous in acute stroke patients, but it does point to the need for caution. The fact that patients must lay supine and motionless for around 25 minutes suggests an increased risk of aspiration. We observed that 18% of our patients had at least one episode of oxygen desaturation to 90% or less, although we did not determine the clinical significance of this. We avoided scanning patients who appeared 'too sick' – others might scan equivalent patients and that could cause harm. Further research is warranted if MR scanning is to become routine.

How might the number of patients be increased?

The number of patients eligible for MR could be increased substantially. 14% of patients (overall) were not scanned because they presented out of hours, and by the following morning, symptoms had resolved or the patient was no longer eligible for the study (greater than 24 hours after symptom onset). These patients could be scanned if the MR was always operational; and perhaps half could be scanned if the MR remained operational until 7pm (to catch patients presenting between 4pm and 6pm).

5.8% of patients were not scanned because the research fellow was absent, or the patient was taken directly to CT (fast-tracked) for thrombolysis. With more training and increased experience of dealing with acute stroke patients, the system would inevitably speed up, and could cope with the absence of key personnel. Hence, MR would still be possible if thrombolysis were being considered, or if one member of the team was away.

Once the patient is within the MR, scanning time must be kept as brief as possible (and no more than 30 minutes unless the patient is particularly well) to maximise the chance of a complete and uninterrupted scan. By following these measures, it may be possible to scan 75-85% of consecutive patients.

There will still be patients who cannot or should not be (MR) scanned

However, there will always be patients who cannot be scanned (claustrophobia, contraindication, scanner down for servicing). It is important to note that all 'un-scannable' patients could have a CT without incident – CT is clearly a vastly more practicable technology for patients with acute stroke.

There are also patients who *should* not be scanned with MR in the acute phase of stroke. The clinician was able to predict who was at high risk of complications with accuracy: these were patients with severe stroke, reduced level of consciousness, or co-existing medical conditions (particularly respiratory problems). These warning signs predicted the need for intervention during, or early termination of the scan. It is possible to identify inappropriate candidates for MR before the scan commences, but the concern is that hypoxia was seen more frequently in patients who were *not* judged to be at high risk of complications. Our experience would suggest that acute stroke patients should be observed within the scanner.

12.6 Summary

- 62% of a consecutive series of patients could be MR scanned within 24 hours of symptom onset

- The reasons for not scanning patients were divided between 'operational' issues (outside scanning time, researcher absent, etc) and 'patient' issues (medically unwell, refused consent, etc.)
- With organisational change, possibly 85% of patients could be scanned
- 33% of patients scanned required some form of intervention, and 20% could not complete the full sequence. These complications were frequently predicted by the clinician before the scanner, and were more likely in patients with severe strokes or when the scan was prolonged
- 20% of patients experienced episodes of hypoxia during the scan. Apart from association with more severe stroke, this was not predictable
- MR entails a small, but probably not inconsequential, risk to patients from hypoxia, aspiration and delay to treatment

Recommendations for further research:

- A study to specifically address the safety issues of MR scanning is required; this might involve monitoring more elderly controls, and a larger number of patients with stroke, so that the age, severity and comorbidity can be examined more closely
- Further studies should determine the optimum scanning sequences, and the benefits of MR in less selected cohorts of patients with acute stroke

Table 12.1 Features of patients recruited into the feasibility study

	MR Feasibility study		All patients in Brain Attack study	
Feature	**Number**	**(%)**	***Number***	***(%)***
Median age (IQR)	76 years	(67-82)	*76 years*	*(67-83)*
Male gender	61	(44%)	*163*	*(49%)*
Median delay from symptom onset to evaluation (IQR)	8 hours	(3-19)	*26 hours*	*(13-51)*
Hypertension	74	(54%)	*159*	*(49%)*
Ischaemic heart disease	36	(26%)	*100*	*(31%)*
Normal conscious level	81	(59%)	*227*	*(68%)*
Median NIHSS (IQR)*	6.0	(4-11)	*4.0*	*(2-10)*
NIHSS group*:				
NIHSS = 0	4	(3%)	*47*	*(13%)*
NIHSS 1-4	44	(37%)	*134*	*(38%)*
NIHSS 5-10	37	(31%)	*82*	*(23%)*
NIHSS >10	33	(28%)	*87*	*(25%)*
OCSP classification				
TACS	24	(17%)	*60*	*(17%)*
PACS	49	(36%)	*108*	*(31%)*
LACS	44	(32%)	*59*	*(17%)*
POCS	10	(7%)	*42*	*(12%)*
Unknown	11	(8%)	*81*	*(23%)*
Final diagnosis:				
Definite or probable stroke	112	(81%)	*220*	*(63%)*
TIA	11	(8%)	*17*	*(5%)*
Possible stroke or TIA	6	(4%)	*48*	*(14%)*
Non-stroke	9	(7%)	*65*	*(19%)*

** 20 in feasibility study without NIHSS scores*

Table 12.2 Clinical features of eligible patients who could and could not undergo MR scanning

	Patients NOT scanned		***Patients scanned***		
Feature	**Number**	**(%)**	**Number**	**(%)**	***P****
Median age (IQR)	77.3 years	(71-86)	74.1 years	(63-81)	.025
Male gender	20	(38%)	43	(51%)	.140
Median delay from symptom onset to evaluation (IQR)	6 hours	(3-15)	12 hours	(3-22)	.073
Hypertension	25	(47%)	49	(58%)	.230
Ischaemic heart disease	13	(25%)	23	(27%)	.742
Exact onset of symptoms	34	(64%)	73	(86%)	.006
Woke from sleep with symptoms	10	(22%)	27	(36%)	.114
Normal conscious level	23	(43%)	58	(68%)	.007
Median NIHSS (IQR)†	11.0	(4-20.5)	5.0	(3.5-8.5)	.027
OCSP classification					.490
TACS	12	(23%)	12	(14%)	
PACS	16	(30%)	33	(39%)	
LACS	16	(30%)	28	(33%)	
POCS	3	(6%)	7	(8%)	
Unknown	6	(11%)	5	(6%)	

** significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables).*
† 20 in not scanned group without NIHSS scores

Table 12.3 Features of the patients judged to be at high risk of complications during MR scanning (n=15)

Study Number	Age	Conscious state	OCSP	NIHSS	Other issue(s)
188	90	Alert	PACS	8	Neck OA; poor level of function after prior strokes
217	89	Drowsy	TACS	27	--
230	80	Drowsy	TACS	21	Recent surgery (TURP)
247	88	Drowsy	TACS	27	--
257	74	Drowsy	TACS	28	Known COAD
284	91	Drowsy	LACS	7	Very frail, poor hearing and vision
305	78	Drowsy	TACS	23	Recent hospitalisation with prostatic problems
328	79	Drowsy	LACS	8	Known COAD
351	80	Drowsy	TACS	20	Other medical problems (on steroids, very frail skin, at risk of pressure sores)
362	80	Alert	PACS	17	--
371	78	Drowsy	TACS	25	History of alcohol abuse
385	76	Alert	PACS	13	Known COAD, required O_2
387	77	Alert	PACS	9	Required O_2, swallowing problems
391	86	Alert	TACS	23	Required O_2
395	71	Alert	POCS	4	Vomited before scan

Table 12.4 Characteristics of patients who had SaO_2 recorded successfully (n=61) and those who did not (n=24).

Feature	SaO_2 recordings possible (n=61) Number	(%)	No SaO_2 recordings possible (n=24) Number	(%)	P*
Median age (IQR)	73 years	(61-82)	77 years	(71-81)	.441
Irregular pulse	13	(22)	6	(26)	.725
Confusion	10	(24)	5	(36)	.411
Decreased conscious level	11	(18)	5	(21)	.766
Aphasia	18	(30)	7	(30)	.975
Median NIHSS (IQR)	5.0	(3-9)	6.0	(4-9)	.356
TACS	9	(15)	3	(13)	.788
Median scan time (IQR)	27 mins	(20-42)	21 mins	(16-30)	.026
Median SaO_2 in ARU (IQR)	97%	(95-98)	96%	(95-98)	.542

** significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables).*

Table 12.5 Characteristics of patients who had successful SaO_2 recordings during scanning (n=61), subdivided into those who had at least one episode of hypoxia (n=11) and those who did not (n=50).

Feature	Episode(s) of hypoxia (n=11)		No hypoxia (n=50)		P*
Median age (IQR)	75 years	(63-82)	72 years	(58-82)	.488
Median SaO_2 in ARU (IQR)	96.5%	(95-98)	97.0%	(95-98)	.794
SaO_2 at start of scanning (IQR)	94.0%	(93-97)	96.0%	(95-98)	.125
Median scan time (IQR)	32 mins	(15-48)	25 mins	(20-39)	.789
Decreased conscious level	1	(8%)	10	(20%)	.670
Median NIHSS (IQR)	5.0	(3-9)	5.0	(3-9)	.858

** significance determined by Mann-Whitney U test for all except conscious level – Fisher's Exact test.*

Table 12.6 Characteristics of patients who required intervention, and those who did not, during MR scanning

Feature	Intervention required (n=27)		No intervention (n=58)		P*
Median age (IQR)	78 years	(67-85)	72 years	(60-81)	.106
Median NIHSS (IQR)	8.0	(4-17)	5.0	(3-9)	.002
Median scan time (IQR)	25 mins	(16-35)	25 mins	(20-39)	.162
Confusion	7	(26%)	9	(16%)	.253
Aphasia	12	(44%)	13	(22%)	.038
Decreased conscious level	7	(26%)	9	(16%)	.253
Premature termination of scan	15	(56%)	2	(3%)	<.001

** significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables).*

Table 12.7 The clinical prediction of the patient's risk of complications during MR scanning

	'High risk' n=15		'Low risk' n=70		P*
Episodes of hypoxia	1	(10%)	10	(20%)	.673
Premature termination of scan	7	(47%)	10	(14%)	.009
Intervention required	10	(67%)	17	(24%)	.004

** significance determined by Fisher's Exact test.*

Chapter 13 : Magnetic resonance brain imaging and the diagnosis of brain attack

13.1 Introduction

This chapter explores the benefits of magnetic resonance (MR) brain imaging in the diagnosis of brain attack. The findings, particularly of the gradient echo (GRE), diffusion-weighted (DWI) and perfusion (PI) sequences will be described in a study of 96 consecutive patients with brain attack. Emphasis will be placed on the results of MR in patients with ischaemic stroke, and how the features seen on MR correlated with baseline clinical features. The impact of the MR on the clinical diagnosis will be explored.

13.2 Aims

(1) To describe the MR findings in patients with brain attack

(2) To correlate imaging findings with baseline clinical features

(3) To determine the sensitivity and specificity for structural and advanced MRI

(4) To describe how advanced MR imaging – particularly diffusion-weighted imaging – influenced the diagnosis of brain attack

13.3 Methods

13.3.1 Patients

Recruitment

The present study recruited consecutive patients who presented to the Western General Hospital with symptoms of brain attack. The clinician must have considered that acute stroke was the likely diagnosis for the brain attack, and the patient must have been assessed by the clinician within 24 hours of symptom onset (defined as time symptoms were first noted). Entry criteria were almost identical to the study of feasibility of MR (although the present study recruited for a longer time); and the general methods to ensure case ascertainment were as described for the clinical studies (see **Section II, Chapter 7**).

There were two 'target' patient groups. The highest priority was assigned to patients who presented with symptoms of cortical stroke within 12 hours of onset. These patients received a longer initial imaging assessment, and were scanned sequentially over three months (to study the pathophysiology of the ischaemic penumbra). Patients with symptoms of brainstem or subcortical stroke, or cortical stroke beyond 12 hours, were assigned a lower priority. These patients received a shorter imaging assessment, and were scanned once. [*NB. This thesis will not address the role of advanced imaging in the study of stroke pathophysiology*].

All patients or their relatives provided their consent to participate in the study.

Clinical assessment

One research fellow (PJH) recruited and assessed all patients. A detailed baseline clinical assessment was performed, and a Brain Attack data form was completed for each patient (see **Appendix 2**). Prior to scanning, the conscious level was assessed again and the National Institute of Health Stroke Scale (NIHSS) repeated if there had been a delay of one hour or more since initially performed.

Investigations

The research fellow organised MR brain imaging for each patient, and arranged for a Doppler ultrasound examination of the extracranial carotid and vertebral vessels either at the same visit or subsequently. Routine blood tests were performed in each patient. Additional investigations (e.g. echocardiogram) were performed at the discretion of the responsible clinician.

If possible, each patient was to receive a computed tomography (CT) brain scan shortly before or after the MR. However, the CT was not always immediately available (because it was often very busy). If the patient were unwell, or had difficulty coping with the MR, I returned the patient to the ward without a CT, as safety and comfort for the patient was paramount.

Final diagnosis

The final diagnosis of the event was determined by consensus of a panel of experts (as described in **Chapters 7 &11**). Meetings were conducted when sufficient experts were available (minimum four clinicians, of whom two were consultants, from a pool of five consultants and three registrars). The research fellow presented the clinical details, and the neuroradiologist (JMW) reviewed the CT scan, structural

MR and DWI. The panel assigned each patient to one of five diagnostic categories (definite, probable and possible stroke, definite transient ischaemic attack (TIA) and non-stroke). The details were recorded on the final diagnosis data form (see **Appendix 5**).

Influence of advanced imaging on the diagnosis sub-study

The present study aimed to determine the impact of brain imaging on the clinician's diagnosis, by assessing the clinician's certainty at each 'level' of the diagnostic process – after the clinical assessment, after CT brain imaging, after structural MR brain imaging, and after the DWI. All patients who successfully underwent MR scanning were studied, but only those who had contemporaneous CT and MR could be compared.

The study was performed at the same time as the consensus panel meetings. Clinicians were asked to complete a data sheet for each patient (see **Appendix 10**), which consisted of a series of lines. Each line was a visual analogue scale ranging from 0-100%. The clinician placed a tick on the line to indicate the level of certainty after each level of the diagnostic process was presented (i.e. history, examination, CT, structural MR, and finally the DWI). A score of 0% indicated that the clinician was certain the diagnosis was non-stroke. A score of 100% indicated complete certainty for the diagnosis of stroke (see **Appendix 10**). Only after the individual clinicians had scored their data sheets (at each level) did I ask the group to make a consensus diagnosis.

To reflect real life, the score was cumulative – each successive diagnostic level was added to the last – so we tested the *additional* effect of MR (rather than

MR as the only imaging modality). This was a pragmatic decision, as there was insufficient time and enthusiasm to show the scans multiple times.

Later, a single observer measured the marks on the data sheet to convert these to a numeric score.

13.3.2 Scanning

Patients were scanned using a 1.5 Tesla GE Signa Echoplanar MR scanner (see **Figure 12.1**) specifically dedicated to research. The study had unrestricted access to the scanner during working hours (with an arrangement that stroke patients took priority over all other patients).

Patients were escorted from the Acute Receiving Unit (ARU) or ward to the scanner by members of the research team. The patient was briefly re-assessed by a radiographer to ensure that there was no contraindication to scanning. If necessary, orbits were x-rayed to exclude metallic foreign bodies. The radiographer provided a detailed explanation of the procedure, fitted earplugs and ensured the comfort of the patient before scanning commenced.

MR brain imaging sequences

Patients who presented with symptoms of cortical ischaemia within 12 hours received the following image sequences: axial diffusion-weighted image (DWI), 20x5mm slices with 1mm slice gap [40 second scan time]; gradient echo (GRE), 20x5mm slices with 1.5mm slice gap [3mins 2secs]; diffusion-tensor images (DTI), 15x5mm slices with 1mm slice gap, repeated ten times [10 x 40 sec]; perfusion imaging (PI), 15x5mm slices with 1 mm slice gap [1min 26secs]; T2 fast spin echo axial images (T2FSE), 30x5mm slices with no gap [3min 22secs], and magnetic

resonance angiography of the circle of Willis (MRA), approximately 116x1.8mm slices with no gap [6min 34secs]. Total sequence time: 21 minutes 44 seconds.

Patients with cortical symptoms beyond 12 hours, brainstem or subcortical symptoms received the following sequences: GRE, 20x5mm slices with 1.5mm slice gap [3min 2secs]; DWI, 20x5mm slices with 1mm slice gap, repeated twice [2 x 40 sec]; PI, 15x5mm slices with 1 mm slice gap [1min 26secs], and T2FSE, 30x5mm slices with no gap [3min 22secs]. Total sequence time: 9 minutes 10 seconds.

If the research fellow felt that a high priority patient was too unwell to tolerate the full sequence, a briefer sequence that substituted two 40 second DWI sequences for the ten 40 second DTI sequences was performed. The order of sequences was critical – it ensured that the key data (the DWI) were obtained first, and if necessary the MRA could be abandoned. Ensuring patient comfort and safety took precedence at all times.

Rationale for sequences

The long scanning time incorporated many different sequences. The GRE sequence is exquisitely sensitive to both acute and chronic haemorrhage (see **Section I, Chapter 6**), which is important if MR is to replace CT. Both DWI and T2 FSE are required to help determine the age of a lesion, and confirm whether the lesion is ischaemic. PI was chosen to document blood flow to the affected area, and to establish if a mismatch existed. The MRA sequence could identify occluded vessels. The only image sequence not in current clinical use – DTI – was chosen for a sub-study that examined the response of brain tissue to ischaemia (in a series of patients with cortical stroke). DTI allows the assessment of both the amount and direction of water diffusion – anisotropy – which may be altered by ischaemia (Pierpaoli *et al.*,

1996). The complex pathophysiology of stroke recovery will not be discussed in this thesis.

13.3.3 Image processing and analysis

After scanning, hard copies of the DWI, GRE, T2FSE and MRA were printed onto photographic film, and were available for immediate inspection and reporting. For the DWI images, only qualitative reports were possible (i.e. lesion present/absent, lesion small/large, area affected). Perfusion images were not printed off, as the quality of the raw images produced by the MR machine are relatively poor. Thus, more detailed analysis of the PI and DWI images (for example lesion volume measurement) required computer-assisted image processing.

The key issue of blinding

Lack of blinding is a major shortcoming of many studies of advanced MR brain imaging (Keir & Wardlaw, 2000). It is difficult to be convinced of the role of imaging when the same clinician recruited the patients, reported the scans, analysed the images, and performed the follow-up assessment. Such a study would not provide objective assessment of the relationships between clinical severity an imaging appearance, or functional outcome and imaging. To minimise these potential biases, we undertook the following steps:

- The clinician (PJH) was blind to the PI data and to measurements on DWI
- The neuroradiologist (JMW) reported the scans independently, blind to the symptoms (this was done separately to the final diagnosis team meetings, where the images were reviewed with the clinicians)

- PI and DWI lesions were identified and outlined for measurement by JMW blind to all other details (and the DWI and PI were done separately and blind to each other)
- The actual measurement of PI and DWI lesion volume and apparent diffusion coefficient (ADC) were performed on computer by a scientist blind to all baseline and follow-up data clinical data, and the DWI and PI were done separately and independently
- The presence of a mismatch between DWI and PI lesions was determined by the neuroradiologist blind to all clinical details

Determining DWI lesion volume and the ADC

This was performed by CSR (PhD candidate) under supervision by JMW. After scanning, the data were saved onto disc and transferred to a UNIX workstation to allow processing. The images were realigned to each other and motion and patient movement artefact was corrected using software developed in-house (by Dr Mark Bastin, medical physicist). At this point (which could take up to 30 minutes per scan), the images were ready for analysis.

DWI lesion volume was determined using ANALYZE™ (Version 7.5, Mayo Clinic, Rochester USA) software. The DWI map (with lesions showing as white blobs) was inspected, and regions of interest were outlined manually. The computer software then calculated volume (area of the lesion multiplied by slice thickness). ADC, a measure of the actual amount of water diffusion, was also determined by ANALYZE™. A contralateral region of interest in normal tissue was highlighted on the DWI map, and both it and the ischaemic lesion were traced onto the ADC map.

The computer calculated the mean ADC in both regions of interest. Thus the ADC value obtained was relative to the contralateral (normal) tissue.

The assessment of PI parameters

The PI sequence consisted of a rapid intravenous injection of gadolinium, followed by repeated scans of the entire brain every 2.5 seconds for 85 seconds (generating 34 time points) which 'tracked' the passage of the tracer agent through the brain. The raw data were exported from the scanner as a DICOM file to a Sun-UNIX workstation for further processing, which was performed by Dr Paul Armitage (Medical Physicist). The first step was to correct for motion artefact, using software developed in-house, and align the scans with each other and the DWI image (as above). The critical importance of correcting for movement artefact (and thus the problem of relying on the films generated by the scanner itself) is illustrated in **Figure 13.1**.

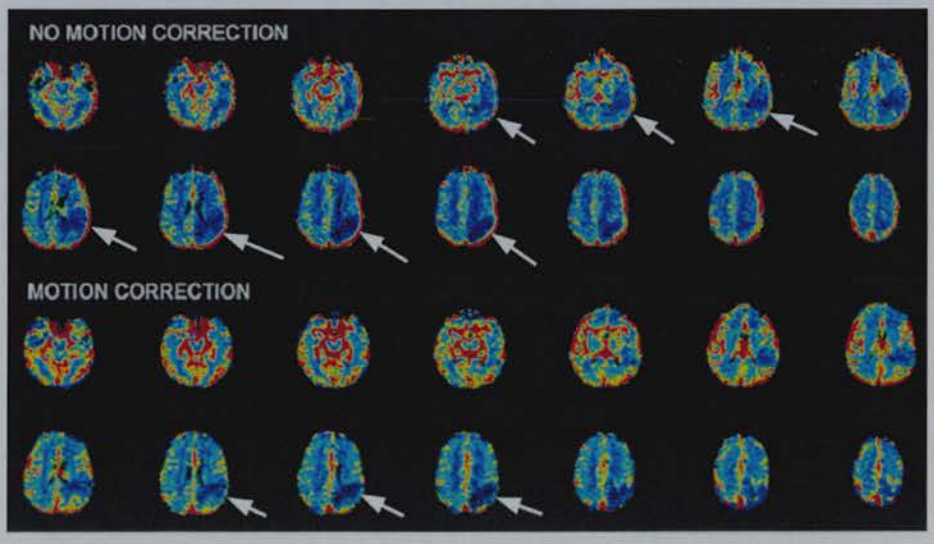


Figure 13.1 Patient movement artefact can overestimate the perfusion abnormality
The dark blue area (arrows) appears more extensive in the upper row of images with no motion correction. Patient's right is on the left side of the page.

The next step in processing was to convert the images to a display of tissue contrast agent concentration (rather than the loss of signal produced by the contrast). This was done automatically using an equation that relates the drop in signal to the signal of the tissue before contrast was given. Once this was performed, the concentration of contrast in each of the 34 slices (for every voxel of brain tissue) was plotted on a concentration versus time graph. A 'gamma variant curve' was fitted to the graphs: cerebral blood volume (CBV) was estimated as the area under the gamma variant curve; mean transit time (MTT) roughly equated to the width of the curve, and cerebral blood flow was determined by dividing CBV by MTT. An arterial input function was not calculated (see **Section I, Chapter 6** for further explanation). Thus the PI parameters were all relative measurements: the lesion was compared with contralateral normal tissue.

Colour CBF and MTT maps were produced and printed for each patient. The neuroradiologist (JMW), blind to clinical details, examined the PI maps in two sittings. The first reading was to identify whether a mismatch between perfusion and diffusion was present (to be discussed in **Chapter 14**). Both PI maps were coded as normal (no perfusion abnormality), focal area of reduced flow consistent with acute ischaemia, or focal area of increased flow/hyperaemia. The second reading, performed blind to the DWI scan result, was to outline the focal regions of abnormal perfusion on the maps, so that lesion volume could be determined semi-automatically using the ANALYZE software (described above for DWI lesion volume).

13.3.4 Statistics

Statistical analyses

Descriptive statistics were used to test the significance of associations and correlations. The data were initially checked for a Normal distribution, which was present only for ADC values. Parametric statistical tests were used for ADC values, but all other data were analysed with standard non-parametric tests. I used the NIHSS and Oxfordshire Community Stroke Project (OCSP) classification as the main markers of stroke severity.

Accuracy of MR imaging

To determine sensitivity and specificity consistent with earlier chapters, I reduced the final diagnostic categories to 'thrombolysis-eligible' stroke (i.e. definite stroke or TIA or probable stroke) or mimic (i.e. definite non-stroke or possible stroke with a plausible non-stroke explanation for the clinical features). The scan findings were dichotomised to relevant stroke lesion (either infarct or haemorrhage) or no acute stroke lesion (normal, non-stroke lesion, old pathology, or atrophy). 95% confidence intervals were determined for the accuracy parameters.

The impact of imaging on the diagnosis

I analysed the data obtained from the clinicians' diagnostic certainty data sheets in several ways (as no single method adequately summarised the results). (1) I plotted a series of line graphs. There was one graph per clinician, with each line on the graph representing an individual patient for which the clinician made a decision. The y-axis represented the percentage certainty, and the x-axis represented the decision nodes (clinical assessment, CT, structural MR and DWI). The graphs

provided an overall picture of how certainty changed, and whether there were any clear trends within and between clinicians. Unusual or outlying patients were identified and described.

(2) I determined the magnitude of change in certainty on moving between each imaging modality (CT, structural MR and DWI). A score of 50% was deemed to be complete uncertainty, and any movement away from this (in either direction) was an increase in certainty (i.e. a 40% increase in certainty could mean going from 50% to 90% certain, or from 50% to 10% certain). For every patient, the raw score at each node was changed to a certainty figure by subtracting the score from 50 and ignoring the direction sign (so that a patient's raw score of 36% became 14%, the same as a patient starting with a score of 64%). [This made certainty for a non-stroke equal to certainty for a stroke]. The change in certainty was simply the difference in certainty between clinical assessment and CT, CT and structural MR, and structural MR and DWI. A change in certainly could be either positive (became more certain) or negative (became less certain). Mean certainties at each decision node were calculated for every individual patient (using the scores of all clinicians who assessed that patient), for every clinician (using all patients that the clinician assessed), and then for all patients (ignoring the fact that patients had been assessed by different groups of clinicians). The change in certainty was analysed using two way ANOVA (adjusting for patients and clinicians).

(3) To give another view of the data, I determined the frequency diagnostic certainty increased, remained the same or reduced for each clinician, and the number of times that each clinician was 100% certain after each imaging modality.

(4) The interaction between severity of stroke and utility of brain imaging was analysed by dividing patients into OCSP subtypes, and four NIHSS categories (NIHSS 0, 1-4, 5-10, >10), and determining mean change in certainty (with 95% confidence intervals) from the clinical assessment to the completion of imaging.

The impact of imaging on lesion localisation

The accuracy of the research fellow's clinical prediction of lesion localisation was compared to the location shown by DWI (in patients with ischaemic or haemorrhagic stroke who had a visible DWI lesion). The OCSP classification was used as the clinical predictor of lesion location. DWI lesions were divided into cortical, large subcortical (e.g. striatocapsular infarct), small subcortical (a 'lacunar infarct' as described by the neuroradiologist) and brainstem. Haemorrhages were divided into subcortical (small or large) and cortical. To be classed as a correct clinical prediction, patients with a TACS or PACS must have had a cortical or large subcortical lesion, patients with a LACS must have had a small subcortical lesion, and patients with POCS must have had a brainstem lesion or cortical infarct affecting the occipital lobe(s).

Statistical packages

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997), Confidence Interval Analysis (version 2.0.0, ©Trevor Bryant 2000) and SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999). Two-way ANOVA was performed using the general linear model function of SPSS, entering certainty as the dependent, and clinicians and patients as fixed variables, to determine change accompanying each new piece of information.

13.4 Results

The study commenced recruitment on 19 September 2000, and completed recruitment on 7 November 2001 (with a break in recruitment from 14/11/00 – 7/1/01 for conferences and holidays). During this time, 96 patients were recruited (no patients were recruited more than once). [NB. The present study recruited an additional 11 patients compared with the feasibility study (**Chapter 12**), as it recruited for a longer period of time].

13.4.1 General Features

Patient demographics

Table 13.1 & 2 give details of the general recruitment and demographics of the 96 patients recruited. The median age of the patient group was 74 years. 54% were seen by the research fellow within 12 hours of onset (median time 9.3 hours), and most were scanned within 13 hours of symptom onset. 37/96 (39%) patients reported a past history of a focal neurological deficit, which had completely resolved in 23 patients. Only three patients were unable to walk prior to the stroke.

Vascular risk factors were common in this cohort: 58% of patients were present or past smokers, 57% reported a history of hypertension, 25% had ischaemic heart disease, and 25% had known atrial fibrillation.

Clinical features of the brain attack

The clinical features of the event that led to recruitment are detailed in **Table 13.3**. A time of onset was estimated for 13 patients (13%), and a further 34 patients (35%) first noticed symptoms on waking. When a patient awoke from sleep with the

deficit, the median time that the patient was last known to be normal was 7.75 hours earlier (IQR 4.4 – 10.8 hours).

Almost 75% of brain attacks involved motor symptoms, and around 50% caused speech disturbance. On examination, 20% of patients were confused, and 20% had reduced consciousness. The median NIHSS score for the cohort was 5 (IQR 3 – 9). 40% were classed as partial anterior circulation syndrome (PACS), 31% lacunar syndrome (LACS), and 14% total anterior circulation syndrome (TACS).

Final diagnosis

The final diagnosis was definite or probable stroke in 85/96 (88%) of patients recruited, TIA in 3/96 (3%), possible stroke in 3/96 (3%) and definite non-stroke in 5/96 (5%) (see **Table 13.4 & Figure 13.2**).

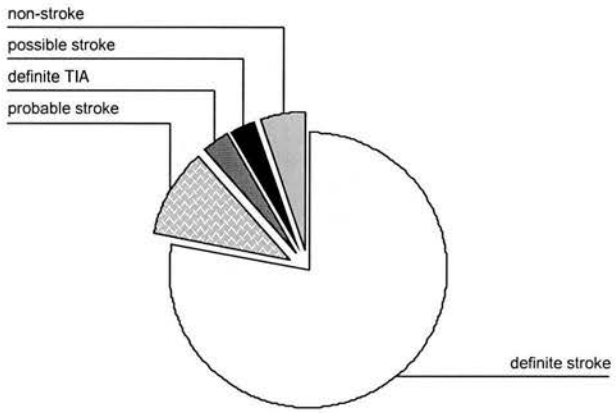


Figure 13.2 Final diagnosis of patients in MR study

13.4.2 Scanning details

37 patients (39%) presented with symptoms of cortical stroke within 12 hours of onset. These high priority patients received the longer scanning sequences

(median scan time 39 minutes, IQR 26-48mins). The remaining 59 patients (62%) received the shorter duration scan sequence (median scan time 21 minutes, IQR 17-26.5mins).

The distribution of time to scanning for the 96 patients is illustrated in **Figure 13.3**. Four patients were scanned after 48 hours. Although not strictly eligible, these patients were scanned, as they were willing to participate, and could still provide useful data.

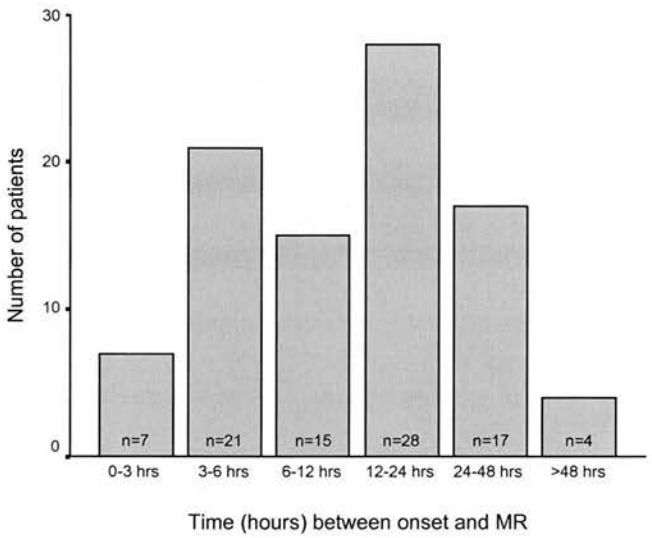


Figure 13.3 Time from symptom onset to scanning (n=92 patients scanned)

Aborted scans

Four patients aborted the scan (due to claustrophobia) before any useful data could be obtained. A further 15 patients could not complete the full imaging protocol (13 were undergoing the longer DTI sequence), although useful DWI and PI data were obtained. 9/37 patients invited to undergo sequential scanning refused after the first scan.

Scan quality

The earliest and briefest images – DWI and GRE – were less affected by movement artefact. Later and longer sequences – T2FSE and MRA – were more likely to be degraded by patient movement (see **Figure 13.4** and also **Figure 13.28**). The neuroradiologist (JMW) was able to provide a qualitative report on all scans.

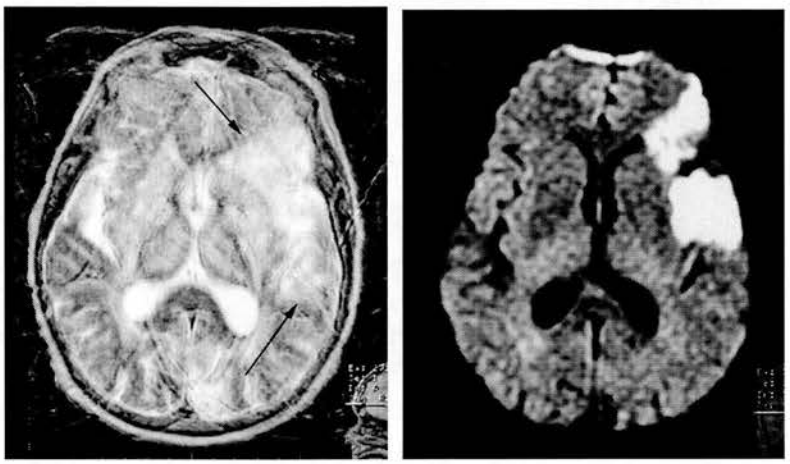


Figure 13.4 Patient movement artefact degraded the T2FSE sequence (see also fig 13.28)
PH387: *Patient presented with a left PACS, MR at 29 hours 30 minutes after onset. T2FSE (left image) is degraded by movement artefact making the hyperintense left MCA infarct more difficult to see (arrows), but the DWI (right) shows an obvious hyperintensity.*

Scan quality was of critical importance for the successful computerised processing of images. DWI lesion volume could not be calculated for six patients, although JMW was able to determine a rough lesion volume by estimating the area of the lesion on the photographic film and multiplying this by the number of slices involved. The ADC could not be calculated for 10 patients, as the data from the MR scanner had become corrupted (thus preventing further analysis). This could not be remedied. PI parameters could not be determined in 22 patients: the patient was unable to tolerate the sequence (n=7), the data was corrupted (n=7), or the sequence was not performed because the lesion identified on MR was not ischaemic (n=8).

13.4.3 MR brain imaging and the detection of stroke mimics

Five patients were diagnosed as definite non-stroke. Two patients [PH250, PH372] had a brain tumour (meningioma and metastasis); in these patients the diagnosis was confirmed by the brain imaging (the lesion was also visible on CT in the patient who had both CT and MR). One patient's symptoms were due to a seizure [PH360], one was due to decompensation unmasking previous stroke signs [PH364], and one was thought to be functional [PH378]. In these three cases, the brain imaging (including DWI) showed no acute lesion. Although the diagnosis was based on the history and examination, it was useful to note that the DWI was negative.

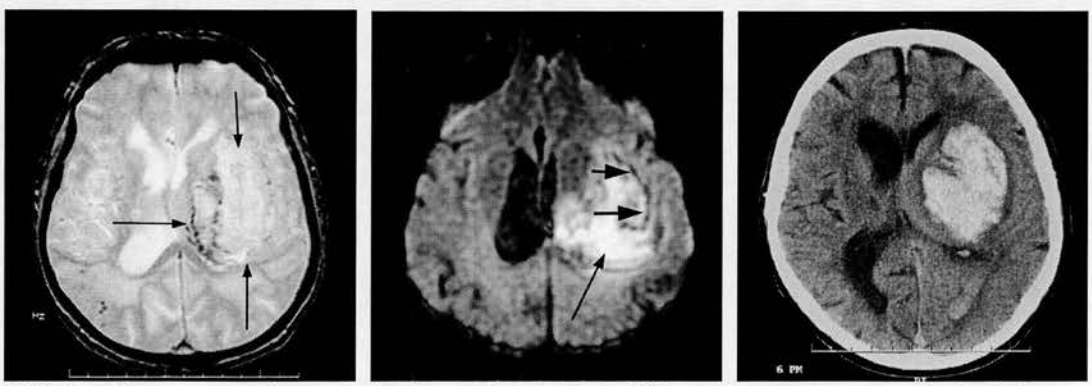
Three patients received a final diagnosis of possible stroke. Two patients [PH222, PH397] presented with symptoms of vestibular disturbance, and all MR sequences failed to disclose an acute lesion. Reaching a consensus final diagnosis was difficult, as some members of the panel were happy to label this as peripheral, but others felt that ischaemia could not be excluded. The other patient [PH388] presented with slurred speech and unsteadiness. On examination, she was confused, dysarthric and unsteady. There was a background of moderately severe cognitive impairment. MR imaging showed atrophy, leukoaraiosis and old petechial haemorrhages, but no acute lesion on DWI. A urinary tract infection was suspected, but there was no laboratory proof of this, so the consensus diagnosis was possible stroke.

13.4.4 The detection of haemorrhage with advanced MR

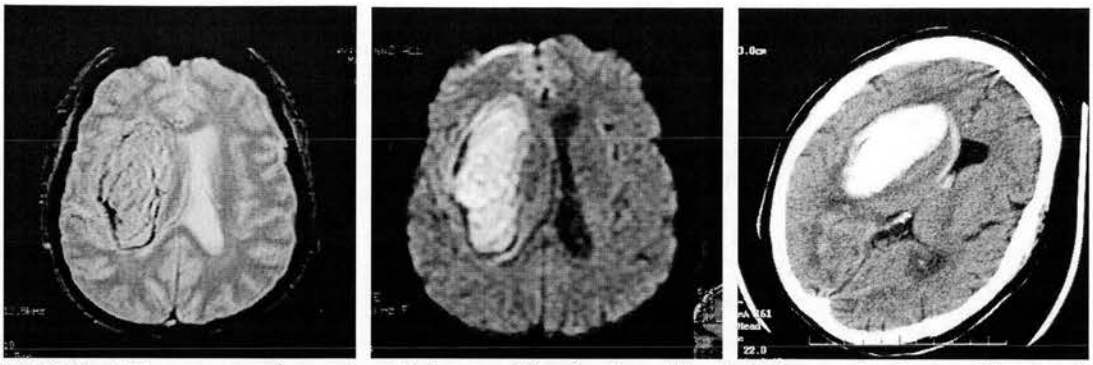
Acute intracerebral haemorrhage

Five patients with acute ICH were scanned with MR before CT (see **Figure 13.5**). Two patients were scanned within a few hours of symptom onset – both presented with a severe clinical syndrome (TACS, NIHSS 22 & 23). The other three patients were scanned greater than 12 hours after symptom onset, and had milder features (classed as PACS, LACS and unsure; NIHSS 12, 3 and 7).

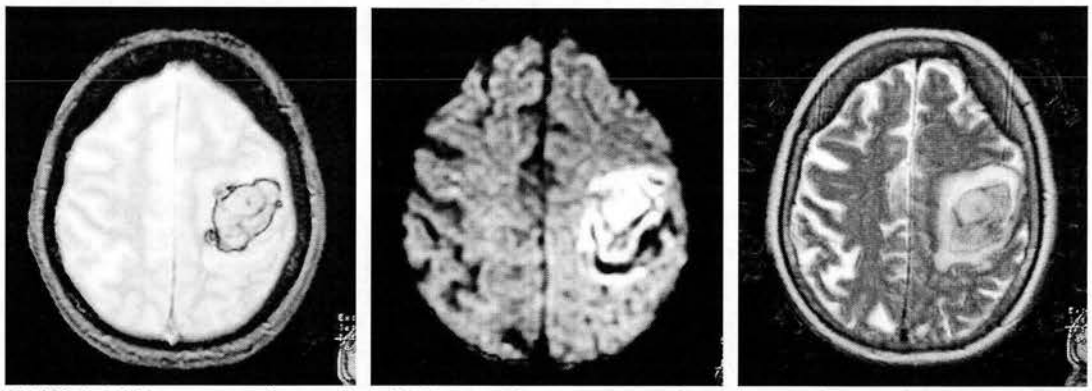
There were several typical features of acute haemorrhage seen on MR. The GRE scan showed an ovoid mass lesion with hypointense (black) margins; the presence of hypointensity was more obvious in patients scanned later. The DWI scan showed a hyperintense (white) lesion, a similar appearance to ischaemia. However, areas of intense hypointensity could often be seen in the lesion on DWI (at the periphery of the lesion when scanned in the first few hours), and the ovoid shape was not the typical wedge shape of an ischaemic lesion. The T2 images (only shown for PH236) were difficult, as the hypointense lines at the rim of the lesion were often not present. In contrast, the CT was very obvious in each case (see **Figure 13.5**).



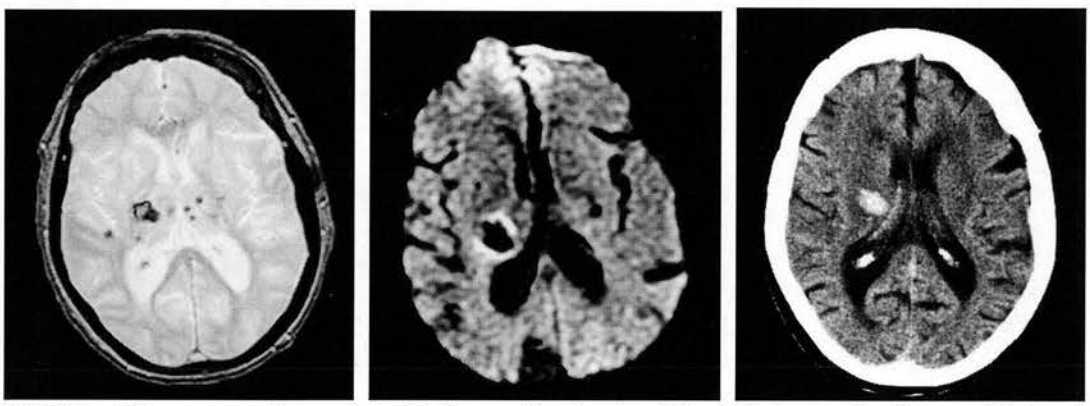
PH391*: MR scan performed at 2 hours 27 minutes following symptom onset. The left image is the gradient echo, middle image is the DWI (large arrows point to the hypointense serpiginous lines often seen), right image is the CT (2 hours 35 minutes).*



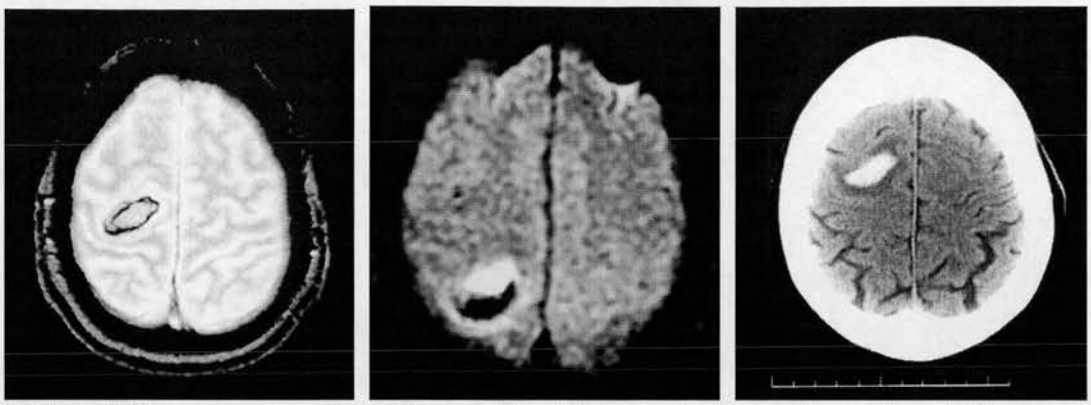
PH243*: MR scan performed at 3 hours 24 minutes. The left image is the gradient echo, middle image is the DWI, and right image is the CT (at 3 hours 38 minutes)*



PH236*: MR scan performed at 12 hours 53 minutes. Left image is the gradient echo, middle image is the DWI and right image is the T2FSE.*



PH284*: MR scan performed at 15 hours 3 minutes. The left image is the gradient echo, middle image is the DWI, and right image is the CT (15 hours 13 minutes).*

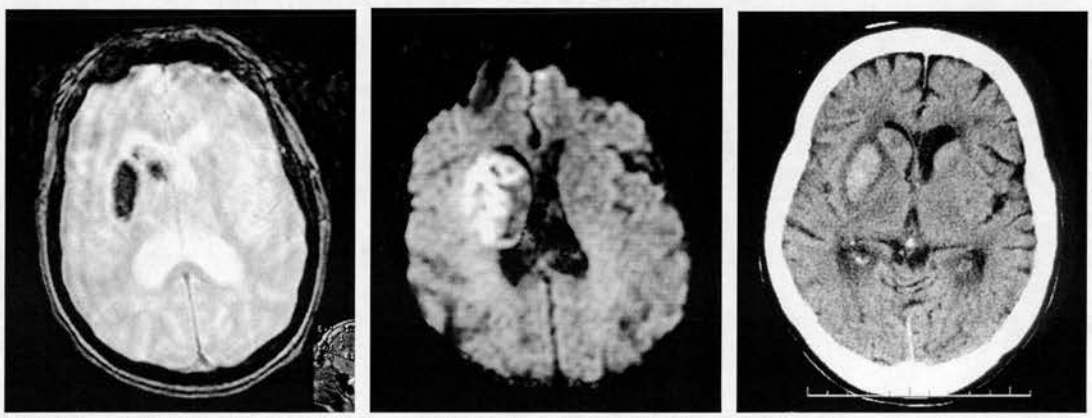


PH265*: MR scan performed at 25 hours. The left image is the gradient echo, middle image is the DWI, and right image is the CT (25 hours 15 minutes).*

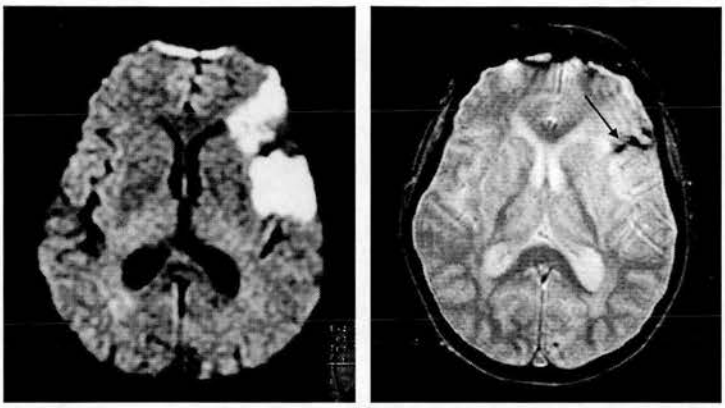
Figure 13.5 The appearance of acute intracerebral haemorrhage on MR in the five patients scanned

Haemorrhagic transformation of an infarct

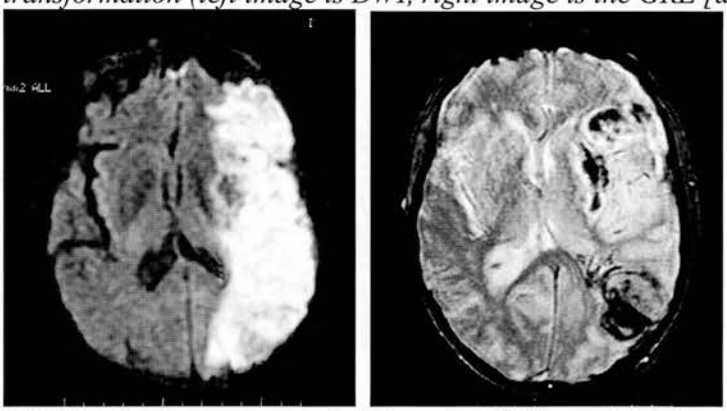
The MR scans identified haemorrhagic transformation of an infarct in three patients, all of whom were scanned after 12 hours (see **Figure 13.6**). The appearance of haemorrhage was characteristic, but not as obvious to the untrained observer as the CT (see PH352, **figure 13.6**). The neuroradiologist considered that patient PH352's lesion was haemorrhagic transformation because there were two lesions (in the caudate and lentiform nucleus) which appeared diffusely petechial with no mass effect.



PH352*: Patient presented with a left TACS. MR performed at 19 hours 45 minutes shows a right striatocapsular infarct with haemorrhagic transformation (left image is the GRE, middle image the DWI). CT 1 hour later (right image) shows the same.*



PH387*: Same patient as* **figure 13.3**. *Patient presented with a left PACS. MR at 29 hours 30 minutes after onset shows a left middle cerebral artery territory infarct with haemorrhagic transformation (left image is DWI, right image is the GRE [arrow points to haemorrhage]).*



PH257*: Patient presented with a L TACS at 2 hours 10 minutes, entered into IST-3 (unknown whether patient received placebo or thrombolysis). MR at 16 hours 36 minutes; DWI (left) showed an extensive hemispheric hyperintensity, and GRE sequence (right) showed extensive haemorrhagic transformation at the edges of the lesion.*

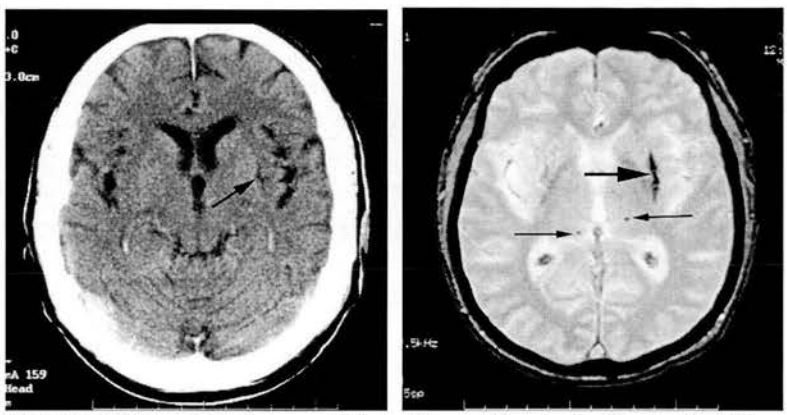
Figure 13.6 Haemorrhagic transformation seen on MR

Remote haemorrhage

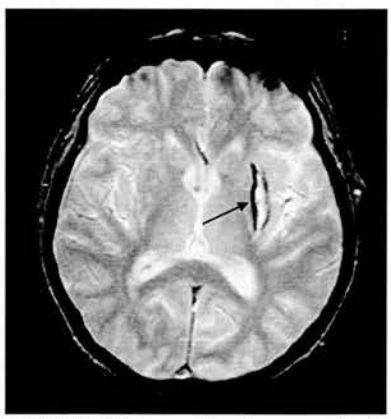
Old discrete haemorrhages

31/92 patients scanned (34%) had evidence of old discrete stroke pathology. 20 patients gave a history of a previous focal neurological deficit (18 patients who had a past history of a focal deficit had no evidence of old stroke pathology on MR). The GRE sequence demonstrated that for 4 of 31 patients (13%, 95% CI 5-39%), the old lesion had actually been a primary intracerebral haemorrhage (PICH). The scans

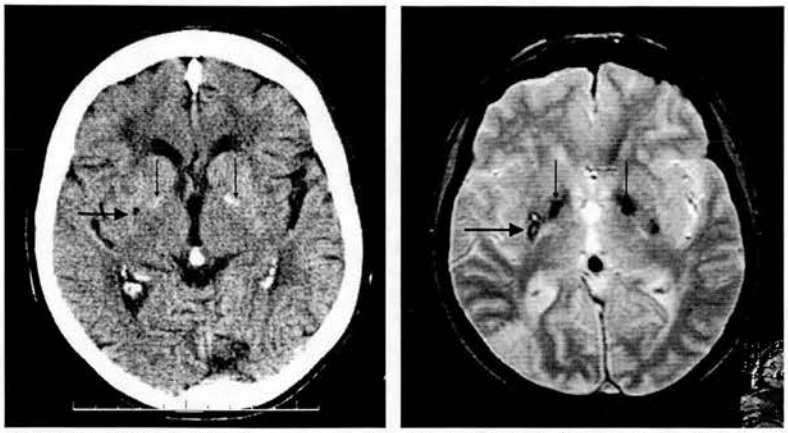
of several patients [PH222, PH393, PH382] are provided in **Figure 13.7**: the CT showed an old slit-like lesion in the basal ganglia, whilst the GRE sequence showed blood breakdown products demonstrating that the stroke had been a PICH.



PH222*: CT on left shows old basal ganglia stroke (arrow), MR on right shows that this event was a primary intracerebral haemorrhage (large arrow) and a few microbleeds (small arrows)*



PH382*: This patient presented with a brief episode of right-sided weakness, GP commenced aspirin. Re-presented several months later with new symptoms – MR shows old bleed (arrow)*



PH393*: This patient presented with a weak left hand, but had a history of multiple events in the past. CT (left) shows an old stroke (large arrow) and basal ganglia calcification (thin arrows). GRE (right) shows a rim of haemosiderin around the old stroke, confirming that it was a bleed (large arrow).*

Figure 13.7 The gradient echo sequence detected old stroke events that were actually haemorrhages

Microbleeds

Ten patients exhibited old microbleeds, seen on the GRE image as small, hypointense (i.e. black) punctate lesions (see **Figures 13.7 & 8**). The frequency in this cohort was therefore 10.9%, with 95% confidence intervals extending from 6.0% to 18.9%. The MR showed an acute infarct in four patients, a PICH in two, and no acute lesion in four (but all had atrophy and or periventricular lucencies). Four of 10 patients had a history of known cognitive impairment, and five had a past history of stroke. The presenting symptoms ranged from mild to severe (NIHSS range 1-23, median 7.5).

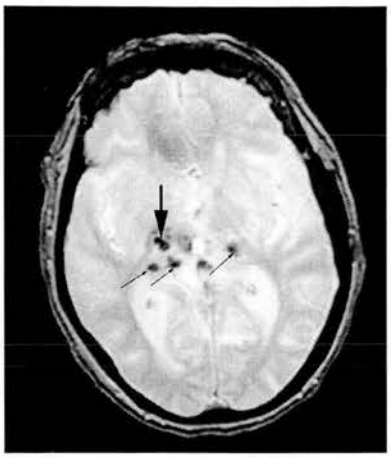


Figure 13.8 Microbleeds seen on the gradient echo MR sequence

This patient presented with an acute PICH (see Figure 13.4), lower extremity of the PICH is marked by large arrow. Small arrows denote microbleeds.

13.4.5 MR brain imaging of ischaemic stroke

82 patients had presumed ischaemic stroke. Of the original 96 patient study cohort, four patients could not tolerate the MR scan, five patients had a definite non-stroke, and five patients had a PICH. The final diagnosis determined by the consensus panel (which was made after viewing the MR) was definite stroke (n=66), probable stroke (n=10), definite TIA (n=3) and possible stroke (n=3). In the following sections I shall describe the findings of advanced MR in the group of patients with definite, probable and possible cerebral ischaemia.

The DWI scan

A hyperintense (or white) lesion was visible on DWI sequence in 64/82 (78%, 95% CI 68-86%) patients. **Figure 13.9** shows that a visible DWI lesion was present in 62 (94%) of those with a final diagnosis of definite stroke, and two (67%) of those with definite TIA. All patients with a final diagnosis of probable or possible

stroke (n=13 in total) had a negative/normal DWI scan (see later for effect on diagnostic certainty).

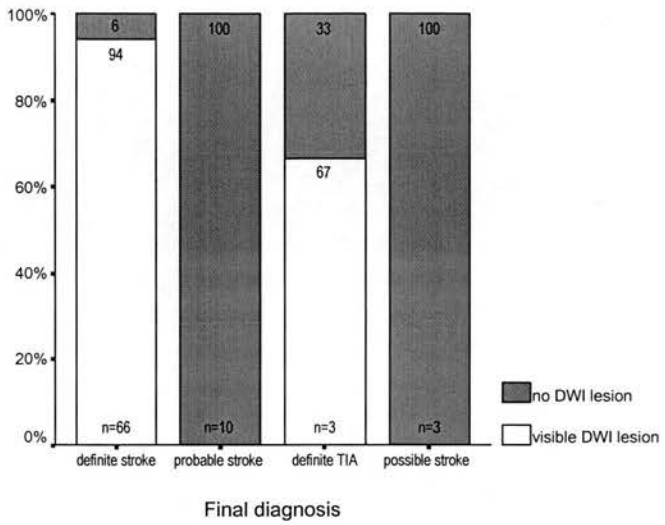


Figure 13.9 Proportion in each diagnostic category with a visible lesion on DWI scan (n=82)

Normal DWI scans

There were 18 (22%) patients with a normal DWI scan: four received a final diagnosis of definite stroke, one received a final diagnosis of transient ischaemic attack, ten were diagnosed as probable stroke, and three as possible stroke. The clinical features of those with and without a visible DWI lesion are compared in **Table 13.5**. The major differences were that patients without a visible lesion were more likely to have brainstem symptoms, an OCSP classification of posterior circulation syndrome, lower NIHSS scores, and signs suggesting brainstem involvement ($p<0.02$ for all). In addition, patients with no lesion on DWI were scanned later than those with a DWI lesion (median 22 hours vs 10 hours, $p=0.06$), but this may have reflected later recruitment of patients with brainstem or milder strokes.

To further investigate the reasons for normal DWI scans, I excluded those with a brainstem lesion (n=8) and reanalysed the data. There was still a significant difference in NIHSS score (median 6.5 for those with a lesion, 3.5 for those with no lesion, p=0.02), and a non-significant trend for those with a DWI lesion to be scanned earlier (median time 9.5 hours vs 22 hours, p=0.12). Those with a visible DWI lesion were more likely to have a cortical syndrome (TACS or PACS) than a lacunar syndrome (61% vs 31%), whilst the reverse was true for those with no visible DWI lesion (33% cortical vs 42% lacunar, p=0.01 for the difference between groups, χ^2).

When those with a final diagnosis of possible stroke or transient ischaemic attack (n=4) were excluded, results were also similar: patients with no visible lesion had a milder clinical syndrome, and the lesion was more likely to be subcortical or brainstem in location.

One patient [PH198] had clinical features of a total anterior circulation syndrome yet had a normal DWI scan. This 98 year old woman woke with symptoms at 8.30am (last normal at 4.30am). On examination, she was mildly drowsy, had a left hemiparesis and gross neglect (NIHSS 11). She was scanned 5 hours and 34 minutes after onset of symptoms (9 hours 34 minutes since last normal). **Figure 13.10** shows the normal DWI scan, and an MRA that demonstrated an occluded right middle cerebral artery.

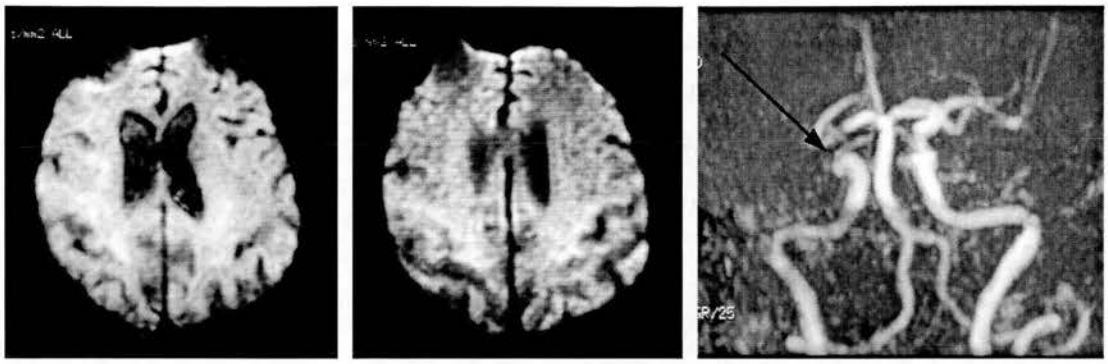


Figure 13.10 A patient with a clinical TACS and an appropriate middle cerebral artery occlusion yet a normal DWI

PH198: *This patient presented with a right TACS (NIHSS 11). MR performed at 5 hours 34 minutes. DWI sequences (left and middle images) showed no evidence of an ischaemic lesion, but the MRA (right image) showed an occluded right middle cerebral artery (arrow).*

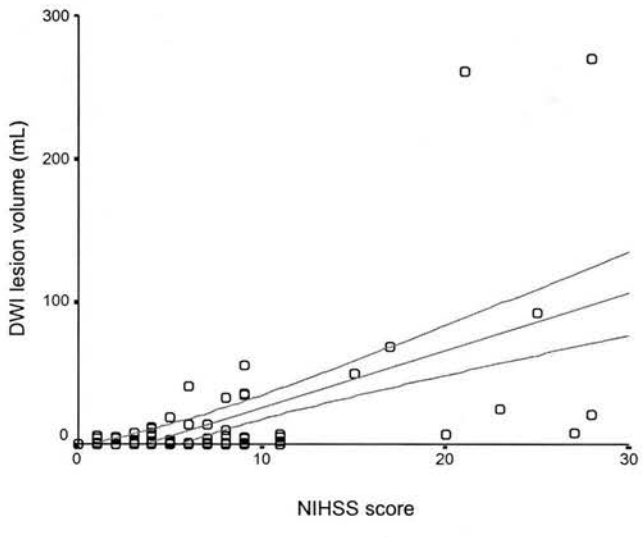
Did lesion volume correlate with stroke severity?

DWI lesion volume data were available for all 82 patients. The median lesion volume was 0.85mL (IQR 0.1-7.6mL), and the mean lesion volume was 14.3mL. Data were dominated by the 18 patients with no visible lesion (volume therefore 0mL), which may have affected the strength of the relationships. Analyses were therefore performed on the whole group, and the subgroup of patients with a lesion.

(1) NIHSS: In **Figure 13.11**, I have plotted the data for all patients with presumed ischaemic stroke (n=82). There was a significant correlation between lesion volume measured on DWI and stroke severity measured by the NIHSS (correlation coefficient, r_S 0.55, $p<0.01$, Spearman's rho). After excluding the patients with no lesion, the association remained significant in the subgroup (r_S 0.51, $p<0.01$, Spearman's rho).

(2) OCSP classification: There was a clear relationship between OCSP classification and DWI lesion volume, with highest volumes observed in those with TACS (see **Table 13.6**), and lowest in those with POCS ($p<0.01$, Kruskal-Wallis).

In the subgroup with a visible DWI lesion, the relationship remained highly significant, although lacunar strokes had the lowest lesion volumes ($p<0.01$, Kruskal-Wallis).



$r^2 = 0.35$, $r_S = 0.55$, $p<0.001$

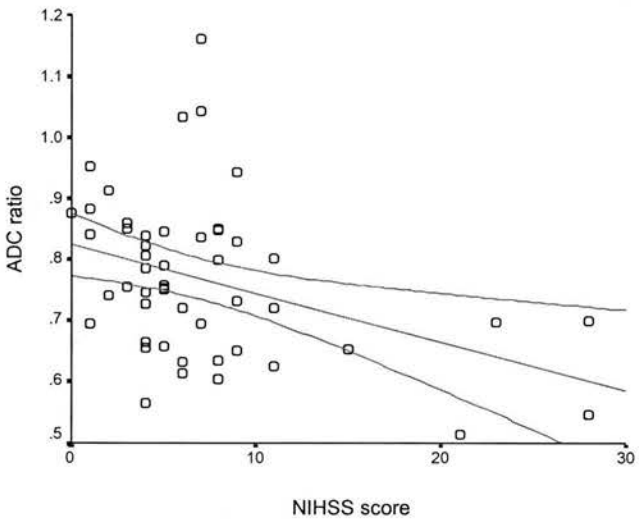
Figure 13.11 Scatterplot of NIHSS versus lesion volume on DWI (with regression line)
Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship (i.e. 35%), r_S is the Spearman correlation coefficient

Apparent Diffusion Coefficient (ADC)

A relative ADC value was calculated for 52 patients. It was not possible to determine ADC in 20 patients with no or very small lesions (due to partial volume effects and other technical reasons pertaining to small lesions), and in 10 patients due to other technical reasons (corrupted data). Of the 52, the final diagnosis was definite stroke in 50 and TIA in two patients. The distributions of age, gender, time to scanning, NIHSS, and OCSP classification were similar to the whole group of 82 patients.

Figure 13.12 shows a significant inverse relationship between NIHSS and ADC (correlation coefficient, r_S -0.35, p=0.01, Spearman's rho). The mean ADCr

(with 95% confidence intervals) for the four OCSP categories is shown in **Figure 13.13**. Overall, there was no significant relationship between mean ADC and OCSP subtype (p=0.08, one-way analysis of variance), and inspection of the graph shows that the mean ADC was actually lower for LACS than for PACS. Patients with a TACS did have a lower mean ADC than PACS, LACS and POCS combined (mean ADC 0.66 vs 0.78, p=0.02, Two-sample t test).



$r^2 = 0.14$, $r_S = -0.35$, $p = 0.01$

Figure 13.12 The relationship between ADCr and stroke severity as defined by NIHSS

Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship (i.e. 14%), r_S is the Spearman correlation coefficient

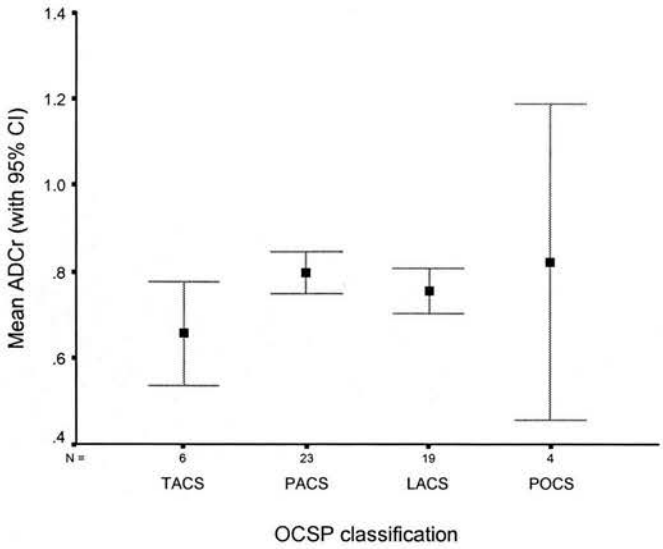
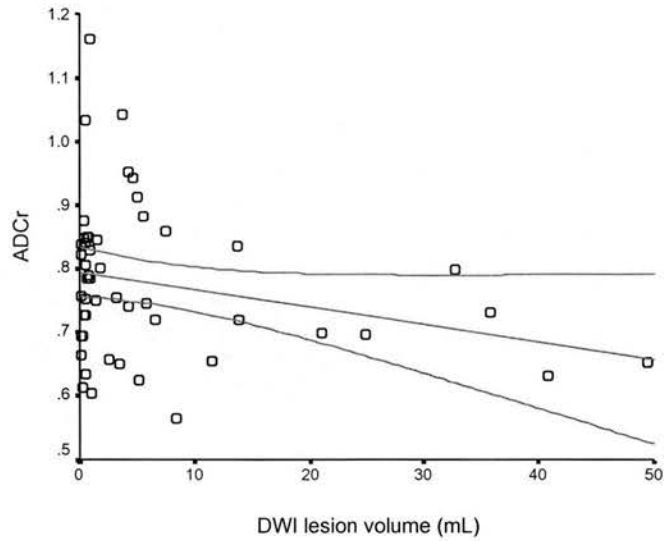


Figure 13.13 The relationship between ADCr and OCSP classification

As the data were Normally distributed (p=0.20, Kolmogorov-Smirnov test for normality) the mean ADCr (with 95% CI) for each OCSP subtype is presented.

Did ADC correlate with DWI lesion volume?

The relationship between ADC and DWI lesion volume is shown in a scatterplot of the 52patients with a measurable ADC (**Figure 13.14**). There was a trend for larger DWI lesion volumes to be associated with lower ADC, but this was a weak correlation that did not reach significance (r_S -0.23, p=0.11, Spearman's rho).



$r^2 = 0.05$, $r_S = -0.23$, $p = 0.11$

Figure 13.14 The relationship between ADC and DWI lesion volume

Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship (i.e. 5%), r_S is the Spearman correlation coefficient

PI parameters

Maps of mean transit time (MTT) and cerebral blood flow (CBF) were available for 68/82 (83%) patients. No PI data were obtained in 14 patients due to patient inability to tolerate the sequence (n=7), or corrupted data that prevented further analysis (n=7). Of the 68, the final diagnosis was definite or probable stroke in 62 (91%), TIA in 3 (4%), and possible stroke in 3 (4%).

The difficulty of interpreting PI maps

PI maps (read with the DWI scans) were coded as no perfusion lesion, focal area of reduced flow consistent with acute ischaemia, or focal area of increased flow/hyperaemia. On the first reading of the PI maps (to determine if a mismatch existed), 23/68 (34%) patients had no PI lesion. On the second reading of the PI maps (to mark the perfusion abnormality so that measurement of lesion volume

could be performed), 27 patients were thought to have had no PI lesion (see **Table 13.7**). This gave a kappa value of 0.81 (very good) for the *intra-observer* reliability of the detection of a PI lesion.

When it came to measuring PI lesion volume, there were 41 patients with a visible PI abnormality (four fewer than after the first inspection). However, a lesion could not be measured in 8/41 (20%) patients. This was because the PI abnormality was in an old stroke lesion (three patients, see **Figure 13.15**), was too small or patchy to measure (three patients, see **Figure 13.16**), or was hyperaemia (two patients, see **Figure 13.17**). Although hyperaemia is an abnormality of perfusion, it is not a deficit of perfusion that could be used to determine mismatch.

Visual examination of the MTT and CBF maps yielded slightly different results – it was possible to have a lesion present on one map but not the other (see **Table 13.8**). When there was disparity in the size of the lesion seen on the two forms of PI, the MTT map was invariably larger (see **Figure 13.18**). Of the 33 patients with a measurable lesion, the MTT map was positive in 29 of 33 scans (88%), the CBF map was positive in 24/33 scans (73%), and 20/33 (61%) patients had lesions on both MTT and CBF maps.

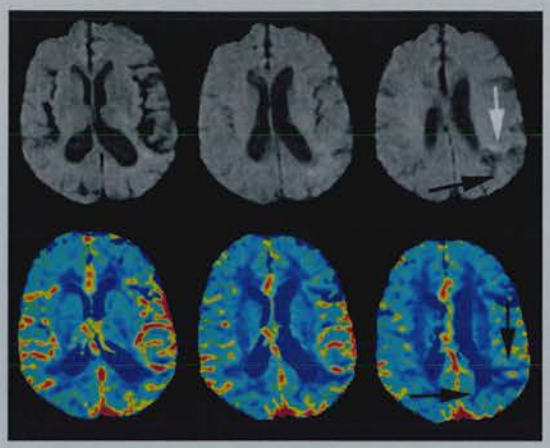


Figure 13.15 Difficulties of measuring a PI abnormality: old stroke lesions

PH260: This patient presented with aphasia and right sided weakness (NIHSS 7). There was a past history of a left middle cerebral artery infarct, and the differential diagnosis was between a seizure or a new ischaemic lesion. The DWI scans (upper row) showed subtle hyperintensity (white arrow) at the margin of the old lesion (black arrow). The CBF maps (lower row) showed a focal area of reduced flow (arrows) to the region corresponding with the old lesion. What part of the reduced flow was new?

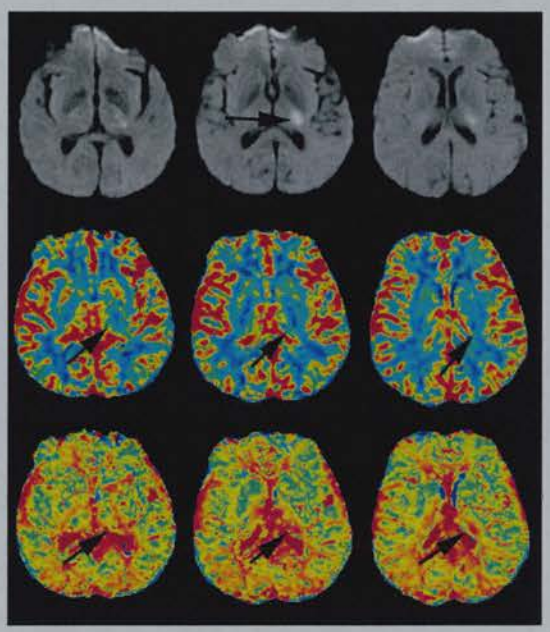


Figure 13.16 Difficulties of measuring a perfusion lesion: small lesions

PH394: This patient presented with right face, arm and leg weakness (NIHSS 5). MR at 3.8hours. The DWI scans (upper row of images) show a left thalamic lacunar lesion (arrow). The CBF (middle row) and MTT (lower row) images show a small region of perfusion abnormality matching the diffusion lesion, but too difficult to draw round and measure.

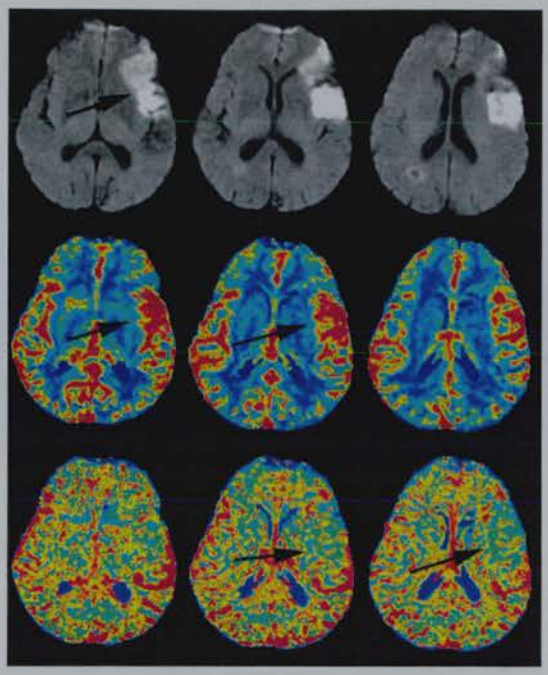


Figure 13.17 Difficulties measuring the PI deficit: hyperaemia

PH387: This patient presented with global aphasia (NIHSS 9). MR at 29.5 hours. The DWI scan (upper row of images) shows a bright ischaemic lesion in the superior branch of the left middle cerebral artery (arrow). The CBF map (middle row) shows a focal area of increased flow (arrows, seen as red) in the same distribution as the DWI abnormality, consistent with hyperaemia and said to be evidence of reperfusion. The MTT maps (lower row) are not as obvious, but also show a focal area of reduced transit. At follow-up, modified Rankin score was two.

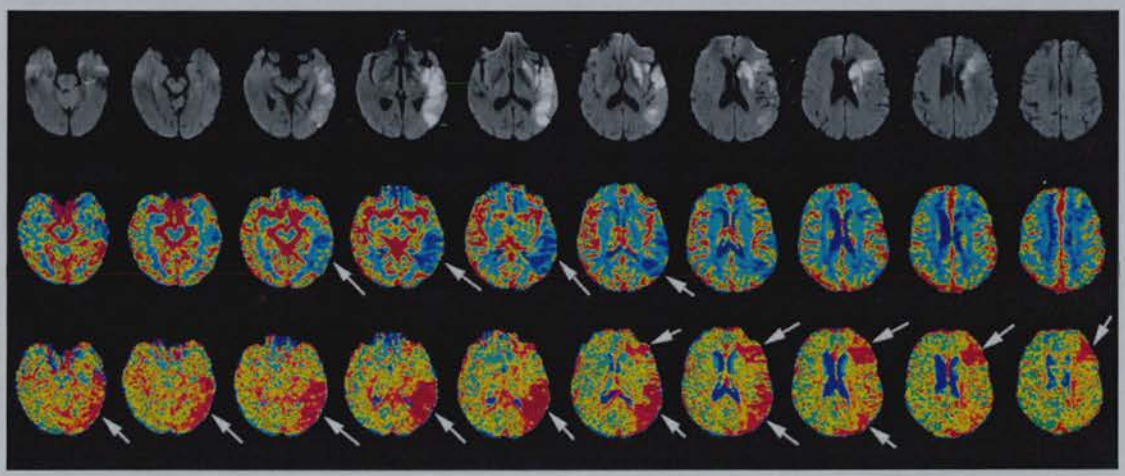


Figure 13.18 Disparity between the size of the perfusion deficit on MTT and CBF maps

PH276: This patient presented with aphasia and weakness of the right face (NIHSS 6). MR at 21.2hours. DWI (top row of images) shows a large left middle cerebral artery distribution hyperintense lesion. The CBF maps (middle row) show a moderate sized focal area of reduced flow consistent with acute ischaemia. The MTT maps (lower row of images) show a much larger area of reduced flow.

No PI lesion

23/68 (34% 95% CI 24-46%) patients with ischaemic stroke had no perfusion deficit (defined as no lesion observed on both MTT and CBF maps on the **first** inspection). The features of patients with and without a visible perfusion abnormality are detailed in **Table 13.9**. The major differences were that patients without a PI lesion were scanned much later (24 hours vs 9 hours, $p<0.01$, Mann-Whiney U), had milder strokes (e.g. median NIHSS 4 vs 7, $p<0.01$, Mann-Whiney U) and more often had a lacunar (61% vs 16%, $p<0.01$, χ^2) or brainstem syndrome (22% vs 4%, $p=0.03$, χ^2). DWI lesion volume was significantly higher in those with a perfusion abnormality (median 4.7mL vs 0.2mL, $p<0.01$, Mann-Whiney U). The final diagnosis was more likely to be a probable than definite stroke in those without a visible PI lesion.

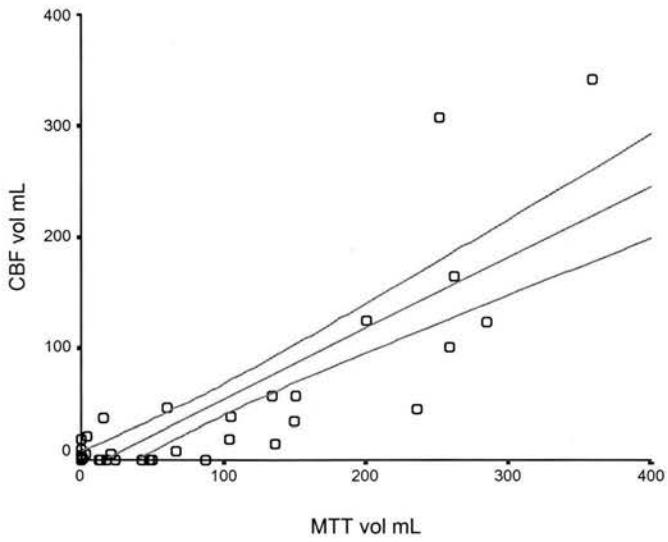
How often was there a PI lesion in patients with no DWI lesion?

18 patients with cerebral ischaemia had no visible lesion on DWI. 14 received perfusion imaging (unsuccessful or abandoned in the remainder). Of the 14, the clinical classification was POCS in five, LACS in four, and PACS in two (three were unknown). Nine of the 14 had no PI lesion. The final diagnosis was probable stroke in six, possible stroke in one and definite stroke in two. Five patients with no DWI lesion had a visible PI lesion; the final diagnosis was definite TIA in one, probable stroke in two, and possible stroke in two (both patients had symptoms of vertigo).

Did lesion volume correlate with stroke severity?

PI lesion volumes were calculated in all 68 patients. The 35 scans with no measurable perfusion abnormality were given a zero volume. On MTT maps, 39

(55%) patients had no lesion, so the median lesion volume was 0mL, mean 49.2mL. Of those with a measurable lesion (29 patients), median lesion volume was 66.2mL and mean 107.3mL. On CBF maps, 44 patients had no lesion, so the median lesion volume was also 0mL, mean 23.3mL. Of the 24 with a measurable lesion, median lesion volume was 35.4mL and mean 66.0mL. There was a strong correlation between MTT and CBF lesion volume (r_S 0.70, $p<0.01$, Spearman's, see **Figure 13.19**).

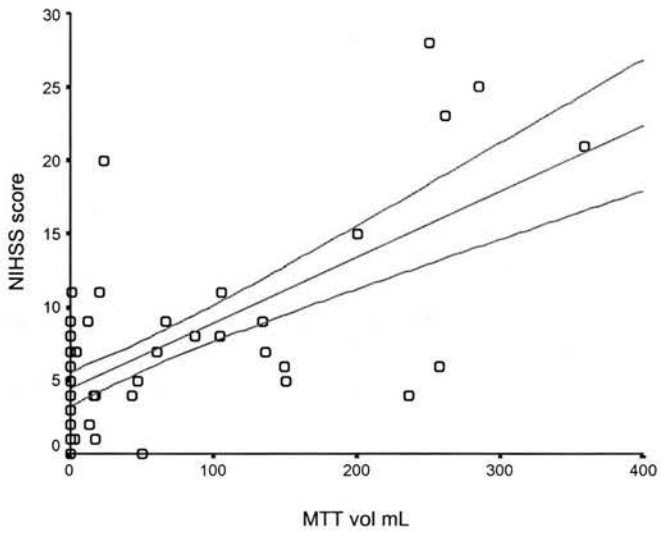


$r^2=0.69$, $r_s=0.70$, $p<0.01$

Figure 13.19 Correlation between lesion volume on CBF and MTT maps

Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship (i.e. 69%), r_S is the Spearman correlation coefficient

(1) MTT and NIHSS: There was a significant relationship between MTT lesion volume and stroke severity (measured by the NIHSS) in all 68 patients (r_S 0.46, $p<0.01$, Spearman's, see **Figure 13.20**). The relationship remained significant if only those with a measurable lesion were included (n=29, r_S 0.45, p=0.02, Spearman's).

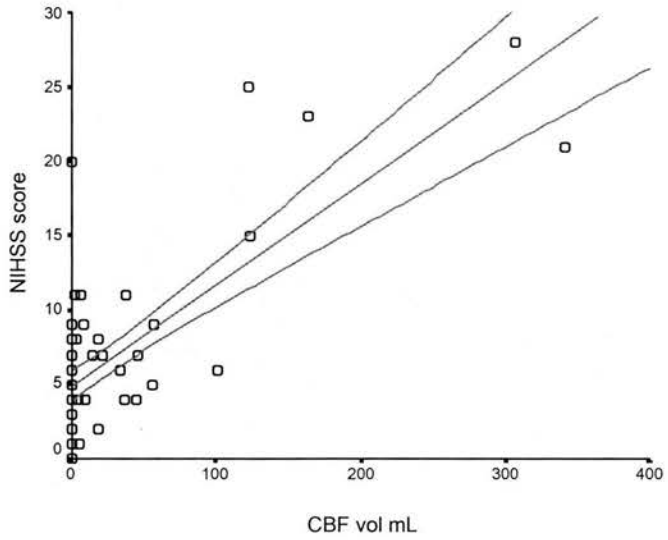


$r^2=0.45$, $r_s=0.46$, $p<0.01$

Figure 13.20 The relationship between MTT lesion volume and NIHSS (all patients, n=68)

Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship, r_S is the Spearman correlation coefficient

(2) CBF and NIHSS: A significant relationship was also observed when CBF was used as the measure of perfusion. **Figure 13.21** shows the relationship for all patients (n=68, r_S 0.46, p<0.01, Spearman's). The relationship was also significant for the subgroup with a measurable lesion (n=24, r_S 0.45, p=0.03, Spearman's).



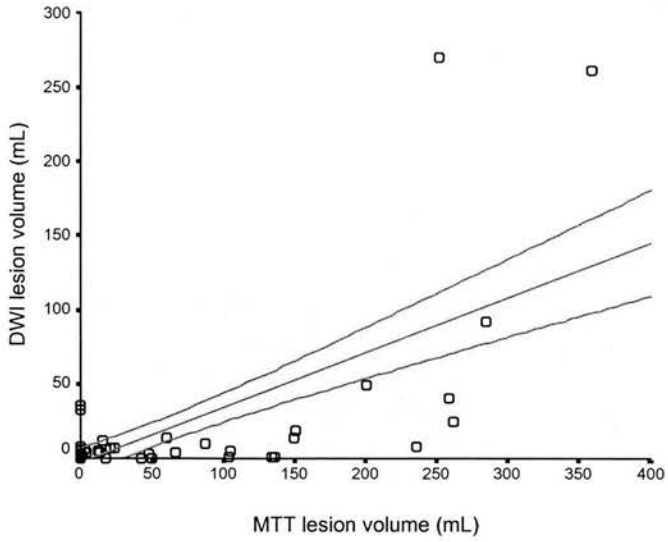
$r^2=0.54$, $r_s=0.46$, $p<0.01$

Figure 13.21 The relationship between CBF lesion volume and NIHSS (all patients, n=68)
Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship, r_S is the Spearman correlation coefficient

Lesion volume on PI and the OCSP clinical classification were associated (see **Table 13.10**), with higher volumes observed for TACS than PACS, LACS and POCS ($p<0.01$, Kruskal-Wallis).

Which correlated better with stroke severity: PI or DWI?

There was a clear relationship between lesion volume on DWI and PI scans (r_S 0.63, $p<0.01$, Spearman's, see **Figure 13.22**). Larger DWI lesions were associated with larger lesions seen on the MTT map, but at lower DWI lesion volumes the association was not as clear (small DWI lesions could have an MTT lesion of up to 100mL). The relationship between MTT lesion volume and NIHSS, and between DWI lesion volume NIHSS, is shown in an overlay scatterplot (**Figure 13.23**). For the 68 patients who had both PI and DWI imaging, the DWI lesion volume (r_S 0.69) was more strongly associated with severity than was MTT lesion volume (r_S 0.45).



$r^2=0.46$, $r_s=0.63$, $p<0.01$

Figure 13.22 The relationship between DWI lesion volume and PI lesion volume (on MTT))

Each point represents a single patient; the straight line represents the line of fit (determined by linear regression) and the surrounding lines represent the 95% confidence intervals for the line of fit. r^2 is the proportion of the variability explained by the relationship, r_S is the Spearman correlation coefficient

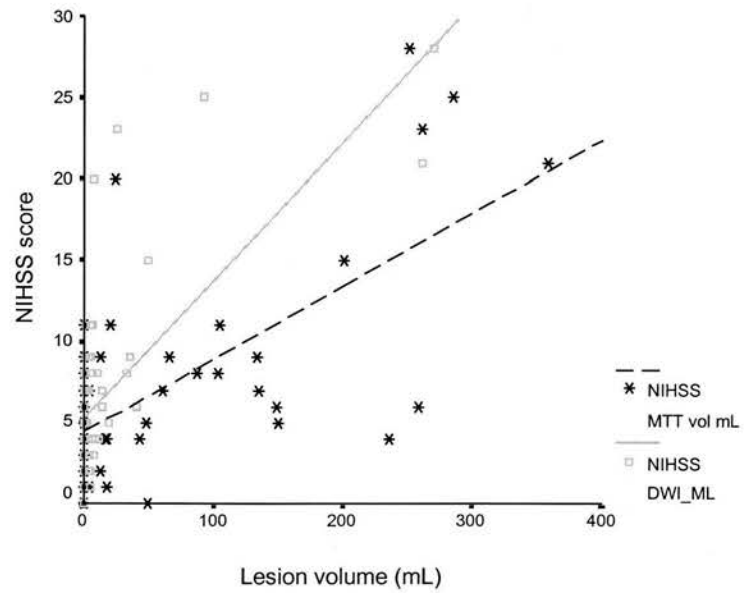


Figure 13.23 How did DWI lesion volume and PI lesion volume compare?

NIHSS-DWI $r_S = 0.69$, NIHSS-MTT $r_S = 0.46$

Each point represents a single patient; the lines represent line of fit for DWI and MTT (determined by linear regression). r_S is the Spearman correlation coefficient

13.4.6 The accuracy of MR brain imaging compared to the final consensus panel diagnosis

MR data were obtained in 92 patients. All patients had structural imaging (gradient echo and T2 images), but one patient [PH372] did not have DWI (the structural imaging showed a brain tumour, so other sequences were performed instead of the DWI).

A CT brain scan was performed in addition to the MR for 62/92 (66%) patients. The CT was performed after the MR in 40/62 (median time between scans 0.8 hours, mean 7.0 hours), and before the MR in 22/62 (median time between scans 1.1 hours, mean 6.2 hours).

The sensitivity and specificity of structural and advanced MR

To assess accuracy parameters consistently with earlier chapters (**Chapters 7,8 & 11**), the final diagnosis was dichotomised to 'thrombolysis-eligible' stroke (definite stroke, TIA or probable stroke, n=84) or mimic (definite non-stroke or possible stroke with a plausible non-stroke explanation, n=8). The measure of imaging accuracy was whether a relevant stroke lesion was seen (which assumed that a negative scan was unhelpful). The expert panel had seen all brain scans when the final diagnosis was made.

I have tabulated sensitivity, specificity, positive and negative predictive value and overall accuracy for the CT brain, structural MR and DWI scan in **Table 13.11**. As the final diagnosis was strongly influenced by the imaging findings, no patients with a mimic were found to have a relevant stroke lesion, thus the likelihood ratio (not shown on the table) for all imaging was infinity, and the specificity and positive predictive value were also 100%. However, the sensitivity of CT and structural MR

was 43% (i.e. a relevant stroke lesion was shown by imaging in less than half of those with a stroke), and the overall accuracy was 48%. In contrast, the sensitivity of the DWI sequence was almost double that of the CT and the structural MR (82%), and overall accuracy was 84%.

When (and how) did DWI help?

The DWI image showed a relevant stroke lesion for 69 patients with a 'thrombolysis-eligible' stroke (sensitivity 82%), whilst the structural MR showed a relevant lesion for 36 patients (sensitivity 43%). The nature of the lesion seen on DWI in the 33 patients with a normal T2 is shown in **Figure 13.24**. The most frequent type of lesion was lacunar (13 patients, 39%, see **Figure 13.25**), followed by several discrete lesions in the middle cerebral artery territory (6 patients, 18%, see **Figure 13.26**) and an individual small lesion in middle cerebral artery territory (6 patients, 18%, see **Figure 13.27**).

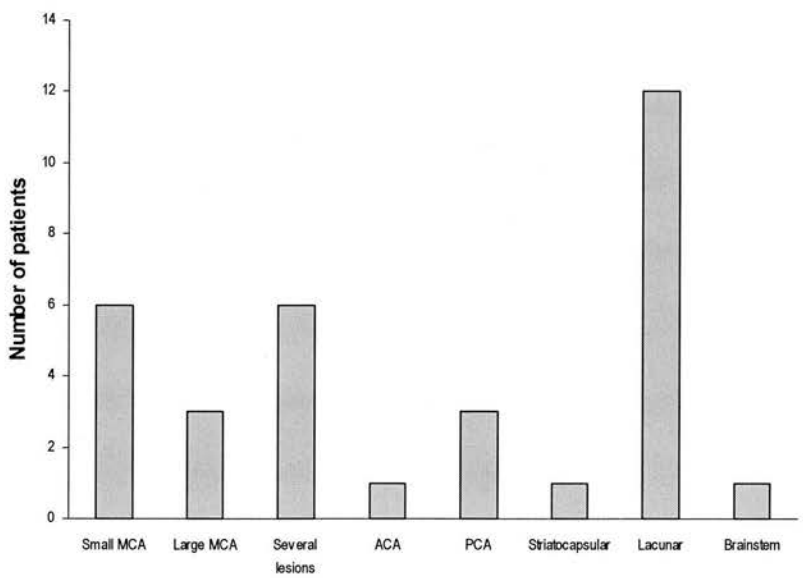


Figure 13.24 Location of the lesion seen on DWI when structural imaging was normal (n=33)

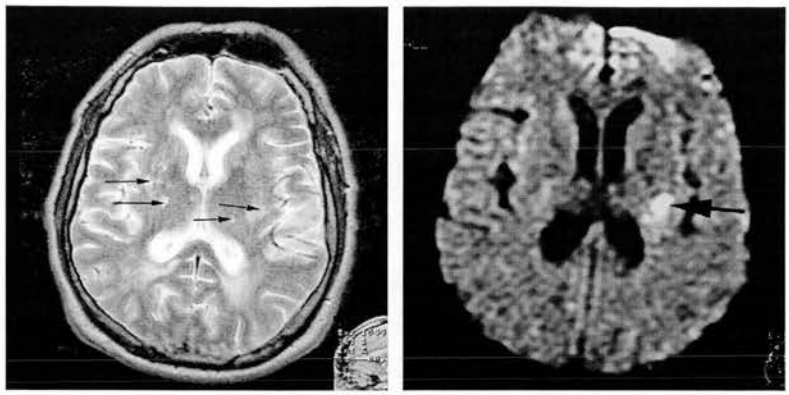


Figure 13.25The DWI scan clearly showed lacunar infarcts

PH300*: MR at 14 hours 24 minutes. T2 image (left) showed several old lacunar lesions and a subtle right thalamic/external capsule lesion (arrows), but there was no way of telling that this was the recent lesion. DWI (right) showed an obvious right hyperintensity (arrow).*

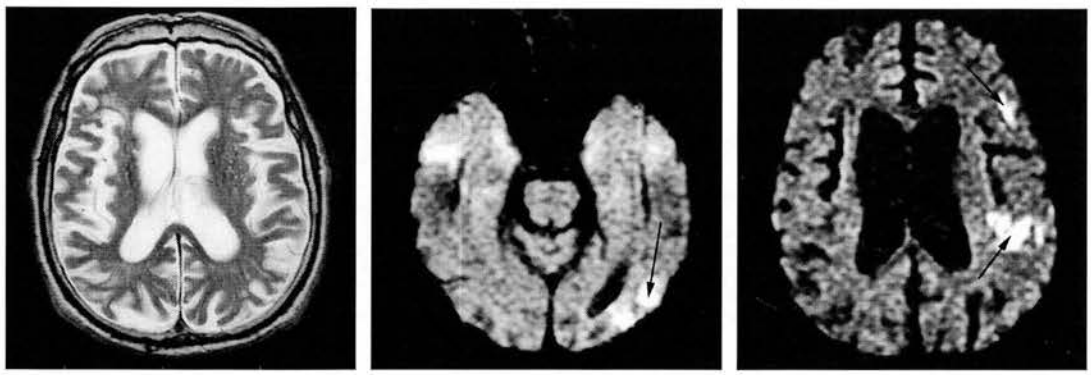


Figure 13.26 The DWI scan showed scattered lesions throughout the middle cerebral territory (not seen on structural MR)

PH354*: Presented with a left PACS. MR at 4 hours 49 minutes. T2 image (left) showed several old lesions in both hemispheres, whilst DWI (middle and right) showed several scattered high signal lesions in borderzone territory (arrows).*

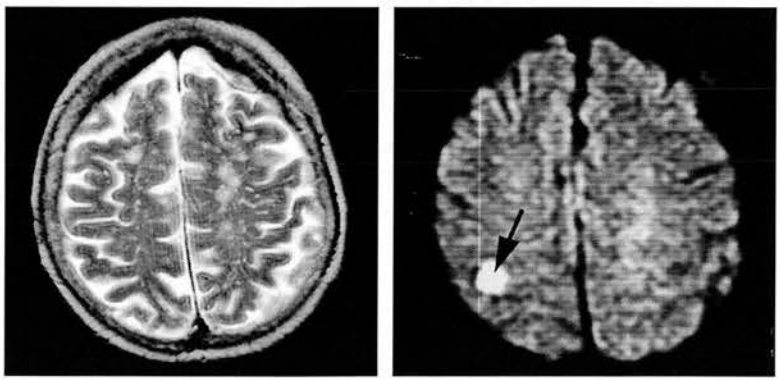


Figure 13.27 The DWI scan showed a small cortical lesion (not seen on structural MR)

PH393 (same patient as in **figure 13.7**)*: Patient presented with a weak left hand. MR at 6.5 hours. T2 image (left) shows leukoariosis and old stroke lesions (not shown), whilst the DWI (right) showed an obvious right parietal hyperintensity (arrow).*

In addition, the DWI was coded as helpful for 19 patients where the structural imaging also showed an ischaemic lesion. In 11 patients (58%) the DWI confirmed that a subtle lesion seen on the T2 image was a relevant infarct (see **Figure 13.28**). In four patients (21%), the DWI identified the one acute lesion amongst several older lesions (see **Figure 13.29**). In the remainder, the DWI was helpful because it showed several lesions (n=2), confirmed that a haemorrhagic lesion was actually haemorrhagic transformation of an underlying infarct (n=1), and showed a smaller lesion than seen on the T2 image (which one might interpret as that reperfusion had occurred).

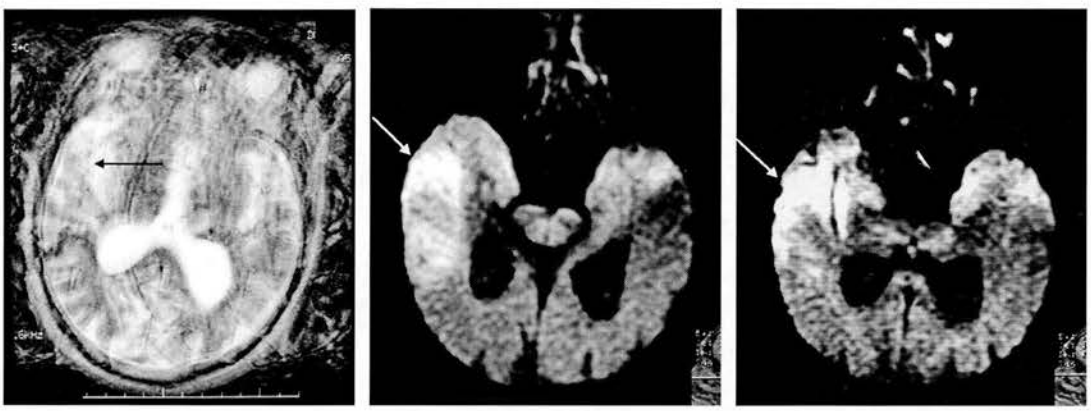


Figure 13.28 The DWI scan confirmed that a subtle abnormality seen on T2 was an acute infarct

PH384*: Presented with a right PACS (NIHSS 5). MR at 2hours 49 minutes. T2 image (left, badly degraded by movement artefact) showed a possible area of increased signal in right parietal region (arrow), whilst the DWI (middle and right images) showed an obvious hyperintensity (arrows).*

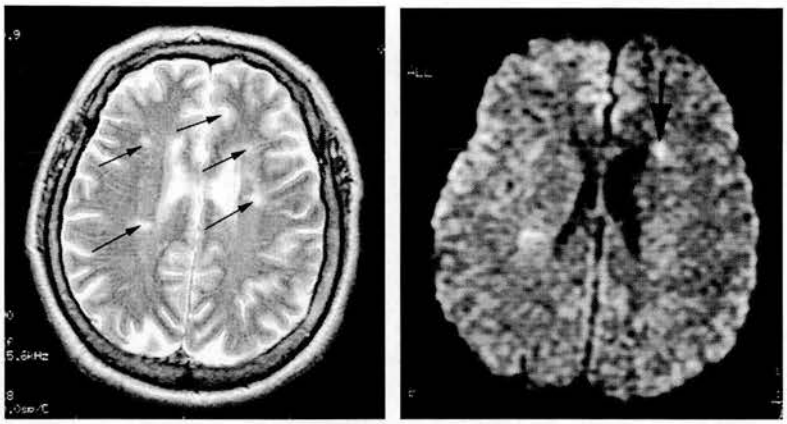


Figure 13.29 The DWI scan identified an acute lesion amongst several lesions seen on T2
PH246*: Presented with left LACS (NIHSS 6). MR performed at 26 hours. The T2 image (left) showed several high signal lesions (arrows), whilst the DWI (right) showed a single left frontal hyperintense lesion (arrow)*

The DWI scan was of no additional benefit in the identification of haemorrhage (n=5). When the DWI was normal (21 of 91 patients who had DWI), it was often difficult to know whether this had been helpful. For those considered to be a definite non-stroke who had DWI performed (n=4), a normal DWI scan was reassuring. For the three patients with a final consensus panel diagnosis of possible stroke, the normal DWI was of little benefit. The DWI was normal in one patient with a definite TIA (imaged shortly after symptoms resolved completely). The clinical features were considered strong enough evidence to classify four patients as definite stroke (one with TACS, three with LACS), and 10 patients as probable stroke (four with POCS, three with PACS, one with LACS and two unsure), despite the absence of a DWI lesion.

13.4.7 The impact of advanced imaging on the clinician's diagnosis

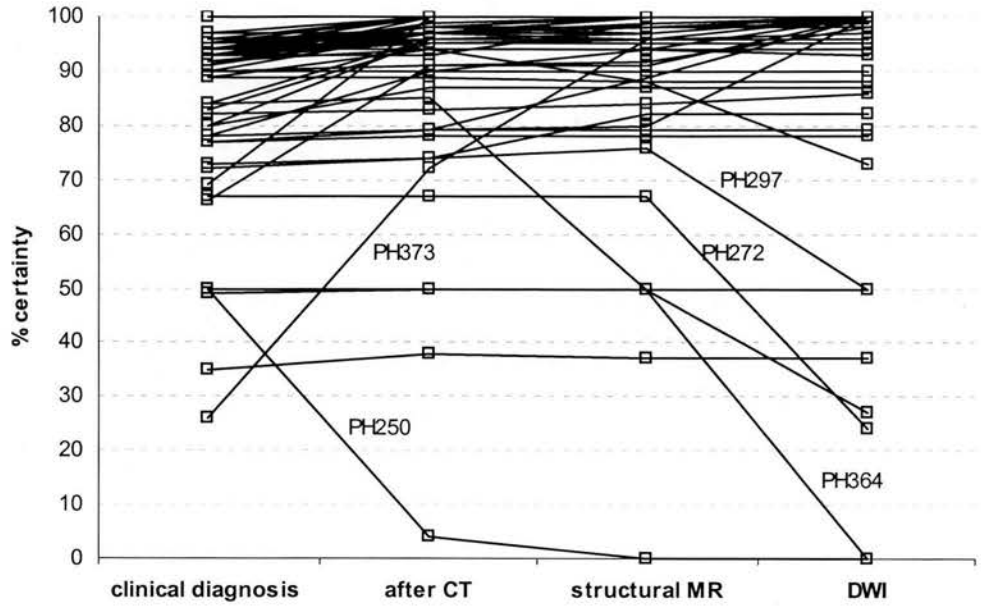
91 patients were available for analysis (four aborted the MR due to claustrophobia, one patient did not have DWI). The 62 patients who had a contemporaneous CT formed the main analysis group, as data were available for all

four levels of the diagnostic process (clinical diagnosis, diagnosis after CT, diagnosis after structural MR, diagnosis after DWI).

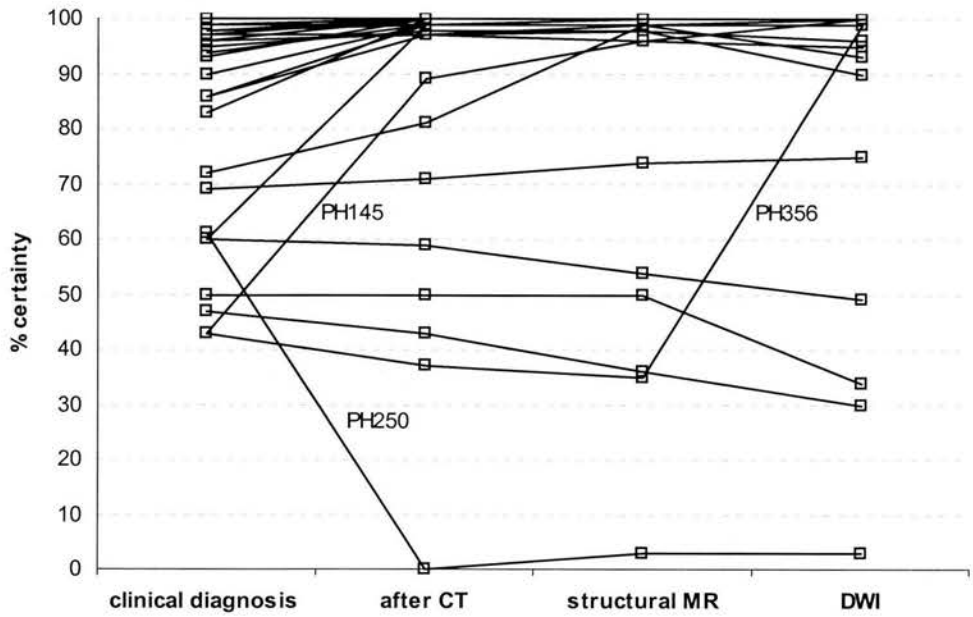
There were four clinicians present at the meeting for 11/62 patients (18%), five were present for 27 patients (44%), six present for 14 patients (23%), and seven clinicians present for 10 patients (16%). Clinicians provided an opinion on an average of 42 patients (range 30 – 58).

Diagnostic certainty

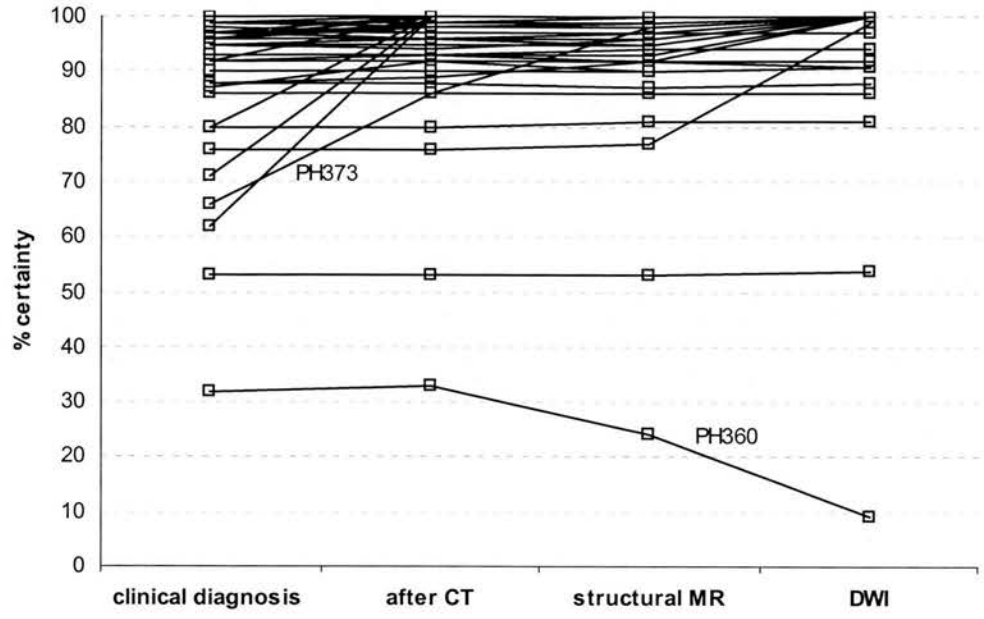
I have plotted percentage certainty at the four levels of the diagnostic process for each clinician, with each line representing a patient, in **Figure 13.30**. Several trends can be distinguished: (1) clinicians were certain about the diagnosis for the majority of patients after the clinical assessment; (2) the CT scan appeared to improve certainty more than either form of MR for most patients; (3) for a small number of patients, the DWI scan increased certainty (for stroke and non-stroke); (4) some clinicians (e.g. clinician six) appeared to rely on imaging more than others (e.g. clinician four), and (5) there were many common patients (some are marked by study number in each graph) who had almost identical lines by each consultant.



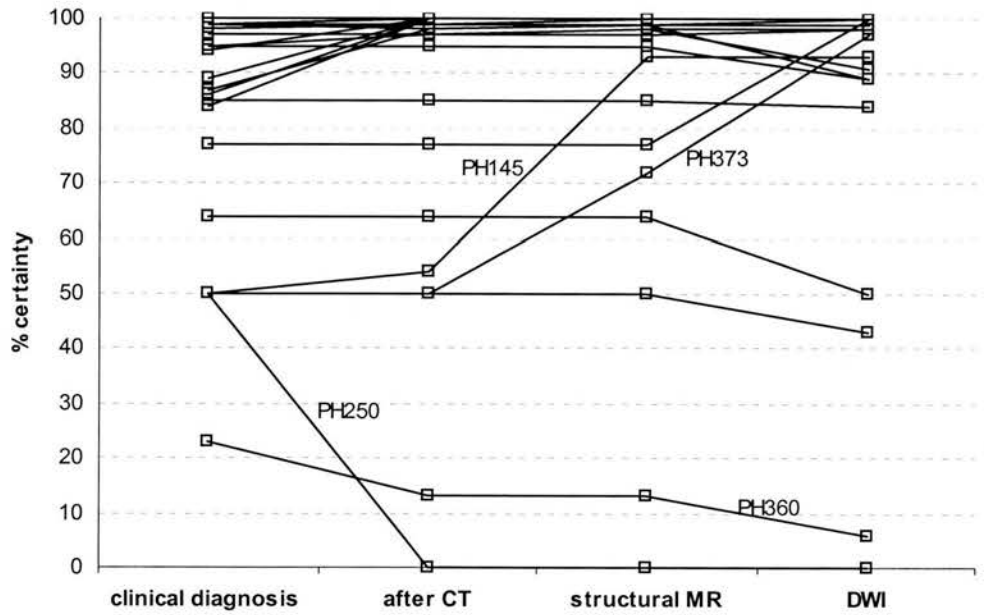
Clinician 1 (n=58)



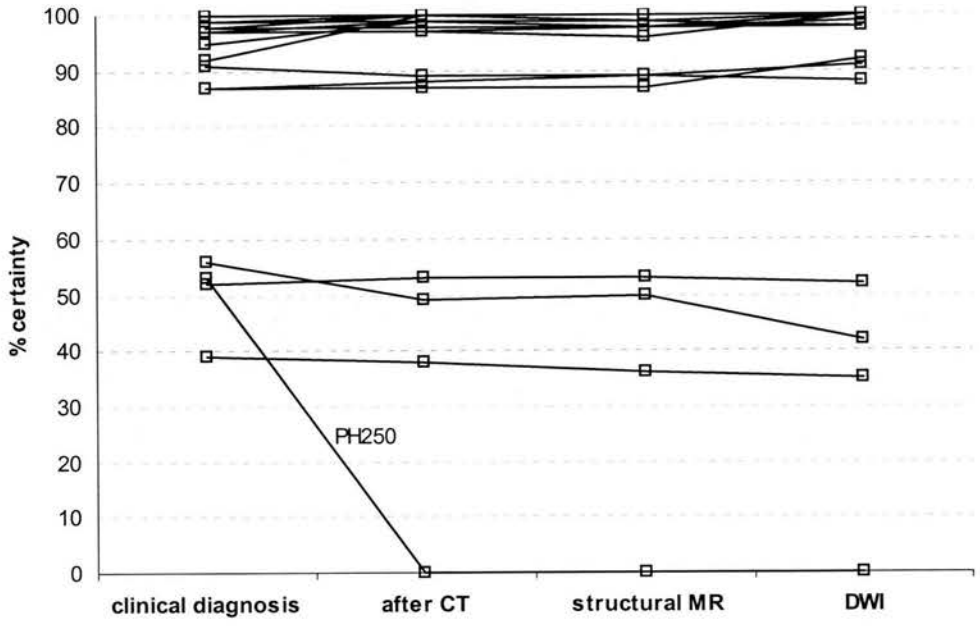
Clinician 2 (n=40)



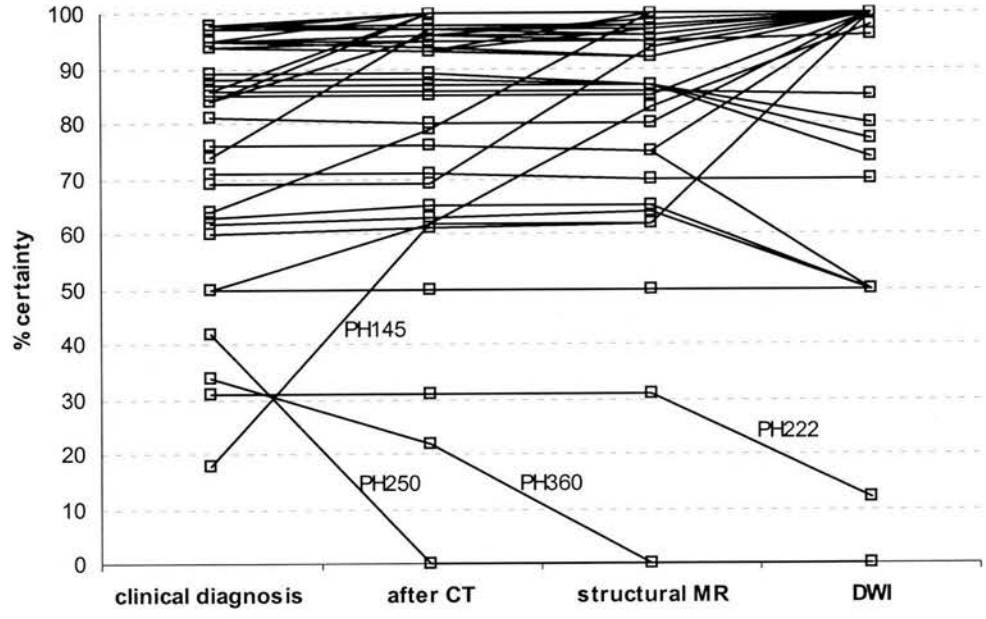
Clinician 3 (n=40)



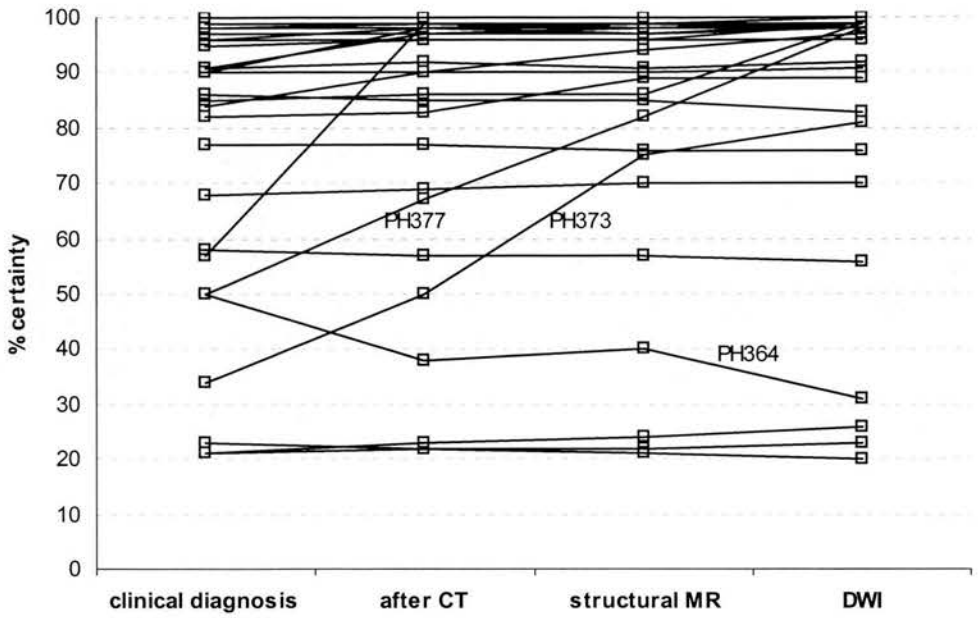
Clinician 4 (n=30)



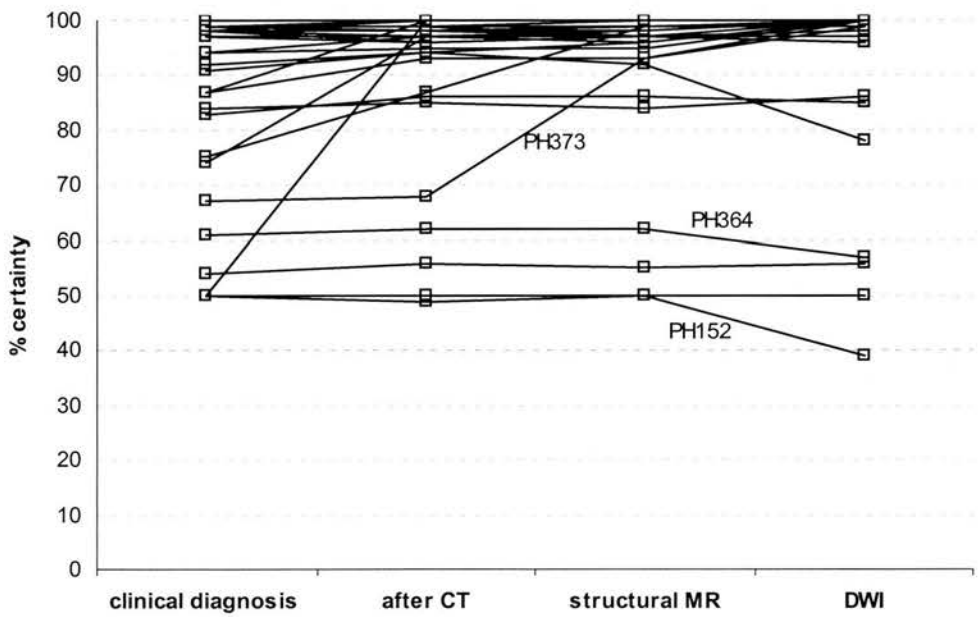
Clinician 5 (n=23)



Clinician 6 (n=55)



Clinician 7 (n=41)



Clinician 8 (n=39)

Figure 13.30 Impact of brain imaging on diagnostic certainty for all clinicians (only patients who had both CT and MR included)

Common patients: the outliers

The mean diagnostic certainty for patients with a final diagnosis of definite stroke was 89.4% after the clinical assessment, and increased to 97.5% after all the imaging. These patients were in the top part of the graph for each clinician. Yet there were some 'outliers' (marked by study number in each graph). Inspection reveals that these patients had almost identical lines for each consultant. PH250 presented with abrupt onset of left-sided weakness (NIHSS 8 on examination), but also had known lung carcinoma. CT showed a solitary high-density lesion, possibly a metastasis, possibly a meningioma. MR confirmed that the lesion was a meningioma. The clinicians were uncertain after the clinical assessment, but convinced after the CT that the diagnosis was non-stroke.

PH360 presented after a probable seizure, with a subtle (and questionable) focal deficit. Most clinicians felt that stroke was possible based on the clinical assessment. The normal CT was a little helpful, but the normal DWI was far more helpful in reducing the certainty that this event had been a stroke. PH364 presented with worsening of neurological deficit from a previous stroke; there had also been symptoms suggesting a chest infection. The CT showed old stroke lesions, but the DWI was normal. Most clinicians were reassured by this, and certainty of a non-stroke cause for symptoms increased.

PH373 presented with progressive neurological impairment, and lacked typical risk factors for stroke. However, CT showed early ischaemic changes, as did the structural MR and DWI. Clinicians 1 & 7 were around 25% certain after the clinical assessment, whilst clinicians 3 & 8 were around 66%, with certainty improving markedly after the CT for two, and after the MR for the remainder.

PH145 presented with speech impairment. The previous night, she had a typical migraine accompanied by visual impairment. On examination, she was confused, and had slight hesitancy of speech (NIHSS 1). The CT suggested subtle early ischaemic changes in the left insular cortex, which was confirmed by both structural MR and DWI. Again, clinicians were uncertain after the clinical assessment, but convinced after the imaging (although some clinicians were more convinced by the CT [e.g. clinician 2], and others by the MR [e.g. clinician 4]).

There were 10 patients with mean certainty of less than 70% after the clinical assessment. After imaging, there was a major change in certainty for six patients (three towards a diagnosis of stroke, three towards non-stroke). The mean change in certainty for all ten patients was 21.8%.

Overall change in certainty with each imaging modality

Table 13.12 displays several measures of how imaging changed diagnostic certainty for the 62 patients who had CT, structural MR and DWI. As anticipated from visual inspection of the line graphs (**Figure 13.30**), CT had the greatest impact on certainty, although the overall effect was modest (3.7%). For 90% of patients, the CT increased mean certainty. The structural MR conferred a small change in certainty compared with the CT (1.1%), but for almost 20% of patients mean certainty was unchanged, and for an equal number of patients, certainty actually reduced. The addition of DWI changed mean certainty by 2.0%, although the range was large. For 18% of patients, the DWI made the clinicians less certain, and for 16% of patients the DWI did not change certainty.

Two-way ANOVA tests for the mean change in certainty between clinical assessment to CT, CT to structural MR, and structural MR to DWI showed that the

mean variation in certainty for patients was significant ($p<0.01$ for each test). There was less variation in certainty for clinicians ($p>0.12$ for each test), although clinician two had the greatest mean change in certainty after CT (5.2%), and clinician six had the greatest change in certainty after MR (2.4% for structural MR, 4.4% for DWI). Clinician four found DWI the least useful (0.3% change in certainty).

How often were clinicians 100% certain of the diagnosis?

Imaging had a major effect on the number of times clinicians were 100% certain that the diagnosis was stroke, as shown in **Table 13.13**. After the clinical assessment, clinicians (with two exceptions) were completely certain for only a few patients. After the CT was presented, certainty of 100% increased to between 15-20% of patients. After the DWI scan, most clinicians were 100% certain of the diagnosis for 60-70% of the patients. The exceptions were clinicians 4 and 8, who were convinced by the history more often than the others; and clinician 7, who was rarely 100% convinced about any patient.

Stroke severity and the impact of imaging on certainty

The impact of imaging on diagnostic certainty when patients were divided by measures of stroke severity was assessed for all 87 patients who had DWI MR (and received a final diagnosis of definite, probable, or possible stroke). As this analysis included patients who did not have CT, the results do not show the additional benefit of DWI over CT.

When divided into OCSP categories (see **Figure 13.31**), imaging had the greatest overall effect on certainty in those with a classification of PACS (mean increase of 9.1%, from 87.8 to 96.9% certain). When divided into NIHSS categories, imaging had the greatest effect on certainty in those with NIHSS 1-4 (mean increase

of 6.7%, from 85.3 to 91.9% certain). There were only four patients with NIHSS of zero, hence confidence intervals were very wide. Those with NIHSS > 10 had a mean increase of 5.3%: from 94.5% to 99.8% certain.

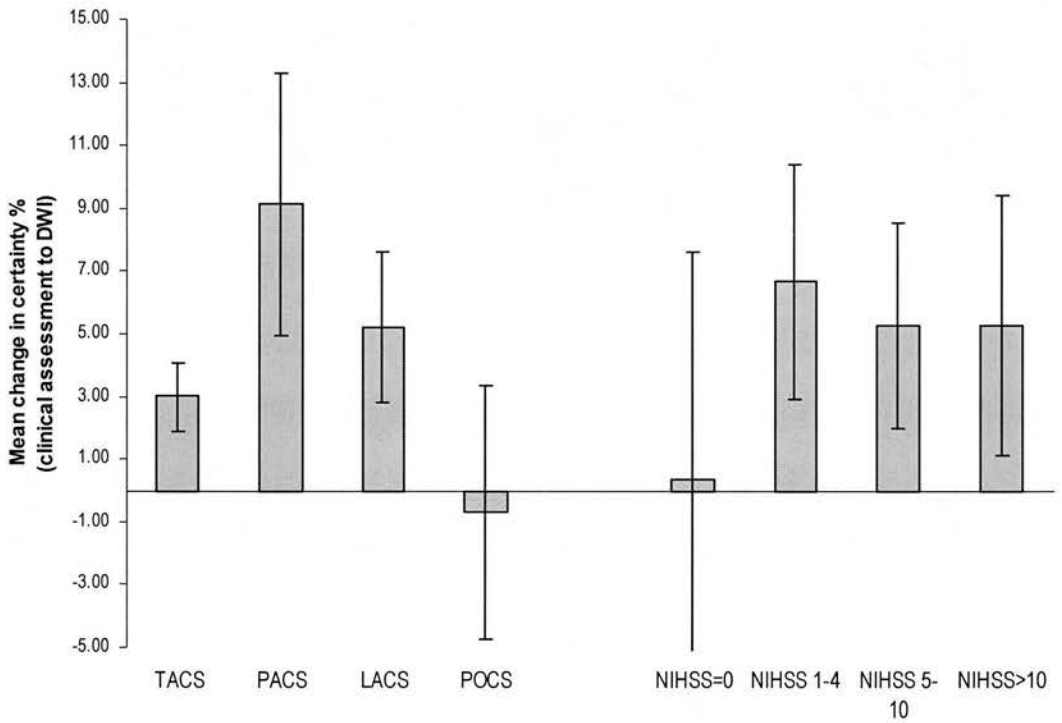


Figure 13.31 Stroke severity and the impact of imaging on diagnostic certainty
Includes all patients with a final diagnosis of stroke who underwent MR with DWI (n=87). The mean change in certainty from clinical assessment to after the DWI is charted on the Y axis, with OCSP classification on the left half of the X axis, NIHSS category on the right half of the axis. Each bar represents the percentage change (plus 95% confidence intervals).

Did clinical lesion localisation agree with the DWI scan?

Although it increased overall certainty for the diagnosis of stroke, the DWI scan disagreed with the clinical prediction of lesion localisation in some cases. 69 patients with a visible DWI lesion and a diagnosis of stroke (haemorrhage or infarct) were analysed. **Figure 13.32** demonstrates the number of patients with cortical, large subcortical, lacunar or brainstem lesions on DWI, divided by OCSP

classification. Of the 12 patients classed as TACS clinically, all had an appropriate lesion (one had a striatocapsular infarct). Of those classed as a PACS, 2/32 (6%) were shown to have had a lacunar infarct by DWI. 7/21 (33%) patients clinically labelled as lacunar stroke turned out to have a cortical lesion. All four patients classed as POCS had an appropriate brainstem or occipital infarct.

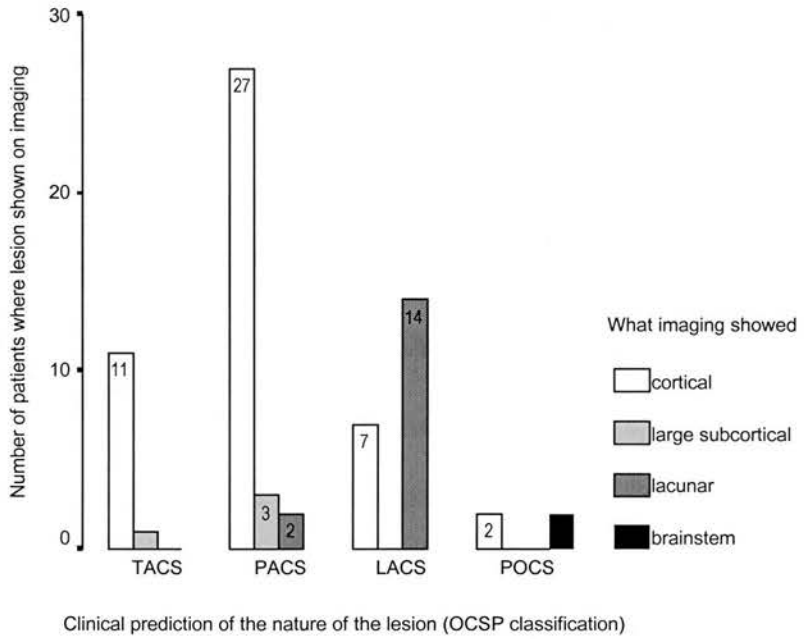


Figure 13.32 How often was clinical lesion location proved to be wrong by the DWI scan?
The X-axis is the clinical prediction of where the lesion is, based on the OCSP classification. The Y axis is the number of patients with a lesion seen on imaging, with the actual imaging result divided into four categories. The clear finding is that 1/3 of those classed as lacunar syndromes actually had a cortical lesion.

Thus, the DWI scan identified an incorrect clinical classification in 9/69 patients (13%, 95% CI 7-23%). Wrong clinical classifications were most commonly seen with patients thought to have had a LACS, and rarely seen in those thought to have had a cortical syndrome (TACS or PACS).

13.5 Discussion

The present study recruited 96 consecutive patients with features of brain attack. 30% were scanned within 6 hours of symptom onset, 96% within 48 hours. Some of the principal findings of this study – the high frequency of normal DWI and PI scans, the difficulty of detecting acute haemorrhage, and the small overall impact of MR on diagnostic certainty – are at odds with many earlier studies. Until now, published reports have concentrated on highly selected patients with severe strokes; the present study selected a broader range of patients and so included milder strokes. If the clinician is to determine the potential of advanced imaging in the 'real world', data from a wide variety of studies are needed.

13.5.1 Is it possible to incorporate advanced imaging techniques into routine clinical practice?

In **Chapter 12**, it was established that MR could be difficult for patients, particularly those with major stroke or co-existing medical conditions. An important finding was that scanning time should be kept to a minimum. However, even our briefest scanning protocol kept the patient in the magnet for 21 minutes (median), even though the sequence time (usually the only figure provided in published reports) was 9 minutes and 10 seconds.

Could the protocol be shortened?

It is possible to reduce scanning time by dropping sequences, but apart from changing the DTI (20 minutes) to DWI (1-2 minutes), it is not obvious which other sequences to drop. Much depends on the impact of sequences on patient management, which shall be considered in the following chapter. For diagnosis, the

key sequences were the gradient echo and diffusion-weighted images, but neither provides good structural detail. The sensitivity of the T2 image, which does provide good structural and anatomical detail, was no better than CT. Could it be dropped? This would make ageing of ischaemic lesions far more difficult, and risk missing tumours, pituitary lesions, leukoaraiosis, atrophy, and abnormalities of bones/orbits/sinuses altogether.

Extensive processing times

Although the MR produces DWI images on photographic film, these are not generally suitable for quantitative analysis. The PI images from the scanner are unsuitable even for visual inspection. If measurement of DWI lesion size, ADC, or PI parameters is important, then extra processing time needs to be allowed. This can limit the usefulness of advanced MR in the acute assessment of stroke (Baird & Warach, 1998).

Despite automated systems designed to analyse images directly from the scanner, we found that DWI lesion volume could not be measured in 6 patients, ADC in 10 patients, and PI parameters in 7 patients because of technical reasons. For all the PI and DWI images, a neuroradiologist needed to trace the boundaries of the lesion to allow the 'automated' program to run. The image processing time was long – up to several hours per patient – but important, as illustrated by the exaggerated size of the perfusion deficit when patient movement was not corrected (**Figure 13.1**). Our physicist estimates that a more streamlined procedure could be performed for clinical purposes, but this would still take around 15-30 minutes per patient (personal communication, Dr Paul Armitage).

For the diagnosis of ischaemic stroke in the present study, extensive post-processing of the MR data to generate measures of perfusion conferred no additional benefit. Fewer than half of our patient sample had a lesion on either measure of PI. Even when present, perfusion abnormalities showed no better correlation with stroke severity than the DWI. However, PI may have potential use for the management of acute ischaemic stroke, which shall be considered in the next chapter.

13.5.2 The diagnosis of brain attack

Despite the claims for MR to be the first line imaging investigation in acute stroke (Lovblad *et al.*, 1998; Prichard & Grossman, 1999; Warach, 2001a), this is one of only two studies that have prospectively scanned an unselected sample of patients presenting with stroke-like symptoms (although in the study of Perkins et al (2001), patients routinely underwent CT brain "within minutes of arrival at the Emergency Department" so patients with bleeds or tumours were not recruited to actually determine whether this is true).

The detection of haemorrhage

Acute intracerebral haemorrhage

The present study recruited five patients with an acute ICH. The MR characteristics of acute haemorrhage (see **Figure 13.4**) were present consistently, but the changes seen were often subtle (in comparison to the obvious appearance on CT). The GRE sequence was the most sensitive image sequence, yet it is not a routine part of the MR evaluation of patients with acute stroke. The appearance of acute haemorrhage on DWI was confusing – it appeared as a white blob, just like ischaemia. With experience, the appearances become obvious (i.e. the black

[hypointense] serpiginous lines at the margin due to paramagnetic effects and the overall shape), but it is instructive to note that the first patient scanned with a hyperacute ICH [PH243] completely flummoxed two experienced neuroradiologists and me!

Our small series of patients support the findings of Patel et al (1996) and Schellinger et al (1999), but do not confirm the latter's claim that MRI is as reliable as CT. More work is required before this claim can be accepted. Our experience would suggest that clinicians and radiologists will need training to become familiar with the MR appearances of haemorrhage.

Remote haemorrhage

The GRE sequence also revealed that 13% of old stroke lesions were actually haemorrhages, and 11% of all patients had cerebral microbleeds. Prior studies have shown that clinically silent microbleeds occur in 6% of healthy elderly subjects (Roob *et al.*, 1999), up to 26% of patients with previous ischaemic stroke (Kwa *et al.*, 1998) and up to 66% of patients with ICH (Roob *et al.*, 2000). Histopathologic analysis of the regions seen on GRE as microbleeds (in patients with ICH) confirmed that are deposits of haemosiderin due to bleeding-prone microangiopathy (Fazekas *et al.*, 1999).

The increased sensitivity of MR to both old ICH and microbleeds has implications for the management of acute ischaemic stroke. A past history of ICH is a contraindication to thrombolytic therapy, although as many as 13% of patients could be inadvertently treated if CT alone is used. The risk of intracranial haemorrhage from thrombolysis in patients with microbleeds is not known (Tong *et al.*, 1999), although there has been a recent report of haemorrhage at the site of a

microbleed following intra-arterial thrombolysis (Kidwell *et al.*, 2002). Similarly, the complication risk of oral anticoagulants in patients with microbleeds is unknown.

TIAs and non-strokes

Five patients whose final diagnosis was non-stroke were scanned. The two patients with brain tumours were easily identified by the structural MR, and the remaining three patients had normal DWI scans. This supports the findings of **Chapter 7**: the diagnosis of many stroke mimics is based on clinical features, not imaging findings. We observed no false positive DWI scans [as has been reported for partial status epilepticus (Lansberg *et al.*, 1999), transient global amnesia (Strupp *et al.*, 1998), hypoglycaemia (Hasegawa *et al.*, 1996) and cerebral venous thrombosis (Doege *et al.*, 2001)]. Interestingly, two patients who presented with vertigo and normal DWI scans had a posterior fossa perfusion deficit. The final diagnosis was possible stroke.

Three patients' deficit resolved completely within 24 hours. These patients were scanned at approximately two, four and nine hours after symptom onset (one patient's symptoms had resolved by the time of scanning). Two patients showed a small lacunar hyperintensity on DWI, and the DWI was normal for the other patient (although the PI scan was abnormal). Several studies have shown that DWI lesions may be seen in up to 48% of patients with TIA (Kidwell *et al.*, 1999; Engelter *et al.*, 1999), particularly when the TIA is prolonged. Thus it appears unlikely that DWI can distinguish between stroke and TIA.

Acute ischaemic stroke

The clear superiority of DWI was demonstrated in the present study: sensitivity of DWI was almost twice that of structural MR and CT. The DWI sequence was well tolerated, and forgiving of patient movement – interpretable images were obtained for all patients who had it. Another advantage of the DWI sequence is that ischaemic lesions are usually obvious. Others have shown that the identification of ischaemia on DWI is more reliable than on CT (Urbach *et al.*, 2000; Fiebach *et al.*, 2001); Lansberg and colleagues (2000a) found that the image interpreter felt lesions were more conspicuous with DWI and so had greater confidence in reporting.

The sensitivity of DWI in the present study (83%) was lower than most previous studies [e.g. 95% (Perkins *et al.*, 2001), 98% (Oppenheim *et al.*, 2000a), 100% (Urbach *et al.*, 2000)]. The likely explanation for this observation is that our patient cohort was milder than other studies, and hence DWI is less effective at detecting small lesions than large cortical lesions. Previous studies selected few patients, often just those with major hemispheric ischaemia, and the mean NIHSS is usually much higher [11.8 in one study (Lansberg *et al.*, 2000b) and 15.5 in another (Tong *et al.*, 1998), compared with our mean NIHSS of 7.0].

This theory is further supported by a comparison of the present study with that of van Everdingen et al (1998). The latter study, selected because it provided more clinical details than most, recruited 42 patients with hemispheric ischaemia (see **Table 13.14**). The mean/median NIHSS scores were not provided. Lesion location was lacunar in six patients (14%) cortical or large subcortical in 32 patients (76%), and no lesion was seen in four patients (10%). Mean lesion volume was higher,

ADC was lower, and the correlation between stroke severity (NIHSS) and lesion volume was stronger in van Everdingen's study than in the present study. Further work is needed to confirm our finding that a change in case-mix towards milder severity results in weaker associations between DWI and stroke.

13.5.3 The normal DWI scan

21/87 (24%) patients with features of brain attack, and no evidence of haemorrhage on imaging, had no discernible lesion on DWI. Despite this, 14 – over 60% – were considered by the panel of experts to have had a probable or definite stroke.

Do other studies report normal (false negative) DWI scans?

The many optimistic reports of 100% sensitivity of DWI (Gonzalez *et al.*, 1999; Urbach *et al.*, 2000) have been tempered by increasing evidence that false negative DWI findings in acute stroke are not rare. Ay et al (1999b) found a normal DWI in 17 of 772 patients (2% false negative rate), Oppenheim et al (2000b) eight of 139 patients (6%), Sunshine et al (2001) seven of 62 patients (11%) scanned within six hours of onset, and Lovblad et al (1998) 18 of 151 patients (12%). False negative DWI was more common in brainstem strokes, very small lesions, and those imaged early. The present study had the highest ever reported frequency of false negative DWI scans (18/82, 22%).

Sunshine et al (2001) reported that all seven of their patients with a normal DWI had abnormal PI scans. All patients were scanned within six hours of symptom onset. Of the patients in the present cohort with normal DWI who had PI (14), an abnormality was seen on either MTT or CBF maps in five patients (and no

abnormality was seen in the remaining nine patients). PI was often negative in patients who were scanned late, had mild symptoms or brainstem strokes – precisely the patients that were more likely to have a negative DWI scan. Only three of our 14 patients with normal DWI were scanned within six hours of symptoms onset (two had no PI lesion, and one patient had a PI lesion), so it is possible that these patients were scanned too late for a PI deficit to still be present. This all seems to suggest that PI is useful only in the first few hours, and for patients with more severe, hemispheric strokes.

Why did the present study find so many normal DWI scans?

Was our scanner not sensitive enough?

We used a state of the art, 1.5 tesla MR unit, DWI images were acquired using echoplanar imaging, using standard techniques, and each image comprised 20 slices of 5mm thickness with 1 mm gap between slices. It is possible that very small lesions (less than 1mm) were missed, and that brainstem lesions were obscured by magnetic susceptibility artefact.

Were patients scanned too early?

Other reports have suggested that false-negative DWI is more likely in the first three to six hours after stroke (Lefkowitz *et al.*, 1999; Oppenheim *et al.*, 2000b; Sunshine *et al.*, 2001). This has been explained on the basis that early lesions may not have had hypoperfusion of sufficient severity or duration to result in cell membrane pump failure (which is thought to cause the DWI hyperintensity). If scanned serially, the very early patient will eventually show a lesion on DWI (Tong *et al.*, 1998; Lefkowitz *et al.*, 1999; Oppenheim *et al.*, 2000b).

However, 13 of our 18 patients with no DWI lesion were scanned after 12 hours. Perhaps the theory that tissue destined for infarction passes through a phase resulting in increased signal on DWI does not apply to all patients. It may be possible that there are several pathways from tissue ischaemia to eventual necrosis, and not all of them result in a bright lesion on DWI. It may be possible that the belief that a bright DWI lesion is caused by cell membrane pump failure is actually wrong – definitive proof for the basis of the diffusion abnormality has not yet been established (Yuh *et al.*, 1999). Or perhaps, in patients with milder symptoms, tissue does not reach the membrane failure phase until after 24 hours. This would suggest the possibility that restoring blood flow might help such patients much later than is currently believed. Data from the present study could help to stimulate further investigation into the pathophysiology of cerebral ischaemia.

Was the ADC a more sensitive marker of ischaemia?

Calculating the ADC allows a precise determination of the rate of water diffusion in and out of cells. Lefkowitz et al (1999) found – in two patients with an initially normal DWI scan – that the ADC was reduced in the area of the eventual lesion, suggesting that there may be a certain ADC threshold for lesions to become obvious on DWI scan. This is an interesting concept, and in future studies we plan to examine the ADC values of regions of tissue with abnormal perfusion but no DWI lesion. At present, calculating an ADC is a time-consuming process, and it should be noted that over half of our patients with no DWI lesion also had no PI lesion, which would make it almost impossible to determine a region of interest for ADC calculation at the time the patient presents.

13.5.4 The clinical impact of advanced imaging

We attempted to determine whether the improved sensitivity of advanced imaging translated into clinical benefit. Three other groups have examined this issue. Lansberg et al (2000a) showed that observer's confidence in identifying acute lesions was greater using DWI than conventional MR; presumably this increased confidence may impact on the clinician's further investigations and management.

Lutsep et al (1997), in a retrospective review of 103 patients, found that DWI was superior to standard MR in eight patients. The DWI detected a lesion not seen on T2 in six patients (two were shown to have a thalamic lacunar infarct, a different vascular territory to the clinical localisation); and in two, the DWI distinguished new from old lesions. Albers and colleagues (2000a) found that DWI helped to clarify the age of the lesion in eight, and demonstrated multiple lesions (suggesting an embolic source) in five of 40 consecutive patients. The DWI altered clinical lesion localisation in seven patients (18%): three were thought to have had lacunar strokes but the DWI showed cortical lesions, three were thought to have had small cortical lesions but the DWI showed a lacunar lesion, and one patient thought to have had a brainstem stroke had a cortical lesion on DWI.

In the present study, DWI altered lesion localisation in 13% (primarily identifying cortical lesions when the clinical classification was lacunar). DWI did not alter the vascular territory in any of our patients. We also observed that the DWI could distinguish new lesions from old, and multiple lesions suggesting an embolic source, in a handful of patients. This has clear implications for the subsequent investigation and management of the patient.

The impact on diagnostic certainty

Although making a correct diagnosis is the first aim of the stroke clinician, and is the rationale for brain imaging, this is the first study to ascertain the impact of MR on clinician's diagnostic certainty. We designed the study to determine the additional benefit of MR over and above CT. We showed that across all patients and clinicians, brain imaging makes a small (but significant) increase in certainty. The CT scan, when performed first, provides the greatest amount of diagnostic information for the clinician. This reflects the fact that for most patients, the diagnosis is almost certain after the clinical assessment alone.

However, DWI was most helpful for the 'difficult' patients: those in whom the clinician was unsure of the diagnosis, and patients with milder strokes. In a small number of patients, DWI can make a large difference in certainty. Overall, the clinician achieves 100% certainty for around 20% of patients with CT, but almost 60% of patients with DWI.

13.5.5 Limitations of the study

There were limitations to the present study. Patients in our sample were relatively mild (median NIHSS 5), old (median age 74.4), and had a high frequency of co-existing medical problems. Our cohort was probably rather different to the types of patients admitted to an academic German (or North American) neurologist-led stroke unit that seem to be reported in the literature [e.g. (Schellinger *et al.*, 2000)]. Our study may have found a higher impact of DWI by including milder stroke patients, because in studies of mainly severe stroke patients, the CT is more likely to show an abnormality, so reducing the value of a positive DWI. On the other

hand, our study found more normal DWI and PI scans, and weaker relationships between imaging and clinical features. To understand this promising diagnostic test better, it is important that MR is tested on a broad range of patients (Powers, 2000).

This study aimed to, and probably succeeded in recruiting a broader spectrum of patients than other studies reported to date. However, due to funding limitations we were unable to recruit consecutive patients with brain attack – patients included were those with a clinical diagnosis of probable or definite stroke. Thus, there was selection bias in the patients who were recruited to this study, and this could have influenced the findings (in particular, the sensitivity and utility of DWI).

Although 96 patients were recruited (and 92 patients were scanned), our sample size was still small. It would have been preferable to include more non-strokes and haemorrhages to strengthen our observations, but resources were limited. Despite recruiting and scanning 82 patients with cerebral ischaemia, numbers for the analysis of calculated parameters (ADC, PI, DWI lesion volume) were diminished for various technical reasons. However, our sample size was considerably larger than most previous studies (Keir & Wardlaw, 2000).

Another limitation was that the final diagnosis was made after the panel of experts had reviewed the CT scan (where there was one), structural MR and DWI with the neuroradiologist. There was thus the potential for bias. If the clinicians were convinced that DWI was always abnormal in ischaemic stroke, a positive study would increase the probability of a positive diagnosis, and so increase the apparent sensitivity of DWI. This is a problem that has been noted by others (Lovblad *et al.*, 1998), but in the absence of a true gold standard for the diagnosis of stroke (D'Olhaberriague *et al.*, 1996), it is difficult to avoid this bias.

13.6 Summary

- In a less selected and probably milder patient group than other reports, we found advanced MR provided a small additional amount of clinically helpful information over and above CT. In a handful of patients, DWI had a major impact on diagnostic certainty, however for most patients the CT was adequate.
- A surprisingly large number of ischaemic events had no DWI corollary; this raises questions about the sensitivity of DWI, and what it is believed to represent.
- The MR appearance of acute haemorrhage is distinctive but subtle, and could easily be missed by unfamiliar observers
- The MR appearance of old haemorrhage, best seen on the gradient echo sequence, can provide information not available on the CT that has implications for risky treatments such as thrombolysis or anticoagulation.
- For most non-strokes, the MR is likely to be normal – the diagnosis remains a clinical one
- Extensive image processing to determine DWI lesion volume, ADC and PI parameters is of limited benefit in the diagnosis of brain attack.

Recommendations for further research:

- The role of MR in patient management needs to be assessed
- We need to determine the ideal imaging protocol
- There should be large, methodologically-sound studies of the reliability of detecting acute haemorrhage on MRI

- We need further investigation into the causes of a normal DWI, and the sequence of pathophysiological changes as shown by PI and DWI and structural MR

Table 13.1 General recruitment details

	MR study patients (n=96)	
Median age (IQR)	74.4 years	(65.1-81.4 yrs)
Male gender	48	(50%)
Median time from onset to examination (IQR)	9.3 hours	(3.1-20.6 hrs)
Onset to examination:		
Within 12 hours	52	(54%)
Greater than 12 hours	44	(46%)
Median time from onset to MR (IQR)	13.2 hours	(5.2-22.6 hrs)

Table 13.2 Patient demographics in MR study

	MR study patients (n=96)	
Past history of stroke	37	(39%)
Prior level of function:		
Walked independently	93	(97%)
Known cognitive impairment	17	(18%)
Vascular risk factors:		
Smoker	56	(58%)
Hypertension	55	(57%)
Ischaemic heart disease	24	(25%)
Diabetes	6	(6%)
Atrial fibrillation	24	(25%)
Peripheral vascular disease	15	(16%)

Table 13.3 Clinical features of MR study patients

	MR study patients (n=96)	
Exact onset known*	83	(87%)
Woke from sleep with deficit*	34	(35%)
Nature of symptoms:		
Visual loss	12	(13%)
Brainstem symptoms†	12	(13%)
Speech disturbance	52	(54%)
Sensory symptoms	28	(29%)
Motor symptoms	71	(74%)
Median systolic blood pressure (IQR)	155mmHg	(144-178mmHg)
Atrial fibrillation	20	(21%)
Confusion‡	16	(20%)
Reduced conscious state	20	(21%)
Median NIHSS (IQR)	5.0	(3.0-9.0)
OCSP classification:		
TACS	13	(14%)
PACS	38	(40%)
LACS	30	(31%)
POCS	10	(10%)
Unsure	5	(5%)
Brain side affected:		
Left	48	(50%)
Right	37	(39%)
Brainstem	8	(8%)

** exact onset defined as time symptoms first noted (time of waking if awoke with symptoms)*
† brainstem symptoms were vertigo, diplopia, or unsteadiness
‡confusion was assessable in 79/96 patients

Table 13.4 Final diagnosis of patients in MR study

Final diagnosis	MR study patients	
Definite stroke	75	(78%)
Probable stroke	10	(10%)
Definite TIA	3	(3%)
Probable stroke	3	(3%)
Non-stroke	5	(5%)

Table 13.5 Clinical features of those with and without a visible lesion on DWI.

	Visible lesion on DWI (n=64)		No visible lesion on DWI (n=18)		
Feature	**Number**	**(%)**	**Number**	**(%)**	**P***
Median time from onset to MR scanner (IQR)	10 hours	(4.9-20)	22 hours	(6.5-26)	.062
Median age (IQR)	77 years	(67-82)	70 years	(62-80)	.292
Past history of stroke	27	(42)	7	(39)	.802
Exact onset	56	(88)	14	(78)	.449
Woke from sleep with deficit	22	(34)	7	(39)	.569
Symptoms:					
Visual	8	(13)	1	(6)	.676
Speech	38	(59)	8	(44)	.259
Brainstem	5	(8)	6	(33)	.012
Sensory	21	(33)	3	(17)	.183
Motor	52	(81)	8	(44)	.005
Confusion†	11	(28)	3	(21)	.739
Decreased conscious level	14	(22)	2	(11)	.502
Median NIHSS (IQR)	6.0	(4-9)	3.0	(1-4)	<.001
OCSP classification:					<.001
TACS	10	(16)	1	(6)	
PACS	31	(48)	3	(17)	
LACS	19	(30)	5	(28)	
POCS	4	(6)	6	(33)	
Unsure	0	(0)	3	(17)	
Brain side affected:‡					<.001
Left	37	(58)	6	(33)	
Right	25	(39)	4	(22)	
Brainstem	2	(3)	6	(33)	

** significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test or Fisher's Exact test (for categorical variables)*
† confusion not determined in 28 patients
‡ side of brain affected could not be determined in two patients with no visible lesion

Table 13.6 OCSP classification and DWI lesion volume

OCSP classification	All patients (n=82)	Subgroup with visible DWI lesion (n=64)
TACS *(n)*	*11*	*10*
Mean (mL)	67.3	74.0
Median (mL)	21.0	22.9
Range (mL)	0 – 269.7	0.9 – 269.7
PACS *(n)*	*34*	*31*
Mean (mL)	11.7	12.8
Median (mL)	4.9	5.1
Range (mL)	0 – 68.4	0.1 – 68.4
LACS *(n)*	*24*	*19*
Mean (mL)	0.8	1.0
Median (mL)	0.4	0.5
Range (mL)	0 – 5.5	0.1 – 5.5
POCS *(n)*	*10*	*4*
Mean (mL)	1.7	4.3
Median (mL)	0	2.6
Range (mL)	0 – 11.5	0.4 – 11.5
Unsure *(n)*	*3*	--
Mean (mL)	0	
Median (mL)	0	
Range (mL)	0	
P value*	*<0.001*	*<0.001*

** significance for the relationship determined by Kruskal-Wallis test*

Table 13.7 Reliability of the observation that there was no relevant PI lesion on either MTT or CBF maps*

	1st reading:		
2nd reading:	No PI lesion	PI Lesion present	Total
No PI lesion	22	5	*27*
PI lesion present	1	40	*41*
Total	*23*	*45*	*68*

Kappa 0.81 for intra-rater reliability (95% CI
** Observer viewed the PI maps with the DWI*

Table 13.8 The two measures of cerebral perfusion often disagreed

	MTT maps:		
CBF maps:	No lesion	Lesion present	Total
No lesion	8	9	*17*
Lesion present	4	20	*24*
Total	*12*	*29*	*41*

In 8 patients, although a lesion was visible, it could not be measured (see text)

Table 13.9 Clinical features of those with and without a visible lesion on either PI image

Feature	Visible lesion on PI (n=45) Number	(%)	No visible lesion on PI (n=23) Number	(%)	P*
Median time onset-MR (IQR)	8.9 hours	(4.4-19.8)	24.7 hrs	(13.5-30.5)	.004
Median age (IQR)	74 years	(68-80)	72 years	(58-82)	.851
Past history of stroke	19	(42)	9	(39)	.806
Exact onset	38	(84)	20	(87)	.782
Woke from sleep with deficit	17	(38)	5	(22)	.333
Symptoms:					
Visual	7	(16)	1	(4)	.250
Speech	26	(58)	9	(39)	.145
Brainstem	6	(13)	4	(17)	.724
Sensory	12	(27)	10	(44)	.161
Motor	34	(76)	16	(70)	.596
Decreased conscious level	11	(24)	1	(4)	.048
Median NIHSS (IQR)	7.0	(4-9)	4.0	(2-5)	.001
OCSP classification:					<.001
TACS	8	(18)	0	(0)	
PACS	24	(53)	3	(13)	
LACS	7	(16)	14	(61)	
POCS	4	(9)	5	(22)	
Brain side affected:†					.040
Left	28	(62)	7	(30)	
Right	14	(31)	10	(44)	
Brainstem	2	(4)	5	(22)	
Final diagnosis:					.029
Definite stroke	40	(89%)	14	(61%)	
Probable stroke	2	(4%)	6	(26%)	
TIA	1	(2%)	2	(9%)	
Possible stroke	2	(4%)	1	(4%)	
No DWI lesion present	5	(11)	9	(39)	.007
Median DWI lesion volume (mL)	4.7	(0.8-12.6)	0.2	(0-0.5)	<.001

** significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test or Fisher's Exact test (for categorical variables)*
† side of brain affected could not be determined in two patients with no visible lesion

Table 13.10 OCSP classification and PI lesion volume

OCSP classification	MTT maps (n=68)	CBF maps (n=68)
TACS *(n=8)*		
Mean (mL)	189	140
Median (mL)	226	123
Range (mL)	0 – 359	0 – 342
PACS *(n=27)*		
Mean (mL)	45	14
Median (mL)	0.6	0
Range (mL)	0 – 258	0 – 101
LACS *(n=21)*		
Mean (mL)	9.4	1.6
Median (mL)	0	0
Range (mL)	0 – 103	0 – 18
POCS *(n=9)*		
Mean (mL)	18	5.6
Median (mL)	0	0
Range (mL)	0 – 135	0 – 37
P value*	*<0.001*	*<0.001*

** significance for the relationship determined by Kruskal-Wallis test*

Table 13.11 Accuracy of CT, structural MR and DWI brain imaging for the detection of a relevant stroke lesion

	CT brain (n=62)*		Structural MR (n=92)		DWI (n=91)†	
Feature	*(95% CI)*		*(95% CI)*		*(95% CI)*	
Sensitivity	43%	*(31-56)*	43%	*(33-54)*	82%	*(73-89)*
Specificity	100%	*(57-100)*	100%	*(68-100)*	100%	*(65-100)*
PPV	100%	*(86-100)*	100%	*(90-100)*	100%	*(95-100)*
NPV	14%	*(6-28)*	14%	*(7-26)*	32%	*(16-53)*
Accuracy	48%	*(36-60)*	48%	*(38-58)*	84%	*(75-90)*

** 62 patients had both CT and MR at the same time*
† DWI was not performed in one patient (with a brain tumour)

Table 13.12 The impact of imaging on diagnostic certainty

	Mean % change in certainty (SD)	Range:		Number of patients where mean certainty:		
		Low	High	Reduced (%)	Remained the same (%)	Increased (%)
Clinical assessment – CT	3.71 (8.68)	-1.53	+44.67	4 / 62 (6.5)	2 /62 (3.2)	56 / 62 (90.3)
CT scan – structural MR	1.09 (5.17)	-1.20	+21.60	12 / 62 (19.4)	12 / 62 (19.4)	38 / 62 (61.3)
Structural MR – DWI	2.02 (7.39)	-12.00	+24.80	11 / 62 (17.7)	10 / 62 (16.1)	41 / 62 (66.1)

The mean change refers to all patients (maximum possible was 50%). The range is the highest and lowest change in certainty for individual patients.

Table 13.13 How often clinicians were 100% certain in their diagnosis

		Number of times clinician was 100% certain that the diagnosis was stroke, after:			
Clinician	***(n)****	**Clinical assessment**	**CT**	**Structural MR**	**DWI**
1	*82*	1 (1%)	12 (15%)	23 (28%)	52 (63%)
2	*64*	3 (5%)	20 (31%)	33 (52%)	47 (73%)
3	*54*	3 (6%)	10 (19%)	16 (30%)	38 (70%)
4	*40*	7 (18%)	11 (28%)	18 (45%)	24 (60%)
5	*41*	3 (7%)	8 (20%)	8 (20%)	22 (54%)
6	*84*	0 (0%)	7 (8%)	20 (24%)	60 (71%)
7	*52*	2 (4%)	2 (4%)	2 (4%)	4 (8%)
8	*63*	13 (21%)	12 (19%)	23 (37%)	41 (65%)

** number of patients for whom each clinician made a diagnosis*

Table 13.14 DWI for the detection of ischaemic stroke: a comparison between the present study and that of van Everdingen et al.

	van Everdingen et al	**Present study**
Number of patients	42	82
Mean age (range)	64 (36-85)	72 (35-99)
Selection criteria	Hemispheric ischaemia	Clinical features of brain attack
Location of lesion:		
Cortical/large subcortical	32 (76%)	48 (59%)
Lacunar	6 (14%)	14 (17%)
Brainstem	0 (0%)	2 (2%)
No lesion	4 (10%)	18 (22%)
Sensitivity of DWI	90%	83%
Mean DWI lesion volume (range)	33mL (0-200)	14.3mL (0-269.7)
Mean ADCr in lesion	0.73	0.80*
Spearman rho correlation between initial NIHSS and DWI lesion volume (r_S)	0.63	0.55†

** ADCr not measured in 10 patients, those with no DWI lesion (18) allocated ADCr of 1.00*
† this figure includes all 82 patients

Chapter 14 : Can MR assist in patient management?

14.1 Introduction

In this final chapter I shall examine how MR may assist the clinician in the management of a patient with brain attack. The first half is devoted to the potential of diffusion-weighted and perfusion imaging in acute ischaemic stroke: could these techniques be used to define the onset of symptoms, predict outcome, or select appropriate patients for treatment? In the second half of the chapter I will examine the additional impact of structural MR and DWI on current patient management.

14.2 Aims

(1) To determine if MR imaging parameters could be used as a surrogate marker of the time from symptom onset.

(2) To determine if the features seen on diffusion imaging might predict outcome from acute ischaemic stroke (and so guide treatment)

A) Does DWI lesion volume predict outcome?

B) Can a recently proposed predictive model for stroke recovery that incorporates DWI lesion volume be independently validated?

(3) How often does a DWI-PI mismatch occur; if absent, why; if present, did it predict a worse outcome?

(4) To determine if MR brain imaging could alter the management of patients with brain attack

14.3 Methods

14.3.1 Patients

The analyses contained in this chapter were performed on patients recruited into the brain imaging study described in **Chapter 13**. Procedures for determining patient eligibility, the clinical assessment, performance of other investigations, and determining the final diagnosis were exactly the same as already described.

Assessment of outcome

Outcome was assessed by modified Rankin Score (mRS) determined at (no sooner than) three months. Death was coded as mRS 6. After ascertaining that the patient was still alive (by hospital records and contact with the general practitioner), the majority of patients were followed-up by telephone. Patients who agreed to undergo sequential imaging were assessed at their final out-patient visit by the research fellow (PJH).

14.3.2 Scanning

The MR sequences were described in the last chapter. Patients received structural imaging – a gradient echo (GRE) and T2 sequence – and 'advanced' imaging – diffusion-weighted (DWI) and perfusion imaging (PI). The analysis of the PI data used mean transit time (MTT) and cerebral blood flow (CBF) maps.

All patients were to undergo an ultrasound examination of the extracranial carotid and vertebral arteries, either at the time of imaging or subsequently.

Methodology particular to the aims of this chapter will be covered below.

The age of the DWI lesion

The neuroradiologist was asked to estimate the age of the lesion seen on DWI. Lesions were categorised as no older than six hours, at least six hours but no more than 12 hours old, and at least 12 hours old. The neuroradiologist judged the age of a DWI lesion by its degree of brightness, how well-defined the margins of the lesion were, and whether a lesion was present on the T2 image. The MR-based estimation of lesion age was compared with the time of stroke onset given by the patient.

The apparent diffusion coefficient (ADC) may provide information that could determine age of the lesion. Several groups have analysed the timecourse of the ADC after stroke (Lutsep *et al.*, 1997; Schlaug *et al.*, 1997; Schwamm *et al.*, 1998; Fiebach *et al.*, 2002). Typically, relative ADC values are reduced at the time of the first MR examination, and then continue to fall, reaching a nadir at 12-24 hours. Thereafter, ADC values begin to rise, returning to normal by around four days. In the present study, a scatterplot of ADC versus time was constructed, and a regression line fitted to look for trends. Patients with outlying results were analysed individually.

DWI parameters and outcome

The methods used to calculate DWI lesion volume and ADC were described in **Chapter 13**. In the present study, univariate and multivariate analyses (see *Statistics*, below) were performed to determine if DWI lesion volume or ADC was capable of predicting outcome.

Determining the presence of a DWI-PI mismatch

The measures of perfusion that were used in the present study were mean transit time (MTT) and cerebral blood flow (CBF). The process of generating these maps from the raw data was described in **Chapter 13**. The neuroradiologist examined the PI maps at two sittings. At the first, the presence of a mismatch was determined by visual inspection of the DWI and PI images. This was designed to simulate the clinical requirement for a rapid decision to guide treatment (and will be the primary analysis of mismatch in the present study).

MTT and CBF maps were analysed and coded separately. We defined mismatch as a focal region of perfusion abnormality that appeared 20% or more greater in volume than the DWI lesion. This is the same definition that has been used by others (Warach *et al.*, 2000; Schellinger *et al.*, 2001). Images were coded as: large mismatch present (PI>DWI in excess of 20%, including patients with no DWI lesion); mismatch present (PI>DWI of about 20%); no mismatch – PI=DWI, and no mismatch – PI<DWI (including patients with no PI lesion). The neuroradiologist interpreted the images blind to all patient details.

A second reading was required to mark any visible focal areas of reduced perfusion so that the PI lesion volumes could be measured on a computer workstation (the same process as for measuring DWI lesion volume, described in **Chapter 13**). The regions of interest were not marked at the same sitting as the determination of mismatch because we wanted the latter to be as quick as possible (to be clinically realistic). The data obtained from the formal lesion volume analysis were compared with the qualitative visual inspection in a secondary analysis. The 'calculated mismatch' (as opposed to the mismatch determined by visual inspection) was defined

as a ratio of PI lesion volume: DWI lesion volume greater than or equal to 1.2. No mismatch was divided into PI=DWI (ratio greater than 0.8 and less than 1.2) and PI<DWI (ratio less than or equal to 0.8). Patients with a PI lesion but no DWI lesion were arbitrarily assigned a DWI volume of 1.0mL for calculation of the ratio. Finally, the volume of perfusion abnormality greater than the diffusion abnormality (thought to represent the ischaemic penumbra) was determined by subtracting DWI lesion volume from the PI lesion (where a mismatch existed).

14.3.3 Influence of advanced imaging on current management strategies sub-study

This sub-study aimed to determine how often – and why – MR imaging changed patient management, compared with CT imaging. A panel of clinicians was asked their opinion about a series of hypothetical management scenarios, using the clinical details and imaging findings of patients recruited. A brief standardised summary of the patient's clinical details was provided by the research fellow (PJH), the brain scans were shown with any abnormality demonstrated by the neuroradiologist (JMW), and the panel recorded their answers to six questions on a data form (see **Appendix 11**). The presentation of the imaging followed the same order for every patient: CT brain scan first, then structural MR, then DWI. CT therefore served as the baseline against which changes were measured. Decisions were cumulative, as the scans for each patient were viewed at the one setting.

It was decided to use hypothetical management scenarios, as relatively few actual management decisions are made on the majority of patients. Most present outside the time window for thrombolysis, most are in sinus rhythm and are not

candidates for long-term anticoagulation, and most do not have a severe carotid stenosis; thus the number of patients whose management could actually be influenced by imaging is tiny. By using the basic clinical details of each patient (e.g. sudden onset right sided weakness, TACS on examination), and asking the clinician to assume that the other important factors were satisfied depending on the question (e.g. presented at two hours, in atrial fibrillation etc), it was possible to use every patient to determine how imaging might affect management.

The scenarios chosen (see **Appendix 11**) reflect the range of therapeutic options available to the stroke physician. At present, acute management of the patient with stroke may involve reversal of anticoagulation if a haemorrhage, or treating ischaemic stroke with intravenous thrombolysis (either open-label, or as part of a clinical trial). [NB. The Department of Clinical Neurosciences are conducting the Third International Stroke Trial, a randomised controlled trial of intravenous thrombolysis for ischaemic stroke (treatment may be given up to six hours from onset)]. Secondary prevention of further stroke may involve consideration of long-term anticoagulation, carotid endarterectomy or altering antiplatelet therapy.

To be eligible for the study, it was therefore necessary that the patient had both CT and MR examinations. The patients were recruited to the MR imaging of brain attack study, as was described in **Chapter 13**. The present study was performed months after the consensus panel and influence of imaging on the diagnosis meetings. To ensure that clinicians were blind to the patient's actual identity, only patient number was used, and no identifying details were used in the brief clinical detail given. Meetings were conducted when at least four clinicians

were available (availability depended on the clinician's other commitments – non-attendance was random).

14.3.4 Statistics

Statistical analyses

Descriptive statistics were used to look for, and test the significance of, relationships and correlations. The data were initially checked for a Normal distribution. This was not present, so standard non-parametric tests were used throughout. I used the NIHSS and Oxfordshire Community Stroke Project (OCSP) classification as the main markers of stroke severity and type. Outcome was dichotomised to 'good', mRS 0-2 (independent), or 'poor', mRS 3-6 (dependent or dead).

Validation of a proposed predictive model for stroke recovery that used DWI lesion volume

Recently, a three item model for the prediction of outcome after stroke has been proposed (Baird *et al.*, 2001). Logistic regression identified three independently predictive variables (DWI lesion volume, NIHSS score, and time from onset to MR scanning), and recursive partitioning was used to categorise the three variables (to provide optimum discrimination between good and poor recovery), and assign points for each category. The total score was the sum of points for each variable, and could range from zero to seven points. 0-2 points indicated a low probability of recovery, 3-4 points a medium probability, and 5-7 points a high probability of recovery (Baird *et al.*, 2001).

To validate the model, I performed a multivariable logistic regression analysis using the same variables originally entered by Baird and colleagues (except 'participation in a drug trial', as this was not relevant in our cohort). I entered seven variables to ensure that my model faithfully replicated that described by Baird et al, even though this was in excess of the ideal events per variable rate [which indicated that only three variables should have been entered in Baird et al's model to avoid overfitting of the model to the dataset (Peduzzi *et al.*, 1996)]. I was unable to perform recursive partitioning to derive categories (and hence points) for the variables selected in my model. Instead, I assigned points and a total score as described in the three-item model, and tabulated the predicted and observed outcome to determine if the model accurately predicted outcome in our patient cohort.

Mismatch

The neuroradiologist classified patients' scans based on visual inspection of the MTT map and DWI scan (designed to replicate the clinical situation). Patients either had a mismatch – where the PI lesion was greater than the DWI lesion (or there was no DWI lesion), or had no mismatch – where the DWI lesion was equal to or larger than the PI lesion (or there was no PI lesion). Standard non-parametric statistical tests were used to assess the significance of differences between the two groups. In addition, the results of visual inspection were compared with the calculated lesion volume results to determine if there were differences between the two methods.

The impact of MR on patient management

Analyses were kept simple, as the main purpose of the study was descriptive. The frequency of management changes in total, and the number of patients affected

by management changes, was assessed for each clinician, and a mean calculated. The nature of the management change, and the imaging findings that prompted the change, were described.

Statistical packages

Data analyses were performed using Microsoft Excel (version 97 SR-2, ©Microsoft Corporation 1997), Confidence Interval Analysis (version 2.0.0, ©Trevor Bryant 2000) and SPSS for Windows (version 10.0.5, ©SPSS Inc. 1999). Logistic regression models were developed using forward stepwise selection of variables, with entry criteria defined as $p<0.05$ and removal criteria defined as $p>0.10$.

14.4 Results

14.4.1 General features

Patient numbers

The analyses reported in this chapter were performed on patients recruited into the brain attack imaging study (reported in the last chapter). 96 patients were recruited in total. 82 patients had cerebral ischaemia, and were the subject of the present analyses of determining time from symptom onset by lesion age, DWI parameters and outcome, and the frequency and implications of a DWI-PI mismatch. 63 patients (of the 96) received CT at around the same time as MR, and were the subjects of the analysis of the impact of imaging on patient management.

Final diagnosis and outcome

The final diagnosis was definite or probable stroke in 85/96 (88%) of patients recruited, TIA in 3/96 (3%), possible stroke in 3/96 (3%) and definite non-stroke in 5/96 (5%) (see **Table 13.4**).

Outcome data were available for all but one patient (this patient had no telephone, no fixed address, and attempts to contact his mother and brother were unsuccessful). At three months, 14/95 patients (15%) had died, 34/95 (36%) were dependent (mRS 3-5), and 47/95 (49%) had a good outcome (mRS 0-2). 51% were therefore dead or dependent (poor outcome).

14.4.2 Could MR be used as a surrogate marker for time of symptom onset?

Using DWI to estimate the age of the lesion

The age of the lesion based on its MR appearances was estimated in the 64 patients who had a visible lesion on DWI (if the scan were normal, it was not possible to determine age of lesion). A precise time of onset was known for 35/64 patients (53%). Onset details were unclear in 29 patients: 21 (33% of the total) awoke from sleep with the deficit, and 8 (13%) whose onset had to be estimated (usually because the patient lived alone and was aphasic on presentation). The MR-estimated age of the lesion was compared to the precisely known age of the lesion.

Table 14.1 shows the estimates of lesion age based on MR appearance against the 'true' age (which has been split into three categories to facilitate comparison). The MR estimate of age was correct in 17/35 patients (49%, 95% CI 33-64%). The positive predictive value of a MR-estimated age of less than six hours was 4/8 (50%, 95% CI 22-79%), whilst it was 11/14 (79%, 95% CI 52-92%) for an

MR-estimated age of greater than 12 hours. Only 4/11 patients (36%, 95% CI 15-65%) who presented within six hours of onset had a correct estimation of lesion age by MR. If dichotomised to age within six hours and greater than six hours – which reflects possible clinical requirements – then the sensitivity of the MR assessment of lesion age less than six hours was 36% (95% CI 15-65%), and the specificity was 83% (95% CI 64-93%).

To explore why the MR timing of lesion age differed from the 'true' age (the precise time symptoms were first noted), the five extreme 'outliers' of **Table 14.1** are considered in more detail. Two patients [PH362, PH363] presented within six hours but were classed as greater than twelve hours by MR appearances. PH362 presented with a moderately severe clinical syndrome (classed as a PACS, NIHSS 17), and was scanned at 5.7 hours. DWI lesion volume was 68mL, and the T2 images showed increased signal, suggesting a lesion at least 12 hours old (see **Figure 14.1**). In contrast, PH363 presented with a moderate syndrome (PACS, NIHSS 9). At 4.3 hours, the scan showed a smaller lesion volume of 5mL, but there was increased signal on the T2 images (again suggesting older lesion age).

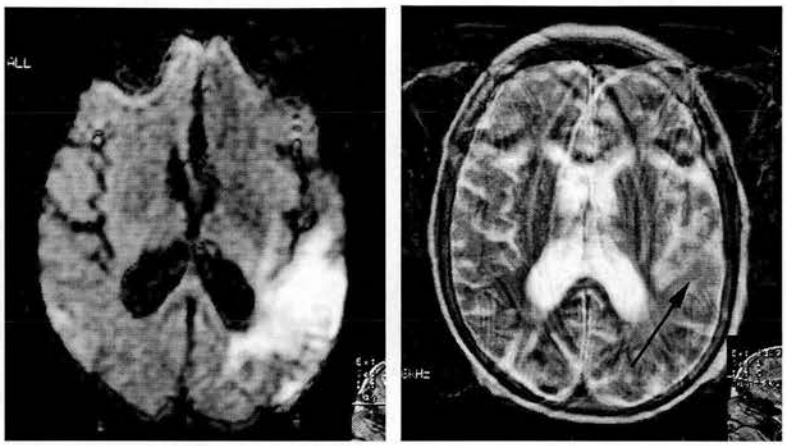


Figure 14.1 The lesion appeared older than it was.

PH362*: presented with a PACS, scanned at 5 hours 42 minutes. DWI image (left) shows a mature hyperintensity in the left temporal region (with a second small right temporal hyperintensity). T2 image (right, degraded by movement artefact) shows early increased signal (arrow). Age of lesion estimated as greater than 12 hours.*

Three patients [PH342, PH352, PH386] were scanned after 12 hours but the lesion was classed as within six hours based on the MR appearances. PH342 presented with symptoms suggesting a lacunar stroke (NIHSS 5), the DWI lesion measured 1.4mL, and the T2 images showed no increased signal. PH352 presented with more severe symptoms suggesting a TACS (NIHSS 9), yet the DWI scan showed a striatocapsular infarct with haemorrhagic transformation (see **Figure 13.5**). PH386 presented with symptoms of a PACS (NIHSS 8) and was randomised into the IST-3. By the time of scanning, the patient had improved significantly, and the DWI showed a subtle lesion (0.4mL) that appeared much younger than it actually was (see **Figure 14.2**).

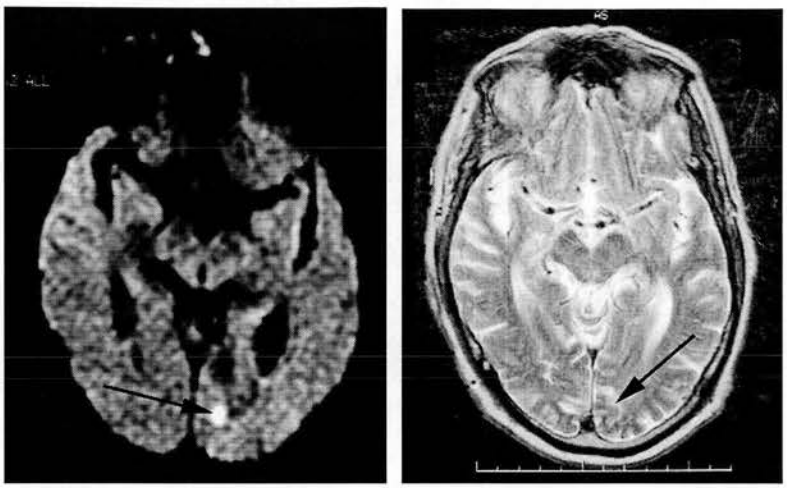


Figure 14.2 The lesion appeared younger than it was.

PH386:*This patient presented with a PACS and was randomised into IST-3 (unknown whether placebo or thrombolysis was given). Scanned at 14 hours 35 minutes. DWI image (left) shows a small increased signal lesion (arrow) corresponding to very subtle increased signal on T2 (arrow, right image). Age of lesion estimated to be less than six hours.*

Thus there were explanations for the individual variations seen, but no uniform features that suggested why some lesions looked a different age on the scan to their real age.

Was there a correlation between ADC and time from symptom onset to scanning?

The relationship between time from symptom onset to scanning and ADC was explored in 52 patients (see **Figure 14.3**). There was a suggestion of a 'J' curve, with ADC values reaching a nadir at around 15-20 hours, then rising again. Clearly numbers were too small to make any firm conclusions [and the latter part of the curve (that actually dips down again) was composed of five patients who were recruited well beyond the planned time limits].

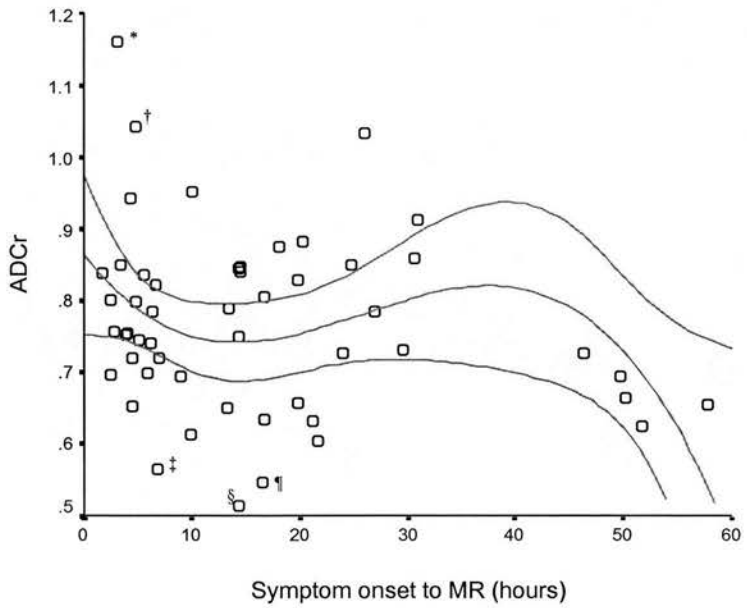


Figure 14.3 The relationship between ADCr and time from symptom onset to scanning
Each point represents a single patient; the central curved line represents the line of fit (determined by cubic regression) and the surrounding lines represent the 95% confidence intervals for the line of fit.
*Outliers (see text for discussion): *PH398; †PH367; ‡PH274; §PH230; ¶PH257*

There were several outlying patients who need further exploration to understand the utility of ADC in timing the age of the lesion. Patient [PH398] had a mean ADC of 1.16 in the lesion, yet was scanned 3 hours after symptoms onset. An ADC greater than one suggests that diffusion in the affected area is actually greater than in the opposite hemisphere, normal brain tissue. ADC >1 might be expected in the subacute to chronic ischaemic lesions. PH398 had awoken at 7.30am, then walked to his GP's surgery for a routine visit. Whilst in the waiting room he developed left sided weakness and visual loss. In the acute receiving unit (ARU), he had a gross left hemianopia, mild-moderate hemiparesis and neglect (NIHSS 7), consistent with a posterior cerebral artery territory infarct. The early DWI scan is shown in **Figure 14.4**. His neurological state deteriorated (NIHSS 13 the following day), and a repeat DWI at 4 days showed a very obvious lesion. The other patient

with an abnormally high ADC [PH367] was scanned at 4.5 hours, but had woken with symptoms and was last completely intact 10.5 hours earlier. Her signs suggested a right PACS (NIHSS 7).

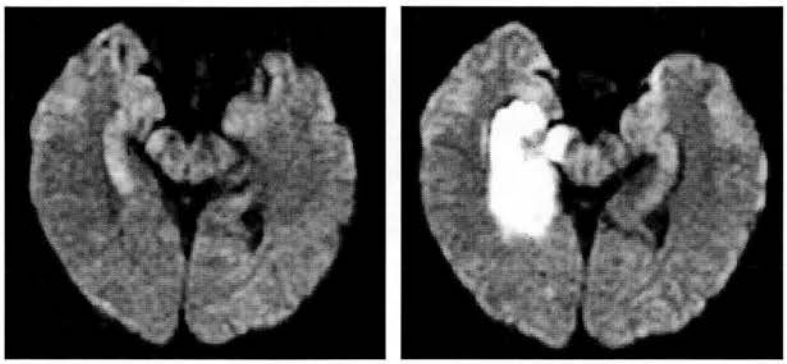


Figure 14.4 A patient with an abnormally high ADC when scanned 3 hours after onset of symptoms

DWI at 3 hours (left scan) showed a subtle hyperintense lesion in the right occipital lobe. Repeat DWI at 4 days (right scan) showed an obvious hyperintensity involving occipital lobe and cerebral peduncle.

Three patients had very low ADC despite being scanned soon after symptom onset. Lowest ADC values usually occur 12 to 24 hours after symptom onset. Patient [PH274] was scanned at 6 hours and 45 minutes, but had woken with the deficit, and was last normal 9 hours earlier. Patient [PH230] was scanned at 13 hours; onset was precise, but the patient had suffered a major stroke (NIHSS 21). Patient [PH257] was scanned 16.5 hours after symptom onset; whilst onset was precise, the stroke was massive (NIHSS 28). Thus an extreme ADC value was often seen in patients with an unclear time of onset or very severe stroke.

14.4.3 The DWI scan and outcome after ischaemic stroke

Analyses were performed on the 82 patients with ischaemic stroke, less one patient in whom follow-up data were unavailable.

Clinical predictors of outcome

There were several potent clinical predictors of outcome: NIHSS, OCSP classification, reduced conscious level, age and cognitive impairment ($p<0.03$ for all) (see **Table 14.2**). Increasing age, more severe stroke and prior dementia predicted a poor outcome (modified Rankin score three to five or death).

DWI lesion volume and ADCr

Imaging features and outcome are detailed in **Table 14.2**. There was a non-significant trend for patients with poor outcomes to present to hospital and be scanned earlier ($p=0.11$). 7/18 (39%) patients with no visible lesion on DWI had poor functional outcome.

There was no statistically significant relationship between outcome and DWI lesion volume, but inspection of **Figure 14.5** demonstrates that those with poor outcome tended to have larger lesions (but the overall relationship was dominated by the preponderance of small DWI lesions). Even when those with no visible DWI lesion were excluded, there was still no significant association between DWI lesion volume and outcome – median lesion volume was 4.0mL (IQR 0.5-8.1) for those with good outcome, and median lesion volume was 4.2mL (IQR 0.8-33.9) for those with poor outcome ($p=0.22$, Mann-Whitney U).

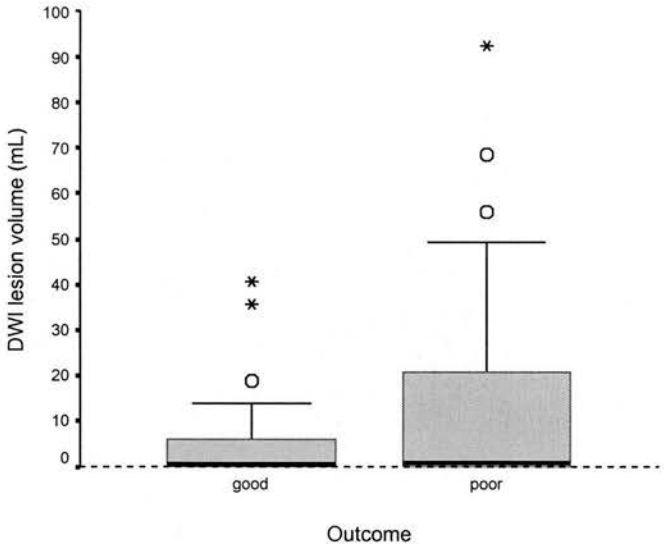


Figure 14.5 Box-and-whisker plot of DWI lesion volume subdivided by good outcome (n=43) and poor outcome (n=38)

The black horizontal line in each box represents the median, with the boxes representing the interquartile range, and the whiskers represent the maximum. Outliers are recorded individually (the two extreme outliers, both in the poor outcome category, are not pictured)

There was no relationship between ADCr and outcome in the 51 patients with both ADCr and outcome data (**Table 14.2**). This group included only those with a visible DWI abnormality (to permit the calculation of the ADCr).

Validation of the three-item model for the early prediction of stroke recovery

The data from the present study were used to independently validate the recently proposed 'three-item scale for the early prediction of stroke recovery' (Baird *et al.*, 2001). The clinical features of the present cohort differed from the training dataset that developed the model (Boston patients). Our patients were slightly older (mean age 72.3 years, vs 69.6 years for Boston patients), the frequency of heart disease was lower (25% vs 46%), the NIHSS scores were lower (mean 7.0 vs 10.5), time to scanning was longer (mean 15.7 hours vs 9.7 hours), and DWI lesion volumes were lower (mean 14.3mL vs 21.1mL). [N.B. As data from our series were

not Normally distributed (and it would appear that neither were the Boston data), statistical tests comparing means for the two groups would have produced spurious results and were therefore not performed.]

Multivariable logistic regression analysis

Age, gender, history of hypertension, history of heart disease, time to scanning, NIHSS score and DWI lesion volume were entered into the logistic regression analysis. Age and NIHSS score were the only significant factors in the model (see **Table 14.3**). With increasing age or stroke severity, the likelihood of a good outcome diminished. The sensitivity of my model for the prediction of a good outcome was 0.86, the specificity was 0.61, and overall accuracy of the model's predictions was 0.74. The model fitted the dataset well (Hosmer and Lemeshow statistic p=0.61). The other variables – including DWI lesion volume and time from onset to scanning – provided no additional prognostic information and were eliminated from the model.

Did the model accurately predict outcome in the present study?

Although multivariable analysis demonstrated that time and DWI lesion volume were not independent predictors of outcome in the present study, the accuracy of Baird et al's (2001) three-item scale was assessed by determining a score for each patient (as indicated by Baird et al). 43 patients were assigned a high total score (5-7 points). Baird et al's model predicted a 91% likelihood of good recovery, but only 58% of our patients actually made a good recovery (**Table 14.4**). The difference between predicted and observed recovery was significant ($p<0.01$, Fisher's exact test).

30 patients were assigned a medium total score (3-4 points), and – as predicted – around half (57%) recovered. Only nine patients received a low total score. Two (22%) recovered, compared with the predicted 7% recovery, but confidence intervals were wide and the difference was not significant (p=0.60) due to low numbers.

14.4.4 PI and outcome

68 patients had perfusion imaging, and functional outcome was assessed for all but one patient. 40 patients had a good outcome, and 27 had a poor outcome. There were 22 patients with no visible PI lesion; 14 of the 22 (64%) were independent, and 8/22 (36%) were dead or dependent at follow-up (p=0.65, χ^2). Median MTT lesion volume for those with a poor outcome was 0.6mL (IQR 0 – 134.1mL), and for those with a good outcome it was 0mL (IQR 0 – 17.1mL)(p=0.08, Mann-Whitney U). There was no significant difference in CBF lesion volume between those with good and poor outcomes (median volume 0mL for both, p=0.30, Mann-Whitney U).

When patients with no visible PI lesion were excluded, the results became clearer. There were 29 patients with a visible lesion on MTT maps. Median lesion volume was 120mL for those who did poorly (n=14), and 20.5mL for the 15 who did well (p=0.04, Mann-Whitney U). Clinically, median NIHSS was 11 in the poor outcome group and 5 in the good outcome group (p<0.01, Mann-Whitney U). Similarly, for the CBF maps (24 patients with a visible lesion), those with good outcome (n=13) had lower median NIHSS (6 vs 11, p<0.01, Mann-Whitney U), but

only a trend for lower median lesion volume (21mL vs 67mL, p=0.15, Mann-Whitney U).

The presence of hyperaemia was detected in seven patients on the CBF map (see **Figure 13.17** in previous chapter for an example). Three were scanned within six hours, one was scanned at seven hours, and the other three were scanned after 12 hours. Five of seven (71%) patients with hyperaemia had a good outcome.

14.4.5 Did DWI-PI mismatch predict outcome after ischaemic stroke?

It was not possible to determine the presence of a mismatch if there were no DWI lesion and PI lesion. This combination occurred in eight patients using MTT maps, and 11/68 patients using CBF maps (the two measures of perfusion used in this study often conflicted, as described in the last chapter, **Table 13.7**).

Mismatch determined by visual inspection of the images

MTT maps

The neuroradiologist classified patients based on a brief visual inspection of the MTT map and DWI scan (designed to replicate the clinical situation). Patients either had a mismatch – where the PI lesion was greater than the DWI lesion (or there was no DWI lesion), or had no mismatch – where the DWI lesion was equal to or larger than the PI lesion (or there was no PI lesion).

Of the 60 classifiable patients using MTT maps, 25 (42%) had a mismatch, and 35 (58%) did not. The clinical features of patients in the two categories are detailed in **Table 14.5**. There were no significant differences between the two groups, although there was a trend for patients with a mismatch to be scanned earlier, have more severe strokes (higher NIHSS and more TACS), and larger DWI lesion

volume. Outcome data were available for 59 /60 patients. As shown in **Figure 14.6**, 52% of those with a mismatch were either dead or dependent, whilst 32% of those without a mismatch were dead or dependent at follow-up (p=0.13, χ^2). The presence of a mismatch was a weak predictor of poor outcome (odds ratio 2.3, 95% CI 0.8 – 6.6).

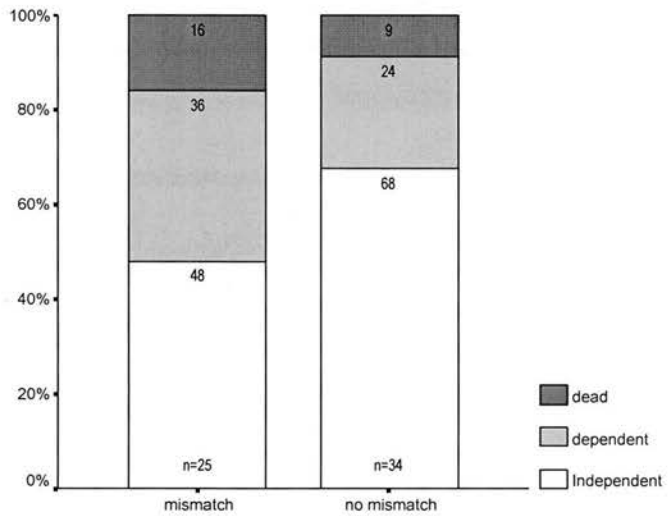


Figure 14.6 Outcome according to visual inspection of the DWI and MTT-PI scans (n=59)

Within the mismatch category were several subcategories. 16 patients had a large mismatch, with the perfusion deficit considerably larger than the DWI lesion (see **Figure 14.7 - 14.9**). In this group, median NIHSS was 8.0, and 9/16 (56%) were dead or dependent at follow-up. Four patients were thought to have a smaller mismatch (PI approximately 20% greater volume than DWI, see **Figure 14.10**): median NIHSS 6.5, and 2/4 (50%) dead or dependent. Five patients had no visible DWI lesion but had a PI abnormality (see **Figure 14.11**): median NIHSS 1.0, and 2/5 (40%) dead or dependent at follow-up.

Patients without a mismatch had either a matching perfusion and diffusion deficit (n=13) or a perfusion lesion that was smaller than the DWI lesion (n=21).

Those with a matching deficit (see **Figure 14.12**) had a median NIHSS of 7.0, and 3/13 (23%) were dead or dependent. Those with a smaller perfusion lesion (see **Figure 14.13**) or no perfusion lesion (see **Figure 14.14**) had a median NIHSS of 4.0, and at follow-up 8/21 (38%) were dead or dependent.

CBF maps

Of the 57 classifiable patients using CBF maps, only 10 (18%) had a mismatch. The clinical features of this group are detailed in **Table 14.6**. There was a non-significant trend for patients with a mismatch to be scanned earlier, have higher NIHSS and fewer lacunar syndromes than patients without a mismatch. Lesion volume on DWI was almost identical. Outcome data were available for 56/57 patients. 4/10 (40%) of those with a mismatch, and 19/46 (41.3%) of those without a mismatch were dead or dependent at follow-up (p=0.94, Fisher's exact). The presence of a mismatch with the CBF map did not predict outcome (odds ratio for a poor outcome 0.9, 95% CI 0.2-3.8).

Disparity between the findings of the CBF and MTT maps was frequently observed. In addition to the ten patients with a mismatch on CBF, there were 12 patients who had a mismatch on MTT maps (but not on CBF) – see **Figures 14.8 & 14.9**.

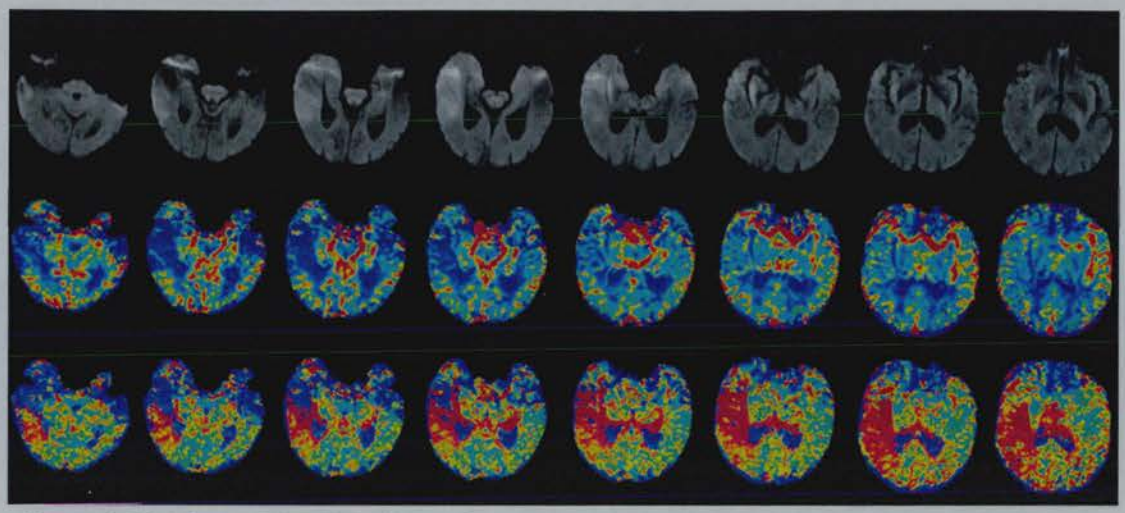


Figure 14.7 A large PI-DWI mismatch

PH384: This patient presented with left face and arm weakness and visual loss (NIHSS 5). MR at 2.82 hours. DWI (upper row of images) shows a right temporal hyperintensity (middle cerebral artery territory). CBF map (middle row) shows a moderately large focal area of reduced perfusion (blue) in the right temporal lobe. MTT map (lower row) shows an extensive area of reduced perfusion (red = delayed transit) in the right temporal and parietal lobes. Both maps were classed as showing a mismatch (PI>DWI).

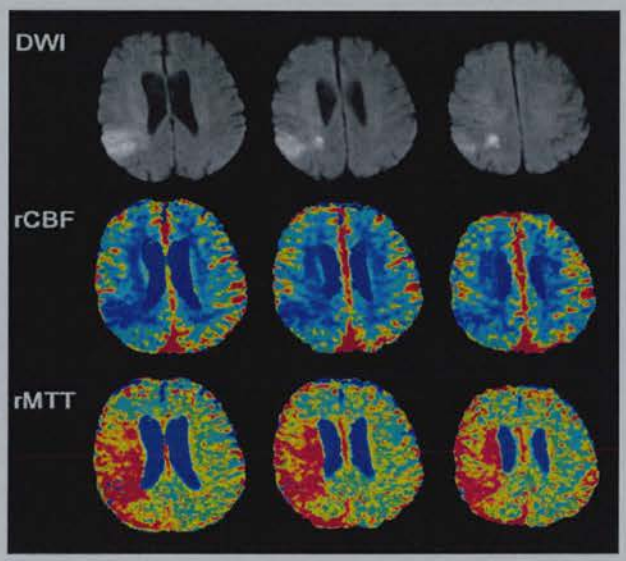


Figure 14.8 A large mismatch on MTT but small CBF lesion

PH399: This patient presented with left hemiplegia, hemianopia and profound neglect (NIHSS 15). MR at 4.43hours. DWI (top row of images) showed a right parietal hyperintensity; CBF map (middle row) showed a matching focal area of reduced flow, and the MTT map (lower row) showed a much larger area of delayed transit.

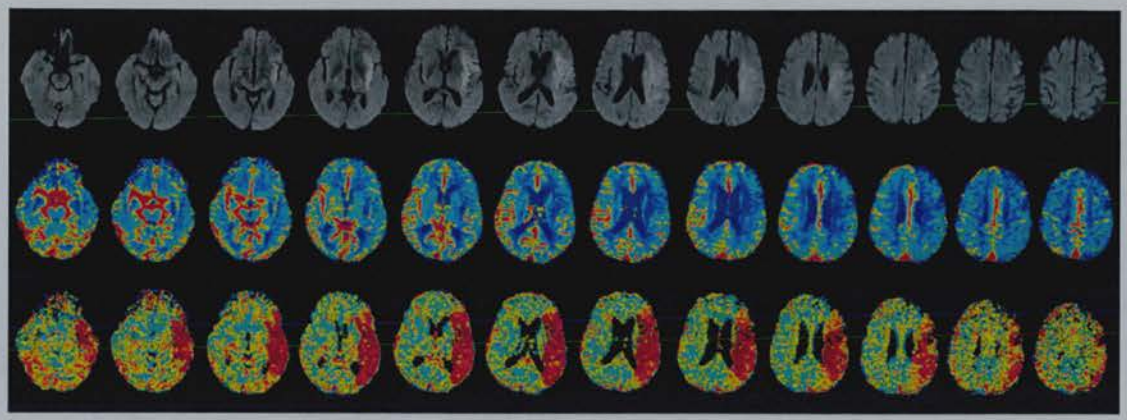


Figure 14.9 A large mismatch on MTT but no CBF lesion

PH305: This patient presented with a left TACS (NIHSS 23). MR at 2.5hours. DWI (upper row of images) shows a large hyperintense lesion in left middle cerebral artery territory. CBF maps (middle row) show slight reduction of flow in the same territory, but the MTT maps (lower row) show marked delayed transit in a larger area than the corresponding DWI lesion. Patient died on day 13.

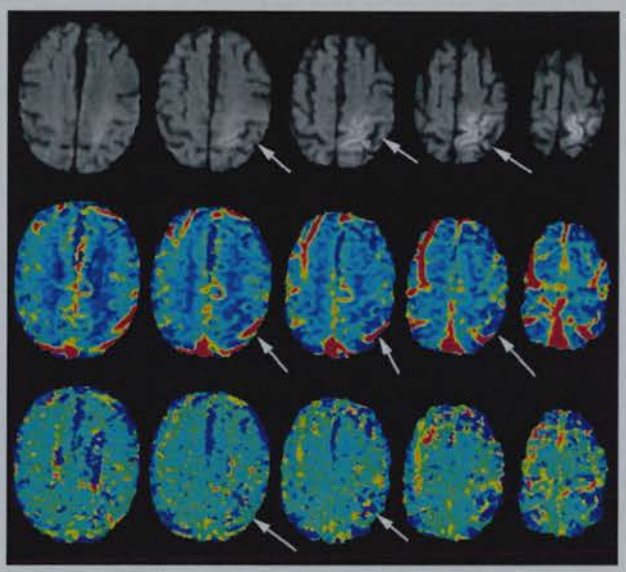


Figure 14.10 A patient with a small mismatch (PI around 20% greater than DWI)

PH188: This patient presented with right sided weakness (NIHSS 8). MR at 9 hours. The DWI (upper row of images) shows a left frontal hyperintensity (arrows). The CBF maps (middle row) show a slightly larger focal area of reduced flow (arrows, but the MTT maps (lower row) are subtle.

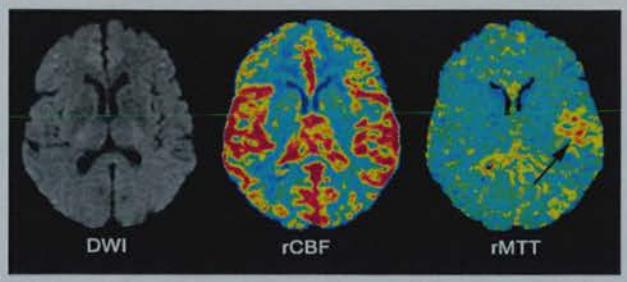


Figure 14.11 A patient with a visible PI lesion but no DWI lesion

PH293: This patient presented with a three hour episode of aphasia, which resolved just before imaging (at 3.9hours). The DWI scan and CBF map show no lesion, but the MTT map shows a focal area of increased transit in the left temporal lobe consistent with acute ischaemia

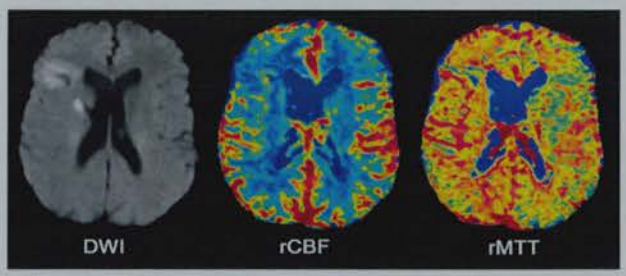


Figure 14.12 A patient with a matched PI and DWI deficit

PH367: This patient presented with left sided weakness and inattention (NIHSS 7). MR at 4.8 hours. DWI shows a hyperintense lesion in the distribution of a branch of the right middle cerebral artery. CBF map shows reduced flow matching the DWI lesion. The MTT map shows possible increased transit throughout most of the right hemisphere

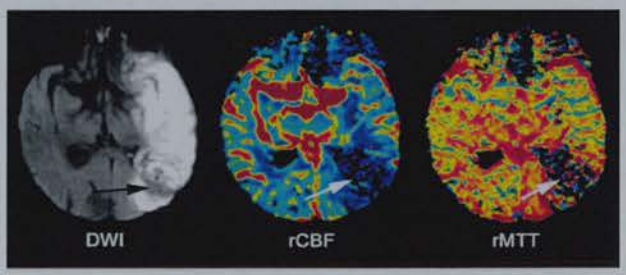


Figure 14.13 A patient with a smaller PI lesion than DWI lesion

PH257: This patient presented with aphasia, right hemianopia and hemiplegia (NIHSS 28). MR at 16.6 hours. The DWI image shows extensive left hemispheric hyperintensity with haemorrhagic transformation posteriorly (arrow). The PI maps show a much smaller area of focal reduced blood flow. The area of haemorrhagic transformation is seen as no flow on PI (white arrows).

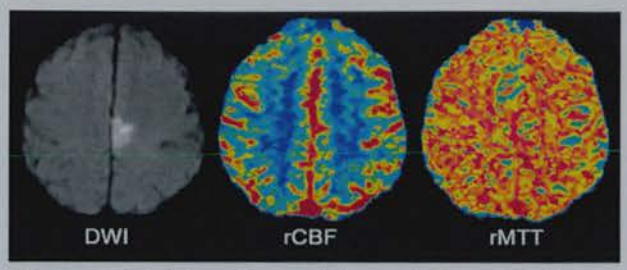


Figure 14.14 A patient with no visible PI lesion

PH212: This patient presented with mild right leg weakness and speech difficulties (NIHSS 3). MR at 4.1 hours. The DWI shows a small hyperintensity in the left frontal lobe. CBF and MTT maps do not show an abnormality.

The influence of time

As the time from symptom onset to scanning increased, the likelihood of observing a mismatch diminished. Using MTT maps, the proportion of patients with a mismatch within six hours was 10/18 (56%); between six and twelve hours was 3/7 (43%); between 12 and 24 hours was 9/23 (39%), and after 24 hours was 3/14 (21%) (see **Figure 14.15**). 8/13 (62%) patients who were scanned within 12 hours and had a mismatch were dead or dependent at follow-up, whilst 3/12 (25%) patients who presented at the same time but did not have a mismatch were dead or dependent at follow-up ($p=0.07$, χ^2).

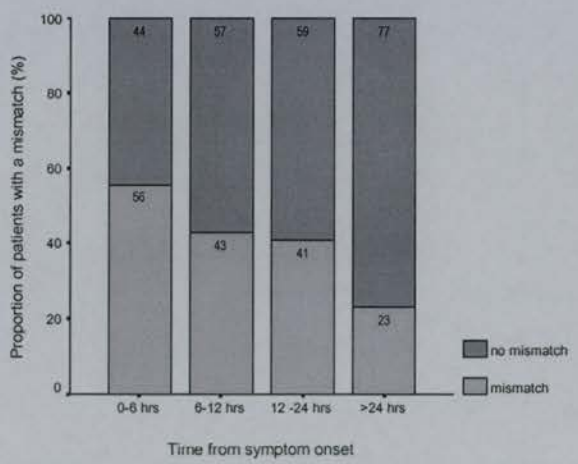


Figure 14.15 The likelihood of seeing a mismatch diminished as time from onset increased

60 classifiable patients using MTT maps, divided into mismatch or not on basis of visual inspection

The latest time that a mismatch was observed was in a patient scanned at 51.8 hours after symptom onset [PH307]. This 81 year old patient presented with right hand weakness and speech loss, on examination the pulse was irregular, there was aphasia and moderate right hemiparesis (NIHSS 11). The clinical classification was PACS. The DWI (see **Figure 14.16**) showed a patchy left internal borderzone ischaemic lesions, but the MTT maps showed a much larger perfusion deficit. At three months, the patient needed considerable support from family (mRS 3).

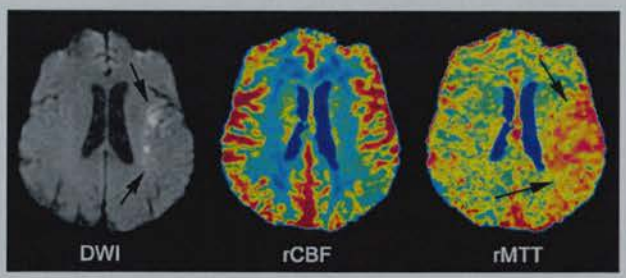


Figure 14.16 The latest patient with a mismatch scanned in the study
PH307: This patient presented with (NIHSS 11). **MR at 51.8 hours**. *The DWI image shows patchy small hyperintense lesions in the internal borderzone region (arrows). The CBF map showed no abnormality, but the MTT map shows a much larger focal area of reduced blood flow (arrows) compared with the DWI.*

The earliest patient with a mismatch in the study was scanned at 2.5 hours after symptoms onset. This 77 year old presented with speech disturbance and reduced consciousness, on examination, GCS was 11, there was global aphasia, a right hemianopia and right hemiplegia (NIHSS 23). The clinical classification was TACS. MRI brain showed an extensive infarct, with PI scans showing a large mismatch (see **Figure 14.9**). The patient died 13 days after onset.

The influence of infarct location on the presence of a mismatch

To determine whether a mismatch was mainly seen in those with cortical rather than lacunar infarcts, patients were divided on the basis of the location and

size of the infarct on the MR. Those with a brainstem infarct (n=2) or a normal structural/DWI scan (n=18) were excluded. Patients with large subcortical lesions were classed as non-lacunar infarcts, along with patients with cortical lesions.

Of the 15 patients with lacunar infarcts, 13 had successful PI scans. None had a mismatch (using the MTT map). Of the 47 patients with non-lacunar hemispheric infarcts, 39 had successful PI scans. 20 had a mismatch and 19 did not. The difference in observed frequency of mismatch between the lacunar and non-lacunar groups was significant, despite the small numbers involved ($p<0.01$, χ^2). Median time to scanning was 14.4 hours for the lacunar infarct group, and 7.1 hours for the non-lacunar group (although three of the lacunar infarct patients were scanned within six hours).

Mismatch determined by careful measurement of lesion volumes

How did visual grading compare with measured volumes?

The neuroradiologist's visual classification of mismatch was compared to the calculated ratios from measurement of DWI and PI lesion volume. Although the initial visual classification included a distinction between those with a large and a small mismatch, only four patients were classed as a small mismatch (so this category was removed). **Table 14.7** shows the comparison using the MTT map. Clinically, the most important distinction would be to identify whether a mismatch was present, and **Table 14.7** shows that 25 patients were classed as having a mismatch, and 19 actually had one according to volume measurements (76% correct). 25 patients also had a 'true' mismatch, of whom 19 (76%) were classed as mismatch after visual inspection. **Table 14.8** shows the comparison using the CBF

map. Here, 10 patients were classed as mismatch after visual inspection of the images, of whom six had a mismatch when measured (60% correct). 19 patients had a measured mismatch, but only six (32%) were actually classed as a mismatch by visual inspection.

Features of patients with a calculated mismatch

The clinical and radiological features and outcome of patients with a calculated mismatch are shown in **Table 14.9** (for the MTT map) and **Table 14.10** (for the CBF map). There was a trend (significant for the MTT map) for clinical features to be more severe in those with a calculated mismatch, and the size of the lesion on DWI and PI was significantly larger in those with mismatch ($p<0.01$ for both CBF and MTT maps, Mann-Whitney U). However, even carefully measured mismatch did not significantly predict outcome: for the MTT map, the odds ratio of a poor outcome if mismatch was present was 1.7 (95% CI 0.6-4.9, $p=0.45$, χ^2), and 1.5 (95% CI 0.5-4.5, $p=0.69$, χ^2) for the CBF map.

Size of the 'penumbra'

For patients with a mismatch, the region of perfusion abnormality larger than the diffusion abnormality may represent the ischaemic penumbra. In our patients with a mismatch, the volume of 'penumbra' ranged from 4.4mL to 236.5mL on MTT maps (median 76.5mL, 25 patients), and from 3.4mL to 139.2mL on CBF maps (median 30.7mL, 19 patients).

The relationship between outcome and size of the 'penumbra' for the MTT map is illustrated in **Figure 14.17**. The median volume of penumbra in the patients who did poorly was 133.3mL, and 54.9mL in those who did well ($p=0.25$, Mann-Whitney U). For the CBF map (see **Figure 14.17**), the median volume was 33.2mL

in the poor outcome group, and 22.7mL for the good outcome group (p=0.33, Mann-Whitney U). Thus, outcome did not appear to be associated with size of the 'penumbra' in the present study.

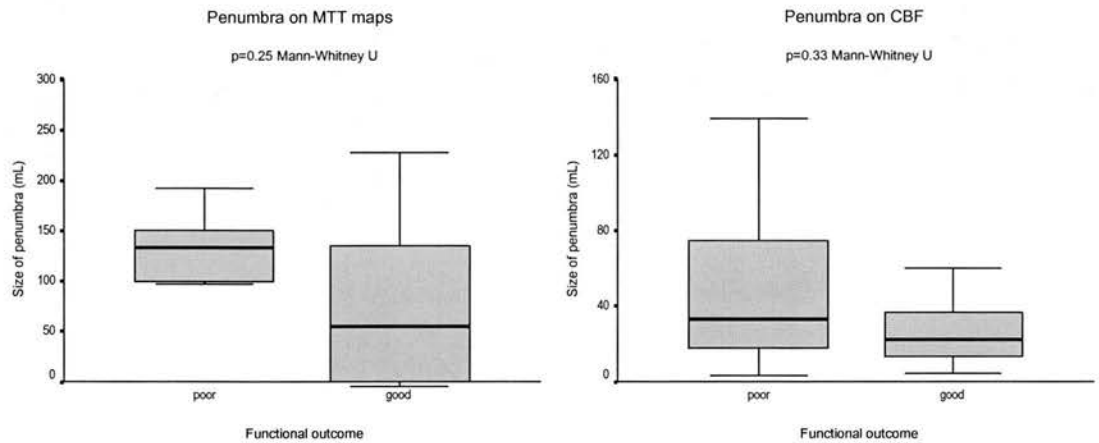


Figure 14.17 The size of the 'penumbra' in those with a mismatch: did it predict outcome? *Box-and-whisker plot of size of penumbra for patients divided into good and poor functional outcome*

Exploring other factors that affect perfusion imaging: the importance of carotid stenosis

Of the 82 patients with a final diagnosis of possible, probable or definite cerebral ischaemia, 72 had a carotid doppler ultrasound examination. Six patients had an ipsilateral carotid occlusion, and a further four patients had 60-99% ipsilateral stenosis. To investigate whether carotid stenosis may have been associated with absence of a perfusion deficit, I plotted the number of patients within 20% bands of ipsilateral carotid stenosis, subdivided by whether a PI lesion was present (**Figure 14.18**). No significant relationship was observed (p=0.66, χ^2). An ipsilateral >60% carotid stenosis or occlusion was more frequent in patients with a regional perfusion deficit.

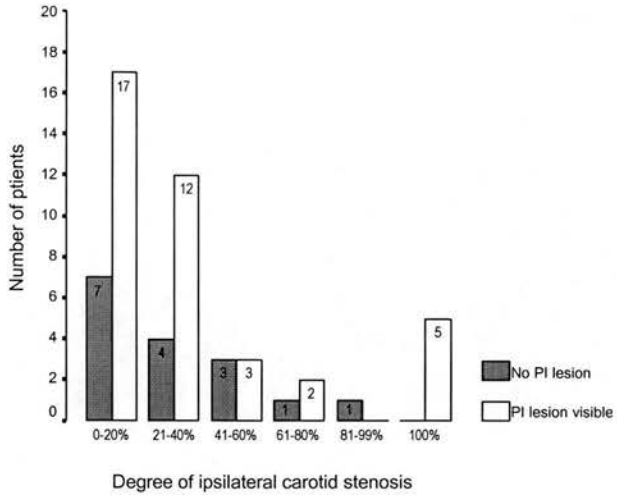


Figure 14.18 The influence of an ipsilateral carotid stenosis on the presence of a visible perfusion abnormality (n=55)

68 patients had PI data, but a carotid ultrasound was not performed in six, and the symptoms referred to the brainstem or could not be localised in seven (hence any stenosis could not be classed as ipsilateral)

An almost identical trend was seen when carotid stenosis was subdivided by whether a mismatch was present (**Figure 14.19**). There was no significant relationship (p=0.17, χ^2), but those with severe stenosis were more likely to have a mismatch.

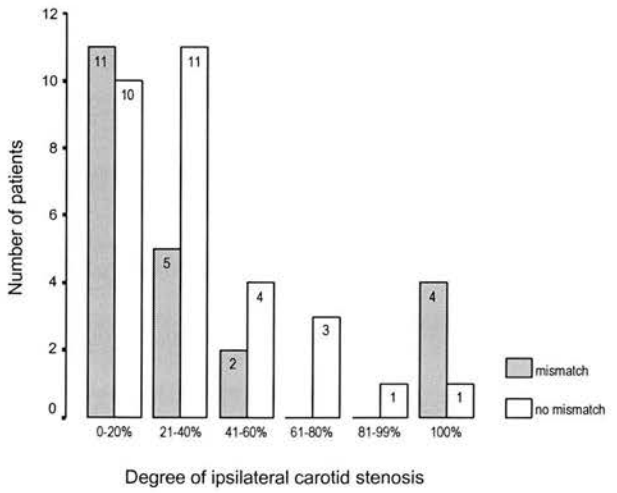


Figure 14.19 The influence of an ipsilateral carotid stenosis on the presence of a DWI-PI mismatch on MTT maps (n=52)

52 patients had all of: a carotid ultrasound, PI scanning, and either a PI or DWI lesion. Ipsilateral refers to side of symptoms - when symptoms referred to the brainstem or could not be localised, patients were excluded.

14.4.6 What was the impact of advanced imaging on current management strategies?

This sub-study examined how often – and why – MR imaging changed patient management, compared with CT. 63 patients were recruited into the study (one more than the influence of imaging on the diagnosis sub-study – an extra CT scan was found). Within the group of 63 patients were four patients with a stroke mimic (seizure, tumour, decompensation, and functional), four patients with primary intracerebral haemorrhage, three patients with haemorrhagic transformation of an infarct, and eight patients with microbleeds. 18/63 (29%) patients had a normal DWI scan.

Five clinicians were present at the meetings when 46 patients were discussed, and four clinicians (the minimum) were present when 17 patients were discussed. An additional two clinicians attended a few meetings, but were excluded from the analysis, as the number of patients an opinion was given for was too low (seven and 15). In total, there were 299 'patient-clinician episodes' (not all clinicians passed an opinion about the same patient).

Clinicians varied in experience and training. Clinicians one and two were academic consultants in stroke medicine, clinicians three and four were academic consultants in neurology, clinician five was a stroke research fellow (commencing geriatric training), and clinician six was a trainee in neurology (18 months before training complete).

The CT was performed after the MR in 41/63 (median time between scans 0.8 hours, mean 7.0 hours, range 48.8 hours), and before the MR in 22/63 (median

time between scans 1.1 hours, mean 6.2 hours, range 23.5 hours). Overall, 43/63 of CT scans were performed within two hours before or after the MR scan.

How often did management change after the MR images?

MR brain imaging – both structural and DWI sequences – resulted in few changes in management. **Table 14.11** shows that, when averaged across all six clinicians, MR resulted in a management change in eight of 49 patients (16%). In six of the eight patients, the change occurred after the structural imaging.

There were clear differences between clinicians. Two found MR to be very helpful (management altered in 26% and 22% of patients), although one placed more emphasis on the DWI (management changed in 14%) than the other clinicians. Two clinicians made few changes after MR imaging (management changed in 7% of patients). There was no pattern observed as to whom found MR useful, in particular, experience had no impact on whether the MR changed management.

On average, each clinician made 294 management decisions. 17 changes were made after MR; 13 after the structural and 4 after the DWI images were shown. Often a finding on MR resulted in a number of changes in one patient. The mean number of changes per patient was 2.4 after structural imaging and 1.5 after DWI.

How did the results of the MR brain imaging change management?

Urgent reversal of anticoagulation

Anticoagulation was reversed urgently for 24/299 (8%) patient-clinician encounters after the CT. After structural MR, there were five management changes: in two (one patient) an initial decision to reverse anticoagulation was changed after the MR showed features suggesting a meningioma (rather than a bleed), and in two

(one patient) the MR showed haemorrhagic transformation of an infarct, not seen on the CT (which was performed 13 hours earlier). One clinician decided to reverse anticoagulation urgently in one patient (whose MR showed old microbleeds only), but then changed back to continuing with anticoagulation after the DWI showed an acute lacunar infarct.

Intravenous thrombolysis

The two hypothetical questions asked whether the clinician would treat a patient at two hours, and at four hours, with intravenous thrombolysis (either open-label or as part of a randomised trial). Three clinicians (3, 4 & 6) would only ever give thrombolysis as part of a randomised trial, and no clinicians would give open-label thrombolysis for the patient presenting at four hours.

For the two-hour patient, there were 68 (23%) decisions to give open-label thrombolysis, 176 (59%) decisions to randomise the patient to a trial, and 55 (18%) decisions to withhold treatment after CT. Mostly, clinicians withheld treatment because the symptoms were due to an intracerebral haemorrhage, or the symptoms were not convincing enough (despite being asked to imagine that symptoms were of severity to warrant treatment). For the four-hour patient, 243 (81%) decisions were to randomise, and 56 (19%) decisions to withhold treatment.

After structural MR, there were 22 changes for the two-hour patient, and 16 changes for the four-hour patient. One clinician decided to change from trial to open-label treatment for a two-hour patient (the structural MR showed atrophy only), and a different clinician made the same decision for a four-hour patient (structural MR was normal). Four decisions were made to change from open-label to trial, for no discernible reason. The remaining 32 changed decisions were from treatment to

nothing. The MR findings that resulted in these changes were: evidence of haemorrhagic transformation (12 decisions in 2 patients); evidence of old haemorrhagic stroke (12 decisions in 3 patients); microbleeds (5 decisions in 2 patients), and atrophy (3 decisions in 1 patient).

After the DWI scan, there were ten changes in management. Three decisions were to do nothing, as the DWI was normal. One decision was to go from no treatment to open label treatment as DWI showed a clear infarct in a two-hour patient, and – in a separate patient – management was changed from no treatment to trial as DWI showed an infarct in a four-hour patient. The five other management decisions were to change from open-label treatment to participation in a trial, as the DWI was normal or showed small lesions (one lacunar, two cortical).

Long term anticoagulation

Clinicians were asked if they would advise long-term anticoagulation for the patient (if in atrial fibrillation). On the basis of the CT, 268 (90%) decisions were to anticoagulate, and 31 (10%) to avoid anticoagulants. Patients with haemorrhage or haemorrhagic transformation were those for whom anticoagulants were avoided, and of these, one clinician altered management after structural MR imaging (as the CT was uncertain whether the lesion was a tumour or a bleed, whilst structural MR was clear that it was a meningioma).

Of those who initially decided to anticoagulate, 19 changed management after the structural MR. The MR findings that resulted in the change were: old haemorrhagic stroke (15 decisions in four patients); haemorrhagic transformation (2 decisions in 2 patients); microbleeds (1 decision) and leukoariosis (1 decision). After

the DWI, one clinician changed management from anticoagulation to none, on the basis of a normal DWI scan.

Carotid endarterectomy

221 (74%) decisions were to proceed with carotid endarterectomy (CEA) if there was an ipsilateral 90% carotid stenosis, and 78 (26%) were against CEA, after the CT had been performed. Clinicians decided not to proceed with CEA when the patient had suffered a haemorrhage or posterior circulation event, and further imaging did not change management. After structural MR, there were five management changes, all against proceeding to CEA. Two patients had clear infarcts in the posterior cerebral artery territory, and three patients had many old lesions evident on the structural imaging (in two there was also evidence of old haemorrhage).

DWI had the largest impact on CEA, with nine changes recorded. In all but one, the changes were against proceeding with CEA. The DWI appearances in the eight patients were: probable/possible posterior circulation vascular territory (7 decisions in 3 patients), and normal scan (1 decision). For one clinician, after deciding against CEA after the structural imaging on the basis of an old haemorrhage, the management was changed back to proceeding with CEA when the DWI showed a small anterior circulation lacunar infarct.

Antiplatelet therapy

The final management scenario asked the clinician about antiplatelet therapy, assuming that the patient were already on aspirin. There were 56 (19%) decisions to continue with aspirin and 26 (9%) decisions to stop aspirin after the CT. Stopping aspirin was observed in the four patients with a bleed (by five clinicians), in the

patient with a meningioma (by five clinicians), and in one patient with haemorrhagic transformation of an infarct (by one clinician) [NB not all the clinicians were present for every patient]. Neither structural nor DWI MR changed these decisions. One clinician had fixed views on aspirin: in 46/47 patients, aspirin was continued, in one patient (with a haemorrhage) aspirin was stopped, and there were no changes after further imaging.

Of the 217 (73%) decisions to intensify antiplatelet therapy, 13 were changed after structural MR. Three clinicians stopped aspirin in one (different) patient each – the structural MR showed old haemorrhage or microbleeds and no evidence of an acute lesion. Ten decisions to change the patient back to aspirin were made – the structural MR showed old haemorrhage (4 decisions in two patients), microbleeds (3 decisions in two patients), leukoariosis (two decisions in one patient), and haemorrhagic transformation of an infarct (one decision). Only two decisions were altered by the DWI: one clinician recommenced aspirin – structural MR showed microbleeds, DWI showed an acute lacunar infarct, and one clinician went from intensified antiplatelet therapy to aspirin when the DWI was normal.

14.5 Discussion

14.5.1 Is it possible to predict the 'age' of a lesion with advanced imaging?

The requirement for a known, precise time of onset is critical to the safe use of thrombolysis. Yet 1 in 3 patients are excluded from treatment as time of symptom onset is unknown (Barber *et al.*, 2001a). Around 25 – 30% of patients wake from sleep with stroke (International Stroke Trial Collaborative Group, 1997; Elliott, 1998), and in the remainder, onset cannot be determined because of speech or other

problems (Barber *et al.*, 2001a). MR imaging offers a potential solution to this problem, because it is independent of the patient's ability to recall the onset of symptoms.

In the present small study, a neuroradiologist with considerable experience in stroke estimated the age of the lesion seen on DWI. The typical changes that occur in the maturation of a DWI lesion were used as the basis for the judgement (Koroshetz & Gonzalez, 1997). The assessment was quick and potentially widely applicable. Using the patient's time of onset as the gold standard (in the subgroup with very precise onset details) showed that there was a discrepancy between the imaging findings and the patient's duration of symptoms.

Similar findings were observed when the ADC was examined. Although others have suggested that this may be a useful marker of lesion age (Fiebach *et al.*, 2002), we did not observe this. ADC values varied significantly in our heterogeneous population of patients, as has been noted in previous studies (Schwamm *et al.*, 1998; Fink *et al.*, 2002). In addition, in most patients there is a further fall in ADC, but the time that it reaches its nadir varies from a few hours to a few days (Lutsep *et al.*, 1997; Schwamm *et al.*, 1998; Fiebach *et al.*, 2002). Thus it would be impossible to define threshold levels for ADC with which to age a lesion accurately. As we demonstrated, an extreme ADC value probably indicates that there is inconsistency in timing.

These findings, although on a small scale, have implications for hyperacute treatments such as thrombolysis. The appearance of the DWI lesion, and the ADC, may provide a more direct estimate of the degree of tissue damage than just relying on time alone. It is clear that time and imaging parameters are measuring different

things. Ideally, treatment should be guided by the degree of tissue damage, for which time is a very crude estimate. These data suggest that some patients who present early have severe damage, and thus may be unsuitable for thrombolysis even within three hours, whilst other patients who presented later had milder damage, and could be suitable for thrombolysis eight or even twelve hours after onset.

14.5.2 The prediction of outcome after stroke

The prediction of outcome after stroke has been the subject of much research, and for obvious reasons: accurate prediction could help to guide management decisions (Counsell & Dennis, 2001). For a treatment such as thrombolysis, it would be ideal to be able to select only the patients likely to benefit, and exclude those who are at high risk of complications and those who are likely to do well without treatment. Such predictions would have to be based on clinical or investigative data that can be obtained from the patient immediately on presentation (rather than at 24 hours, or one week, as was the focus of many previous studies, e.g. (Johnston *et al.*, 2002)).

There has been much interest in the potential of MR to predict outcome. Several small studies demonstrated that there was a strong correlation between baseline DWI lesion volume and outcome, with a higher lesion volume predicting a worse prognosis (Lovblad *et al.*, 1997; van Everdingen *et al.*, 1998; Barber *et al.*, 1998; Beaulieu *et al.*, 1999). More recently, two studies showed that DWI lesion volume at baseline independently predicted outcome (Thijs *et al.*, 2000; Baird *et al.*, 2001). In both studies, logistic regression was performed, and the other independent

predictors were age, NIHSS and delay to imaging (Thijs *et al.*, 2000), and NIHSS and time (Baird *et al.*, 2001).

However, these two studies have been criticised for failing a number of methodological standards (Hand *et al.*, 2001; Counsell *et al.*, 2001). The studies were retrospective, the sample sizes were small, the patients were highly selected (just hemispheric strokes), and the models violated key rules of logistic regression [e.g. 12 variables were entered into the model when there were only 24 outcome events (Thijs *et al.*, 2000)]. We thus aimed to perform an external validation of Baird and colleagues' (2001) three item scale.

In our own series of 82 patients, we found that the three stage model failed to usefully predict outcome, particularly in those predicted to have a good outcome. We found that DWI lesion volume provided no additional prognostic information – either on univariate or multivariate analyses. In our sample of patients, the most important predictors of outcome were age and NIHSS score.

Why did DWI lesion volume not predict outcome?

Not withstanding the methodological flaws of the models produced, probably the major explanation for our findings is case-mix. Our patient sample was an unselected group of patients who presented with brain attack. This reflects real-life. We included patients who turned out to have had transient ischaemic attacks, and possible strokes. Our patients were older, had more comorbidity, and had milder stroke severity than the patients previously reported. The two previous studies had major selection bias: only 66 patients from a potential 347 (19%) were selected for Baird et al's study (2001), and Thijs et al (2000) excluded those with prestroke

disability, lacunar subtype and normal DWI scans. Both identified patients retrospectively.

The clear implication of the present study is that for patients with milder stroke severity, or lacunar or brainstem strokes, imaging adds little to the prediction of outcome over and above age and NIHSS score. The importance of the NIHSS has been a consistent finding in many other studies (Muir *et al.*, 1996; Adams, Jr. *et al.*, 1999; Uchino *et al.*, 2001). An explanation for the discordance of results between the present study and other imaging studies can be seen in **Figure 14.20** [reproduced from (Adams, Jr. *et al.*, 1999)]. The mean baseline NIHSS of our cohort has been plotted on the curve, along with that of Baird et al's study (it was not possible to include Thijs et al's study). Our cohort is on part of the curve where the slope is very steep, particularly if the curve for lacunar stroke is also included. Where the slope is very steep, small changes in NIHSS can result in major changes to the likelihood of a good outcome. It would be difficult for any factor to add to NIHSS in the prediction of outcome. Conversely, Baird et al's cohort (and other similar studies) is further down the curve. Lacunar strokes were excluded, and it can be seen that the slope becomes less steep. Here, the relationship between NIHSS and outcome is not as strong – small changes in NIHSS have less effect on outcome – and so it becomes possible for other features like DWI lesion volume to add independent information.

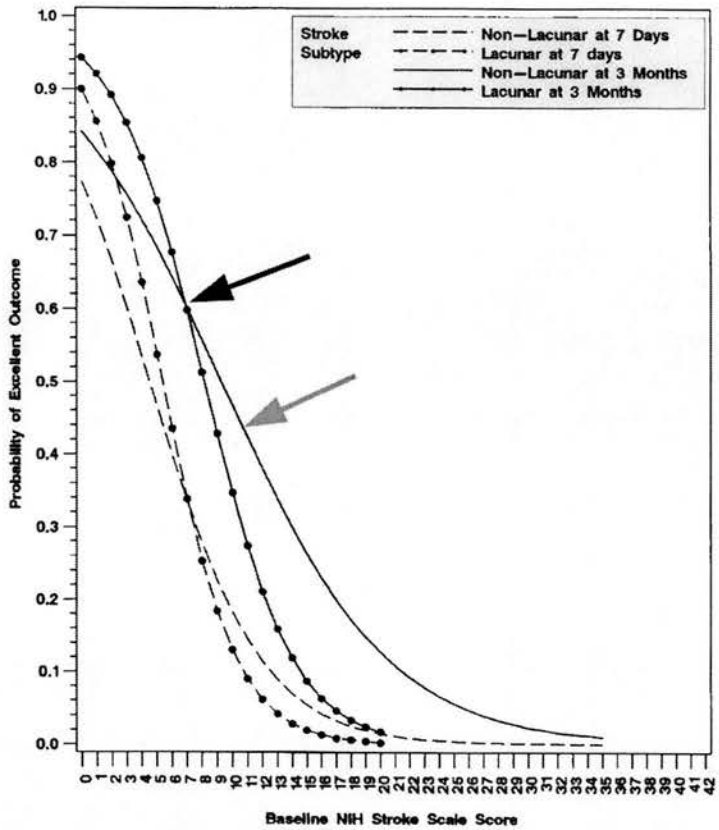


Figure 14.20 The influence of baseline stroke severity on outcome

The Y axis plots the probability of an excellent outcome, and the X axis plots baseline NIHSS score. The straight line is the three month outcome for non-lacunar stroke, and the straight line with dots is the three month outcome for lacunar stroke. The black arrow marks the mean NIHSS in the present study, the grey arrow marks the mean NIHSS of Baird et al's study. Reproduced from (Adams, Jr. et al., 1999).

Limitations of the study

The present study is subject to a number of limitations. In order to replicate Baird et al's study, I contravened many of the unofficial rules of logistic regression. However, as the aim was to validate an existing study (and they had contravened the rules to produce their model), I felt this was acceptable. I used the modified Rankin score as a measure of outcome, but it would have been desirable to combine this with a measure of neurological deficit (such as a repeat NIHSS at 3 months) to determine how much of the poor outcome was due to the stroke (Lyden & Hantson, 1998).

14.5.3 The DWI-PI mismatch – what more does it tell us?

The combination of perfusion and diffusion-weighted imaging has also attracted much interest as a predictive tool. It is thought that the region of perfusion compromise that is larger than the region of abnormal diffusion (thought to represent the ischaemic core of an infarct) is an approximation of the ischaemic penumbra – tissue that should respond to reperfusion therapy. Thus, demonstration of a mismatch might identify patients suitable for thrombolysis after three hours (Albers, 1999; Warach, 2002; Parsons *et al.*, 2002). In the absence of treatment, lesion growth is said to occur in patients with a mismatch (Tong *et al.*, 1998; Barber *et al.*, 1998; Beaulieu *et al.*, 1999)

Most of the previous studies have been subject to numerous methodological problems (Keir & Wardlaw, 2000), principally selection bias. Despite the logical attractiveness of such theories, questions remain. How often does a mismatch occur in unselected patients? What is the implication of finding a mismatch? How feasible is the process of determining a mismatch? There is currently a randomised controlled clinical trial ['DIAS', Desmotoplase In Acute ischaemic Stroke] in progress that aims to test a new thrombolytic agent, with entry to the trial based on demonstration of a mismatch. We aimed to determine if such a trial was feasible in our unit.

Practical difficulties of determining if a mismatch is present

We demonstrated that determining the presence of a mismatch is challenging. The initial problem is the extensive processing of the data required to generate perfusion maps, which has been the major limiting factor for widespread use of PI (Baird & Warach, 1998). Now, PI packages are often available with the MR

scanner, but these have limitations (Calamante *et al.*, 2002). One of the most time consuming aspects of post-processing is correction of motion artefact, but if this is not performed, the volume of the lesion may be seriously over-estimated (see **Figure 13.1**).

The next problem is that there is no ideal single measure of perfusion. The four different measures – mean transit time (MTT), time to peak (TTP), cerebral blood volume (CBV) and cerebral blood flow (CBF) – have advantages and disadvantages. TTP and MTT maps are most widely used, because the lesion boundaries are more distinct (Parsons *et al.*, 2001). In the present study, we found the MTT maps far easier to read, and consequently visual inspection of the MTT map more accurately defined a mismatch than did the CBF map. However, Parsons and colleagues (2001) found that the CBF map most accurately defined tissue in the mismatch region that was at risk of infarction (the MTT map overestimated the final infarct size). In our study, there was often discordance between the two measures of perfusion.

A method for overcoming the extensive processing required to calculate DWI and PI lesions is to base decisions on a brief visual inspection of the DWI film and PI maps. This is the basis for recruitment to the DIAS trial. We replicated this scenario in the present study, but also calculated the actual lesion volumes. This required an additional reading of the PI maps, which resulted in some changes to the initial classification of the PI lesion. We demonstrated major differences in the nature of the mismatch as identified by visual inspection and by lesion calculation, but it is by no means clear which method is 'correct'. Our data suggests that in future,

researchers should clearly specify what method of perfusion they used, how it was processed and then analysed, so that the results can be interpretable.

A final problem was the difficulty of interpreting the PI maps, which was highlighted in Chapter 13 (see **Figures 13.15-13.18)**. PI maps can be difficult to report when there are old stroke lesions, very small (particularly lacunar) lesions, and even extracranial carotid stenosis (Neumann-Haefelin *et al.*, 2000). Few studies to date have mentioned these problems, possibly because the patients in these studies have been so highly selected.

The significance of a 'mismatch'

A mismatch was observed in 42 % of patients on MTT maps, and 18% (by visual inspection) to 33% (by calculation) of patients on the CBF map overall. This is far less than the 75% suggested by others (Parsons *et al.*, 2001), but ours was a more heterogeneous group, and time to scanning varied. In patients scanned within six hours, 56% had a mismatch (on MTT maps) and these patients did worse.

Overall, in our cohort, the presence of a mismatch did not predict outcome. Our patients were not treated with thrombolysis, which may prevent lesion growth and improve outcome in those with a mismatch (Parsons *et al.*, 2002). We did not perform further scans on the majority of patients, so we do not know whether the ischaemic lesions in those with a mismatch enlarged, as is proposed. Our data would suggest that in a milder cohort of patients scanned at later time intervals, the presence of a mismatch is of little clinical value.

This data helps to define the place of diffusion and perfusion MRI. In patients who present early, with symptoms of a severe stroke, the demonstration of a mismatch may be of benefit in guiding further treatment.

Limitations

The present study was subject to many limitations, some of which have been highlighted above. Our sample size was small (though larger than many prior studies). We measured outcome as the modified Rankin score, which may be insensitive to subtle changes (but is arguably more relevant to the patient). To test the underlying theories of the perfusion-diffusion mismatch, sequential scans were required (but this was beyond the scope of this thesis, though is part of the underlying study). There may well have been significant associations between lesion growth and the presence of a mismatch, even though the clinical associations were not significant [as was found in the original report by Barber et al (1998)]. It has been proposed that quantifying the severity of the perfusion deficit better predicts the proportion of the mismatch that is likely to go on to infarction (Neumann-Haefelin *et al.*, 1999). Whilst interesting, this offers little to the clinician who needs to make a rapid decision at the bedside.

14.5.4 Do the results of advanced imaging change the clinician's management?

Many have argued for widespread availability of advanced MR on the basis that it provides far greater information about ischaemic lesions than CT (Prichard & Grossman, 1999; Hacke & Warach, 2000; Warach, 2001b). MR – particularly the DWI and GRE sequence – improves accuracy of the diagnosis of stroke, and can be extremely helpful to the clinician in a handful of patients. Does this translate into changes in patient management? Earlier studies have not addressed this directly. Improved management is assumed to flow from the greater information that DWI

shows about the stroke. For example, Albers et al (2000a) demonstrated that DWI can show 'potentially clinically relevant findings' not seen on the CT which may affect management – such as multiple lesions suggesting an embolic source, or altered lesion location.

The present study is the first to directly assess the impact of structural MR and DWI on patient management. A panel of clinicians of varying experience was given a series of hypothetical management, and changes in management were recorded. We demonstrated that MR altered management in 16% of patients (on average). Surprisingly, the structural images altered management far more often than the DWI.

MR had the greatest impact on the scenarios involving thrombolysis, where the demonstration of any form of blood – haemorrhagic transformation, old primary intracerebral haemorrhage, or microbleeds – on the gradient echo sequence resulted in the clinician deciding against treatment. DWI had the greatest impact on the endarterectomy scenario, where the clinician decided against recommending surgery on seven occasions when the lesion localised to the posterior circulation. The results obtained were highly consistent – similar changes were made by the clinicians on the same patients.

Limitations of the study

The methodology of the study – a series of hypothetical scenarios that required many assumptions – may be criticised as not being realistic. The evidence obtained from this study is indirect, albeit closer to actual patient management than earlier studies. The ideal methodology would be to use real patients, but this would require enormous numbers. The aim was to assess how much MR influenced patient

management (over and above CT), so the use of scenarios was an efficient way of minimising individual patient factors and maximising the influence of imaging in decision-making.

Other limitations of the present study include the variation in time between CT and MR, and the clinicians' own biases. 32% of CT scans were obtained greater than two hours earlier or later than the MR. In one patient, the CT (obtained 13 hours before the MR) showed early ischaemic changes, and the MR showed haemorrhagic transformation; clinicians were happy to give thrombolysis after the CT, but avoided it after the MR. The study was also hampered by clinicians' own biases – evidenced by several who would only enter a patient into a trial of thrombolysis (and the department itself is currently conducting a trial of thrombolysis), and one clinician who did not believe that any antiplatelet agent was superior to aspirin. I attempted to minimise the influence of bias by including many clinicians from different backgrounds and with different levels of expertise. Despite that, the findings probably represent a uniform approach to management that may or may not be representative of wider practice.

Finally, it would have been desirable to show the PI images, to assess the impact of mismatch on clinician's decisions about thrombolysis. This was not possible, as the extensive processing required to generate PI images meant they were unavailable till after the study was complete. Additionally, given the departmental bias towards a randomised trial of thrombolysis without imaging-based entry criteria, it is doubtful that PI-DWI data would have altered decisions.

What are the implications of the management sub-study?

Imaging is less important to management than clinical factors

Imaging probably has less relevance to management than it does for diagnosis. Management of individual patients depends on many clinical factors (such as: did the patient present within the time window, was the stroke severity sufficient, was the patient's premorbid state good enough to consider surgery or anticoagulation, etc.). In contrast, there are relatively few imaging factors that influence management. CT alone is capable of detecting most of these, leaving little extra benefit to be gained by MR. Hence, in the present study, MR caused a management change in 104/1794 (6%) scenarios.

The impact of imaging varied for each clinician. I hypothesised that junior doctors would find MR more useful than senior doctors, who are used to working with CT. However, level of experience, and clinical background (neurology vs stroke medicine), did not influence whether the clinician found MR useful. This has resource implications: there is little use in performing extra imaging if the clinicians will not act on the findings.

More research is needed

We observed that structural imaging resulted in 81/104 (78%) of the changes. The major finding that prompted these changes was the demonstration of haemorrhage on the GRE sequence, or leukoaraiosis on T2 sequence in a smaller number of patients. The demonstration of a relevant lesion on DWI, or the absence of a lesion on DWI, had little impact.

Many decisions to avoid proven treatments were made on the basis of conjecture rather than evidence. Although leukoariosis *on CT* has been shown to

independently predict cerebral haemorrhage complicating anticoagulation in those with cerebral ischaemia 'of presumed arterial origin' in one trial (Gorter, 1999), the importance of this factor in cerebral ischaemia secondary to atrial fibrillation, and how CT findings relate to MR findings, has not been established. A recent case report (Kidwell *et al.*, 2002) suggested that microbleeds might be associated with remote haemorrhage complicating thrombolysis, but called for a large prospective study. There is an urgent need for more research into the influence of microbleeds, old bleeds, and leukoariosis on the risks of thrombolysis and oral anticoagulants.

Why was little 'positive' use made of the MR?

There were 104 altered management decisions in the present study. 93 changes were 'negative' (i.e. the clinician decided not to give a treatment, randomise the patient in a trial, or not intensify antiplatelet therapy). Only 11 'positive' changes to management were made. Why did MR findings result in so few decisions to act more aggressively?

One possible explanation is that despite MR imaging, clinicians may act on the expectation that the scan will be negative: management decisions are made after the clinical assessment and can only modified downward by subsequent imaging. For example, any abnormality on CT – haemorrhage or major signs of ischaemia – would prompt the clinician to avoid thrombolysis. In the present study, the few patients with microbleeds or old haemorrhage on MR influenced management far more than the larger number of patients with a negative DWI. If this is true, clinicians will need to change their mind-sets away from CT if the full potential of MR is to be realised.

More complex imaging might restrict management choices

The present study has shown that the more complex the imaging, the less likely it is that patients will receive risky treatments such as thrombolysis. In addition, we found that only 56% of our patients who presented within six hours had a DWI-PI mismatch. It may be desirable that trials impose entry criteria to ensure a new drug is tested in a homogeneous population (Warach, 2002). However, it must be recognised that this strategy increases the complexity of the requirements for the trial, and dramatically restricts eligibility. Where evidence suggests that a treatment is beneficial – thrombolysis for ischaemic stroke within three hours of onset (Wardlaw *et al.*, 2001a), anticoagulation for atrial fibrillation (Koudstaal, 2002) – efforts ought to be directed towards ensuring every eligible patient receives treatment.

14.6 Summary

- The present study selected a broader spectrum of patients, and therefore provides useful data on the utility of MR in real life
- Imaging may provide a more direct estimate of the degree of tissue damage than can be determined by using time from symptom onset
- The present study found that DWI lesion volume did not predict outcome, and was unable to validate a simple predictive model proposed by others. Imaging parameters probably have less prognostic influence in patients with small cortical, lacunar or brainstem infarcts, than in those with large hemispheric infarcts

- Perfusion abnormalities are correlated with the baseline neurological deficit and DWI appearance. On its own, PI does not provide additional prognostic information
- In combination with DWI, PI does identify a subgroup of patients with mismatch. These patients have larger DWI lesions, and more severe neurological deficit. The presence of a mismatch did not predict outcome in our cohort
- The determination of mismatch is currently technically difficult, and the significance of the various perfusion parameters remain uncertain
- The additional impact of MR (over CT) in current management was small. The MR resulted in a change in management for 16% of patients (ranged from 7% to 26% of patients depending on the clinician). The demonstration of blood on structural images had the greatest impact on management. Usually, an abnormality seen on imaging stopped the clinician from acting.

14.6.1 Recommendations for further research

- Further prospective studies of a broad selection of patients are required to establish the role of MR in routine clinical practice
- More information on the association between time and imaging parameters is required to determine how to combine these two measures to ensure that patients benefit from thrombolysis

- The best measure of perfusion needs to be determined, and clear criteria established to identify a mismatch. If lesion volumes must be calculated, then processing times needs to be reduced to make the process viable
- The pathophysiology of ischaemic stroke needs further exploration: what does a mismatch signify, does the DWI lesion represent infarcted tissue, what is the significance of a mismatch seen many hours after onset?
- Further research into the impact of advanced imaging on real management of patients is required

Table 14.1 Accuracy of determining the age of the lesion based on its MR appearances (n=35*)

	Precisely known onset			
MR-estimated age of lesion	0-6 hours	6-12 hours	>12 hours	**Total**
Within 6 hours	4	1	3†	*8*
6-12 hours	5	2	6	*13*
After 12 hours	2†	1	11	*14*
Total	*11*	*4*	*20*	*35*

** patients who did not wake with symptoms, and could give an exact time of onset. A DWI lesion had to be present to allow an estimation of lesion age.*
† 'extreme outliers' – see text for explanation

*Table 14.2 Clinical features, DWI and outcome in MR study (n=81)**

Factor	Functional outcome in the MR study				p†
	Good (n=43)		Poor (n=38)		
Clinical features					
Median age (years) (IQR)	69.8	(60.1-77.2)	80.0	(72.2-83.7)	<.001
Median time (hrs) from onset of symptoms to scanning (IQR)	14.6	(5.6-24.7)	9.4	(4.7-19.8)	.107
Male gender	21	(49%)	20	(53%)	.733
Cognitive impairment	3	(7%)	11	(29%)	.009
Hypertension	23	(54%)	23	(61%)	.798
Ischaemic heart disease	9	(21%)	11	(29%)	.194
Past history of stroke	14	(33%)	19	(50%)	.111
In atrial fibrillation	7	(16%)	11	(29%)	.171
Median systolic blood pressure (mmHg) (IQR)	155	(140-178)	164	(149-180)	.233
Reduced conscious state	0	(0%)	16	(42%)	<.001
Median NIHSS (IQR)	4.0	(3.0-7.0)	8.0	(5.0-12.0)	<.001
OCSP classification:‡					.027
TACS	1	(2%)	10	(26%)	
PACS	21	(49%)	13	(34%)	
LACS	12	(28%)	11	(29%)	
POCS	7	(16%)	3	(8%)	
DWI features					
No visible DWI lesion	11	(26%)	7	(18%)	.439
Median DWI lesion volume (mL) (IQR)	0.6	(0.1-6.2)	1.6	(0.2-22.0)	.222
ADC (IQR)¶	0.76	(0.71-0.85)	0.75	(0.65-0.82)	.342

** outcome was assessed by modified Rankin Score. Data not available for one patient*
† significance determined by Mann-Whitney U test (for continuous variables) and χ^2 test (for categorical variables).
‡ OCSP classification unknown in three patients
¶ ADC and outcome data available for 51 patients (29 good outcome, 22 poor outcome)

Table 14.3 Logistic regression model of stroke recovery

Variable	Coefficient	Odds Ratio (95% CI)
Constant	5.89	-- --
Age	-0.06	0.94 (0.89-0.99)
NIHSS score	-0.19	0.83 (0.72-0.96)

Table 14.4 Predicted and observed outcome using the three-item scale

		Baird et al (n=129)*		Present study (n=81)		
Three-item total score	**Predicted % recovery**	**Number recovered / total**	**% recovered (95% CI)**	**Number recovered / total**	**% recovered (95% CI)**	**P†**
0-2	7%	3 / 42	7 (0-15)	2 / 9	22 (3-60)	0.60
3-4	46%	21 / 40	53 (37-68)	17 / 30	57 (37-75)	0.45
5-7	91%	41 /47	87 (77-97)	25 / 43	58 (42-73)	<0.001

** data from combined Boston and Melbourne patient groups (Baird et al., 2001)*
† significance for the difference between predicted recovery by the logistic model and observed recovery in Brain Attack series (determined by Fisher's exact test)

Table 14.5 Features of patients according to whether mismatch present using visual inspection of MTT map (n=60)

Factor	Imaging category: Mismatch (n=25)		No mismatch (n=35)		P^*
Median age (yrs) (IQR)	76.3	(69.1-80.7)	72.4	(60.1-81.9)	.319
Time to scanner (hrs) (IQR)	8.9	(4.0-20.5)	14.6	(6.1-26.0)	.142
Median NIHSS (IQR)	7.0	(3.5-10.0)	5.0	(4.0-8.0)	.203
OCSP classification:†					.130
TACS	5	(20%)	3	(9%)	
PACS	12	(48%)	15	(43%)	
LACS	4	(16%)	14	(40%)	
POCS	2	(8%)	3	(9%)	
Median DWI lesion volume (mL) (IQR)	5.0	(0.6-16.4)	0.9	(0.5-5.5)	.179
Poor outcome‡	13	(52%)	11	(32%)	.129

** Significance determined by Mann-Whitney U test for continuous variables, and χ^2 test for categorical variables*
† OCSP classification could not be determined for two patients with PI>DWI
‡ Outcome data not available for one patient (who had no mismatch)

Table 14.6 Features of patients according to whether mismatch present using visual inspection of the CBF map (n=57)

Factor	Imaging category: Mismatch (n=10)		No mismatch (n=47)		P^*
Median age (yrs) (IQR)	76.9	(72.6-82.1)	74.2	(62.3-81.2)	.390
Time to scanner (hrs) (IQR)	5.8	(3.0-16.6)	14.5	(5.6-24.7)	.075
Median NIHSS (IQR)	7.0	(4.8-8.3)	5.0	(4.0-8.0)	.506
OCSP classification:†					.119
TACS	1	(10%)	7	(15%)	
PACS	16	(60%)	20	(43%)	
LACS	1	(10%)	17	(36%)	
POCS	1	(10%)	3	(6%)	
Median DWI lesion volume (mL) (IQR)	2.2	(0.1-11.0)	1.8	(0.5-7.5)	.536
Poor outcome‡	4	(40%)	19	(41%)	.940

** Significance determined by Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables*
† OCSP classification could not be determined for two patients with PI>DWI
‡ Outcome data not available for one patient (who had no mismatch)

Table 14.7 The agreement between visual classification of mismatch and calculation of lesion volumes using the MTT maps

	Calculated lesion volumes:			
	Mismatch	***No Mismatch***		
Visual classification:	PI>DWI	PI=DWI	PI<DWI	**Total**
Mismatch (PI > DWI)	19	0	6	*25*
No Mismatch:				
PI=DWI	5	1	7	*13*
PI < DWI	1	1	20	*22*
Total	*25*	*2*	*33*	*60*

Table 14.8 The agreement between visual classification of mismatch and calculation of lesion volumes using the CBF maps

	Calculated lesion volumes:			
	Mismatch	***No Mismatch***		
Visual classification:	PI>DWI	PI=DWI	PI<DWI	**Total**
Mismatch (PI > DWI)	6	0	4	*10*
No Mismatch:				
PI=DWI	10	2	6	*18*
PI < DWI	3	2	24	*29*
Total	*19*	*4*	*34*	*57*

Table 14.9 Features of patients according to whether a calculated mismatch was present using the MTT map (n=60)

Factor	Calculated category: Mismatch (n=19)		No mismatch (n=38)		P^*
Median age (yrs) (IQR)	77.6	(70.3-80.3)	72.4	(60.2-82.0)	.333
Time to scanner (hrs) (IQR)	6.8	(4.2-18.2)	16.6	(7.1-26.0)	.030
Median NIHSS (IQR)	7.0	(4.0-11.0)	5.0	(3.0-8.0)	.021
OCSP classification:†					.058
TACS	6	(24%)	2	(6%)	
PACS	12	(48%)	15	(43%)	
LACS	3	(12%)	15	(43%)	
POCS	3	(12%)	2	(6%)	
Median DWI lesion volume (mL) (IQR)	6.5	(1.7-16.4)	0.6	(0.4-3.2)	.001
Median CBF lesion volume (mL) (IQR)	18.2	(0-56.8)	0	(0-0)	<.001
Poor outcome‡	12	(48%)	12	(35%)	.326

** Significance determined by Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables*
† OCSP classification could not be determined for two patients
‡ Outcome data not available for one patient (who had no mismatch)

Table 14.10 Features of patients according to whether a calculated mismatch was present using the CBF map (n=57)

Factor	Calculated category: Mismatch (n=19)		No mismatch (n=38)		P^*
Median age (yrs) (IQR)	76.5	(69.8-79.4)	74.2	(62.5-82.1)	.826
Time to scanner (hrs) (IQR)	6.3	(3.9-21.2)	14.6	(6.8-24.1)	.176
Median NIHSS (IQR)	7.0	(4.0-11.0)	5.0	(3.0-8.0)	.063
OCSP classification:†					.079
TACS	5	(26%)	3	(8%)	
PACS	10	(53%)	16	(42%)	
LACS	2	(11%)	16	(42%)	
POCS	2	(11%)	2	(5%)	
Median DWI lesion volume (mL) (IQR)	8.3	(0.9-24.9)	0.9	(0.4-5.6)	.001
Median MTT lesion volume (mL) (IQR)	38.3	(18.2-101)	0	(0-0)	<.001
Poor outcome‡	9	(47%)	14	(38%)	.492

** Significance determined by Mann-Whitney U test for continuous variables, and χ^2 test or Fisher's exact test for categorical variables*
† OCSP classification could not be determined for one patients with no mismatch
‡ Outcome data not available for one patient (who had no mismatch)

Table 14.11 The impact of MR on patient management

Clinician	Total number patients	Patients affected by management changes: Number changed (%)	Structural MR (%)	DWI (%)	Management decisions: Number changed / total (%)	Structural MR (%)	DWI (%)
1	*62*	8 (12.9)	7 (11.3)	1 (1.6)	18 / 372 (4.8)	17 (4.6)	1 (0.3)
2	*62*	16 (25.8)	13 (21.0)	4 (6.5)	36 / 372 (9.7)	32 (8.6)	4 (1.1)
3	*36*	8 (22.2)	4 (11.1)	5 (13.9)	26 / 216 (12.0)	13 (6.0)	13 (6.0)
4	*43*	3 (7.0)	2 (4.6)	1 (2.3)	4 / 258 (1.6)	3 (1.2)	1 (0.4)
5	*47*	9 (19.1)	7 (14.9)	2 (4.3)	17 / 288 (6.0)	15 (5.3)	2 (0.7)
6	*45*	3 (6.7)	1 (2.2)	2 (4.4)	3 / 270 (1.1)	1 (0.4)	2 (0.7)
Mean	*49*	7.8 (16.0)	5.7 (11.6)	2.5 (5.1)	17.3 / 294 (5.9)	13.5 (4.6)	3.8 (1.3)

Conclusion

Implications for clinical practice

Brain attack is a medical emergency. At the beginning of the 21st century, there is a very promising treatment for acute ischaemic stroke – thrombolysis – and many other therapeutic options for patients with any form of stroke – stroke unit care, surgery for intracerebral haemorrhage, and aspirin. The challenge is to ensure that all eligible patients receive the best care possible.

Patients who present to hospital with a brain attack comprise a heterogeneous group of serious medical conditions – not all will have a cerebral infarct. This thesis has demonstrated the key components of the clinical assessment that accurately distinguish between stroke and mimic at the bedside. We identified the reliable components of history and examination. Three streamlined models were produced, which varied from a four item tool (designed for a nurse) to an eight item tool (for a trainee or expert in neurology).

Evidence suggests that around 50% of patients currently arrive at hospital within six hours of symptom onset, yet only a small fraction receives thrombolysis. The major stumbling block appears to be the long delay from arrival to assessment and investigation. The data gathered in this thesis could be used to improve the clinical assessment of brain attack, by promoting a rapid confident clinical diagnosis, and thus prompt referral for neuroimaging.

There is little doubt that imaging has an enormous contribution to make in the diagnosis and management of acute stroke. Every patient with brain attack needs to

be imaged; the question is what is the best imaging method for the individual patient? CT is available, rapid and cheap. It demonstrates haemorrhage with accuracy and reliability, and shows great potential for the diagnosis of hyperacute ischaemia. Conversely, MR imaging is difficult, time consuming and unavailable to the vast majority of patients. Yet MR has great potential in expanding our understanding of the pathophysiology of acute ischaemia, and may be helpful for clinical diagnosis and management.

This thesis has shown that MR is not yet ready to replace CT as the imaging of choice for patients with brain attack. In a less selected – and more representative patient sample – MR showed little extra advantage. However, in certain situations, advanced brain imaging might be preferred: for the patient with an unclear diagnosis; to identify if an old lesion were a haemorrhage; to distinguish a new lesion from old, and possibly to help guide treatment in patients who present early with a major stroke. For most, the CT scan remains the unquestioned 'cardiogram of the brain' (Buchan, 2001). Given its ease, safety and availability, CT is likely to remain at the forefront of patient assessment for some time.

Implications for research

I would hope that this work might stimulate further research into the clinical assessment, with particular emphasis on the validity and reliability of symptoms and signs in the first few hours. Simple clinical research has enormous potential to assist in training less experienced doctors and nurses. The key questions that deserve further attention are: (1) is it possible to identify the patient with a TIA on

presentation; (2) how useful is the OCSP clinical classification in the first few hours, and (3) can the models developed be validated in an independent dataset?

I have identified many imaging issues that require further clarification. Work is currently underway to explore, in far greater detail, the safety of MR imaging acute stroke patients. There is much more to be learnt about the pathophysiology of acute stroke, and how this is represented on the MR scan. A larger study involving severe patients may shed further light on such problems as the best measure of abnormal perfusion, defining the ischaemic penumbra, and determining if there are reliable (and practical) imaging methods for identifying viable brain tissue.

The experience of recruiting and scanning patients, analysing the data obtained, and writing up this thesis has given me an excellent insight into why earlier studies have been so small and highly selected. There is no doubt that patients are difficult to scan with MR, and as stroke is a heterogeneous condition, there is often great – and disappointing – variation in the results obtained. However, I think it is important that all results are reported, not just those that best fit with an attractive theory. More studies of MR should be performed prospectively, in diverse but clearly described patient groups. Most importantly, one must not suspend one's critical faculties when reading a paper on imaging!

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Appendix 1: Medline Search Strategy

1. exp basal ganglia cerebrovascular disease/ or exp brain ischemia/ or exp carotid artery diseases/ or exp cerebrovascular accident/ or exp intracranial arterial diseases/ or exp intracranial arteriovenous malformations/ or exp "intracranial embolism and thrombosis"/ or exp intracranial hemorrhages/ or exp vasospasm, intracranial/ or exp vertebral artery dissection/ or Cerebrovascular disorders/
2. (stroke$ or cva or cerebrovsc$ or cerebral vascular).tw.
3. ((cerebral or brain or vertebrobasilar) and (isch?emi$ or infarct$ or thrombo$ or emboli$)).tw.
4. ((cerebral or brain or subarachnoid) and (haemorrhage or hemorrhage or haematoma or hematoma or bleed$ or aneurysm)).tw.
5. diagnosis/ or diagnos$.tw.
6. "diagnostic techniques and procedures"/
7. exp Neurologic Examination/ or diagnostic techniques, neurological/
8. physical examination/
9. exp medical history taking/
10. ((clinical or neurologic) adj5 (assessment or diagnosis or picture or investigation or information or examination or features or method$ or criteria or prediction)).tw.
11. assessment battery.tw.
12. scoring system$.tw.
13. clinical score$.tw.
14. medical history.tw.
15. or/5-14
16. exp basal ganglia cerebrovascular disease/di or exp brain ischemia/di or exp carotid artery diseases/di or exp cerebrovascular accident/di or exp intracranial arterial diseases/di or exp intracranial arteriovenous malformations/di or exp "intracranial embolism and thrombosis"/di or exp intracranial hemorrhages/di or exp vasospasm, intracranial/di or exp vertebral artery dissection/di or Cerebrovascular disorders/di
17. 1 or 2 or 3 or 4
18. 15 and 17
19. 16 or 18
20. diagnosis, differential/
21. diagnostic errors/
22. false negative reactions/
23. false positive reactions/
24. observer variation/
25. "sensitivity and specificity"/
26. clinical competence/
27. reproducibility of results/
28. ((inter?rater or inter?observer) adj5 (reliability or variation)).tw.
29. (accurate adj5 (assessment or diagnosis or identification or differentiation or discrimination)).tw.
30. stroke?like.tw.
31. (true stroke or pseudostroke).tw.
32. mimic$.tw.
33. misdiagnosis.tw.
34. predictive value of tests/
35. or/20-34
36. 19 and 35

Patient label

Appendix 2: BRAIN ATTACK ASSESSMENT FORM

EXAMINER: PJH / JK / BL / other:
*Study number*_____

Patient's Phone number: (_____) _____ _____ WARD _____

Patient's GP & Clinic Phone Number: _____

1. TIMING

When did the patient arrive in ARU (or hospital)? *(As logged in by the nursing staff)* Date: / / Time: *(24 hour clock)*

When was the patient seen by the examiner? Date: / / Time:

2. PRELIMINARY DIAGNOSIS

Primary referral source: ARU ☐ Other ☐ Comment _____

Who made the referral: Doctor ☐ Nurse ☐

The referring diagnosis: Stroke ☐ Non-stroke ☐ Unsure ☐

GP diagnosis: Stroke ☐ Non-stroke ☐ No diagnosis ☐ No GP letter ☐

Diagnosis before assessing the patient: *(end of the bed assessment)*	Def. Str ☐	Prob. Str ☐	Poss. Str ☐	Non-stroke ☐
Diagnosis after taking the history:	Def. Str ☐	Prob. Str ☐	Poss. Str ☐	Non-stroke ☐
Diagnosis after the examination:	Def. Str ☐	Prob. Str ☐	Poss. Str ☐	Non-stroke ☐

3. SOURCE OF HISTORY

Who/what was the PRIMARY (or major) source of history?

- ☐ Patient
- ☐ GP Letter
- ☐ Relative
- ☐ Ambulance
- ☐ Inpatient Medical Notes
- ☐ Other_____

Were there any SECONDARY sources of history?

- ☐ **None**
- ☐ Patient
- ☐ GP Letter
- ☐ Relative
- ☐ Ambulance
- ☐ Inpatient Medical Notes
- ☐ Other_____

Is there inconsistency or discrepancy between primary and secondary source for:

Time of onset of this event (>30 minutes difference)? ☐ Yes ☐ No

Evolution of symptoms since onset of this event ☐ Yes ☐ No

Presence or absence of major symptoms (e.g. vomiting, LOC) ☐ Yes ☐ No

*If **yes** for any of the above, please comment:*

4. PAST HISTORY

Was the patient known to have cognitive impairment before this event? Y ☐ N ☐ Unknown ☐

Was the patient able to walk independently before this event? *(without the aid of another person, but can use a stick or aid)* Y ☐ N ☐ Unknown ☐

Does the patient have any of the following conditions: *(tick any that apply)*

☐ Migraine ☐ Known malignancy

☐ Epilepsy ☐ Psychological disturbance *(requiring any treatment)*

Is the patient a smoker (incl. given up <12 months)? Y ☐ N ☐ Unknown ☐

Is the patient an ex-smoker >12 months? Y ☐ N ☐ Unknown ☐

Is there a history of Ischaemic heart Disease (angina, AMI, CABG)? Y ☐ N ☐ Unknown ☐

Is there a history of hypertension? *(including drug treatment at any time)* Y ☐ N ☐ Unknown ☐

Is there a history of Diabetes Mellitus? *(Including diet control)* Y ☐ N ☐ Unknown ☐

Is there known Atrial Fibrillation? Y ☐ N ☐ Unknown ☐

Is there known peripheral vascular disease? *(int claud or prior surgery)* Y ☐ N ☐ Unknown ☐

Was there a history of focal neurological deficit in the past? Y ☐ N ☐ Unknown ☐

If **yes**, had it resolved completely before this event? Y ☐ N ☐ Unknown ☐

What was the deficit, if any? *(tick those that apply)*

Communication disorder ☐ Visual disorder ☐ Swallowing problem ☐

Motor deficit ☐ [Left ☐ Right ☐] Other ☐ Balance or co-ordination problems ☐

Comment:

5. HISTORY OF THIS EVENT

Can the exact time that symptoms were **first** noted be determined? *(time that symptoms came on or patient awoke)*

Yes ☐ → If **yes**, onset was: Date: / / Time:

Did the patient wake from sleep with the deficit? Yes ☐ No ☐

If yes, last time known to be normal / / Time:

No ☐ →

If time that symptoms first noted can **not** be determined, tick one:

☐ Onset is not assessable *e.g. unconscious – comment*_____

☐ The exact onset is unclear

☐ Other _____

APPROX TIME OF ONSET

/ / time:

Can the patient or relative recall exactly what the patient was doing at time of onset? Yes ☐ No ☐

Are the symptoms now stable?

Yes ☐ → Evolution to maximal deficit took ____ *Minutes (1 day = 1440mins)*

No ☐ → Are the symptoms still getting worse? Yes ☐ No ☐

Has there been any improvement in symptoms? Yes ☐ No ☐

Was the patient generally well in the week before these symptoms started? Yes ☐ No ☐

If **no**, *comment:*

Was there a **definite** history of focal neurological symptoms? Yes ☐ No ☐

If yes, tick any of the following that apply:

Visual loss ☐ Diplopia ☐ Loss of function of speech or language ☐

Loss of balance ☐ Vertigo ☐

Other brainstem symptoms ☐ Comment _____

Face:	Arm:	Hand:	Leg:
Loss of feeling ☐	Loss of feeling ☐	Loss of feeling ☐	Loss of feeling ☐
Loss of power ☐	Loss of power ☐	Loss of power ☐	Loss of power ☐
Loss of function ☐	Loss of function ☐	Loss of function ☐	Loss of function ☐
Altered sensation ☐	Altered sensation ☐	Altered sensation ☐	Altered sensation ☐

The symptoms have affected left ☐, right ☐, both ☐ sides; Or there are no lateralising symptoms ☐

Any other symptoms? _____

Is the patient able to walk independent of another person at present? Yes ☐ No ☐ Unknown ☐

Has the patient lost consciousness *(at any time since onset)*? Y ☐ N ☐ U ☐

Has the patient vomited *(at any time since onset)*? Y ☐ N ☐ U ☐

Is there a definite history of headache during this event? Yes ☐ No ☐ Unknown ☐

If history of headache, is it distressing to the patient? Yes ☐ No ☐

If history of headache, *tick any that apply*
☐ The headache commenced before the event
☐ The headache started when the event started
☐ The headache commenced after the event started

Has the patient had a seizure since symptom onset? Yes ☐ No ☐ Unknown ☐

If **yes**, date of first seizure / / Number of seizures

Comment

6. GENERAL EXAMINATION

Vital signs: *Pulse* *BP* / *Temp* *SaO2*

CVS:
Irregular pulse Yes ☐ No ☐
Cervical bruits Yes ☐ No ☐ *If **yes**, Left* ☐ *Right* ☐
Valvular Heart Disease Yes ☐ No ☐ *Specify* _____
Clinical heart Failure Yes ☐ No ☐ *Specify* _____
Absent periph pulses? Yes ☐ No ☐ *If **yes**, Left* ☐ *Right* ☐

Respiratory: *Abnormal signs?* Yes ☐ No ☐

If yes, comment:

Abdomen: *Abnormal signs?* Yes ☐ No ☐

If yes, comment:

Are there any other abnormal physical signs? Yes ☐ No ☐

If yes, comment:

Does the patient have an overwhelming co-morbid condition *(making assessment difficult)*? Yes ☐ No ☐

If yes, comment:

Conscious State: *(Circle the most appropriate number that describes the level of consciousness)*

Reaction Level Scale

Mentally responsive — *Responds verbally, makes eye contact, obeys commands, responds to light stimulation (touch) or strong stimulation (loud verbal/shaking)*

1 **Alert**. No delay in response
2 **Drowsy or confused**. Responds to light stimulation, but drowsy or disoriented in time, place or person
3 **Very drowsy or confused**. Responds only to strong stimulation

Unconscious — *Test response to painful stimulation – sternal rub or nailbed pressure*

4 **Localises** to site of pain, does not ward off pain
5 **Withdraws** from painful stimulus
6 **Flexion** to pain
7 **Extension** to pain
8 **No response** to pain

Glasgow Coma Score

Eye Opening:		**Best motor:**		**Best verbal:**	
Never	1	None	1	None	1
To pain	2	Extend to pain	2	Noises only	2
To sound	3	Abnormal flexion to pain	3	Inappropriate	3
Spontaneously	4	Flexion to pain	4	Confused	4
		Localises to pain	5	Normal	5
		Normal	6		

Confusion tests: Can you test for confusion?

☐ No → ☐ The patient is unconscious
☐ The patient is aphasic *If so, can the patient be engaged (follow your face)?* Yes ☐ No ☐
☐ Other _____

☐ Yes

Do not attempt the tests for confusion - pass on to the neurological examination

Is the patient oriented to:	Time? *(nearest hour)*	Yes ☐	No ☐
	Day?	Yes ☐	No ☐
	Month?	Yes ☐	No ☐
	Year?	Yes ☐	No ☐

Can the patient state all 7 days of the week backwards, starting with Sunday? Yes ☐ No ☐

7. NEUROLOGICAL EXAMINATION

Signs are on Left ☐ Right ☐ Both/Bilateral signs ☐; No Lateralising signs ☐; There are no signs ☐

Legend for completing this section: Y=yes, N=no, U=unsure/unassessable. Tick one box for each question

Vision

Is there a **LEFT** hemianopia? Y ☐ N ☐ U ☐
If **yes**, is it partial ☐, complete ☐
Is there **LEFT** visual inattention? Y ☐ N ☐ U ☐

Is there a **RIGHT** hemianopia? Y ☐ N ☐ U ☐
If **yes**, is it partial ☐, complete ☐
Is there **RIGHT** visual inattention? Y ☐ N ☐ U ☐

Eye Movements

Are the eyes deviated to the **left**? Y ☐ N ☐ U ☐
Is there nystagmus to the **left**? Y ☐ N ☐ U ☐
Is there **LEFT** III/IV/VI nerve lesion? Y ☐ N ☐ U ☐

Are the eyes deviated to the **right**? Y ☐ N ☐ U ☐
Is there nystagmus to the **right**? Y ☐ N ☐ U ☐
Is there **right** III/IV/VI nerve lesion? Y ☐ N ☐ U ☐

Speech & Language

Can patient point to the ceiling with unaffected side? Y ☐ N ☐ U ☐

Is verbal output: Normal ☐ Slow ☐
Slurred ☐ Unintelligible ☐ No verbal output ☐

Face

Can patient lift **LEFT** eyebrow? Y ☐ N ☐ U ☐
Can patient lift **RIGHT** eyebrow? Y ☐ N ☐ U ☐
Is there asymmetry of the smile? Y ☐ N ☐ U ☐

Arm weakness	***L***	***R***
The arm does not drift	☐	☐
The arm drifts	☐	☐
Unable to lift arm off bed	☐	☐
Unassessable	☐	☐

Leg weakness	***L***	***R***
The leg does not drift	☐	☐
The leg drifts	☐	☐
Unable to lift leg off bed	☐	☐
Unassessable	☐	☐

Hand weakness: fine finger movements are:

LEFT: Normal ☐ Reduced ☐ U ☐

RIGHT: Normal ☐ Reduced ☐ U ☐

Cerebellar signs

There is finger-nose ataxia out of proportion to weakness **L**: Y ☐ N ☐ U ☐ **R**: Y ☐ N ☐ U ☐
There is heel-shin ataxia out of proportion to weakness **L**: Y ☐ N ☐ U ☐ **R**: Y ☐ N ☐ U ☐

Sensory signs

Is there **LEFT** sensory loss? Y ☐ N ☐ U ☐
Is there **RIGHT** sensory loss? Y ☐ N ☐ U ☐

Reflexes

Asymmetry of the biceps jerk? Y ☐ N ☐ U ☐
Asymmetry of the knee jerk? Y ☐ N ☐ U ☐

Visuospatial dysfunction

Is there sensory extinction? Yes on **L** ☐ Yes on **R** ☐; N ☐ U ☐
Is the patient aware of the deficit? **NO** on **L** ☐ **NO** on **R** ☐; **Yes** ☐ U ☐ ; No deficit ☐
Does the patient recognise his/her own hands? Y ☐ N ☐ U ☐
Are there any other "parietal" signs:_____

Plantar response

Left flexor ☐	Left extensor ☐	Left equivocal or mute ☐	Unsure on left ☐
Right flexor ☐	Right extensor ☐	Right equivocal or mute ☐	Unsure on right ☐

8. DIAGNOSTIC FORMULATION

Were any important tests (that helped the diagnosis) immediately available? Y ☐ N ☐

If **yes**, ECG ☐ Glucose ☐ _____ Other

Are the neurological signs consistent with the symptoms? Y ☐ N ☐ No neurological signs ☐

Do the neurological deficits conform to a known vascular territory *(e.g. ACA, MCA, PICA)* Y ☐ N ☐ No signs ☐

Did the patient fulfil Newcastle FAST criteria for acute stroke (on admission)? Yes ☐ No ☐

Newcastle FAST criteria:

GCS>5 **+ one of**	**F**acial weakness (unequal smile or obvious weakness)	☐
	Arm weakness (one arm drifts or falls rapidly)	☐
	Speech problems (word finding difficulties or slurred speech)	☐

Diagnosis at end of assessment:

DEFINITE STROKE ☐ PROBABLE STROKE ☐ POSSIBLE STROKE ☐ NON-STROKE ☐

Specify:

Clinical Classification: NO SIGNS ☐

TACS ☐	PACS ☐	LACS ☐	POCS ☐	Unsure ☐
Side of brain lesion:	Left ☐	Right ☐	Brainstem ☐	Unsure ☐

9. COMMENTS

Any additional comments about the patient?

Comment:

Any comments about the form?

Comment:

How long did it take to see the patient? ____ Minutes

How long did it take to fill out this form? ____ Minutes

*Study number*_____ *Patient label*

NIH Stroke Scale *Please circle the most appropriate response for each section*

1a Level of Consciousness (LOC)	0	Alert – *keenly responsive*
	1	Drowsy – *arousable by minor stimulation to obey, answer, or respond*
	2	Stuporous – *requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)*
	3	Comatose – *responds only with reflex motor or autonomic effects or totally unresponsive, flaccid*
1b LOC Questions	0	Answers both correctly
	1	Answers one correctly
	2	Incorrect
		Patient is asked to state the month & his/her age
1c LOC Commands	0	Obeys both correctly
	1	Obeys one correctly
	2	Incorrect
		Patient is asked to open & close eyes, grip & release normal hand
2. Best Gaze	0	Normal
	1	Partial gaze palsy – *gaze is abnormal in one or both eyes, no forced deviation/total gaze paresis*
	2	Forced deviation – *or total gaze paresis not overcome by oculocephalic maneouvre*
3. Visual Fields	0	No visual loss
	1	Partial hemianopia
	2	Complete hemianopia
	3	Bilateral Hemianopia – *including cortical blindness*
4. Facial Palsy	0	Normal
	1	Minor - *flattened nasolabial fold, asymmetry on smiling*
	2	Partial – *total or near total paralysis of lower face*
	3	Complete - *absent facial movement in upper and lower face on one or both sides*
5. Best Motor RIGHT ARM	0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable*
6. Best Motor LEFT ARM	0	No drift – *holds limb at 90 degrees for full 10 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable*
7. Best Motor RIGHT LEG	0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable*
8. Best Motor LEFT LEG	0	No drift – *holds limb at 45 degrees for full 5 seconds*
	1	Drift - *drifts down but does not hit bed*
	2	Some effort against gravity
	3	No effort against gravity
	4	No movement
	x	*Untestable*
9. Limb Ataxia	0	Absent
	1	Present in 1 limb
	2	Present in 2 or more limbs
10. Sensory	0	Normal
	1	Partial loss – *patient feels pinprick is less sharp or is dull on affected side*
	2	Dense loss - *patient is unaware of being touched on face, arm, leg*
11. Best Language	0	No dysphasia
	1	Mild – moderate dysphasia *obvious loss of fluency or comprehension, without significant limitation on ideas expressed or form of expression. Makes conversation about provided material difficult or impossible, e.g. examiner can identify picture or naming card from patient's response.*
	2	Severe dysphasia - *all communication is through fragmentary expression; great need for inference, questioning, and guessing by the listener who carries burden of communication. Examiner cannot identify materials provided from patient response*
	3	Mute *no usable speech or auditory comprehension.*
12. Dysarthria	0	Normal articulation
	1	Mild – moderate dysarthria - *patient slurs some words, can be understood with some difficulty.*
	2	Unintelligible or worse - *speech is so slurred as to be unintelligible (absence of or out of proportion to dysphasia) or is mute/anarthric*
	x	Untestable
13. Neglect	0	No neglect
	1	Partial neglect - *Visual, tactile, auditory, spatial, or personal inattention or extinction to bilateral simultaneous stimulation in one of the sensory modalities*
	2	Complete neglect - *Profound hemi-inattention or hemi-inattention to more than one modality. Does not recognise own hand or orients to only one side of space*

Notes for completion of NIHSS:

Administer stroke scale items in the order listed. Record performance in each category after each subscale exam. Do not go back and change scores. Follow directions provided for each exam technique. Scores should reflect what the patient does, not what the clinician thinks the patient can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the patient should not be coached (i.e., repeated requests to patient to make a special effort).

1a. Level of Consciousness: The investigator must choose a response, even if a full evaluation is prevented by such obstacles as an endotracheal tube, language barrier, orotracheal trauma/bandages. A 3 is scored only if the patient makes no movement (other than reflexive posturing) in response to noxious stimulation.

1b. LOC Questions: The patient is asked the month and his/her age. The answer must be correct - there is no partial credit for being close. Aphasic and stuporous patients who do not comprehend the questions will score 2. Patients unable to speak because of endotracheal intubation, orotracheal trauma, severe dysarthria from any cause, language barrier or any other problem not secondary to aphasia are given a 1. It is important that only the initial answer be graded and that the examiner not "help" the patient with verbal or non-verbal cues.

1c. LOC Commands: The patient is asked to open and close the eyes and then to grip and release the non-paretic hand. Substitute another one step command if the hands cannot be used. Credit is given if an unequivocal attempt is made but not completed due to weakness. If the patient does not respond to command, the task should be demonstrated to them (pantomime) and score the result (i.e., follows none, one or two commands). Patients with trauma, amputation, or other physical impediments should be given suitable one-step commands. Only the first attempt is scored.

2. Best Gaze: Only horizontal eye movements will be tested. Voluntary or reflexive (oculocephalic) eye movements will be scored but caloric testing is not done. If the patient has a conjugate deviation of the eyes that can be overcome by voluntary or reflexive activity, the score will be 1. If a patient has an isolated peripheral nerve paresis (CN III, IV or VI) score a 1. Gaze is testable in all aphasic patients. Patients with ocular trauma, bandages, pre-existing blindness or other disorder of visual acuity or fields should be tested with reflexive movements and a choice made by the investigator. Establishing eye contact and then moving about the patient from side to side will occasionally clarify the presence of a partial gaze palsy.

3. Visual: Visual fields (upper and lower quadrants) are tested by confrontation, using finger counting or visual threat as appropriate. Patient must be encouraged, but if they look at the side of the moving fingers appropriately, this can be scored as normal. If there is unilateral blindness or enucleation, visual fields in the remaining eye are scored. Score 1 only if a clear-cut asymmetry, including quadrantanopia is found. If patient is blind from any cause score 3. Double simultaneous stimulation is performed at this point. If there is extinction patient receives a 1 and the results are used to answer question 11

4. Facial Palsy: Ask, or use pantomime to encourage the patient to show teeth or raise eyebrows and close eyes. Score symmetry of grimace in response to noxious stimuli in the poorly responsive or non-comprehending patient. If facial trauma/bandages, orotracheal tube, tape or other physical barrier obscures the face, these should be removed to the extent possible.

5–8. Motor Arm and Leg: The limb is placed in the appropriate position: extend the arms (palms down) 90 degrees (if sitting) or 45 degrees (if supine) and the leg 30 degrees (always tested supine). Drift is scored if the arm falls before 10 seconds or the leg before 5 seconds. The aphasic patient is encouraged using urgency in the voice and pantomime but not noxious stimulation. Each limb is tested in turn, beginning with the non-paretic arm. Only in the case of amputation or joint fusion at the shoulder or hip may the score be "x" and the examiner must clearly write the explanation for scoring as an "x."

9. Limb Ataxia: This item is aimed at finding evidence of a unilateral cerebellar lesion. Test with eyes open. In case of visual defect, insure testing is done in intact visual field. The finger-nose-finger and heel-shin tests are performed on both sides, and ataxia is scored only if present out of proportion to weakness. Ataxia is absent in the patient who cannot understand or is paralyzed. Only in the case of amputation or joint fusion may the item be scored "9", and the examiner must clearly write the explanation for not scoring. In case of blindness test by touching nose from extended arm position.

10. Sensory: Sensation or grimace to pin prick when tested, or withdrawal from noxious stimulus in the obtunded or aphasic patient. Only sensory loss attributed to stroke is scored as abnormal and the examiner should test as many body areas [arms (not hands), legs, trunk, face] as needed to accurately check for hemisensory loss. A score of 2, "severe or total," should only be given when a severe or total loss of sensation can be clearly demonstrated. Stuporous and aphasic patients will therefore probably score 1 or 0. The patient with brain stem stroke who has bilateral loss of sensation is scored 2. If the patient does not respond and is quadriplegic score 2. Patients in coma (item 1a=3) are arbitrarily given a 2 on this item.

11. Best Language: A great deal of information about comprehension will be obtained during the preceding sections of the examination. The patient is asked to describe what is happening in the attached picture, to name the items on the attached naming sheet, and to read from the attached list of sentences. Comprehension is judged from responses here as well as to all of the commands in the preceding general neurological exam. If visual loss interferes with the tests, ask the patient to identify objects placed in the hand, repeat, and produce speech. The intubated patient should be asked to write. The patient in coma (question 1a=3) will arbitrarily score 3 on this item. The examiner must choose a score in the patient with stupor or limited cooperation but a score of 3 should be used only if the patient is mute and follows no one step commands.

12. Dysarthria: If patient is thought to be normal an adequate sample of speech must be obtained by asking patient to read or repeat words from the attached list. If the patient has severe aphasia, the clarity of articulation of spontaneous speech can be rated. Only if the patient is intubated or has other physical barrier to producing speech, may the item be scored "9", and the examiner must clearly write an explanation for not scoring. Do not tell the patient why he/she is being tested.

13. Extinction and Inattention (formerly Neglect): Sufficient information to identify neglect may be obtained during the prior testing. If the patient has a severe visual loss preventing visual double simultaneous stimulation, and the cutaneous stimuli are normal, the score is normal. If the patient has aphasia but does appear to attend to both sides, the score is normal. The presence of visual spatial neglect or anosagnosia may also be taken as evidence of abnormality. Since the abnormality is scored only if present, the item is never untestable.

Appendix 3: Clinical Assessment Scales

The Glasgow Coma Score

Best motor response	*Points*	**Eye opening**	*Points*	**Best verbal response**	*Points*
Normal	*6*	Spontaneously	*4*	Normal	*5*
Localises to pain	*5*	To sound	*3*	Confused	*4*
Flexes to pain	*4*	To pain	*2*	Inappropriate	*3*
Abnormal flexion to pain	*3*	Never	*1*	Noises only	*2*
Extends to pain	*2*			None	*1*
None	*1*				

The Reaction Level Scale

Score:	**Clinical State**
1	Alert (no delay in response)
2	Drowsy or confused (responds to light stimulation, but drowsy or disoriented in time, place or person)
3	Very drowsy or confused (responds only to strong stimulation)
4	Localises to site of pain, does not ward off pain
5	Withdraws from painful stimulus
6	Flexion to pain
7	Extension to pain
8	No response to pain

Oxfordshire Community Stroke Project (OCSP) stroke subtype

OCSP subtype		**Clinical features**
TACS	Total anterior circulation syndrome	Either (a) homonymous hemianopia, hemiparesis and higher cerebral dysfunction (e.g. aphasia or neglect); or (b) drowsiness plus hemiparesis and higher cerebral dysfunction
PACS	Partial anterior circulation syndrome	Two of three components of a TACS, higher cerebral dysfunction alone, or restricted motor/sensory loss
LACS	Lacunar syndrome	Pure motor or pure sensory disturbance, sensory-motor disturbance or ataxic hemiparesis. Motor/sensory signs must involve at least two of face, arm and leg.
POCS	Posterior circulation syndrome	Ipsilateral cranial nerve palsy with contralateral motor/sensory deficit, bilateral motor/sensory deficit, disorder of conjugate gaze, cerebellar dysfunction, or isolated homonymous hemianopia

Appendix 4: IMAGING FORM

Patient Name:

Date of Birth:

Hospital Number:

*Study number*_____

FIRST CT SCAN

Date of scan: / / Time:

Result: Normal ☐

Recent infarct on appropriate side ☐

Recent haemorrhage on appropriate side ☐

Other lesion on appropriate side ☐

Comment:

Old discrete lesion(s) ☐

Periventricular lucencies ☐

Cerebral atrophy ☐

Any other lesion? ☐

Comment:

Was contrast given? Yes ☐ No ☐

Was the lesion seen **only** with contrast? Yes ☐ No ☐

Comment

FURTHER CT SCAN

Date of scan: / /

Did it provide any additional information (over and above first scan)? Yes ☐ No ☐

If **yes**, please comment:

MRI SCAN

Date of scan: / / Time:

Result: Normal ☐

Recent infarct on appropriate side ☐

Recent haemorrhage on appropriate side ☐

Other lesion on appropriate side ☐

Comment:

Old discrete lesion(s) ☐

Periventricular lucencies ☐

Cerebral atrophy ☐

Other lesion ☐

Comment:

Was DWI performed? Yes ☐

Did it provide any additional diagnostic information? Yes ☐

Comment

ADDITIONAL IMAGING

Carotid Duplex performed during admission? Yes ☐ No ☐

Result:

Left ICA ☐ Normal

☐ Minor atheroma

☐ Stenosis %

Right ICA ☐ Normal

☐ Minor atheroma

☐ Stenosis %

Is there a documented vertebral vessel abnormality? Yes ☐ No ☐

Comment:

Were any other important imaging tests performed?
Detail:

Appendix 5: FINAL DIAGNOSIS

Patient Name:

Date of Birth:

Hospital Number:

*Study number*_____

1. TIMING

Date of meeting: / /

Present at meeting: RIL ☐ MSD ☐ PAGS ☐ CPW ☐ GM ☐ JK ☐ PJH ☐ JMW ☐

BW ☐ EK ☐ CLMS ☐ Other: _____

2. FINAL DIAGNOSIS

☐ DEFINITE STROKE — DEFINITE TIA ☐

☐ PROBABLE STROKE — POSSIBLE TIA ☐

☐ POSSIBLE STROKE

☐ NON-STROKE *Specify:* _____

3. HOW WAS THE DIAGNOSIS MADE? *(tick one for each section only)*

Demographics & History:

☐ Definite stroke/TIA ☐ Probable stroke/TIA ☐ Possible stroke/TIA ☐ Non-stroke

Examination:

☐ Definitely compatible with stroke ☐ Probably compatible with stroke ☐ Possibly compatible with stroke ☐ Not compatible with a stroke (non-stroke)

Imaging:

☐ Relevant stroke lesion ☐ Relevant non-stroke lesion ☐ No relevant pathology seen ☐ Previous stroke pathology ☐ Not done

4. COMMENTS

Appendix 6: Accuracy of clinical diagnosis of stroke – 2x2 tables

GP diagnosis

	Final diagnosis	
Clinical diagnosis	Stroke	Mimic
Stroke	146	53
Mimic	7	9

ARU diagnosis

	Final diagnosis	
Clinical diagnosis	Stroke	Mimic
Stroke	190	54
Mimic	26	51

Research fellow's 'end of bed' assessment

	Final diagnosis	
Clinical diagnosis	Stroke	Mimic
Stroke	216	62
Mimic	25	47

Research fellow's diagnosis after history only

	Final diagnosis	
Clinical diagnosis	Stroke	Mimic
Stroke	223	52
Mimic	18	57

Research fellow's final clinical diagnosis

	Final diagnosis	
Clinical diagnosis	Stroke	Mimic
Stroke	206	19
Mimic	35	90

Appendix 7: THE INTERRATER RELIABILITY STUDY DATA FORM

When did the examiner see the patient? Date: / / Start time:

Who gave the history? Patient ☐ Patient and relative ☐ Relative/other ☐

HISTORY

1.	Does the patient have high blood pressure? *(including drug treatment at any time)*	Y ☐ N ☐ unknown ☐
2.	Is the patient a smoker? *(including giving up <12 months ago)*	Y ☐ N ☐ unknown ☐
3.	Does the patient have ischaemic heart disease?	Y ☐ N ☐ unknown ☐
4.	Does the patient have atrial fibrillation?	Y ☐ N ☐ unknown ☐
5.	Does the patient have peripheral vascular disease?	Y ☐ N ☐ unknown ☐
6.	Does the patient have diabetes?	Y ☐ N ☐ unknown ☐
7.	Does the patient have a history of focal neurological deficit before this event?	Y ☐ N ☐ unknown ☐

HISTORY OF THIS EVENT

8.	Can the exact time the symptoms were first noted be determined?	Y ☐ N ☐
	If yes, what was the exact time of onset?*	Date: / / Time:
9.	Did the patient wake from sleep with the deficit?	Y ☐ N ☐ unknown ☐
	If yes, what was the last time known to be normal?	Date: / / Time:
10.	Can the patient recall what they were doing at the time of onset?	Y ☐ N ☐ unknown ☐
11.	Has there been any improvement since the onset of symptoms?	Y ☐ N ☐ unknown ☐
12.	Are the symptoms now stable?	Y ☐ N ☐ unknown ☐
13.	Has the patient been generally well in the week before the symptoms started?	Y ☐ N ☐ unknown ☐
14.	Is there a definite history of focal neurological deficit?	Y ☐ N ☐ unknown ☐
15.	If yes, was there hemianopia/quadrantanopia;	Y ☐ N ☐ unknown ☐
	was there loss of speech or language function;	Y ☐ N ☐ unknown ☐
	was there sensory loss;	Y ☐ N ☐ unknown ☐
	was there loss of power;	Y ☐ N ☐ unknown ☐
	did the symptoms affect the left side;	Y ☐ N ☐ unknown ☐
	did the symptoms affect the right side;	Y ☐ N ☐ unknown ☐
	did the symptoms affect both sides?	Y ☐ N ☐ unknown ☐
16.	Did the patient have a headache during the event?	Y ☐ N ☐ unknown ☐
17.	How confident are you about the findings from the history?*	high ☐ low ☐

GENERAL EXAMINATION

18.	Is the patient alert?*	Y ☐ N ☐
19.	Is the patient drowsy?	Y ☐ N ☐
20.	Is the patient unconscious?	Y ☐ N ☐
21.	Is the patient confused?	Y ☐ N ☐ unexamin. ☐

NEUROLOGICAL EXAMINATION

22.	Does the patient have arm weakness?	Y ☐ N ☐ unexamin. ☐
	Does the patient have hand weakness	Y ☐ N ☐ unexamin. ☐
	Does the patient have face weakness	Y ☐ N ☐ unexamin. ☐
	Does the patient have leg weakness?	Y ☐ N ☐ unexamin. ☐
	Is the patient able to walk?*	Y ☐ N ☐ unexamin. ☐
	Does the patient have visual loss?	Y ☐ N ☐ unexamin. ☐
	Does the patient have speech problems *(dysarthria)*?	Y ☐ N ☐ unexamin. ☐
	Does the patient have a language problem*(dysphasia)*?	Y ☐ N ☐ unexamin. ☐

	Does the patient have sensory disturbance?	Y ☐ N ☐ unexamin. ☐
	Does the patient have visual neglect?	Y ☐ N ☐ unexamin. ☐
	Does the patient have sensory neglect?	Y ☐ N ☐ unexamin. ☐
	Does the patient have any other form of visio-spatial dysfunction (e.g. dressing apraxia)?	Y ☐ N ☐ unexamin. ☐
23.	Is the right side affected?	Y ☐ N ☐
24.	Is the left side affected?	Y ☐ N ☐
25.	Are both sides affected?	Y ☐ N ☐
26.	How confident are you about the results of the examination?	high ☐ low ☐

FINAL DIAGNOSIS

27.	Do you think the patient has had a stroke?	Y ☐ N ☐
28.	If yes, is there a left-sided brain lesion?	Y ☐ N ☐
29.	is there a right-sided brain lesion?	Y ☐ N ☐
30.	is there a brain-stem lesion?	Y ☐ N ☐
31.	what OCSP-classification would you give this patient?*	TACS ☐ PACS ☐ LACS ☐ POCS ☐ Unexamin. ☐
32.	How confident are you about the final diagnosis?	high ☐ low ☐

Finish time:

INSTRUCTIONS

Observer one explains the proceedings and asks for the patient's consent in participating in the study e.g.: 'We are doing research on the diagnostic tests we use in the hospital for people who we think might have had a stroke. To make these tests more reliable we have to compare the results from different observers. I would like to ask you a few questions and to do a few tests. My colleague will come to see you after me and will repeat some of the questions and tests. Would you mind participating?'
Observer one and two do not communicate with each other during or in between assessments. Assessment forms are put in a sealed envelope immediately after the assessment.

Circle your initials.
Circle which observer is 'one', the first to see the patient, and which one is 'two', the second to see the patient.
Note the date as DD/MM/YY
Note the times as on a 24 hour clock.
Score the answer by ticking the 'yes' or 'no' box (or 'unexaminable') for the examination. Score all the questions.

HISTORY

2. If the patient denies being a smoker but stopped less than 12 months ago, score this question as 'yes'.

HISTORY OF THE EVENT

8. When the symptoms were noticed when waking up, note the waking time as time of onset.
17. If your clinical impression was made with a high level of confidence score 'high'; if you were not confident score 'low'.

GENERAL EXAMINATION

18. Judge this on observation and score 18, 19 or 20 as 'yes' when applicable and as 'no' when not. Score one of 18, 19 or 20 as 'yes' and the other two as 'no'.
19. See 18.
20. See 18.

NEUROLOGICAL EXAMINATION

22. 'Able to walk' means without help from another person; walking aid may be used.
26. If your clinical impression was made with a high level of confidence score 'high'; if you were not confident score 'low'.
31. If the patient has had a stroke a choice has to be made between TACS (total anterior circulation infarct), PACS (partial anterior circulation infarct), LACS (lacunar infarct), POCS (posterior circulation infarct).
LACS: patients present with a pure motor or pure sensory stroke, sensor-motor stroke, ataxic hemiparesis (cerebellar type ataxia with pyramidal signs), dysarthria clumsy had syndrome, or acute focal movement disorders.
TACS: patients present a combination of new higher cerebral dysfunction (dysphasia, dyscalculia, visiospatial disorder); homonymous visual field defect; and ipsilateral motor and/or sensory deficit of at least two areas of face, arm and leg.
Impaired consciousness rendering testing impossible is interpreted as a deficit.
PACS: patients present with two of the three components of the TACS, higher cerebral dysfunction alone or with motor/sensory deficit more restricted than those classified as LACS (confined to one limb, or to face and hand but not the whole arm).
POCS: patients present with any of the following: ipsilateral cranial nerve palsy plus contralateral motor and/or sensory deficit, bilateral motor/sensory deficit, disorder of conjugate eye movement, cerebellar dysfunction without ipsilateral long-tract deficit (ataxic hemiparesis), or isolated homonymous visual field defect.

Appendix 8: Reliability study raw data

Vascular risk factors

Hypertension

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	31	10	7	48
	no	6	26	2	34
	unknown	4	3	8	15
Total		41	39	17	97

Smoker within 12 months

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	17	2	3	22
	no		56	3	59
	unknown	1	7	8	16
Total		18	65	14	97

Ischaemic Heart Disease

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	17	4	6	27
	no	4	50	2	56
	unknown	1	3	10	14
Total		22	57	18	97

Atrial fibrillation

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	8	7	3	18
	no	4	53	3	60
	unknown	2	4	12	18
Total		14	64	18	96

Peripheral vascular disease

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	5	3	4	12
	no	7	51	8	66
	unknown	1	5	13	19
Total		13	59	25	97

Diabetes mellitus*

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	3	2	1	6
	no		62	5	67
	unknown		3	10	13
Total		3	67	16	86

**This question was added after the study commenced*

PHx focal neurological deficit

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	21	7	7	35
	no	6	40	4	50
	unknown	1	4	8	13
Total		28	51	19	98

History of presenting complaint

An exact time of onset can be determined

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	46	9	55
	no	9	34	43
Total		55	43	98

The patient woke from sleep with deficit

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	15	5	1	21
	no	5	39	6	50
	unknown	3	7	16	26
Total		23	51	23	97

The patient can recall what he/she was doing at onset

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	40	10	1	51
	no	9	13	9	31
	unknown	2	6	7	15
Total		51	29	17	97

Improvement since symptom onset

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	34	7	4	45
	no	4	25	7	36
	unknown	2	5	10	17
Total		40	37	21	98

Symptoms now stable

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	64	5	7	76
	no	2	2	1	5
	unknown	1	1	15	17
Total		67	8	23	98

Patient was well in the week before onset

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	41	9	5	55
	no	11	13	3	27
	unknown	4	2	10	16
Total		56	24	18	98

Definite history of focal neurological deficit

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	60	3	6	69
	no	3	6	3	12
	unknown	4		13	17
Total		67	9	22	98

Hemianopia/quadrantanopia

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	4	2		6
	no	5	49	5	59
	unknown	1	4	19	24
Total		10	55	24	89

Loss of speech or language

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	25	5	6	36
	no	5	29	1	35
	unknown	2	2	14	18
Total		32	36	21	89

Sensory loss

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	14	5	1	20
	no	3	35	6	44
	unknown	1	5	19	25
Total		18	45	26	89

Loss of power

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	44	5	6	55
	no	3	11	2	16
	unknown	1	4	13	18
Total		48	20	21	89

Symptoms affect the left side of the body

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	23	3	4	30
	no	3	29	7	39
	unknown	1	4	14	19
Total		27	36	25	88

Symptoms affect the right side of the body

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	16	7	7	30
	no	2	34	5	41
	unknown	1	3	14	18
Total		19	44	26	89

Symptoms affect both sides of the body

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	1	3	1	5
	no	6	50	9	65
	unknown		4	14	18
Total		7	57	24	88

Headache

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	14	4	2	20
	no	4	51	5	60
	unknown	2	2	13	17
Total		20	57	20	97

Physical examination

The patient is alert

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	75	7	82
	no	2	14	16
Total		77	21	98

The patient is drowsy

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	10	1	11
	no	5	82	87
Total		15	83	98

The patient is unconscious

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	4		4
	no		94	94
Total		4	94	98

The patient is confused

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	11	10	4	25
	no	4	50	5	59
	unknown	2	3	7	12
Total		17	63	16	96

Arm weakness

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	51	7	1	59
	no	9	29		38
	unknown			1	1
Total		60	36	2	98

Hand weakness

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	51	5	2	58
	no	5	32		37
	unknown		2	1	3
Total		56	39	3	98

Face weakness

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	29	9	1	39
	no	13	43	1	57
	unknown		1	1	2
Total		42	53	3	98

Leg weakness

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	41	10	1	52
	no	10	32		42
	unknown		1	2	3
Total		51	43	3	97

The patient could walk

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	27	9		36
	no	5	42	3	50
	unknown	1	3	6	10
Total		33	54	9	96

Visual loss

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	12	5	2	19
	no	7	56	3	66
	unknown	4	5	4	13
Total		23	66	9	98

Dysarthria

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	19	15	1	35
	no	10	41	4	55
	unknown	2		6	8
Total		31	56	11	98

Dysphasia

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	27	9		36
	no	7	51		58
	unknown		1	3	4
Total		34	61	3	98

Sensory disturbance

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	21	9	2	32
	no	8	42	1	51
	unknown	5	4	6	15
Total		34	55	9	98

Visual neglect

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	3	4	8	15
	no	5	47	4	56
	unknown	2	9	16	27
Total		10	60	28	98

Sensory neglect

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	12	2	5	19
	no	4	44	5	53
	unknown	1	7	18	26
Total		17	53	28	98

Other forms of neglect

Count

		Observer 2			
		yes	no	unknown	Total
Observer 1	yes	2	4	3	9
	no	3	42	15	60
	unknown	1	9	19	29
Total		6	55	37	98

Signs affect the right

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	35	8	43
	no	7	48	55
Total		42	56	98

Signs affect the left

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	32	7	39
	no	5	54	59
Total		37	61	98

Signs affect both sides of the body

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	1	3	4
	no	4	90	94
Total		5	93	98

Diagnostic formulation

The patient has had a stroke

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	76	3	79
	no	4	15	19
Total		80	18	98

Left-sided brain lesion

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	37	2	39
	no	2	35	37
Total		39	37	76

Right-sided brain lesion

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	28	4	32
	no	3	41	44
Total		31	45	76

Brainstem lesion

Count

		Observer 2		
		yes	no	Total
Observer 1	yes	2	2	4
	no	3	68	71
Total		5	70	75

OCSP classification

Count

		Observer 2				
		TACS	PACS	LACS	POCS	Total
Observer 1	TACS	13	5			18
	PACS	4	20	4	1	29
	LACS		5	13	1	19
	POCS	1	2		7	10
Total		18	32	17	9	76

Patient label

Appendix 9: MR STUDY – IN-SCANNER DATA FORM

*Study number*_____

1.TIMING

The date of this assessment	Date:	/ /	Complication risks
Arrived at scanning suite	Time:		The patient's risk is: HIGH / LOW
Entered MR scanner	Time:		*Comment:*
Out of MR scanner	Time:		

Were Xray Orbits required? Yes ☐ No ☐ If yes, why: ☐ Aphasic, ☐ Comatose, ☐ Metal work

2. PRE-SCAN EXAMINATION

Conscious State: *(Circle the most appropriate number that describes the level of consciousness)*

Reaction Level Scale

Mentally responsive — *Responds verbally, makes eye contact, obeys commands, responds to light stimulation (touch) or strong stimulation (loud verbal/shaking)*

1 **Alert**. No delay in response
2 **Drowsy or confused**. Responds to light stimulation, but drowsy/disoriented in time, place or person
3 **Very drowsy or confused**. Responds only to strong stimulation

Unconscious — *Test response to painful stimulation – sternal rub or nailbed pressure*

4 **Localises** to site of pain, does not ward off pain
5 **Withdraws** from painful stimulus
6 **Flexion** to pain
7 **Extension** to pain
8 **No response** to pain

Glasgow Coma Score

Eye Opening:		**Best motor:**		**Best verbal:**	
Never	1	None	1	None	1
To pain	2	Extend to pain	2	Noises only	2
To sound	3	Abnormal flexion to pain	3	Inappropriate	3
Spontaneously	4	Flexion to pain	4	Confused	4
		Localises to pain	5	Normal	5
		Normal	6		

NIHSS: Same as at initial assessment? Yes ☐ No ☐
If **NO,** please complete NIHSS form

3. OBSERVATIONS WITHIN SCANNER

Time 0 = _____

	0min	5min	10m	15m	20m	25m	30m	35m	40m	45m	50m	55m	60m
Pulse													
SaO2													
BP													

Was any intervention required? No ☐ Yes ☐
If **YES** was it: ☐ Medical – detail: _____
☐ Nursing – detail: _____
☐ Reassurance – detail: _____
Did the patient ring the panic button? Yes ☐ No ☐
Was the full scan completed? Yes ☐ No ☐
If scan aborted, why? ☐ Claustrophobia ☐ Confusion ☐ Medically unwell ☐ Equipment failure ☐ Other

Comments:

Any other problems in the scanner? No ☐ Yes ☐
If yes, please detail:

Finish time: ☐

Appendix 10: The CT-MR diagnosis study data form

CT –MR STUDY: FINAL DIAGNOSIS

PATIENT NUMBER: PH 360

Date of meeting: 2/11/01

You are clinician: (please tick) RIL ☐ MSD ☐ PAGS ☐ CPW ☑ GM ☐ JK ☐ CLMS ☐ EK ☐

BW ☐ Other: _____

FINAL DIAGNOSIS

INSTRUCTIONS - Please put a cross on the line. If you are 100% sure the diagnosis is stroke/TIA, put a cross at the left end; if you are 100% sure the diagnosis is non-stroke, put a cross at the right end. A cross through the middle point means you cannot be sure whether the diagnosis is stroke or non-stroke.

A. Your diagnosis on the basis of... HISTORY

Stroke/TIA |---------- *Non-stroke*

B. Your diagnosis on the basis of... HISTORY & EXAMINATION

Stroke/TIA |---------- *Non-stroke*

C. Your diagnosis on the basis of... HISTORY, EXAMINATION & CT SCAN ☐ No CT done

Stroke/TIA |---------- *Non-stroke*

D. Your diagnosis on the basis of... HISTORY, EXAMINATION & MR

Stroke/TIA |---------- *Non-stroke*

E. Your diagnosis on the basis of... HISTORY, EXAMINATION & DWI

Stroke/TIA |---------- *Non-stroke*

81. Found unresponsive, left, 6 hr ? h. stroke
Diabetic BP+

Appendix 11: The CT-MR management scenarios study data form

CT –MR STUDY: FINAL DIAGNOSIS

PATIENT NUMBER: PH 357

Date of meeting: 5/9/01

You are clinician: (please tick) RIL ☐ MSD ☑ PAGS ☐ CPW ☐ GM ☐ JK ☐

Other: _____

HYPOTHETICAL MANAGEMENT SCENARIOS

A. ACUTE MANAGEMENT

	After CT:	After MR:	After DWI:
1. If this patient were on warfarin for AF, and INR was 3.3, would you reverse the anticoagulation urgently?	☐ Yes ☑ No	☐ Yes ☑ No	☐ Yes ☑ No
2. If this patient were 60 years old, otherwise well, and presented at 2 hours, would you?	☑ Open label tPA ☐ Randomise to IST-3 ☐ Nothing	☑ Open label r-tPA ☐ Randomise to IST-3 ☑ Nothing	☐ Open label tPA ☐ Randomise to IST-3 ☑ Nothing
3. If this patient were 60 years old, otherwise well, and presented at 4 hours, would you?	☐ Open label tPA ☑ Randomise to IST-3 ☐ Nothing	☐ Open label tPA ☑ Randomise to IST-3 ☑ Nothing	☐ Open label tPA ☐ Randomise to IST-3 ☑ Nothing

B. SECONDARY PREVENTION

	After CT:	After MR:	After DWI:
1. If this patient is in AF, and has no contraindications, would you anticoagulate in the long term?	☑ Yes ☐ No	☑ Yes ☑ No	☐ Yes ☑ No
2. If this patient were male, fit and well, made a good recovery from stroke, and had a 90% ipsilateral carotid stenosis, would you refer for CEA?	☑ Yes ☐ No	☑ Yes ☐ No	☑ Yes ☐ No
3. If this patient were in sinus rhythm, and already on aspirin, assuming they make a good recovery from stroke, would you?	☐ Stop aspirin ☐ Continue aspirin ☑ Intensify antiplatelet therapy (*eg clopidogrel*)	☐ Stop aspirin ☑ Continue aspirin ☑ Intensify antiplatelet therapy (*eg clopidogrel*)	☐ Stop aspirin ☑ Continue aspirin ☐ Intensify antiplatelet therapy (*eg clopidogrel*)