The aetiology, investigation and outcome of ischaemic stroke in childhood.

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Abstract

The aetiology, investigation and outcome of ischaemic stroke were studied in a population of 128 children.

Cerebrovascular abnormalities were present in the majority of children; in many cases these conformed to specific diagnostic categories, with implications for management. In contrast, previously unrecognised non-vascular risk factors for stroke were relatively rare. In particular, the prevalence of inherited prothrombotic states was no higher in children with stroke than in control populations.

Although magnetic resonance angiography was useful in identifying cerebrovascular lesions, conventional cerebral angiography had a continuing and definable role in the investigation of the child with ischaemic stroke.

In the investigation of outcome after ischaemic stroke a simple questionnaire investigating parents' perception of residual disability was shown to correlate well with therapists' and neuropsychological assessment. Over half the children in this population had significant residual deficits; the incidence of recurrent stroke was 17% over 5 years. A younger age at the time of stroke was associated with worse outcome. However, prognosis was not influenced by other clinical factors. In a subgroup of 38 children with lesions in the territory of a middle cerebral artery, although the location of the lesion was not related to outcome, outcome was poor in all patients who had infarcted at least 10% of intracranial volume had. Lesion size could, therefore, be used to identify patients at high risk of long term disability for future treatment trials. These findings support the view that there is a role for both acute treatment and secondary prevention in children with ischaemic stroke.

This study has characterised in detail a large population of children with ischaemic stroke and has given rise to several practical recommendations about the investigation and management of such patients.

Contents

List of figures

List of tables

1. Introduction

1.1. Definition of terms

Ischaemic stroke

Ischaemic stroke has been defined by the World Health Organisation as *"rapidly developed clinical signs of focal (or global) disturbance of cerebral function lasting for more than 24 hours, or leading to death, with no apparent cause other than of vascular origin"*[2]. However, this definition should not be directly applied to the paediatric population as firstly, the differential diagnosis of acute hemiparesis in childhood is wider than in adults and, secondly, some of the conditions which lead to cerebral infarction in childhood (e.g. mitochondrial disease) do not have an obvious vascular basis.

An alternative definition was used in the American National Survey of Stroke which is as follows[3]: *Stroke is a clinical syndrome consisting of neurological findings, sudden or rapid in onset, which persists for more than 24 hours and whose vascular origins are limited to a) thrombotic or embolic occlusion of a cerebral artery resulting in infarction or b) spontaneous rupture of a vessel resulting in intracerebral or subarachnoid haemorrhage. This definition excludes occlusion or rupture due to traumatic, neoplastic or infectious processes which produce vascular pathology".* Although cerebral infarction is identified as the end point of ischaemic stroke, cases without vascular occlusion or those due to trauma are excluded by this definition.

To ensure that a uniform population of children was considered for the purposes of this study, acute ischaemic stroke was defined as *"an acute focal neurological deficit of*

greater than 24 hours duration with evidence of cerebral infarction in a vascular distribution on brain imaging".

Transient ischaemic attack (TIA) was defined as *"an acute focal neurological deficit lasting less than 24 hours, probably of ischaemic origin, without evidence of cerebral infarction".*

Reversible ischaemic neurological deficits (RIND) was defined as *" an acute focal neurological deficit lasting less than 1 week, thought to be of ischaemic origin, without evidence of cerebral infarction".*

Childhood was defined as the first 18 years of life. The *neonatal period* was defined as the first 28 days of life.

"Symptomatic stroke" was defined as stroke in a child who was known to have a previous medical condition which is associated with stroke e.g. congenital cardiac disease.

"Idiopathic stroke" was defined as stroke in a child who was previously well.

"Unexplained stroke" was defined as stroke without any identified vascular or non-vascular risk factors.

Moyamoya syndrome was defined as stenosis or occlusion of large cerebral arteries with collateral vessel formation[4].

1.2. Historical background

The initial accounts of ischaemic stroke in children in the late 19th century considered the clinical syndrome of "acute hemiplegia of childhood". In 1897 Freud summarised the features of this clinical syndrome: *" a previously healthy child without hereditary predisposition suddenly becomes ill ...The aetiology of the illness remains unknown or is sought in a simultaneously occurring infectious disease. The initial symptom may be violent, with fever, convulsions or vomiting, or may be slight or insignificant...speech impediment and aphasia are frequent and usually temporary; hemianopsia and paralysis of the eye muscles are rare...mental disturbance of varied degree is usually apparent"*[5]. Gowers was the first to describe arterial thrombosis as a cause of "acute hemiplegia" in children[6]. However, as Bickerstaff noted in 1964[7], *"by the use of this title, which is purely descriptive, one may be misled into thinking that a firm clinical diagnosis has been made"*. Factors such as a febrile prodrome[8], age and focal seizures at onset were thought to influence eventual outcome in these children[9,10,11,12,13].

Although some of these patients are likely to have had ischaemic stroke, with cerebral infarction, the conclusions of these early studies have not always been upheld in studies of children with radiologically confirmed ischaemic stroke. The differential diagnosis of acute hemiplegia in childhood is wide[14] and without imaging data it is difficult to ascertain the degree of overlap between clinical syndromes such as "acute hemiplegia of childhood" and HHE (hemiplegia, hemiconvulsions and epilepsy) described by Gastaut[15] and their relationship to cerebrovascular disease and cerebral infarction.

The introduction of computerised tomography (CT) and magnetic resonance imaging (MRI) has made relatively rapid and accurate diagnosis of cerebral infarction possible.

With the use of MRI, in particular, it has become evident that the clinical correlates of acute cerebral infarction in childhood may be very variable[16]. Identification of patients using imaging criteria has enabled comparisons to be made between studies. Given the small numbers of patients reported in individual series this is important, and is likely to become more so if treatment trials are considered.

Some previous studies have not included cases of ischaemic stroke in children with predisposing conditions e.g. cardiac disease or meningitis (see Appendix 1). There is clearly a distinction between stroke in such children (referred to in this study as "symptomatic" stroke) and stroke which occurs "out of the blue" in a previously well child (referred to here as "idiopathic" stroke) . The similarities and differences between these groups have not previously been examined in detail. It has not been clear whether their natural history is comparable and whether or not a uniform approach to investigation and management should be adopted.

1.3. Epidemiology

The peak incidence of ischaemic stroke in childhood is in the toddler age group. Such cases encompass many of those previously subsumed under the rubric of "acute infantile hemiplegia"[13,17,18,19,20,21,22]. However, no age group is exempt and cases occur throughout the childhood years.

The difficulties of establishing the true incidence and prevalence of ischaemic stroke in childhood are related to the relatively low directly related mortality[23] and to the variation of population characteristics. Local factors such as the prevalence of moyamoya

syndrome (which is endemic in Japan) and sickle cell anaemia are important when considering the incidence in specific populations.

The first epidemiological data on ischaemic stroke in childhood is contained in the report of the Joint Committee for Stroke Facilities[23]. Death certificate data indicated that mortality from cerebrovascular disease (ICD codes 330 - 334) in America between 1959 - 1961 was $15/10^6$ for children under 5 and $7/10^6$ for children aged 5 - 14. This is comparable to the reported rates in the UK over that period. However, two community based studies found that the prevalence of "hemiplegia due to stroke" in children was 11.7 - 13.1/100 000, suggesting that the death certificate data may have provided an underestimate of the true prevalence[23].

Schoenberg[24] employed the medical records linkage system in use in Rochester, Minnesota, to retrospectively investigate the incidence of stroke in childhood between 1965 and 1974. He found that the incidence of all stroke in children under 15 years to be 2.52/100 000/year (95% confidence intervals 0.69 - 6.45/100 000/year). The incidence of ischaemic stroke specifically was 0.63/100 000/year. However, among the drawbacks of this widely quoted study are: i) its reliance on purely clinical grounds for inclusion and ii) the use of a study population which was not widely representative of urban American populations, and in particular with as low prevalence of sickle cell anaemia. In 1983, Eeg-Olffson[25] reported an incidence of stroke of 2.1/100 000/year in the Linkoping municipality of Sweden between 1970 - 1979; the incidence of ischaemic stroke specifically was 0.86/100 000/year, similar to the rate previously reported by Schoenberg.

Following the advent of CT, Satoh[17] reported that the incidence of radiologically determined ischaemic stroke in children under the age of 16 in the north-east region of Japan (excluding cases of moyamoya syndrome) was 0.5/100 000/year. It is of note that the number of new cases increased over the course of the study period (1974 - 1989) from 2 to 7 cases per year. This was attributed to improved recognition of ischaemic stroke in children due to the increasing availability of CT over this period[17].

Broderick found that the incidence of first - ever stroke (ascertained by CT) in a metropolitan population in the USA in 1988 was 1.2/100 000/year (95% confidence intervals 0.3 to 2). Sixteen percent of the population in this region were black. Although these figures are similar to those previously reported by Schoenberg[24], the prevalence of sickle cell anaemia in this population in this study may explain the higher incidence compared to the Japanese study which was conducted along similar lines.

A recent, prospective population based study in Dijon, France[26] between 1985 and 1993 found that the annual incidence of ischaemic stroke in this population was 7.91/100 000/year (95% confidence intervals 2.56 to 14.57). The diagnosis in all cases was confirmed by CT scan and, after 1987, by MRI. Ascertainment was high in this study as data was collected from all local hospitals as well as from federal records (in order to identify patients resident in the area who fell ill elsewhere) and death certificates. This may account for the much higher incidence of stroke reported in this study compared to the previous studies discussed.

The Canadian Pediatric Ischemic Stroke Registry, an ongoing population based national study in Canada which has ascertained more than 280 cases to date, has found that the

incidence of arterial ischaemic stroke to is 0.91/100 000/year. The combined incidence of arterial ischaemic stroke and ischaemic stroke due to cerebral venous thrombosis is 1.23/100 000/year. Of note, 1/3 of the children in this study are in the neonatal age group and the age related incidence of stroke is highest in this age group (G. de Veber - personal communication).

Overall, therefore, the incidence of ischaemic stroke in childhood appears to be between 0.5 and 8/100 000 children per year. Though considerably lower than the incidence of ischaemic stroke in adults (around 179/100 000 per year[27]), it is comparable to the incidence of brain tumour in the paediatric population (around 3/100 000 per year).

1.4. Pathophysiology of ischaemic stroke

The pathophysiology of focal cerebral ischaemia can be considered at two levels: that of the cerebrovascular and haematological factors leading to vascular occlusion and that of the cellular consequences of focal cerebral hypoperfusion[28].

1.4.1. Arterial occlusion

Focal ischaemia in humans is usually the result of arterial occlusion, due either to *in situ* thrombosis or to vascular occlusion by embolus. The underlying basis of vascular occlusion differs between adults and children. In the former, atheroma, most commonly in the extracranial carotid circulation, acts as a nidus for platelet aggregation and subsequent propagation of distal emboli; emboli may also arise from the heart, especially in patients with atrial fibrillation.

Although embolism is said to be a more common mechanism than thrombosis in children,[14,21] this is somewhat speculative. The angiographic evidence for this is that, in most cases, large vessels are involved, arguing for a proximal source of emboli. In the absence of a communication between the right and left side of the heart this source must be in the heart or great vessels. However, potential embolic sources in these sites are rarely discovered in children with stroke. Although in some cases diffuse vascular involvement with evidence of systemic inflammatory disease provides some evidence of intrinsic cerebrovascular disease, this is by no means the case in the majority of patients. Other circumstantial evidence favouring thrombotic vascular occlusion may be the presence of a prothrombotic state. However, in most cases, the distinction between thrombotic and embolic stroke remains rather speculative.

The sympathetic nervous system may have an important role in mediating arterial occlusion in children with ischaemic stroke[29]. The evidence for this is that cervical sympathectomy both in animals and children has improved ICA stenosis or occlusion[4,30] albeit with usually transient effect. Sympathetic stimulation has been shown to increase vascular permeability which, in the context of systemic inflammation, could render the affected vessels susceptible to focal arteritis[29]. The observations of Bickerstaff and Shillito that stroke was frequently preceded by pharyngeal infection, which have been recently revisited, also lend credence to this hypothesis[31,32,33,34].

The mechanisms underlying stroke in children are likely to be diverse and related to whether or not the child has another predisposing illness (i.e. whether they fall into the "symptomatic" or " idiopathic" category as previously defined). Although embolic

occlusion is likely to be the commonest mechanism in children with structural cardiac disease, intrinsic cerebrovascular disease may also be important in this group[35,36]. In children with sickle cell anaemia, endothelial hyperplasia in large arteries may act as a focus for thrombosis and distal embolisation. The pathological basis of observed arterial abnormalities in children who develop stroke "out of the blue" is not well understood.

1.4.2. Haemostatic system

The haemostatic system relies on interaction between the vessel wall, platelets and the coagulant-anticoagulant systems, with the aim of maintaining a fluid circulation while initiating coagulation at sites of vascular damage[37]. The contribution of the vascular endothelium is mediated by the vasomotor and platelet anti-aggregant effects of prostacyclin and nitric oxide, by the interaction of thrombomodulin (expressed at the endothelial surface) and the protein C anticoagulant system.

Damage to vascular endothelium results in loss of the platelet repelling glycosaminoglycan layer and exposure of collagen to the circulation. This has a procoagulant effect on platelets. Reduced synthesis of prostacyclin, thrombomodulin, plasminogen activator and ecto-ADPase exacerbate this procoagulant tendency[38]. Platelets are damaged by contact with damaged vascular endothelium, resulting in cleavage of platelet membrane phospholipids. Ultimately, this leads to production of thromboxane A_2, which mediates release of the procoagulant platelet contents, as well as promoting vasoconstriction and platelet aggregation[37].

The extrinsic pathway of the coagulation cascade is driven by tissue factor, a ubiquitous protein from which the circulation is normally protected by the vascular endothelium[37]. Endothelial damage, therefore, also initiates the extrinsic pathway of the coagulation cascade.

1.4.3. Thresholds of cerebral blood flow

The sequelae of arterial occlusion are dependent on the severity and duration of the ischaemic insult and collateral circulation, as well as on systemic factors, such as body temperature[39]. The concept of thresholds of cerebral blood flow relates the level of reduction of cerebral blood flow to its pathophysiological consequences. It is relevant to the present discussion to consider 3 such thresholds: those for electrical failure, ion homeostasis and energy failure. The threshold necessary for maintaining cerebral electrical activity in animal models of focal ischaemia is in the region of 15-20ml/100g brain tissue/min[40,41,42], whereas the threshold below which cellular ion homeostasis is disrupted is in the region of 10 - 12ml/100g/min[40,41,42]. The threshold for cellular energy failure is similar to that for ion homeostasis and this is effectively the threshold for neuronal death[40]. However, tissue acidosis, oedema and disruption of protein synthesis may occur at higher levels of cerebral blood flow.

1.4.4. Infarct core and penumbra

It is useful to consider tissue which is damaged as a result of a focal ischaemic injury in terms of a "core", where there has been profound hypoperfusion, metabolic and electrical

failure, and the "penumbral" region, where cerebral blood flow has been reduced to a level which results in electrical silence but where some metabolic activity persists[28,43,44,45]. This concept is fundamental to the drive to seek therapies for acute stroke. The core of the infarct dies very rapidly and therapeutic strategies have therefore been directed towards limiting the extent of, and salvaging tissue in, the penumbral region.

Although infarction has traditionally been defined by histological evidence of tissue necrosis[44], irreversible tissue damage occurs before necrosis is apparent. Rather than considering traditional definitions of infarct core and penumbra, it may be more useful to consider tissue as irreversibly damaged or potentially salvageable[44,46] In subsequent discussion, the term "ischaemic penumbra" will be used to refer to potentially salvageable tissue whereas the "infarct core" will refer to tissue which is irreversibly damaged.

1.4.5. Mechanisms of cellular damage in focal ischaemia

The biochemical mechanisms involved in ischaemic tissue damage are summarised in simplified form in figure 1(1)[28,44,40,47,48,49]. Adenosine triphosphate (ATP) is the energy source for many cellular processes and is normally derived from oxidative phosphorylation. Cellular energy failure is the result of a reduction of cerebral blood flow below the threshold required to maintain ATP production by this route. This results in a switch to anaerobic glycolysis, with a resultant increase in lactate and tissue acidosis.

Cellular energy failure also results in disruption of cellular ion homeostasis. This leads to extrusion of K^+ from the cell and accumulation of intracellular Na^+, Cl^- and water, resulting in cytotoxic oedema, and accumulation of intracellular calcium which is an

important mediator of neuronal death. Other mechanisms which are implicated include activation of lipolysis (resulting in production of free fatty acids and arachidonic acid); protein phosphorylation (resulting in the activation of intracellular enzymes); proteolysis (resulting in free radical formation and disruption of the cytoskeleton)[47]; and activation of nitric oxide synthase, leading to production of nitric oxide and release of excitotoxic amino acids such as glutamate[28,40,47,50]. Glutamate release also stimulates production of nitric oxide which (is directly neurotoxic) as well as production of free radicals[51]. The products of arachidonic acid metabolism result in production of inflammatory mediators as well as promoting production of thromboxane A_2 over prostacyclin, promoting vasoconstriction in the microcirculation and platelet aggregation[47].

The inflammatory response is also important in focal ischaemia[52,53]. Leukocytes bind to endothelial cells in ischaemic tissue; surface molecules on the leukocyte, termed integrins, interact with endothelial receptors such as ICAM-1 and ICAM-2. Leukocyte adhesion promotes release of proinflammatory cytokines such as IL-1, IL-2, IL-6, IL-8 and TNFα. These factors not only promote thrombosis and leukocyte infiltration but also have a direct effect on cellular differentiation, proliferation and apoptosis within the central nervous system[54]. Several recent studies have shown that preceding infection is a risk factor for stroke and the inflammatory response may partly explain this association[55] although at present this explanation remains speculative[33]. A higher brain temperature, which may be associated with infection, seems to potentiate many of the pathways of damage discussed above[56,57].

The mechanisms discussed above represent some of the pathways responsible for neuronal death by necrosis. Recent work has shown that focal ischaemia may result in

neuronal death by apoptosis or "delayed cell death". The mechanism of cellular death may be determined by the duration and severity of the ischaemic insult, as protein synthesis (which requires cerebral blood flow of at least 30-35ml/100g/min), is required for cell death by apoptosis[44]. Mild ischaemia may, therefore, result in apoptotic cell death in contrast to severe ischaemia, which will favour cell death by necrosis. Focal ischaemia is known to induce expression of "early response genes" both locally and in sites distant from the infarct core. Expression of these genes is thought to modulate expression of other, "late effector genes", which may influence tissue damage and recovery. It has been hypothesised that apoptotic cell death requires induction of genes promoting and suppression of genes inhibiting apoptosis. This may be one role of the early response genes[58].

Extension of infarction from the infarct core to the "penumbra" is thought to be mediated by waves of depolarisation (recurrent anoxic depolarisation), similar to spreading depression[28,43,47,59,60]. Spreading depression is characterised by waves of slowly moving, transient, reversible depression of cortical electrical activity which spread from the site of onset with a speed of 2 to 5 mm per minute[59]. Comparison between transient depolarisations in penumbra and classical induced spreading depression is controversial. Spreading depression in normal tissue does not lead to histological damage whereas transient depolarisations in ischaemic tissue are associated with increased infarct size[45,59]. In ischaemic tissue, transient depolarisations, thought to be triggered by extracellular K^+ accumulation and glutamate release, increase energy demand which cannot be met by an increase in cerebral blood flow and are thought thereby to promote conversion of potentially salvageable tissue into areas of infarction[43,,51,59,60,61,62]. Microvascular

compromise and accumulation of polymorphonuclear leukocytes in the penumbral region may also be involved in promoting conversion of penumbral tissue to infarction[44].

Although restoration of cerebral blood flow has, in animal models, been shown to limit the size of infarction[43], it may, paradoxically, worsen tissue damage by exacerbating oedema and promoting oxidative damage mediated by free radicals. This mechanism is known as "reperfusion injury"[40,41]. Disruption of the blood brain barrier may result in haemorrhagic transformation of an ischaemic lesion, with associated mass effect[63]. Restitution of blood flow also results in delivery of leukocytes; leukocytes are involved in initiation of an inflammatory cascade and may also result in occlusion of the cerebral microcirculation[54,64].

Focal ischaemia may have effects remote from the site of origin. Cerebral diaschisis is a reversible reduction in cerebral activity at a site distant from the ischaemic focus[65]. Positron emission tomographic (PET) studies have provided evidence of reduced cerebral blood flow in the hemisphere contralateral to the ischaemic focus[65].

Therapeutic strategies for stroke have focused on countering the mechanisms involved in ischaemic damage as outlined above in order to salvage tissue in the ischaemic penumbra. Broadly, they can be divided into attempts to restore tissue perfusion (such as thrombolysis and anticoagulation) and neuroprotective approaches. The latter include use of calcium channel blockade, glutamate receptor antagonists, free radical scavengers and inhibitors of the inflammatory cascade[41,44,63].

The duration of the time window for salvage of penumbral tissue is one which has preoccupied researchers working on potential acute therapies. A recent trial of rTPA in acute ischaemic stroke in adults suggested that thrombolysis was of benefit in patients treated within 3 hours of onset of the deficit[66]. However, the timing of the progression of ischaemic but salvageable tissue to infarction is likely to be a dynamic process, influenced by variables unique to individual patients such as the severity and duration of the ischaemic insult and the availability of collaterals[44,63].

1.5. Clinical features of acute ischaemic stroke in children

The clinical features of acute ischaemic stroke in older children and adolescents closely resemble those seen in adults but the presentation may be less typical in infants[14]. Children with acute ischaemic stroke usually present with completed stroke although syndromes meeting the definition of TIA and RIND are also seen. Transient ischaemic attacks may herald a more permanent neurological deficit in up to 60% of cases[13,67,68,69]; occasionally the neurological deficit may wax and wane before becoming permanent[70]. Headache is a commonly reported prodromal symptom[71].

The distinction between thrombosis and embolism in difficult to make with certainty on clinical grounds. Clinical features suggestive of cerebral embolism include an abrupt onset of the deficit which reaches maximum intensity rapidly and the occurrence of seizures[14,72,73,74]. Rarely, recanalisation is associated with a improvement in the clinical deficit. Cerebral thrombosis has a more insidious onset and the deficit may develop gradually over hours or days[14,72]. However, these "typical" clinical presentations are rarely encountered and, in practice, the distinction is extremely difficult.

Acute hemiparesis is the commonest manifestation of acute ischaemic stroke in childhood, accounting for up to 90% of cases[70,75,76,77]. Pure motor strokes are said to be commoner in children than in adults[78]; it is not clear whether this is because other signs are not reliably detected in children. Although clinically, expressive aphasia in rare in children, formal evaluation of language reveals that both receptive and expressive language function may be impaired[79]. Although more usually seen in children with cortical damage, language dysfunction may also be a consequence of subcortical lesions[70,77,80,81].

With the availability of detailed neuroimaging it is apparent that the clinical deficits attributable to ischaemic stroke are varied and include cerebellar syndromes, seizures, coma and quadriparesis, depending on the site of the ischaemic lesion[19,67,76,82]. Hemianopia is a difficult sign to detect with certainty in young infants and its frequency is probably underestimated. Higher sensory dysfunction may not be apparent clinically but may be influence the child's subsequent course during rehabilitation. Hemichorea may be a presentation of moyamoya syndrome or of ischaemic lesions involving the striatum[76,82]. Cerebral infarction may occur "silently" in children at risk e.g. in those with sickle cell anaemia[16]. Although the nature of the initial deficit does not seem to be directly related to eventual outcome[19], depression of conscious level at presentation is predictive of poor outcome[18].

The reported incidence of seizures associated with acute stroke varies widely from 14 - 73%[26,76,77,83] but, overall, are more common in children than in adults[71,83].

1.6. Imaging in acute ischaemic stroke

1.6.1. Computerised tomography (CT)

Computerised tomography was the first technique to enable accurate diagnosis of acute cerebral infarction[84]. Technological improvements have resulted in improved detection of ischaemic lesions[85] as well as enabling more rapid imaging. In the acute situation most children presenting with focal neurological deficits will be imaged with CT in the first instance to identify intracranial haemorrhage, which may have urgent treatment implications. The disadvantages of CT in acute ischaemic stroke relate to poor contrast, poor visualisation of posterior fossa structures and inability to image cerebral vasculature.

Raybaud[86] summarised the computerised tomographic features of ischaemic stroke in children. In the acute phase, vasogenic oedema results in low density (see figures 1(2) and 1(3)); luxury perfusion may result in contrast enhancement of the lesion. Occlusion of the large cerebral vessels with thrombus is occasionally visualised. In the next stage (1-2 weeks) there is uniform low density within the infarct as a result of tissue necrosis. There may be a ring of oedema at the boundaries of the infarct and there is no contrast enhancement. The oedema disappears before scarring occurs (2 - 5 weeks). The lesion appears to have very low density and haemorrhagic phenomena may be seen within the infarct. From 2 months onwards, the lesion has the appearances of a glial scar and there may be local atrophy. The distribution of the lesion (within the distribution of an artery) provides supportive evidence that the lesion is an infarct.

Although more recent studies in adults report that up to 70% of patients with infarction have abnormal CT scans within 4 hours of onset[85,87], CT may be entirely normal within the first 24 hours after cerebral infarction[76,88]. In adults, areas of low attenuation apparent very early after the onset of the clinical deficit are associated with a poor outcome[85,87].

1.6.2. Magnetic resonance imaging (MRI)

Magnetic resonance imaging is able to provide detailed structural imaging of the entire brain (including the posterior fossa) and cerebral circulation in any plane. Newer techniques are able to provide information about cerebral functional status. This is achieved without exposing the patient to ionising radiation and therefore serial studies can be performed. In experienced hands, detection of cerebral haemorrhage with MRI is as good as with CT[89]. In paediatric practice imaging may require sedation or anaesthesia.

The signal in MR images is derived from the nuclei of the hydrogen atoms (i.e. protons) in water and fat. In the presence of an externally applied static magnetic field, the nuclei are excited by the application of a radiofrequency magnetic field, and the signal generated from the nuclei detected by a radiofrequency receiver coil. After the nuclei have been perturbed from their equilibrium state, they will return to this condition by processes known as relaxation. The return of the longitudinal component of the magnetisation to its initial condition is an exponential process, with a time constant known as T1. This form of relaxation is thus referred to as T1 or longitudinal relaxation. The loss of coherent magnetisation in the transverse plane is also an exponential process in which the relevant time constant is referred to as T2. The reduction of the transverse component of the magnetisation is therefore known as T2 or transverse relaxation. Image contrast will

depend on the acquisition parameters used and the T1, T2 and proton density characteristics of each region of tissue. For example, images in which the contrast is dependent primarily on the T1 relaxation time differences (so called T1-weighted images) can be generated using a short TR (time to repeat). Similarly, T2-weighted images can be obtained by the use of a long TE (time to echo), while proton density images (images in which the signal intensity is primarily dependent on the distribution of hydrogen nuclei) can be obtained by minimising any relaxation time weighting; i.e. by the use of a long TR and a short TE. By choosing a suitable combination of parameters, optimal contrast (e.g. between grey matter, white matter, CSF and abnormal tissue) can be achieved.

Experimental studies suggest that the changes apparent on MRI in cerebral infarction relate to alterations in regional brain water distribution. Within minutes of an ischaemic insult, with sufficient reduction of cerebral blood flow, there is failure of Na-K-ATP pumps resulting in cytotoxic oedema, with retention of free water in the intracellular compartment; if ischaemia is sustained, subsequent breakdown of the blood-brain barrier results in vasogenic oedema[90].

The earliest MR finding in ischaemic stroke is the absence of flow void or the presence of arterial enhancement with contrast MRI[90]. In the earliest stages of an infarct there is prolongation of both T1 and T2. Swelling may be recognisable by enlargement of structures or distortion of adjacent structures within 2 hours on T1-weighted images; signal change on T2-weighted imaging is apparent from 8 hours onwards, corresponding to the timing of development of vasogenic oedema. Subsequently, the infarcted area will appear dark on T1-weighted images. Overall, T1-weighted imaging is relatively insensitive compared to T2-weighted imaging[90]. In the chronic stage, the characteristics

the infarct is of high signal on T2-weighted images and low signal on T1-weighted images[91]. A rim of signal hyperintensity on T2-weighted imaging may be appreciated around the area of the infarct which corresponds histologically in chronic infarcts to areas of Wallerian degeneration[92]; in acute cases this area may represent penumbral tissue[91].

The sensitivity of CT and T2-weighted MRI are similar, and relatively poor, within 2 to 3 hours of clinical stroke. Beyond this period, the sensitivity of T2-weighted MRI is clearly greater[85,87,88,93]. However, a few cases of pathologically proven cerebral infarction with normal MRI have been reported[93]. The improved sensitivity of MRI has been shown to have clinical implications for both diagnosis and treatment of acute ischaemic stroke in adults[94]. Although MRI has been shown to be useful in the diagnosis of both arterial and venous cerebral infarction in children, the clinical implications of this have not been reported in detail, except in children with sickle cell anaemia[95]. In this group, MRI has been shown to be superior to CT in the detection of cerebral infarction both in terms of timing and extent, especially in the case of microvascular lesions involving the white matter[96,97].

Diffusion-weighted MRI is a relatively new technique which, in animal models, is able to demonstrate changes within minutes of an ischaemic insult. Changes on diffusion-weighted MRI have also been demonstrated in adults with stroke; the most acute studies in humans have been carried out around 100 minutes after the onset of the clinical deficit and have demonstrated signal hyperintensity at this stage[98]. The natural history of changes on diffusion-weighted imaging in cerebral infarction is of signal hyperintensity (due to cytotoxic oedema and consequent reduction in the diffusional motion of water), peudonormalisation of the signal and then signal hypointensity (reflecting free diffusion

of water) as tissue necrosis occurs. Quantification of the signal is possible with mapping of the apparent diffusion coefficient (ADC). Signal hyperintensity on diffusion-weighted imaging was thought to correlate with membrane pump failure but subsequent experimental work has suggested that it is a better reflection of tissue acidosis[99,100]. Diffusion-weighted imaging has been shown to be more sensitive than conventional T2-weighted MRI in the detection of very acute ischaemic brain lesions. Lesions can be identified at an earlier stage and the limits of the ischaemic lesion are better appreciated[101,102].

A question which has aroused much interest is whether diffusion-weighted imaging enables visualisation of the ischaemic penumbra. Although cases of acute diffusion-weighted imaging signal hyperintensity which do not progress to infarction have been described in adults and in children with stroke, in the acute stage it has not been possible to differentiate these cases from those which progress to infarction[98,100,103].

Early identification of ischaemic lesions using diffusion-weighted imaging has been shown to be clinically useful in adults in enabling targeting of subsequent investigations[102]. Diffusion-weighted imaging may also be of benefit in identifying patients who may benefit from very early thrombolytic therapy. It has recently been shown that in acute MCA territory stroke, lesion volumes on diffusion-weighted imaging correlate with initial clinical severity and outcome[104]. This may enable more accurate characterisation of patients for inclusion in therapeutic trials.

Perfusion-weighted MRI maps cerebral blood volume and enables identification of hypoperfused tissue in ischaemic stroke[44,105]. Deficits on early perfusion-weighted

imaging have been shown to correlate better with the eventual area of infarction than areas of signal hyperintensity on diffusion-weighted imaging . Studies combining diffusion and perfusion-weighted imaging in acute stroke have shown that the area of initial perfusion deficit is larger that the area of acute diffusion-weighted imaging signal hyperintensity; it has been suggested that the areas with a perfusion deficit and restricted diffusion represent infarcted tissue while the areas of mismatch reflect potentially salvageable tissue[44]. The combination of early diffusion- and perfusion-weighted imaging has been shown to be superior to T2-weighted imaging in predicting outcome in adults with ischaemic stroke[105].

1.6.3. Imaging the cerebral circulation

1.6.3.1. Conventional angiography

Conventional cerebral angiography remains the gold standard of defining cerebrovascular anatomy. The resolution is sufficient to enable visualisation of the pre-capillary arterioles. Intra-arterial digital subtraction angiography is now the standard method of conventional cerebral angiography.

There are concerns about the complications of conventional cerebral angiography in the investigation of patients after ischaemic stroke. These include haematoma and vessel trauma at the site of arterial puncture, the risk of stroke and the possibility of precipitating painful crisis in patients with sickle cell anaemia. The incidence of complications is also related both to patient factors and operator factors. Experience of conventional

angiography in children is limited in many centres[106]. In adults, the presence of cerebrovascular disease is also associated with a higher risk. Sellar found that the risk of permanent neurological deficit after conventional angiography in a patient with symptomatic cerebrovascular disease was 1%; however more recent studies (with the advantage of newer equipment etc) put this figure at around 0.1%[106]. There are no figures reported for the complication rate in children. However, with adequate preparation and experience, conventional angiography can be carried out relatively safely in most children. Technical advances, such as soft tipped catheters, the use of arterial catheter sheaths and non-ionic contrast agents, have improved safety[106,107].

The timing of angiography in relation to the acute stroke is important. Delay may result in under-detection of vascular pathology, as vascular occlusion may recanalise, but contrast injection in patients with a leaky blood brain barrier may result in exacerbation of brain swelling[108].

1.6.3.2. Magnetic resonance angiography

Magnetic resonance angiography makes use of the fact that blood is flowing in order to provide a means of differentiating blood vessels from static tissue. There are a number of different techniques used to achieve this. These can be grouped as: *magnitude contrast*, in which signal from flowing blood is either re-phased or de-phased on successive images, from which a difference images eliminates static tissue leaving only blood vessels; *phase contrast*, in which the amount of phase change accumulated in the presence of a magnetic field gradient is used to generate an image of the blood vessels; and *time-of-flight*, in

which "new" magnetisation flowing into an imaging slice is used to produce higher signal than in surrounding static tissues. This last method relies on applying successive radiofrequency pulses sufficiently quickly that static tissue does not have enough time to relax and is therefore saturated, whereas in-flowing blood which has not experienced the previous radiofrequency pulses gives rise to a much larger signal.

Magnetic resonance angiography is superior to MRI in the detection of cerebrovascular abnormalities[109,110]. Vessels of more than 1 mm diameter can be visualised; this includes all the large and some of the medium sizes intracranial arteries. Abnormalities on MRA correspond well to areas of cerebral infarction detected using MRI[111,112,113]. Magnetic resonance venography enables visualisation of slow flow such as that in the cerebral venous system.

In adult stroke patients the sensitivity and specificity of MRA compared to conventional angiography has been reported to be 97% and 98.9% respectively[114]. Kandeel[115] reported that the sensitivity and specificity of MRA relative to conventional cerebral angiography in the detection of cerebral vasculopathy in children with sickle cell anaemia were 81% and 94% respectively. Both false negative and false positive evaluations for stenotic and occlusive lesions of the large vessels occurred with MRA. The sensitivity was especially poor for lesions of the ACA and posterior circulation (54% and 50%). The sensitivity of MRA is best for normal vessels and vessel occlusion; the severity of stenotic lesions tends to be over-estimated[116]. Turbulent flow, which may be a particular problem in children with a hyperdynamic cerebral circulation (such as those with sickle cell anaemia), can generate significant artefact[117]. Magnetic resonance angiography has been well established

in paediatric practice and is particularly useful given the technical difficulties associated with conventional angiography in children and the potential for serial studies[113,117,118,119,120].

1.6.3.3. Transcranial Doppler ultrasound

Pulsed Doppler ultrasound using a low frequency probe enables measurement of cerebral blood flow velocity in the basal cerebral vessels[121]. Both the transtemporal or transorbital approaches may be used; examination of the MCA, terminal ICA, ACA and basilar artery are possible. The limitations of this technique include the absence of a bony window in 5 - 15% of adults, insensitivity to mild degrees of stenosis and symmetrical abnormalities, inaccessibility of the distal portions of the MCA and vertebrobasilar system, and the reliance on operator skill. Transcranial Doppler ultrasound is particularly useful for serial studies in "at-risk populations" and, as the technique can be used at the bedside, is suitable for the investigation of the cerebral circulation in critically ill patients.

Experience with TCD in the detection of cerebrovascular abnormalities in childhood is greatest in children with sickle cell anaemia. The value of TCD in predicting stroke by detecting cerebrovascular disease in this group of children was first demonstrated by Adams in 1992[122]. High velocity (>190cm/s) in the MCA is suggestive of vessel stenosis[122] whereas low velocity suggests vessel occlusion[123]. In a subsequent study, Adams found that TCD had a sensitivity of 90% and specificity of 100% when compared to conventional angiography for detection of >50% stenosis in the large intracranial arteries[124]. In a longitudinal study, maximal velocity >200cm/s in the MCA significantly predicted stroke in children with sickle cell anaemia[123].

1.7. Clinico-pathological ischaemic stroke syndromes

Clinico-pathological stroke syndromes are well described in adults but are less well defined in children This may be related to the difficulties of delineating subtle neurological symptoms and signs in young children. However, it is useful to distinguish between individual clinico-pathological syndromes, as this may provide some guidance about natural history. The following discussion will summarise the clinical features and pathological mechanisms of lesions in the territories of the major cerebral arteries.

1.7.1. Anterior circulation infarction

Ischaemic stroke in childhood affects the anterior cerebral circulation far more commonly than the posterior circulation. The MCA territory is most frequently involved[17].

1.7.1.1.1. Middle cerebral artery territory (MCA) infarction

(see figures 1(5(i - iii))

Occlusion of the proximal MCA results in contralateral hemiparesis and hemi-anaesthesia which is more marked in the arm than in the leg[73]. There may also be contralateral visual field impairment. Lesions of the dominant hemisphere may result in aphasia, which is usually mixed[73,79].

"Malignant " MCA territory infarction is a term describing infarction of the entire vascular territory of this artery[125,126]. This usually results from occlusion of the terminal

ICA or proximal MCA. The sequelae are usually severe[125,126], in part due to herniation secondary to cerebral oedema[127,128](see figure 1(5)).

1.7.1.1.2. Subcortical infarction

Subcortical infarction with involvement of the basal ganglia is a frequently observed pattern in childhood stroke[17,26,70,129,130](see figure 1(6)). The clinico-pathological syndrome of striatocapsular infarction is due to infarction in the territory of the lateral striate branches of the MCA, resulting in a typically "comma" shaped infarct on CT involving the head of the caudate, anterior limb of the internal capsule and the putamen[131]. Striatocapsular lesions account for 5% of lesions in adults with stroke but around 50% in paediatric series[26,132]. Such lesions are thought to be more frequent in children with apparently "idiopathic" stroke; however, preceding chickenpox, vasculitis, head injury, meningitis and chemotherapy have been described as risk factors[133,134].

The mechanisms are attributable to large rather than small vessel disease, and include proximal MCA occlusion in patients with good collateral circulation or partial MCA occlusion with occlusion of the lateral striate arteries but some preservation of distal flow[132,135]. In adults, over half the patients have evidence of a carotid or cardiac source of emboli[136]. Minor head trauma with stretching of the lateral lenticulostriate perforators is also thought to be a possible mechanism in children[132,134,137].

Ipsilateral hemisphere or capsular TIA preceding stroke are frequently noted in adults and children[131]. The clinical syndrome is of hemiparesis, worse in the arm. Cortical deficits such as aphasia, neglect or apraxia may occur[132,136,138]. Motor sequelae are related to

directly to lesions of the internal capsule and corona radiata[133]. Damage to areas distant from the lesion may occur as a result of diaschisis and Wallerian degeneration of the pyramidal tracts.

Adults with striatocapsular infarcts frequently have a significant incidence of residual cognitive dysfunction. This is thought to be due to involvement of adjacent cortical tissue in the ischaemic penumbra, diaschisis or direct disruption of cortico-basal ganglia-thalamo-cortical circuits[80131,139]. Although outcome is said to be good in childhood[67,70] subcortical lesions in children may be associated with cognitive[80], attentional and behavioural disorders[140].

1.7.1.2. Internal carotid artery (ICA) occlusion

Occlusion of the terminal ICA results in infarction in the territories of the anterior cerebral and middle cerebral arteries. Hemiparesis and hemi-anaesthesia usually affect the upper and lower limbs to a similar extent; involvement of the ophthalmic artery may result in monocular blindness[73]. Direct involvement of the sympathetic chain may result in an ipsilateral Horner's syndrome. Lesions resulting from ICA occlusion tend to be large and may be associated with depression of conscious level and significant mass effect[126]. However, gradual occlusion may lead to the development of moyamoya collaterals, with a distinctive clinical picture, as described later.

1.7.1.3. Anterior cerebral artery (ACA) occlusion

Isolated ACA occlusion is rare in childhood; infarction in this territory results in a contralateral motor deficit more marked in the lower limb[73]. The territory of the ACA is usually involved together with that of the MCA in cases of ICA occlusion.

1.7.2. Borderzone infarction

(see figure 1(7))

The arterial borderzones are the areas at the junction between territories of supply of major cerebral arteries[141]. The anterior borderzone refers to the boundary between the ACA and MCA; the posterior borderzone refers the junction of the MCA and PCA territories and the internal borderzone is the junction between territory supplied by the deep perforating branches of major arteries and the medullary arteries which arise from the superficial pial plexus. The internal borderzone anatomically corresponds to the corona radiata and centrum semiovale[141].

Although lesions in the arterial borderzones classically arise after reduction in cerebral perfusion e.g. after severe hypotension[141], they may also result from severe stenotic or occlusive lesions of the carotid bifurcation[142]. In adults, there is evidence that infarction is secondary to distal microemboli rather than to hypoperfusion, although this remains controversial[142]. Diffuse small vessel occlusion, possibly due to disorders of thrombosis, has also been noted in cases of bilateral borderzone infarction. In children, borderzone infarction is most frequently seen with sickle cell anaemia and is thought to be related to perfusion failure[143]. Bladin[141] observed that internal borderzone infarction in adults was associated with significant cognitive sequelae and this also appears to be the case in children[144].

1.7.3. Posterior circulation infarction

Posterior circulation stroke is much less common than anterior circulation stroke in childhood[145,146,147]. The posterior cerebral circulation supplies the occipital lobes, thalamus, brainstem and cerebellum. Basilar artery occlusion may result in bilateral infarcts. Cerebellar infarcts may not be clearly visualised on CT and should be considered where the posterior fossa appears "tight" on CT[145,146]. Lesions in this territory may produce cranial nerve signs, gaze paresis, visual field defects, vertigo or cerebellar signs in addition to hemiparesis, depending on the location of the infarct. In contrast to lesions in the anterior circulation, disorders of language or cognition are not a prominent feature[73,148].

Overall, there is a marked male preponderance (in excess of 80%)[146,149,150]. Though this may partly relate to cervical trauma[149], structural abnormalities of the cervical vertebrae also occur more frequently in males[151]. Vascular mechanisms which have been implicated include VA dissection with subsequent thrombosis and distal embolisation (see figure 1(8)), vasospasm and thrombosis during attacks of basilar migraine, and structural anomalies such as a hypoplastic VA, hypoplastic posterior communicating artery or cervical vertebral anomalies[145].

1.8. Aetiology of ischaemic stroke in children

The aetiology of stroke in an individual child can be considered in terms of vascular and non-vascular risk factors. Clearly, the profile of risk factors is different in elderly and

young stroke populations. A recent study has suggested that a further distinction can be drawn between paediatric and young adult groups (with a proposed age cut-off at 15 years) in terms of the distribution of risk factors[21] and that a large proportion of cases in the paediatric age group may remain unexplained. This is supported by the findings of previous studies, as is evident in Appendix 1.

1.8.1. Cerebral vessels

The importance of cerebrovascular abnormalities in ischaemic stroke in childhood was recognised very early in studies of "acute infantile hemiplegia"[7,9,11,152,153]. The prevalent hypothesis in these studies was that vascular inflammation or "arteritis", related to pharyngeal inflammation, was responsible for the changes observed in cerebral vessels[7,11,153,154]. However, although this hypothesis is now regaining popularity in light of recent work establishing an association between preceding infection and ischaemic stroke[31,32], these observations were based solely on angiographic appearances. The angiographic findings in some of these cases would be compatible with pathological entities other than arteritis, such as carotid dissection or fibromuscular dysplasia[11,155]. Recent evidence has also suggested that preceding infection may be an important risk factor in these specific patterns of cerebrovascular disease[156].

Most angiographic studies were focused on anatomical classifications of cerebrovascular lesions, based on angiographic morphology [11,152,154].

Such classifications can be summarised as follows:

1. Intracranial large vessel occlusion or stenosis (see figures 1(9(i - ii)) 1(10(i - ii)))

2. Extracranial large vessel occlusion or stenosis
3. Large vessel occlusion or stenosis with collateral formation (moyamoya syndrome)
4. Branch vessel occlusion
5. Small vessel disease

The implications of cerebrovascular abnormalities for treatment and prognosis in children with "acute infantile hemiplegia" remained unclear. Solomon[10] concluded that the presence of a cerebrovascular abnormality was indicative of a more favourable prognosis in children with acute hemiplegia. However, this probably related to the heterogeneity in the patients studied, who included a large proportion who would now be classified as having HHE, with a correspondingly poor prognosis.

More recent studies of children with radiologically confirmed ischaemic stroke have also found a high frequency of cerebrovascular abnormalities[70,157]. Shirane[157] found that 85% of such children had cerebrovascular abnormalities. The distribution of abnormalities was similar to those previously described (where the terminal ICA and proximal MCA were the most frequently affected vessels[7,10,11,153,157]). Of note, when angiography was repeated after an interval of 1 year in Shirane's study, 55% of the abnormalities seen in the acute phase had improved or resolved[157]. This had been previously noted[7] and invoked as evidence of a transient cerebral vasculitis secondary to cerebral inflammation though other explanations, such as embolic occlusion and recanalisation could account for these findings.

In a recent study, Chabrier[158] defined an entity termed "transient cerebral arteriopathy". This is a disorder which was predominantly seen in young children, with often multifocal

large vessel stenosis or occlusion, which usually improved or resolved on serial angiography. Of note, many of the patients had had recent *Varicella zoster* infection. It is likely that this is the same entity described in the earlier studies by Bickerstaff, Shillito and Shirane[7,153,157]. Unfortunately, without serial imaging it is not possible to distinguish these children from those who develop progressive cerebrovascular disease. Improvement or resolution of cerebrovascular lesions does not correlate with clinical improvement[11].

More recently, is has been recognised that a significant proportion of cerebrovascular abnormalities seen in children with ischaemic stroke fall into some well defined categories namely moyamoya syndrome, arterial dissection, inflammatory cerebrovascular disease and fibromuscular dysplasia. These diagnostic entities will be discussed in further detail.

1.8.1.1. Moyamoya syndrome

(see figures 1(11(i - ii)))

First described by Shimizu and Takeuchi in 1955[159], "moyamoya" is a Japanese term which in translation means "something hazy like a puff of cigarette smoke drifting in the air"[4]. In the context of cerebrovascular disease, moyamoya syndrome refers to the angiographic appearance produced by stenosis or occlusion of the terminal ICA, sometimes with involvement of the ACA and MCA, with a mesh of basal collateral vessels. Moyamoya syndrome can occur either in isolation (when it is referred to as idiopathic moyamoya or moyamoya disease) or in association with a number of other conditions. It is not possible to make a distinction between these two groups on angiographic grounds. In contrast to the Japanese experience where most cases are

idiopathic, in a Western series, 80% of cases were secondary and only 20% of cases were idiopathic[160].

Moyamoya syndrome is endemic in Japan where 0.07% of the population are affected; 2.7 - 7% of Japanese cases are familial[161,162,163]. It has now become clear that both primary and secondary moyamoya syndrome occur world-wide, although much less often than in the Japanese, in whom a genetic susceptibility has been postulated. The frequency of the HLA B51, AW24, BW46 and BW54 genotypes[164]in Japanese patients with idiopathic moyamoya syndrome[165] would support this hypothesis as would the description of this condition in twins[162,166] and an increased occurrence in family members of affected individuals[163,167]. Cases have also been described in non-Japanese families[168,169]. In Japan, the age distribution shows 2 peaks, in the first and fourth decades[4]. There is a female preponderance in idiopathic cases.

Pharyngeal inflammation with sympathetic hyperstimulation has been put forward as a possible mechanism for the development of moyamoya syndrome[29,161]. There is some experimental evidence for this in that injection of foreign protein into dogs produced similar vascular changes; these were reduced in dogs who had had prior superior ganglionectomy. Both perivascular sympathectomy and cervical ganglionectomy have also been associated with reduction in the frequency of TIA and cognitive stabilisation or improvement[4]. However, in a case-control study, there was no evidence that the incidence of preceding infection was higher in children with moyamoya syndrome than age-matched controls[120].

Histological findings have included intimal thickening, excessive convolutions or deficiencies of the internal elastic lamina and thinning of the vascular media. Perforating vessels may show microaneurysm formation and along with the thinning of the elastic lamina, this may account for some cases of intracerebral haemorrhage[4,74]. Both fresh and mature thrombus have been apparent at the sites of vascular occlusion. It has been suggested that microthrombi may induce the intimal thickening seen in the cerebral vessels of patients with moyamoya syndrome[170]. No inflammatory changes have been seen in vessels at post-mortem[171].

The usual presentation in childhood is with recurrent TIA or stroke[120]. Other presentations include epilepsy, progressive cognitive decline, chorea, headache[74,161,172], or intracranial haemorrhage[173], which is more commonly seen in adults[4]. Neurological sequelae are evident in around 75% of cases; there is also a significant mortality[174]. Cognitive impairment affects 21 - 50% of all patients and is more frequent than in children with large vessel abnormalities without moyamoya collaterals[175]. This is worst in children with cerebral infarction and is also related to the duration of the disease[120,172]. During EEG recordings, hyperventilation may reveal the characteristic pattern of "re-buildup" but this manoeuvre is dangerous as it is a reflection of cerebral ischaemia due to hypocapnic vasodilatation[4,163,171,175].

Computerised tomographic appearances include multiple low density areas (related to areas of infarction), multiple flow voids in the basal ganglia and generalised atrophy. Magnetic resonance imaging is more sensitive. Areas of infarction appear as high signal areas on T2-weighted images while the flow voids (of the collateral circulation) are often

best seen on T1-weighted images. Infarcts tend to be located in the arterial borderzones and in subcortical regions[159].

The incidence of recurrent ischaemic symptoms is high. Surgical treatment (discussed in section 1.9.2) may prevent recurrent cerebral ischaemic symptoms and stabilise cognitive function[4].

1.8.1.2. Arterial dissection

(see figure 1(12))

Arterial dissection has only recently gained wide recognition as an important cause of stroke in the young and may cause up to 20% of cerebral infarction in children and young adults[176,177,178]. Dissection may affect both the extracranial and the intracranial sections of either the anterior or the posterior cerebral circulation. In children, in contrast to adults, the anterior circulation is more frequently affected. Although overall the most frequently affected vessel is the supraclinoid ICA in all ages[176,178,179], the intracranial ICA is more frequently affected in children than in adults. The incidence of VA dissection is thought to be around 1/3rd that of spontaneous ICA dissection[180]. The V1 and V3 segments of the VA are not attached to bony structures and are therefore most susceptible. The most frequently affected segment in cases of "spontaneous" VA dissection is the V3 segment, adjacent to the C1 and C2 vertebrae[180,181,182].

In dissected vessels, a tear results in the passage of blood into the vessel wall. This either causes reduction in the calibre of the true lumen of the affected vessel, thrombosis of the dissection flap with local occlusion or distal propagation of emboli, or formation of a

pseudoaneurysm if blood tracks between the vascular media and adventitia[183,184]. Stroke usually occurs because of arterial embolism, although reduced perfusion plays a part in some cases[185]. In the extracranial carotid artery and VA, the plane of dissection is usually within the arterial media which is the least elastic layer of the vessel wall and therefore most likely to rupture as a result of trauma[186]. In intracranial vessels, dissections are subintimal as the medial layer in these vessels is relatively simplified[178,179]. Rarely, this may result in subarachnoid haemorrhage as blood leaks or ruptures through the adventitial layer[178,187]. The dissection may extend distally from the site of origin[176] or multiple vessels may be involved at presentation. This occurs in around 25% of cases and is more common in young patients[178,188,189].

Although dissection is often precipitated by trauma, either direct or indirect, this may be relatively trivial or may be absent[178,184]. Some cases occur in the context of generalised connective tissue abnormalities[178,190], atherosclerosis[160], fibromuscular dysplasia[179,191], in association with migraine[177,192,193], in patients with carotid artery redundancy[194] or as part of a syndrome comprising arterial dissection, cystic medial necrosis and lentiginosis[195]. Preceding infection has recently also been implicated[156]. However, most cases occur in otherwise normal individuals. The identification of familial cases, involvement of multiple vessels, association with structural cardiac abnormalities and increase in the incidence of intracranial aneurysms in patients with arterial dissection provides some circumstantial evidence that some patients are likely to have an underlying vasculopathy or developmental abnormality in cells derived from the embryological neural crest[36,196].

Diagnosis is often delayed, even in cases with an antecedent history of injury[177,183], and a high index of clinical suspicion is required in order to target appropriate investigations.

Although the appearances of dissection are well described in many of the early papers on cerebral angiography (especially in children who had had blunt pharyngeal trauma[7,10,11,23,197]), it was not recognised as a diagnostic entity until relatively recently. Stroke may occur some time after the injury as, after the formation of a dissection flap, it may take some time for thrombotic or embolic vascular occlusion to occur[187,198]. Suggestive clinical features include facial, head and neck pain (which may affect >90% of patents[177,178]), Horner's syndrome, a bruit[179] and pulsatile tinnitus[199]. Cranial nerve palsies involving the V^{th}, IX^{th} - XII^{th} cranial nerves have also been described[189]. Occipital or cervical pain and symptoms of vertebrobasilar ischaemia may be the presenting features of VA dissection[180,181,200]; head tilt is occasionally a feature in childhood[201].

There is a significant incidence of recurrence, which is greater in younger patients[196] and in those with a family history of arterial dissection[202]. Overall, the risk of recurrent dissection is in the order of 2% in the first month and 11.9% over 10 years[196].

1.8.1.3. Cerebral vasculitis

(see figure 1(13) and 1(14))

Confusion arises because many authors have used the terms "vasculitis" and "arteritis" loosely, often when referring to a clinical or radiological description rather than a pathological one. Strictly, the term "vasculitis" should be used to refer to a pathological process with a number of diverse aetiologies[203]."Cerebral vasculitis" is defined as inflammation of the cerebral circulation, either as part of a systemic vasculitic process or,

in the instance of isolated angiitis of the central nervous system (IAC) , as inflammation confined to the cerebral vessels[204].

Cerebral vasculitis may be responsible for around 20% of stroke in young adults; the prevalence in childhood is unknown[176]. CNS involvement in children, resulting in stroke, has been reported in polyarteritis nodosa[23,73], Bechets disease[205], Kawasaki disease[73], Takayasu disease[69,73,206] and Henoch-Schoenlein purpura[176,207]. Cerebral vasculitis may also arise secondary to infection, neoplastic disease (lymphoma), toxins (amphetamines, cocaine) or connective tissue disorders such as systemic lupus erythematosis[23,176,208,209]. Evidence of a systemic vasculitic process should be sought in all children with cerebral vasculitis but especially in those with recurrent stroke, encephalopathy, multifocal neurological deficits, fever, rashes, renal impairment or raised inflammatory markers[176].

Isolated angiitis of the central nervous system (IAC) affects mainly small and medium sized arteries and is confined to the central nervous system[210]. Although the mean age of onset is 46 years[211], this has been as young as three years[212]. Reports of adult cases greatly exceed those in children; it is unclear whether this accurately reflects the incidence of the disease or whether there is under-reporting or under-detection of paediatric cases.

The cause of IAC is unknown[208] although it has been suggested that there may be an infective trigger[212]. Cell mediated vascular injury results in ischaemia, thrombosis, haemorrhage and vasoconstriction with subsequent tissue injury[208].

Apart from acute infarction, clinical features (which relate to ischaemia or hypoperfusion) include headache, encephalopathy, seizures, cognitive dysfunction, cranial nerve palsies

and multifocal neurological deficits[208]. Presentation with stroke in the absence of other deficits is unusual[212]. Similarly, systemic symptoms are also unusual. The course is usually progressive with stepwise periods of deterioration[212] and there may be acute exacerbations. Inflammatory markers such as the erythrocyte sedimentation rate, C reactive protein, white cell count, platelets, immune complexes and autoantibodies are usually negative. Around 50-60% of patients have a mild CSF pleiocytosis or elevated CSF protein[212]. Electroencephalography is abnormal in 75% of cases but is rarely diagnostic. Detailed ophthalmological examination may reveal evidence of a retinal vasculitis in some cases[203].

The six paediatric cases of IAC reported in the literature have all presented with acute cerebral infarction. Histological confirmation was only reported in 1 patient, who had normal cerebral angiography[213]. The other cases relied on cerebral angiography for diagnosis, although all responded to anti-inflammatory therapy[214,215,216]. Moore[217] has proposed the following diagnostic criteria for IAC :

1. Recent onset of headaches, cognitive dysfunction and multifocal neurological deficits unless the initial illness has a severe and progressive course
2. Angiographic changes suggestive of vasculitis
3. Exclusion of systemic disease and infection
4. Leptomeningeal +/- parenchymal biopsy confirming vascular inflammation.

However, only patients at the severe end of the spectrum will be identified using these criteria[217].

The clinical course is variable. Some patients appear to have a relatively benign course without any treatment[211,218], others respond well to immunosuppressant therapy[219]. Some have a relentlessly progressive course culminating in severe disability and death.

Magnetic resonance imaging in cerebral vasculitis reveals areas of infarction, cortical swelling, meningeal enhancement, foci of high signal in the white matter and areas of haemorrhage[209].Multifocal white matter lesions without cortical changes have led to the misdiagnosis of multiple sclerosis in adults and children[213]. Lesions may also be mistaken for neoplasms[203,211]. Magnetic resonance imaging may also be normal in patients with clinical symptoms and abnormal cerebral angiography. Although MRA will enable visualisation of occluded or stenotic large vessels, smaller vessels will not be visualised.

Cerebral biopsy has been advocated in order to gain histological confirmation of the diagnosis. Moore[220] quotes the risk of permanent deficit associated with this procedure to be around 1%. MRI may guide tissue sampling from radiologically abnormal sites; if none are accessible, the non-dominant frontal lobe or temporal tip may be targeted. Ideally, meninges as well as parenchymal tissue should be sampled as this improves the diagnostic yield[212]. However, the multifocal nature of the disease means that cerebral biopsy has a significant false negative rate, which ranges in different series from 25 - 74%[203,212,220].

1.8.1.4. Fibromuscular dysplasia

Fibromuscular dysplasia is a condition which affects small and medium sized vessels and is characterised pathologically by alternating areas of vascular fibrosis and dilatation.

Typically, the condition affects middle aged women[69,160,221]; however, cases in children with ischaemic stroke are well documented[176,222,223]. Overall, cervicocephalic fibromuscular dysplasia accounts for 25 to 30% of all cases[176,222]. 60 - 80% of patients with fibromuscular dysplasia of the cervical ICA have bilateral involvement [222]. The childhood variety is atypical in that hyperplasia of the intima rather than the media is observed. The diagnosis should be considered in patients with hypertension as this may be the result of renal artery involvement[69].

Diagnosis is usually made on the basis of angiographic appearances of the "string of beads appearance" due to the alternating segments of stenosis and dilatation. However, the smooth walled, non-progressive stenotic tubular form occurs more frequently in children than in adults and may be difficult to distinguish from other causes of large vessel stenosis[160]. The "string of beads" appearance may be mimicked by inflammatory vascular disease[86] or by radiological artefact[221]. Some authors have advocated diagnostic biopsy of the superficial temporal artery[221] but this may be misleading in a condition which may be focal or multifocal.

1.8.2. Cardiac disorders

A third to a half of ischaemic stroke in children is associated with cardiac disease[73,114]. Around 3% of children with congenital cyanotic cardiac disease suffer stroke[78,99], usually before the age of 2 years[224]. The possible mechanisms by which cardiac disease can result in stroke are:

1. Intracardiac thrombosis and subsequent embolism

2. Polycythaemia (secondary to cyanosis) causing vascular occlusion
3. Relative anaemia
4. Perfusion failure secondary to low cardiac output
5. Bacterial endocarditis and embolisation of infected material[225]
6. Right to left shunts and paradoxical embolism
7. Cerebral venous thrombosis[226]
8. Cardiac surgery, catheterisation or angiography[71,227]
9. Associated cerebrovascular disease[36,228]

More than one mechanism may be important in an individual patient.

The risk of stroke associated with congenital cardiac disease is greatest in the major admixture anomalies such as Fallot's tetralogy or transposition of the great arteries[205,226]. Many studies of childhood stroke specifically exclude children with known congenital cardiac lesions as they are thought to be less "interesting" than other children with stroke. However, cerebral infarction is a significant cause of morbidity and mortality in this group of already disadvantaged children[227]. Cardiac embolism does not explain all causes of stroke and, unless patients are investigated in detail, other, treatable, causes of stroke may be missed[228]. Acquired cardiac disease such as cardiomyopathies[73,78,224], cardiac rhabdomyomas[78] and myocardial infarction[224,229] have also been described in association with ischaemic stroke; both congenital and acquired cardiac arrhythmias may also predispose to stroke[70,78,230,231,232].

Despite improvements in cardiac surgery, children with surgically corrected cardiac defects remain at risk at developing stroke[233,234,235]. Although children undergoing cardiac surgery are at risk of global cerebral ischaemia, focal neurological deficits are well

recognised in the immediate post operative period and may result in long term neurological sequelae[236]. For example, the incidence of post-operative stroke in children undergoing the Fontan procedure is in the region of 2 - 3%[233,237]. Mechanisms leading to stroke in children who have had cardiac surgery include intra-operative factors (e.g. air emboli) and post-operative factors, such as the presence of foreign material within the heart, stasis of blood in vascular stumps or alterations in intracardiac haemodynamics, left to right shunts, cardiac arrhythmias and elevated systemic venous pressure resulting in systemic venous thrombosis[233,236,237].

The relationship between common minor structural anomalies such as mitral valve prolapse and PFO and stroke in young adults has received much attention. Mitral valve prolapse affects 5 - 7% of all children but is rarely associated with stroke in this age group (2654, 1404). Although several series have reported a high frequency of mitral valve prolapse in young adults with stroke, the frequency with which this occurs in the normal population, especially in women, means that the link between mitral valve prolapse and premature stroke remains unproven[225,238].

Paradoxical emboli (from the systemic venous circulation or the right side of the heart to the brain) rely on the presence of a connection between the right and left sides of the heart. This can be a major structural anomaly such as a ventricular or atrial septal defect or more minor anomalies such as PFO, ASD, atrial septal aneurysm or a pulmonary arteriovenous fistula[73,224,225]. A physiological shunt through a PFO can be demonstrated on contrast echocardiography in 10 - 18% of otherwise healthy individuals[238]. The prevalence of PFO in young adults with otherwise unexplained stroke is in the order of 32 - 55%[238,239,240,241]. Right atrial pressure is not sustained at a high level in these patients but is

thought to rise transiently due to a Valsalva manoeuvre resulting in right to left shunting of blood[238]. The presence of an atrial septal aneurysm may confer additional risk[240,242,241]; mitral valve prolapse is a commonly associated abnormality[243].

The detection of shunting though a PFO is possible using either bubble contrast transthoracic echocardiography; transoesophageal echocardiography or TCD are more sensitive[242,244,245,246,247,248,249,250]. However such examinations require the patient to perform a Valsalva manoeuvre in order to increase right heart pressure, which is difficult in children. Alternatively, pressure on the liver may increase systemic venous return and have a similar effect. The frequency of PFO in the normal population makes the association with stroke circumstantial, in the absence of a definite systemic source of embolus[238,241,251]. A recent study has suggested that, in contrast to the young adult stroke population, paradoxical embolism is not a common mechanism of ischaemic stroke in children[21].

1.8.3. Sickle cell anaemia and ischaemic stroke

Two hundred and fifty thousand children with homozygous sickle cell anaemia (HbSS) are born each year world-wide[252]. Clinical stroke affects 6-9% of individuals with sickle cell anaemia under 20 years of age. However, this may only represent 75% of the children who have evidence of cerebral infarction on MRI[16,253]. The risk of stroke is over 250 times greater in children with sickle cell anaemia than in their contemporaries[254] and, untreated, two-thirds of them will have a recurrence[253]. The risk of stroke is greatest in the childhood years and is highest in children aged 2-5 years[255]. Although traditionally the risk of stroke has been thought to be less in patients with HbSC and HbSβthalassaemia phenotypes[256], a

recent study suggests that although lower than in patients with the HbSS phenotype, it is appreciable[255]. Ischaemic stroke is far commoner than haemorrhagic stroke in younger children[255].

In 1939, Bridger made the observation of occlusion of large cerebral arteries due to endothelial proliferation in a 7 year old girl with sickle cell anaemia and stroke. However, at this time, attention focused on microvascular occlusion with sickled red cells and thrombus as the mechanism of stroke[256]. A later angiographic study by Stockman demonstrated large vessel occlusion in 6 out of 7 patients with sickle cell anaemia and stroke. The focus of attention was then redirected towards the large cerebral vessels, where it has remained[257]. Histological studies have supported this view; the terminal ICA and proximal MCA are the most frequently affected vessels[258]. Recent reviews of the angiographically documented cases have suggested that large vessel abnormalities were evident in 60 - 95% of the published cases[256,259].

The vasculopathy is thought to be due to intimal proliferation and fibrosis secondary to chronic endothelial trauma by the deformed, sickled erythrocytes[256]. Abnormal adherence to the vascular endothelium is thought to lead to endothelial damage as the red cells are washed away by the rapidly flowing blood. Exposure of subendothelial structures may then promote platelet aggregation and thrombosis[260,261]. Occlusion arises by obliteration of the vascular lumen by fibrotic tissue or thrombus; embolus from a proximal arterial source may also result in distal large vessel occlusion[258,259]. Although occlusion of the vasa vasorum of the large vessels has also been postulated as a mechanism, there is no post-mortem evidence to support this and intracranial vessels are thought to lack vasa

vasorum[256]. The development of basal collaterals may lead to the radiological appearances of moyamoya syndrome[257,262,263].

Large vessel disease does not entirely account for the patterns of cerebral infarction seen in patients with sickle cell anaemia. In particular, this is supported by the observations that some patients have had normal cerebral arteriograms at the time of stroke[256]. Other factors of importance are microvascular disease (due to occlusion of terminal arterioles by deformed sickled erythrocytes[256,264]) and "anaemic infarction" (perfusion failure in the arterial borderzones resulting from low cerebrovascular reserve secondary to the cerebral hyperaemia of chronic anaemia)[78,143,256]. There is also evidence to suggest a procoagulant tendency in patients with sickle cell anaemia[73,265,266,267]. A low level of HbF appears to be a risk factor for stroke[260] and this has become the target for therapeutic intervention[256]. Other risk factors for stroke in this population include a high white cell count[268], low haemoglobin[255], recent chest crisis[255], adenotonsillar hyperplasia[73,269] and cardiomegaly[73]. A recent study which showed that hyperhomocysteinaemia (possibly related to low serum folate) was a risk factor for stroke in individuals with sickle cell anaemia awaits confirmation in a prospective study in a larger cohort[270].

Although dural venous sinus thrombosis has been observed in a few patients at post-mortem[256], the frequency of cerebral venous thrombosis in patients with sickle cell anaemia is unknown. The frequency of cerebral venous thrombosis may be underestimated in patients with sickle cell anaemia as the commonest presenting features of this, headache and seizures, are relatively common in children with sickle cell anaemia[256].

Stroke in sickle cell anaemia usually occurs "out of the blue". A few cases may be heralded by TIA[254] while others may occur in the context of severe anaemia secondary to an aplastic crisis or acute splenic sequestration[5,254,268]. Hemiparesis, seizures, dysphasia and visual failure are the most frequently observed presenting features of stroke[253,254,268,271]. Formal neurological examination has a sensitivity in the order of 70% for the detection of abnormalities in children with cerebral infarcts on MRI[16]. "Soft" neurological signs rather than formal long tract signs are more sensitive for identifying children with otherwise "silent" cerebral infarction[272].

The commonest pattern of infarction on CT and MRI involves the arterial borderzones[16,256,273]; such lesions are analogous to those seen in patients with severe hypotension or severe ICA stenosis and lend weight to the hypothesis that perfusion failure and large vessel disease are important mechanisms[256]. The anterior, posterior or internal borderzones may be involved[16]. Areas of infarction may also correspond to the territories served by large vessels[273].

The prevalence of clinically "silent" lesions on MRI ranges from 11 - 24%[5,16,263]. Lesions involving cortical structures or the basal ganglia, as opposed to the white matter, tend to be accompanied by a clinical event[263]. Clinically silent lesions may be significant in terms of their effect on cognitive function in particular[274,275] and may predict further, clinically overt, stroke[263].

The value of TCD in identifying patients with increased risk of stroke was first demonstrated by Adams[122] and has subsequently become widely recognised[111]. As previously discussed. the sensitivity and specificity of MRA is high compared to

conventional cerebral angiography in the detection of cerebral vasculopathy in this population[115]. Deficits apparent using functional imaging techniques such as PET and T2* MRI have been shown to precede clinical and MRI evidence of cerebrovascular disease and require further investigation[160].

Primary prevention of stroke has aroused much interest in this population. Adams' work suggesting that the risk of stroke in the 3 years following an abnormal TCD study was in the order of 40%[123] made this an appropriate group to target. A recent study in which asymptomatic patients with cerebral blood flow velocities of more than 200cm/s in the ICA or MCA on TCD were randomised to either conservative treatment or blood transfusion was terminated early because of a highly significant reduction in the incidence of stroke in the transfused group[276]. However, as previously discussed, transfusion therapy has risks. Moreover, the logistics of mass screening and transfusion therapy will be a significant challenge for health care provision in areas where there is a high prevalence of sickle cell anaemia. Having identified a particularly high risk group, the efficacy of other primary preventative strategies, such as bone marrow transplantation or hydoxyurea, remains to be seen.

1.8.4. Prothrombotic states

The prevalence of inherited prothrombotic states is between 1:2500 to 1:5000[277,278]. They are more commonly associated with venous rather than arterial thrombosis[279]. Even in individuals at risk, the tendency to thrombosis appears to be multifactorial; in some patients, a combination of genetically determined predispositions to thrombosis may be important, while in other patients there may be acquired risk factors for thrombosis such

as antiphospholipid antibodies, immobilisation, infection, malignant disease or drug therapy[280]. With reference to ischaemic stroke, the tendency to venous thrombosis may be relevant in patients with a communication between the right and left sides of the heart, with a potential route for paradoxical embolisation[37].

1.8.4.1. Protein C deficiency

Protein C exerts its anticoagulant effect by inactivating activated factor V and activated factor VIII and activating fibrinolysis. Inheritance of protein C deficiency is autosomal dominant with variable penetrance. While homozygous protein C deficiency may be associated with neonatal *purpura fulminans* and is usually fatal, the prevalence of symptomatic heterozygosity for protein C deficiency is 1 in 16 000. Up to 1:60 individuals in healthy blood donor populations have low levels of protein C[281]. Although the risk of venous thrombosis (including cerebral venous thrombosis[282]) is increased in heterozygotes, this is variable and may depend on co-existence of other environmental or genetic risk factors for thrombosis. Normal levels of protein C are lower in children than in adults; adult values are not reached until at least 4 years of age[283]. Acquired protein C deficiency can occur in the acute phase of thrombosis, in disseminated intravascular coagulation, hepatic disease, and in patients receiving certain chemotherapeutic agents (such as L-aspariginase and flourouracil[284]) and warfarin.

1.8.4.2. Protein S deficiency

Protein S is a vitamin K dependent protein which is a cofactor for the anticoagulant effect of protein C. It exists in two forms; 40% circulates in a free fraction while the remainder is bound to C4b, part of the complement system. The free fraction is responsible for the anticoagulant effect of protein S. Protein S deficiency is inherited in an autosomal dominant manner[285]. The prevalence of primary protein S deficiency in the healthy population is 7/1000[286]; secondary deficiencies are also well recognised. The most common association is with inflammatory illnesses in which the complement system is activated, leading to an increase in the levels of C4b of up to 400%, increased binding of protein S to C4b and a secondary free protein S deficiency[287]. Other causes include nephrotic syndrome, liver dysfunction and warfarin therapy. Protein S deficiency following infection with *Varicella zoster* is thought to be mediated by antibodies directed against protein S[288].

1.8.4.3. Antithrombin III deficiency

Antithrombin III inactivates circulating thrombin and activates factors IX, X, XI and XII[38,37]. Hereditary antithrombin III deficiency is inherited as an autosomal dominant trait. Asymptomatic heterozygous antithrombin III deficiency has a frequency of 1 in 2000[37]. Dysfunctional antithrombin III molecules have been described which result in functional antithrombin III deficiency[37]. Acquired deficiencies occur in the context of nephrotic syndrome, disseminated intravascular coagulation, protein losing enteropathy and L-aspariginase therapy[289]. As with the other anticoagulant proteins, transient antithrombin III deficiency may occur in the context of acute thrombosis. The risk of venous thrombosis associated with antithrombin III deficiency is relatively high; 85% of patients will experience a thrombotic event before the age of 50[37].

1.8.4.4. Activated protein C resistance and the factor V Leiden mutation

Activated protein C resistance (APC resistance) is a prothrombotic condition originally described by Svensen and Dahlback[290] in which there is resistance to the anticoagulant effects of activated protein C. Inactivation of factor Va by activated protein C proceeds in an ordered manner with cleavage first at the Arg506 site followed by cleavage at the Arg306 and Arg679 sites[291]. In 95% of cases the APC resistant phenotype is secondary to an Arg506Gln mutation in the factor V gene, termed the factor V Leiden mutation[292]. More recently, mutations have been identified in the Arg306 site[291,293].

The factor V Leiden mutation is the commonest hereditary risk factor for venous thrombosis, affecting 21% of patients in unselected populations[294]; inheritance is autosomal dominant. The relative risk of venous thrombosis is increased seven times in heterozygotes and thirty times in homozygotes[295]. Recently the prevalence of APC resistance and the factor V Leiden mutation in patients with cerebral venous thrombosis has been shown to be around 20%[296,297,298,299]. The prevalence of heterozygosity for the factor V Leiden mutation in the healthy population is extremely high and is strongly affected by ethnicity[300]; this may also be true for the mutations at the Arg306 site[291]. There is also some evidence to suggest that the prevalence of this mutation is higher in healthy neonates compared to healthy elderly people, suggesting that age may be an important factor in determining prevalence[301]. A study of blood donors in the north of England found that the local prevalence was 3.5%[302]

Both genotypic and phenotypic evaluation are important as patients can have APC resistance without the factor V Leiden mutation[303]; the positive predictive value of the APC resistance test for the factor V Leiden mutation can be improved by using factor V deficient plasma in the APC resistance ratio assay[304].

The factor V Leiden mutation is not associated with an increased risk of ischaemic stroke in adults[305]. However, some reports have suggested an association with juvenile stroke[306,307]. Fisher[308] has recently suggested that APC resistance not associated with the factor V Leiden mutation may be a risk factor for stroke in some populations.

1.8.4.5. Antiphospholipid antibodies

Antiphospholipid antibodies are directed against protein phospholipid complexes[309]. The target for the lupus anticoagulant appears to be thrombin, whereas anticardiolipin antibodies are thought to be directed against β2-glycoprotein[37]. The lupus anticoagulant is detected by its effect in prolonging clotting time in phospholipid dependent tests of clotting function (e.g. KCT (kaolin clotting time), aPTT(activated partial thromboplastin time), DRVVT (dilute Russell's viper venom time)); confirmation of an abnormality requires demonstration that the defect is not corrected by the addition of donor plasma[188]. Anticardiolipin antibodies are detected by immunoassay, usually ELISA, and can be of the IgG or IgM class.

The lupus anticoagulant prolongs the aPTT because negatively charged phospholipid is an essential cofactor in fibrin generation. However, the procoagulant effect of antiphospholipid antibodies are thought to be mediated via inhibition of the protein C

anticoagulant system, inhibition of prostacyclin formation and increasing platelet aggregability and adhesiveness[309,310], modulated by protein cofactors such as β2-glycoprotein I[311].

Antiphospholipid antibodies may occur in association with autoimmune diseases such as systemic lupus erythematosis, Beçhets disease, livedo reticularis or in otherwise healthy individuals. The term primary antiphospholipid syndrome refers to patients who have antiphospholipid antibodies without systemic lupus erythematosis but with at least one of the following clinical features - recurrent foetal loss, thrombosis or thrombocytopaenia. Antiphospholipid antibodies may also occur transiently after infective illness (especially IgM anticardiolipin antibodies) or in association with certain drugs such as phenothiazines or phenytoin[309]. Anticardiolipin antibodies are found in 2 -5% of the healthy population, a figure which increases to 51% in 80 year olds[312,313]. Angelini[314] studied 42 healthy children and found that although none had IgG anticardiolipin antibodies, 5% had IgM anticardiolipin antibodies. The pathological significance of IgM anticardiolipin antibodies is uncertain[311].

Individual patients may have only one of these abnormalities[313]. Greaves suggests that patients who have both the lupus anticoagulant and anticardiolipin antibodies are more likely to suffer from thrombotic events than those with anticardiolipin antibodies alone. There is evidence to suggest that the actual level of the antibody may be important in determining pathogenicity[311].

1.8.5. Metabolic disorders and ischaemic stroke

1.8.5.1. Homocystinuria and hyperhomocysteinaemia

Homocystinuria is a recessively inherited disorder caused by a number of enzyme deficiencies (the commonest of which is of cystathione β-synthase) resulting in increased levels of homocysteine in blood and urine[74]. Arterial disease is a well recognised feature of this disorder, affecting 50% of untreated patients under the age of 30 years[315]. This is thought to be result from the toxic effect of homocysteine on vascular endothelium which leads to increased platelet aggregation and patchy endothelial loss[38,74]. Structural abnormalities of blood vessels have also been seen in this condition suggesting that there is damage to the intima and media of medium to large sized intracranial arteries[74]. Patients are at particular risk of developing vascular occlusion after invasive vascular procedures such as cerebral angiography[74]. Patients who develop thrombotic events are at greater risk of further events[74].

Hyperhomocysteinaemia has been shown to be an independent risk factor for cerebrovascular disease in adults[316,317,315]. The prevalence of heterozygosity for cystathione βsynthase deficiency in the population is around 1: 200[318] while heterozygosity for the thermolabile variant of methylenetetrahyrofolate reductase may affect 5 - 50% of the population[315]. Hyperhomocystinaemia may also have a nutritional basis (vitamin B12 and folate deficiencies, renal failure) or may be due to treatment with drugs such as methotrexate or anticonvulsants[315]. Inhibition of thrombomodulin at the vascular endothelial surface may explain the thrombotic tendency in patients with mild hyperhomocysteinaemia[37]. The relationship between hyperhomocysteinaemia and

cerebrovascular disease in childhood remains largely unexplored; however, this association may be important in children with sickle cell anaemia[270]. A case of moyamoya syndrome in child who was heterozygous for homocystinuria with an abnormal methionine loading test has been described[134] - an association which merits further investigation.

1.8.5.2. Hyperlipidaemia

Hyperlipidaemia in childhood may be primary or secondary. Familial hypercholesterolaemia (due to a defect or absence of LDL-cholesterol receptors) affects 1:1 000 000 children in the UK. The gene frequency is 1 in 500[319]. One percent of children in the UK have either familial combined hyperlipidaemia or polygenically determined hypercholesterolaemia. The prevalence of familial combined hyperlipidaemia is around 3 times that of familial hypercholesterolaemia[319].

HDL-cholesterol has a protective effect on endothelial cells while LDL-cholesterol is toxic[320]. Other factors which increase the risk of stroke in adults are high levels of total cholesterol and triglycerides, low levels of high density lipoprotein (HDL-cholesterol), high levels of low density lipoprotein (LDL-cholesterol) and high levels of lipoprotein a[320,321]. Levels of serum lipids may be transiently depressed in the immediate period following stroke[320,321] and timing of measurements in relation to the acute event is, therefore, important. Other factors which should be considered in evaluating whether lipid values are raised are the variation in the relative contribution of HDL and LDL to total cholesterol in childhood and adolescence[322] and the influence of gender[319] and ethnicity[320].

Although the relationship between hyperlipidaemia and coronary atheroma is well established, the relationship with cerebrovascular disease is less clear, both in adults and children[319]. The literature has, in the past, been confounded by the difficulties in correlating hyperlipidaemia with evidence of vascular disease in the cerebral circulation in either cases or controls. In a review, Tell concluded that there was an association between lipid abnormalities and cerebrovascular atheroma, but that this relationship was more important with increasing age[320]. However, given the relative rarity of atheroma in childhood[6,8,323,324], hyperlipidaemia is likely to be a less important risk factor for stroke in children than in adults.

Although two studies have suggested that hyperlipidaemia is associated with ischaemic stroke in children[67,325], this has not been a consistent finding in the previous literature[70,147,326,327]. In the study carried out by Glueck[325], 10 out of 11 children with otherwise unexplained stroke had lipid abnormalities (raised LDL cholesterol, raised triglycerides or low HDL cholesterol). Although the rate of "premature" (under 60 years of age) vascular disease in the first degree relatives of these children was said to be higher, the incidence in a control population was not considered. Conventional angiography was carried out in 5 cases and showed a wide variety of findings, such as normal vessels, arterial dissection and diffuse arteritis. The lesion locations (in the intracranial vessels) and the nature of the described abnormalities would argue against atheroma as the underlying pathology. Furthermore, similar abnormalities have been demonstrated in the vessels of children without lipid abnormalities.

Abram[67] found a high prevalence of lipid abnormalities in children with otherwise unexplained stroke. There was a relatively long interval between the stroke and measurement of lipids in this study (mean 7.4 years). Of the 36 patients investigated, 28% of the children had high triglycerides, 19% had high total cholesterol, and 17% had a low HDL-cholesterol; 53% had a depressed apolipoprotein A-1/B ratio. However, the authors note that "specific lipid abnormalities did not predict angiographic features or location of ischaemic events".

1.8.6. Infection

1.8.6.1. Fever and infection

Much interest has focused on the role of infection preceding stroke in children. As previously discussed, several studies in the 1960's found a high incidence of antecedent pharyngeal inflammation[7,153]. Considering the more recent literature, Riikonen[147] found that the incidence of infection within 21 days preceding the stroke was higher in a group of 44 children with ischaemic stroke than in age matched controls. However, specific infectious agents were only identified in 7 patients. Nagaraja observed that 23% of Indian children with ischaemic strokes had had a preceding fever although no specific causes were identified for this[129]. A case control study in Finland found that recent febrile infection was associated with 9 times greater risk of developing cerebral infarction in patients under 50 years of age when compared to controls[328]; in 80% of cases such infections affected the respiratory system. Both bacterial and viral infections, especially of the respiratory tract, appear to be important[33]. Chronic and recurrent infections, for

example dental sepsis, also appear to be associated with an increased risk of ischaemic stroke[34].

Although activation of the thrombotic system, inhibition of the anticoagulant system, thrombocytosis, the effect of pro-inflammatory cytokines on the vascular endothelium and generation of antiphospholipid antibodies have been advanced as possible mechanisms to explain this association[31,329], inflammatory and prothrombotic markers are similar in cases and controls[33]. Hyperthermia secondary to fever may be an important adverse prognostic factor[329]. As infection has been implicated in the pathogenesis of ICA dissection, there may be a link with structural vascular abnormalities[156].

1.8.6.2. Bacterial meningitis

Cerebral infarction is a common complication of bacterial meningitis, affecting over a quarter of cases[330]. Children with meningitis secondary to *Streptococcus pneumonia, Haemophilus influenzae*, gram negative organisms and tuberculous meningitis[73,160,331] are especially vulnerable, as are younger children[73]. Although infarction is often unilateral, bilateral signs may be evident at presentation, reflecting more widespread cerebral derangement; seizures are frequent[330].

Bacterial meningitis leads directly to inflammation of intracranial vessels as they are immersed in purulent exudate[69]. Vasospasm, possibly mediated by proinflammatory cytokines, is also thought to occur. Although all sizes of vessel are involved[332], vasospasm tends to affect large arteries. Tuberculous meningitis may be complicated by a necrotising panarteritis, with secondary thrombosis and vascular occlusion[331]. Ischaemic lesions and

evidence of cerebrovascular involvement, detected as increased cerebral blood flow velocity on TCD, are associated with a poor outcome[331,332].

1.8.6.3. *Varicella zoster*

Chickenpox is a common childhood exanthem due to infection with *Varicella zoster*, predominantly affecting children under the age of 10 years. Ichiyama found that in Japan 1:6500 cases of chickenpox are complicated by ischaemic stroke[333]. In a recent case-control study in Belgium, Sebire found a significantly higher incidence of chickenpox within the previous 9 months in children with stroke compared to age matched controls[334]. Although stroke has sometimes been described as a delayed complication of chickenpox, it may also complicate the acute illness.

Several mechanisms have been implicated[335]. Firstly, there may be primary cerebrovascular abnormalities, such as occlusion or stenosis of large vessels[336], due to both focal or diffuse arteritis (mediated either by direct viral invasion or due to an immunological reaction to the infection)[337,338]. Secondly, it has been demonstrated that these patients may develop a prothrombotic tendency, due either to the formation of antibodies against the anticoagulant protein, protein S, increased binding of protein S to C4b or to low levels of protein S and protein C levels due to consumption in the thrombotic process[339,340]. Demonstration of thrombotic vascular occlusion, without evidence of a local vasculitic reaction, by Eidelberg[341] would provide support for the role of thrombosis in the pathogenesis of ischaemic stroke associated with chickenpox.

1.8.7. Trauma

Trauma may cause ischaemic stroke by several mechanisms and is a prominent cause of stroke in the young. In one series, cerebral infarction in a quarter of patients under the age of 45 was attributed to trauma[198]. In the carotid circulation there is usually a history of external trauma whereas in the vertebrobasilar circulation trauma may result from neck movement during normal activities[198]. Penetrating injuries may cause direct arterial trauma but these are usually overt[30].

Blunt pharyngeal trauma (caused for example by a child falling with a pencil in the mouth) may directly injure the ICA in the tonsillar fossa and result in local thrombotic occlusion[10,68,73]. Minor cranio-cervical trauma may cause arterial dissection or injury even in children with apparently normal arteries[342].

Direct trauma to the posterior circulation may, as in the anterior circulation, cause stroke either by thrombotic occlusion or in association with VA dissection. The VA's may be indirectly sheared by a rotational injury to the cervical spine or directly traumatised by being forced against the bony prominences[343]. Imaging of the cervical spine in flexion and extension may be required to reveal instability at the C1/C2 level[150] and either an anterior-posterior view or CT imaging of the cervical spine may be necessary to detect subtle spinal fractures[343,344]. Such bony injuries may result in VA trauma and subsequent arterial dissection.

The VA's are especially vulnerable to rotational or nodding movements and stretching at the level of the atlanto-axial or occipito-atlantoid joints[149,150], to forced lateral flexion in

the third part (V3) as they run postero-medially on the upper surface of the atlas towards the midline[150] and to flexion/extension or lateral neck movements at the levels of the C3 to C6 vertebrae[149]. Post-mortem angiography has shown that physiological degrees of neck hyperextension and 45° neck rotation results in narrowing of the VA at the level of the atlanto-axial junction[345]. Children with developmental variants of the posterior circulation or atlanto-axial junction e.g. congenital non-fusion of the odontoid[68], atlanto-axial instability or subluxation (in, for example, Down's syndrome, mucopolysaccharidoses and juvenile rheumatoid arthritis[78]) may be especially vulnerable to the effects of position. However, compromise of circulation on head rotation may occur even in the absence of any structural abnormalities[346]. "Physiological" alterations in head posture such as looking over the shoulder while reversing a car, painting a ceiling, standing on the head or performing yoga may have been reported in association with stroke[198,342]. Carotid artery injury may also be associated with hyperextension and contralateral neck rotation and skull base fractures[183].

Mild head trauma has been reported to be associated with basal ganglia infarction[130,347,348]. The mechanism which has been proposed to explain this involves stretching or shearing of the lenticulostriate arteries as a result of the traumatic insult.

1.8.8. Malignant disease

Stroke affects around 4% of all children with cancer[349] and is most commonly seen with lymphoreticular malignancies and neuroblastoma. Both cerebral arterial and venous thrombosis may occur[310]. The mechanisms involved relate to direct effects of the malignancy, to tumour metastases (in neuroblastoma)[78], to treatment (L asparaginase

(arterial or venous thrombosis), methotrexate, adriamycin (cardiomyopathy) radiotherapy (cerebral vasculopathy)), the coagulopathy associated with malignant disease[310] or to intercurrent infection[349]. Most events occur within the first year after diagnosis[349]. The long term risk in survivors who may, for example, have received cranial irradiation (which is associated with a mineralising microangiopathy or the development of moyamoya syndrome) is unknown. Stroke has been reported over 20 years after treatment with radiotherapy[350].

1.8.9. "Idiopathic" ischaemic stroke

Between one third and two thirds of all cases of ischaemic stroke in childhood are unexplained[21,70,75,74,351,352,353]. The term "idiopathic stroke" is often loosely applied as the extent to which the many causes of ischaemic stroke have been excluded varies greatly between series. Even in cases where there is a well recognised predisposition to stroke, the mechanism in individual cases may not be clear; cause and effect is often not clearly established, for example in the case of the inherited prothrombotic states[281].

Mintz[354] reported that 4 children with otherwise idiopathic stroke were heterozygous for the class 1 major histocompatibility antigen HLA B51; three children with non-idiopathic stroke and 3 children with other diseases did not have this genotype. The association of this HLA type with other inflammatory diseases (such as Bechet's disease and Kawasaki's disease) led them to speculate as to whether these children are vulnerable to inflammatory cerebrovascular disease, possible mediated by a viral trigger. Another group has shown that this genotype is associated with idiopathic moyamoya syndrome in Japan[165].

The high frequency of moyamoya syndrome in Japan suggests that the vulnerability to cerebrovascular disease in childhood may be at least partly genetically determined[169]. The recognised association between structural abnormalities of the heart[355] or cutaneous lesions[160] and cerebrovascular abnormalities also suggests the possibility of an abnormality in the genes controlling vascular development in affected individuals. Additionally, the importance of common, genetically determined, risk factors for vascular disease, such as mild hyperhomocysteinaemia, in children with ischaemic stroke remain undetermined. Environmental factors which merit further consideration in this group are the role of acute infection, especially *Varicella zoster*, and of minor cranio-cervical trauma.

1.9. Treatment of acute ischaemic stroke

Ischaemic stroke in adults is fast becoming a treatable condition[356,357,358]. Except for revascularisation in moyamoya syndrome and blood transfusion in sickle cell anaemia, there is no data regarding the safety and efficacy of treatments in children. An editorial on the treatment of acute ischaemic stroke in adults in 1995 concluded that *"it is evident from systematic overviews that too few patients have been studied and that much larger trials are needed"*[359]. This is a much greater problem in the paediatric stroke population where numbers of patients are much less. The approach in the adult population has been to conduct very large scale multicentre trials with good statistical power and to collate systematic reviews of the published literature in order to provide a meta-analysis of the available evidence[359].

1.9.1. Treatment of stroke in sickle cell anaemia

Exchange blood transfusion is the mainstay of treatment in acute stroke in children with sickle cell anaemia; this will immediately reduce the percentage of HbS and increase the haematocrit[256]. The aim is to reduce to percentage of HbS to under 30%. General factors such as maintenance of hydration, attention to blood pressure and treatment of sepsis should be given due attention.

1.9.2. Anticoagulation in ischaemic stroke

The purpose of anticoagulant therapy in acute ischaemic stroke is to reduce further thrombus formation by impairing the clotting cascade[27], with the dual aims of limiting the extent of cerebral infarction and preventing further embolic events. Despite the fact that both heparin and warfarin are relatively "old" drugs, systematic evidence about the risks and benefits of anticoagulation in acute ischaemic stroke has only recently become available.

Sandercock[360] reviewed the published literature on anticoagulation in acute ischaemic stroke in 1993 and concluded that there were inadequate data to draw conclusions about the safety and efficacy of heparin in the treatment of acute ischaemic stroke. The main safety issue was the risk of bleeding complications, particularly the risk of haemorrhagic transformation of infarcts, related to the use of anticoagulation. The International Stroke Trial was a randomised open trial with a factorial design in 20 000 adults with ischaemic stroke designed to investigate the safety and efficacy of unfractionated heparin and aspirin

in acute ischaemic stroke[361]. The study found that subcutaneous unfractionated heparin was associated with significant risk and no benefit in terms of early mortality and morbidity.

Low molecular weight (fractionated) heparin is associated with fewer bleeding complications than conventional intravenous heparin and can be given subcutaneously. In 1995 a trial involving 312 patients concluded that low molecular weight heparin improved morbidity after ischaemic stroke with no excess risk[362]; however 3 other studies of fractionated heparin or heparinoids failed showed an increased mortality with no net benefit in the treated groups[363].

Although the Stroke Council of the American Heart Association were unable to make recommendations on the role of heparin in acute cardioembolic stroke, heparin continues to be commonly used in this situation, in both children and adults. Immediate anticoagulation for infarction associated with cardiogenic brain embolus is associated with a high rate of haemorrhagic transformation[225] and it is important to evaluate the risk-to-benefit in individual cases. Spontaneous haemorrhagic transformation is also common in cardioembolic stroke with an incidence of around 40%, and is both more common and associated with a worse outcome in patients with large lesions[46]. However, anticoagulation appears to reduce the incidence of early recurrent stroke which is up to 12% in the first fortnight in adults[46,225,363]. It may, therefore, be prudent to initiate anticoagulation in patients with moderate or small lesions but to delay such therapy, at least for 48 hours, in patients with larger lesions, already associated with significant mass effect[46,73]. A moderate level of anticoagulation (INR of 2 -3) is currently recommended by the Cerebral Embolism Task Force[238]. Although heparin conferred a significant reduction

in early recurrent stroke in over 3000 patients with atrial fibrillation studied as part of the International Stroke Trial, there was also an increase in the incidence of intracranial haemorrhage, such that no net benefit accrued[361].

Anticoagulation has been advocated in patients with arterial dissection affecting extracranial vessels as the dissection flap may act as a nidus for thrombus formation and propagation of distal emboli. The use of anticoagulation in intracranial arterial dissection is controversial due to concerns about precipitating haemorrhage. The available evidence suggests that treatment is most effective if initiated very early, before infarction has occurred[177]. There is a rationale for the use of anticoagulation even in patients in whom infarction has occurred as there may be potential for the prevention of further embolic events, but the efficacy of this strategy remains unproven.

1.9.3. Aspirin

Aspirin exerts its anti-platelet action by inhibiting platelet cyclo-oxygenase; it also inhibits the production of thromboxane A_2 from platelets and prostacyclin in the vascular endothelium. After acute stroke, there is platelet activation in the peri-infarct zone with sludging in the microcirculation and platelet aggregation due to the local actions of thromboxane[364]. Inhibition of this effect is the basis of using aspirin to treat acute ischaemic stroke. The maximal antiplatelet effect of aspirin is apparent within 20 minutes[365].

In an overview of the role of aspirin given acutely after ischaemic stroke in adults, including the results from two large randomised controlled trials, the International Stroke

Trial[361] (IST) and the Chinese Acute Stroke Trial[366] (CAST), Sandercock concluded that immediate aspirin therapy was associated with a moderate reduction in early recurrent ischaemic stroke and death. The risk of intracranial haemorrhage was 1 in 1000. The IST used an aspirin dose of 300mg and CAST used a dose of 160mg. He therefore concluded that all patients without evidence of intracranial haemorrhage or contraindications to aspirin should receive 160 - 300 mg aspirin for 2 weeks and 75 - 150 mg a day thereafter for secondary prevention. Combining the data from CAST and the IST, the overall advantage conferred by aspirin is to prevent 10 deaths or recurrent strokes per 1000 patients treated.

The net benefit of aspirin given acutely is relatively small and large numbers of patients need to be treated in order to demonstrate benefit. The risk-to-benefit ratio of the use of aspirin acutely in children with ischaemic stroke remains unexplored. The use of aspirin in childhood is additionally complicated by the reported association with Reye's syndrome. This seems to be a genuine observation given the dramatic reduction in the incidence of this disorder after reduction in the use of aspirin as an analgesic or antipyretic agent in childhood[367,368,369,370]. As well as children with concurrent viral infections (including *Varicella*), children who are on long term aspirin for rheumatic diseases are also at risk[368]. However, as there is some evidence to suggest that the risk of developing Reye's syndrome is related to aspirin dose[370], the risk may be less with low dose aspirin.

1.9.4. Thrombolytic therapy

The aim of thrombolytic therapy in acute ischaemic stroke is to restore cerebral perfusion and to limit damage by salvage of tissue in the penumbral region of the infarct. Thrombolytic agents which have been investigated for use in acute ischaemic stroke include streptokinase, urokinase and recombinant tissue plasminogen activator (rTPA)[371,372]. In a review of randomised controlled trials of thrombolytic therapy in acute ischaemic stroke for the Cochrane Collaborative Stroke Review Group (total of 3500 patients randomised), Wardlaw and Warlow drew the following conclusions[371]: thrombolytic therapy was associated with a 9% increase in death in the first fortnight, 7% increase in the rate of symptomatic and 5% in the rate of fatal intracranial haemorrhage; overall there was a 25% relative reduction in death or dependence at 3-6 months (corresponding to 65 patients with improved outcome for every 1000 treated)[371,,372].

In 1995, publication of the NINDS rTPA study (which had a randomised, double blind design) in around 300 patients indicated that administration of rTPA to adults with ischaemic stroke within 3 hours of onset was associated with a net benefit in terms of morbidity at 3 months[66]. Although there was a significantly higher incidence of intracranial haemorrhage in the treated group, there was no significant increase in mortality at 3 months. Early mortality was not specifically discussed. The results of this study and subsequent licensing of rTPA for acute ischaemic stroke by the Food and Drug Administration in the USA were the first definitive indications that acute ischaemic stroke may be treatable in clinical practice. However, the safety of rTPA, which is possibly related to the dose used, remains an issue for concern[373] and the time window for treatment (3 hours) is very narrow. Overall, despite the positive results of the NINDS trial, Warlow concluded that there is insufficient evidence from the published literature to

make any conclusive recommendations about the use of thrombolysis to treat acute ischaemic stroke[371].

1.9.5. Surgical decompression

Surgical decompression (either resection of ischaemic tissue or resection of the non-dominant frontal lobe) in adults with " malignant MCA territory infarction" is associated with improved mortality, although morbidity remains high[374]. There may be a role for aggressive monitoring and management of raised intracranial pressure, including the use of cranial decompression, in the treatment of children with large territorial infarcts[183].

1.9.6. Control of temperature

As previously discussed, it has been observed that hyperthermia has been shown to adversely affect outcome in adults with stroke[375,376,377]. There is a strong case to support active management of fever, by underlying sepsis and by use of antipyretic agents such as paracetamol[57].

Although cooling the brain is used as a neuroprotective strategy in patients undergoing cardiopulmonary bypass, the role of hypothermia in patients with focal ischaemia relatively unexplored. Experimental evidence would suggest that even relatively small reductions in brain temperature are associated with significant reductions in lesion size[56,57]. A recent study in adults with malignant MCA territory infarcts showed that mild hypothermia was associated with a reduction in intracranial pressure and in cerebral

oedema on CT[376]. Brain temperature may be reduced either by cooling the whole body (although this may be associated with systemic metabolic derangement) or by selectively cooling the head by, for example, using a cooling helmet[378].

1.10. Outcome

In contrast to adults, it is commonly perceived that the outcome after ischaemic stroke in childhood is favourable. However, objective evidence for this view is lacking. Around 75% of children with cerebral infarction have residual sequelae[99](see Appendix 2). Deficits in motor, linguistic, sensory and cognitive domains may result in significant functional disability [73,379]. The importance of this is that the potential for preventing disability must enter into the risk-to-benefit equation when considering acute and secondary therapies for stroke. Overall, mortality after ischaemic stroke is relatively low[24,70,75,351] though it may be higher in children with sickle cell anaemia[253,268,271].

The assessment of outcome after stroke in childhood has been made difficult by the lack of any validated scales comparable to the Barthel or Rankin scales in adult[380]. Patients included in previous studies have been relatively heterogeneous in terms of age and diagnosis. For example, most studies which include children with ischaemic stroke also include children with haemorrhagic stroke, neonatal stroke or "acute infantile hemiplegia" or have excluded specific groups of patients such as those with cardiac disease or stroke as a result of trauma[9,18,19,70,82]. If outcome is predictable by any clinical factors at the acute stage then this would also be of value in selecting patients for acute treatments. Although some authors have previously tried to define the factors which predicted outcome[10,18,19,82],

these studies have also been in "mixed" populations. Both outcome and prediction of outcome in children with ischaemic stroke are, therefore, relatively poorly described.

Although the high prevalence of residual motor impairment after ischaemic stroke is well recognised[10,24,26,70,381,382], little is known about the frequency of cognitive, language and behaviour impairment. In practical terms, there is little information for parents about what to expect; appropriate rehabilitation for children is also lacking[383]. Improved definition of motor, language, cognitive and behaviour deficits would also enable the use of appropriately targeted rehabilitative strategies.

In contrast to the outcome after stroke in other children (where motor impairment is the most frequent residual deficit[384]), cognitive impairment is the most frequent residual effect of stroke in children with sickle cell anaemia. Silent cerebral infarction is associated with significant cognitive sequelae in this population[274,275]. There is evidence to suggest that the IQ of children with sickle cell anaemia without stroke is lower than that of sibling controls[385], possibly secondary to early nutritional state[386]. However, stroke further impairs cognitive function[384,387] and recurrent stroke worsens this on each occasion[253].

1.11. Recurrence

Although the question of the risk of recurrent stroke is one which occurs immediately to parents, this subject has received very little attention in the literature. Most studies of ischaemic stroke are retrospective and there is no longitudinal data on the risk of stroke in adolescent and adult life. It is commonly held that ischaemic stroke does not recur[86] but this is clearly not the case[76,67,147]. Recurrence is most commonly described in children with

"symptomatic stroke" (i.e. in those with another underlying diagnosis)[76,67,147] In children with sickle cell anaemia the risk of recurrent stroke in untreated patients is around 65%[253]. Children with idiopathic moyamoya syndrome are also known to be at high risk of recurrent stroke and TIA[4,120]. The risk of recurrence has not been systematically investigated for children with apparently idiopathic stroke.

1.11.1. Prevention of recurrent stroke in children with sickle cell anaemia

Blood transfusion has been shown to reduce the incidence of recurrent stroke in children with sickle cell anaemia from 67% to 10%[253,260,388] and is currently recommended as secondary prevention for children who have had at least one stroke. Most clinicians aim to maintain the level of HbS between 20% and 30% and to keep the haemoglobin above 10g/dl (to suppress production of HbS in the bone marrow)[254]. However, recurrent stroke on transfusion has occurred at levels of HbS of 15 - 20% and some authors recommend maintaining the HbS below 15%[256]. Such a level is rarely achievable in practice and increases further the already significant risks of iron overload associated with transfusion[253,254]. The other risks of transfusion therapy include transmission of blood borne infection (including HIV) and sensitisation to blood products[256]. As well as reducing the percentage of HbS and ameliorating the chronic anaemia, blood transfusion also improves the cerebral hyperaemia in patients with sickle cell anaemia[256]. However, at best, transfusion "stabilises" vascular lesions[260,389,390].

The optimal duration of transfusion remains unresolved; the peak period for recurrent stroke is in the following 3 years and some authors have recommended that transfusion therapy is continued only for this period[253,256]. However, transfusion is only protective for

the duration of treatment and the high risk of recurrent stroke after transfusion is discontinued[389,390,391] means that some clinicians elect to continue transfusion for a longer period. Some have recommended relaxing the transfusion regime after the initial 3 years and accepting higher HbS levels of 40 - 50% after this. Although there has been limited experience with this strategy, there are reports that it has been successful in preventing stroke recurrence[254].

Bone marrow transplantation cures sickle cell anaemia and is therefore a permanent solution[392]. In practice however, the availability of suitable donors will mean that this treatment is only available to a relatively small number of children, even in countries where bone marrow transplantation is feasible. Other measures which have been tried include the use of agents such as hydoxyurea which increase the level of HbF[393,394]. As previously discussed, adenotonsillar hyperplasia may be a significant risk factor for stroke and the role of early adeno-tonsillectomy merits further investigation. Surgical revascularisation in a child with sickle cell anaemia and moyamoya syndrome has recently been described[395]. The role of surgery in such patients and the implications for ongoing transfusion therapy will require further exploration.

1.11.2 Surgical revascularisation

Transcranial revascularisation is the mainstay of treatment for idiopathic moyamoya syndrome. The aim of this is to bypass the site of large vessel occlusion or stenosis and to promote the formation of a collateral circulation to reperfuse ischaemic tissue. Three procedures have been used: direct vascular anastomosis (usually superficial temporal artery to MCA), encephaloarteriodurosynangiosis (EDAS) (where the superficial temporal

artery and a strip of galea are mobilised and laid over the pial surface of the brain) and encephalo-myosynangiosis (EMS) (where a strip of temporalis muscle is laid directly over the cortical surface). Modified EDAS refers to the situation where the arachnoid is opened as part of the EDAS operation. Direct anastomosis is technically difficult, may disrupt transdural collaterals and has been reported to be associated with clinical deterioration in some cases[396,397,398] although, in general the results are better than for indirect revascularisation procedures[71,397,399]. Some patients who have indirect revascularisation may benefit from later direct anastomosis[71] and the results of using a combination of direct and indirect techniques are encouraging[400]. Patients should be monitored after surgery, either with serial angiography, or with serial MRA, SPECT, PET and psychometry in order to ensure that ischaemic symptoms do not recur and cognitive function is stable[401].

Surgery is often considered late on the course of the disease by which time many children have significant residual deficits. This is not only true in Europe[402] and North America[174] but also in Japan[120]. Delays arise not only in diagnosis but also in referral for surgery. The Japanese experience would suggest that surgery should be considered in symptomatic children (i.e. in those with TIA or stroke) and in those with evidence of cerebral hypoperfusion and decreased cerebrovascular reserve on SPECT or PET[403], rather than relying solely on the angiographic appearances. Controlled trials of surgery and the optimal surgical technique are needed in order to strengthen the already convincing case for surgery.

In 1985, a multi-centre study investigating the role of superficial temporal artery to MCA anastomosis for symptomatic ICA stenosis or occlusion in adults reported that surgery did

not confer any appreciable benefit[404]. However, the design of this study has been widely criticised[402]; there are also inherent differences between the adult and the paediatric populations. A recent study by Ohno[405] suggests that extracranial - intracranial (EC - IC) bypass may be useful in preventing recurrent TIA and promoting revascularisation in children with long-standing large vessel occlusion without collateral. Given the frequency of this pattern of vascular disease in children with ischaemic stroke, this approach merits further investigation.

1.11.3.Aspirin

Aspirin has been shown to reduce the incidence of recurrent stroke and TIA after stroke in adults by 20-50%[65,273]. Aspirin has also been shown to be effective in preventing stroke in adults with a potential cardioembolic source[46]. The dose of aspirin is controversial; different trials in adults have used doses ranging from 30mg/day to 1300mg/day.

The indications for and benefits of long term aspirin in the prophylaxis of recurrent stroke in childhood remain unclear. Solomon recommends use of aspirin in children with evidence of platelet hyperaggregability, those with angiographic arterial abnormalities and those with embolic stroke who are unable to tolerate anticoagulation. She suggests a dose of 75mg for children under 35kg and 150mg for those over 35kg[72]. In a recent textbook, Matthews suggests that children with ischaemic stroke may be given 40 to 80 mg of aspirin per day but freely admits that there is no evidence to support this recommendation[71]. Further data is needed in order to enable comparison of the risks of long term, low dose aspirin and the benefit conferred in terms of preventing recurrent stroke.

1.11.4.Warfarin

There is good evidence to support the use of long term warfarin in adults with stroke due to atrial fibrillation[27], in terms both of safety and efficacy, with an INR in the range of 1.2 to 1.5. There is a significant risk of minor haemorrhage on warfarin but significant haemorrhage is no more common on warfarin than in control patients. In children, warfarin is used in patients with cardiac lesions or arrhythmias which could predispose them to embolic events; the level, duration and efficacy of such treatment has not been formally investigated.

1.11.5. General measures

Although it is unclear whether children who have had ischaemic stroke are at increased risk of stroke in adult life, it would seem prudent to advise avoidance of known risk factors for stroke in later life. The include some "lifestyle" factors such as smoking, dietary fat intake and use of the oral contraceptive pill as well as medical risk factors such as hypertension and diabetes mellitus

Rationale for present study

Much of the previous literature on stroke in children comprises studies of relatively small numbers of patients, often with heterogeneous characteristics e.g. no distinction between ischaemic and haemorrhagic stroke (see appendix 1). Other authors have chosen to exclude specific groups of children e.g. those with cardiac abnormalities. Early studies (before CT was available) tended to include patients with acute hemiplegia and the possibility of alternative pathologies in such patients has been discussed on page 16. Finally, many previous studies have tended to be purely descriptive and have not provided clear information to guide clinical practice.

A further consideration is that although the role of many modern investigative techniques (e.g. MRI, MRA) have been explored in adults with ischaemic stroke, this has not been specifically addressed in children with ischaemic stroke. The role of invasive techniques (such as contrast cerebral angiography) has been unclear with the increasing availability of newer, non-invasive modalities (such as MRA). Furthermore, the importance of specific aetiological factors (e.g. prothrombotic states) has not been considered other than in anecdotal reports.

The present study was undertaken to investigate the characteristics of a large, unselected population of children presenting to a single institution in the modern era, using the definition of stroke given on page 14. The focus of this study was on the questions of clinical importance detailed on page 110.

Figure 1(1):Mechanisms of cell death after focal ischaemia

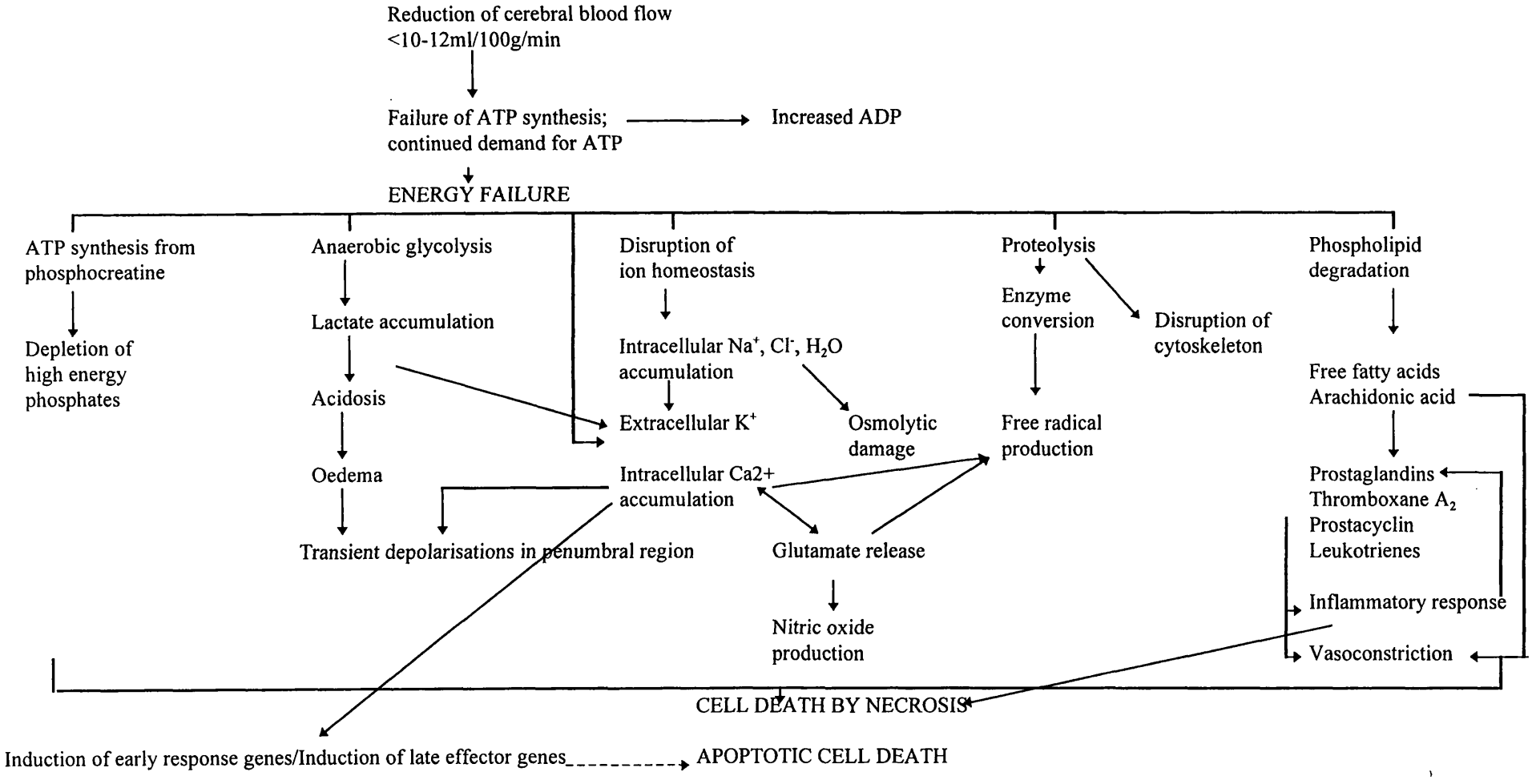


Figure1(2): Early CT scan appearances of cerebral infarction

CT scan taken within 12 hours of onset of R hemiparesis (patient 45) showing low density in the territory of the L MCA, compatible with an early infarct.

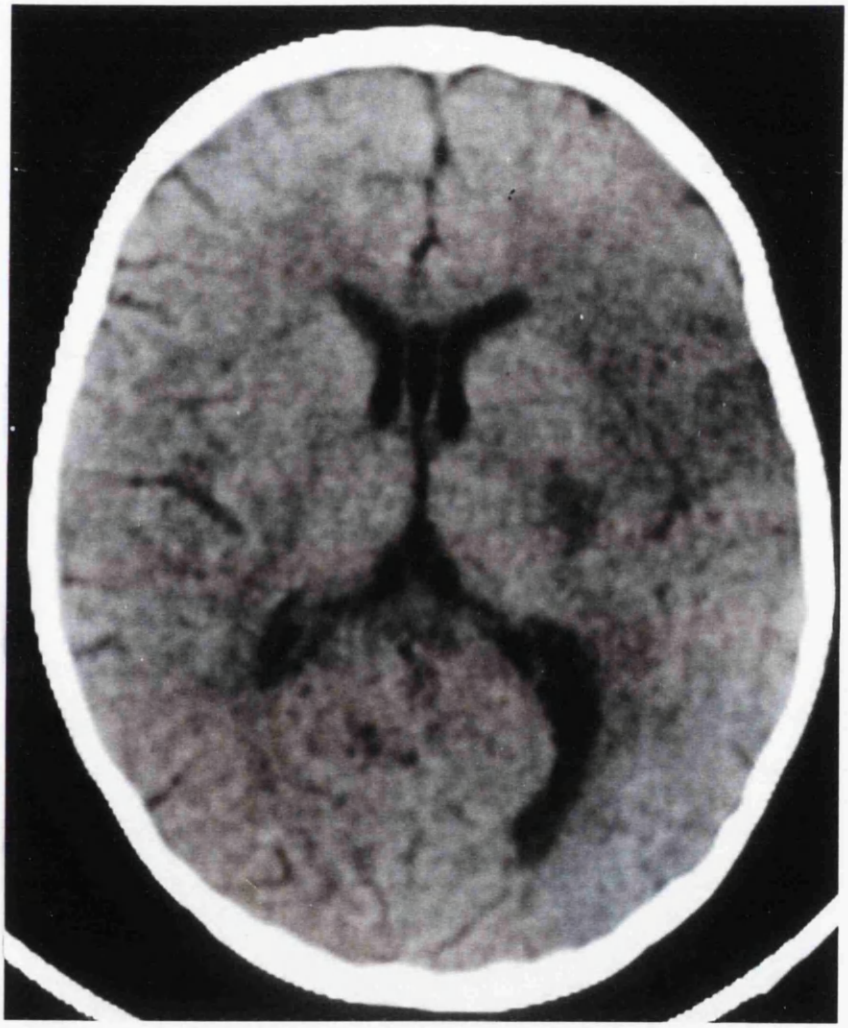


Figure 1(3): CT scan appearances of mature infarct

CT scan taken 5 days after the onset of R hemiparesis (patient 82) showing an infarct in the territory of the L MCA with some mass effect.

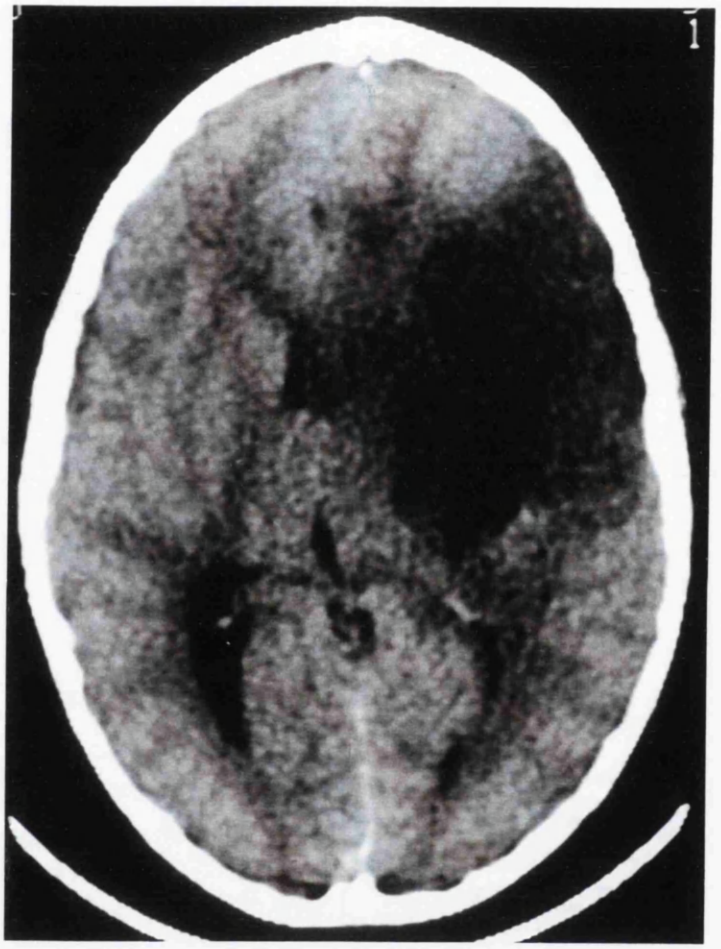
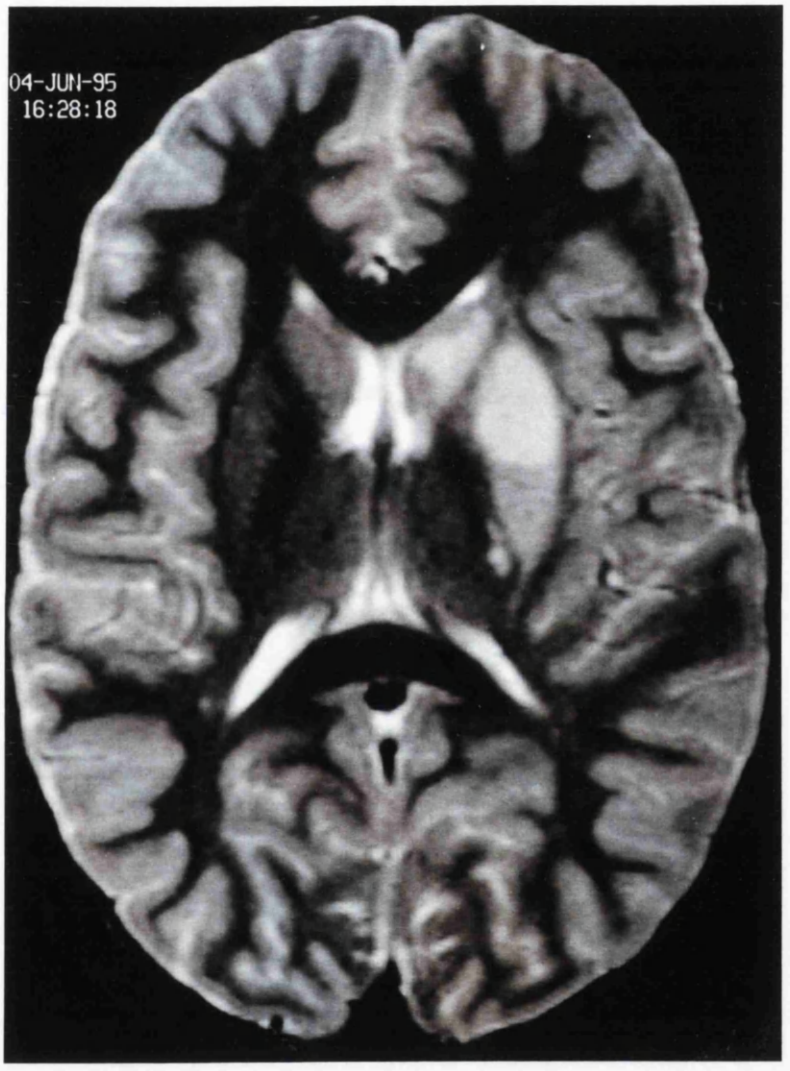


Figure1(4): Extension of MCA territory infarct (patient 82):

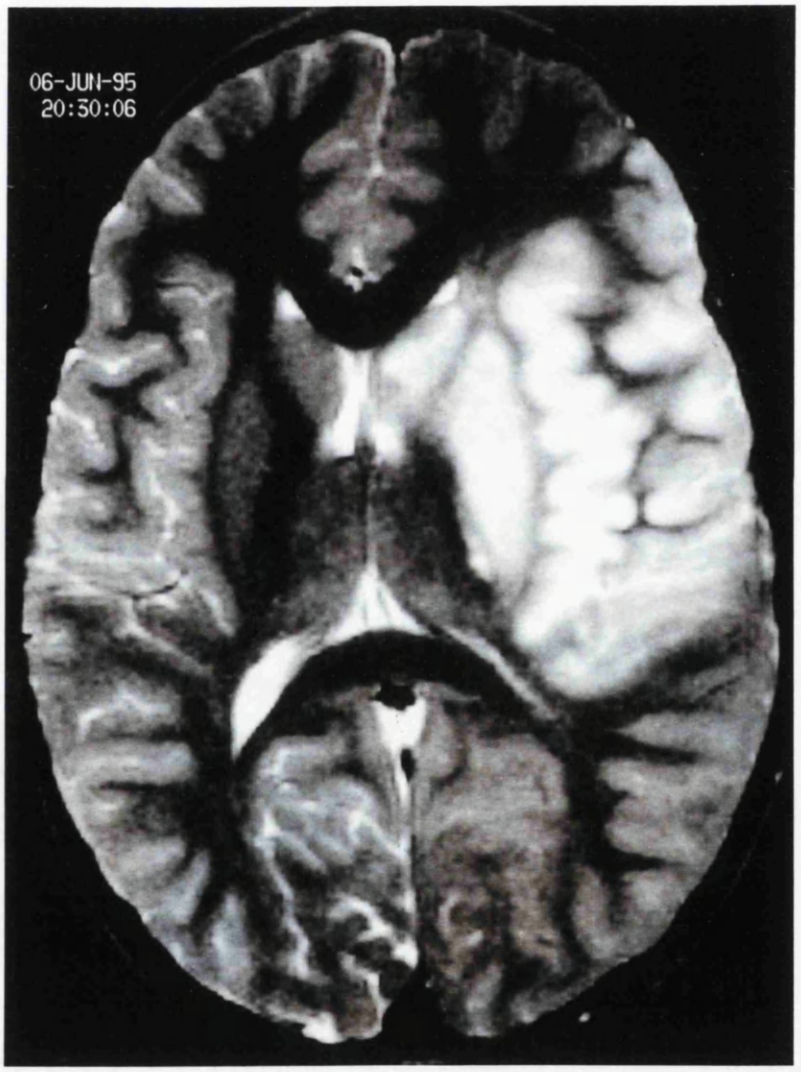
1(4(i)) Subcortical infarct

T2-weighted MRI 36 hours after onset of R hemiparesis showing high signal in L caudate and lentiform nuclei. The MRA at this time suggested stenosis of the proximal L MCA.



1(4(ii)) Extension to involve cortical tissue.

T2-weighted MRI at 4 days following clinical deterioration. This occurred the day after the patient had had a conventional cerebral arteriogram which had showed L MCA occlusion. The scan shows extension of the previous area of high signal to involve adjacent cortical tissue, with swelling and mass effect



1(4(iii)) Mature lesion.

T2-weighted MRI at 12 days showing some persistent signal change and atrophy in the territory of the L MCA.

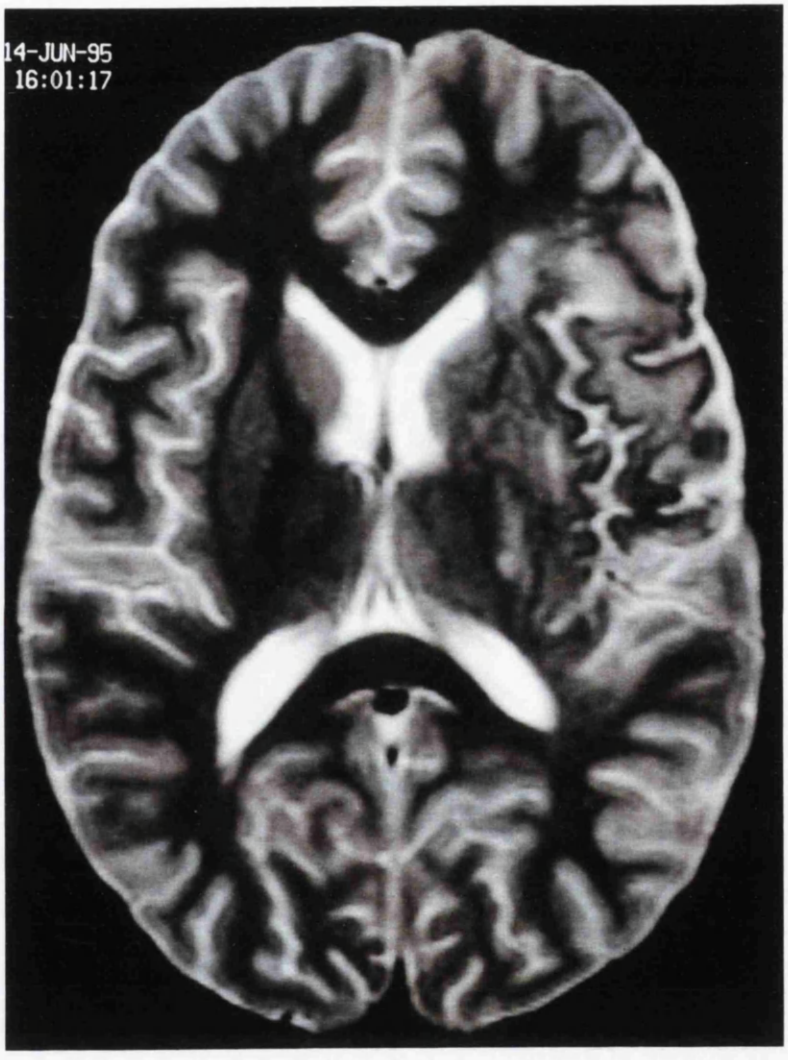


Figure1(5): "Malignant" MCA territory infarct.

T2-weighted MRI showing high signal in the territory of the L MCA and an additional area of signal change in the L posterior borderzone with mass effect and midline shift (patient 50). The patient was unconscious, with hypertension and bradycardia.

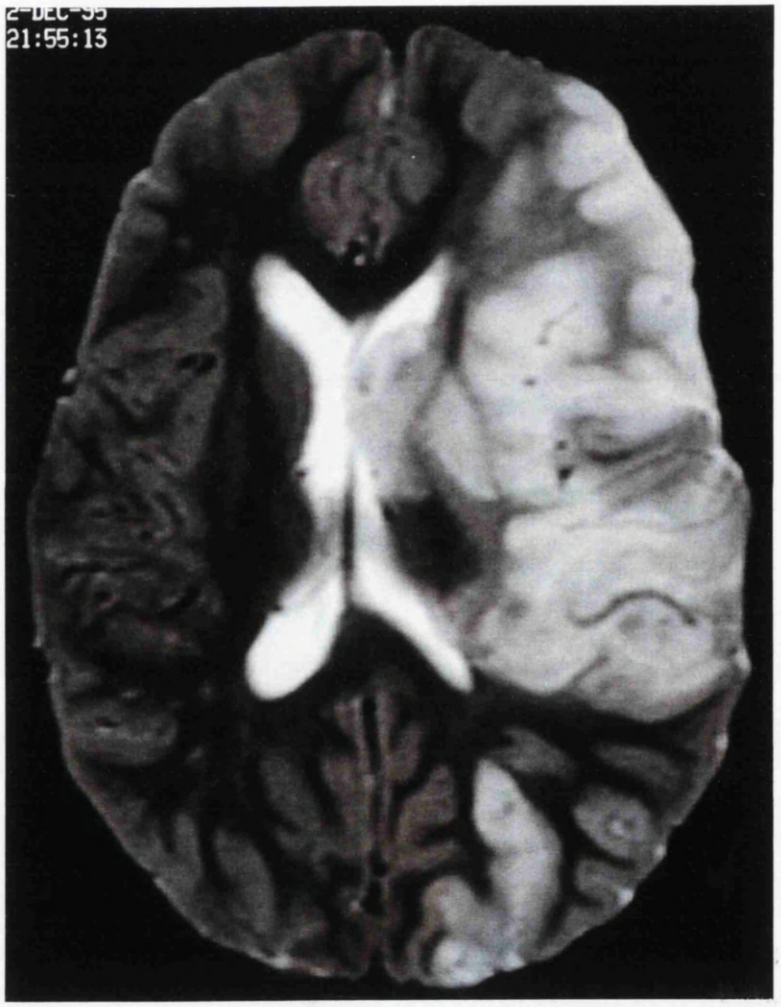


Figure1(6): Subcortical infarction.

T2-weighted MRI showing well circumscribed high signal lesion in L lentiform nucleus (patient 104).

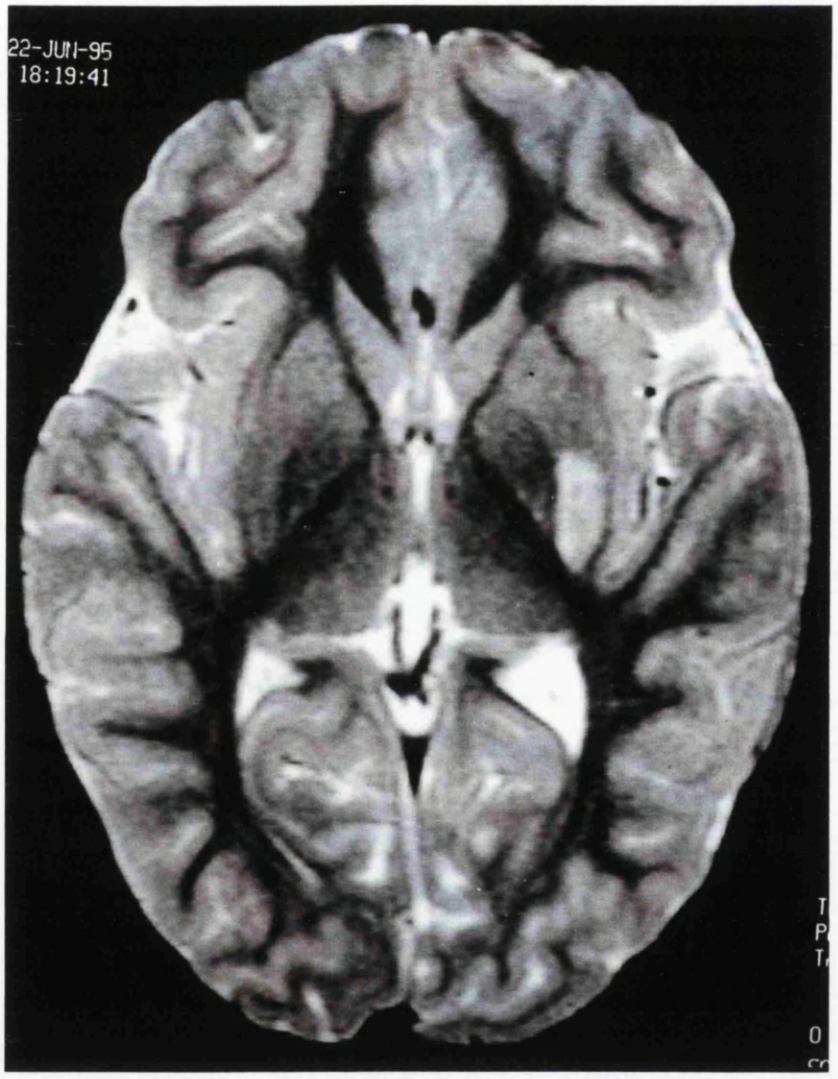


Figure 1(7): Borderzone infarction.

T2-weighted MRI showing high signal lesions in both anterior borderzones and R posterior borderzone (patient 29). The patient had a normal conventional cerebral arteriogram.

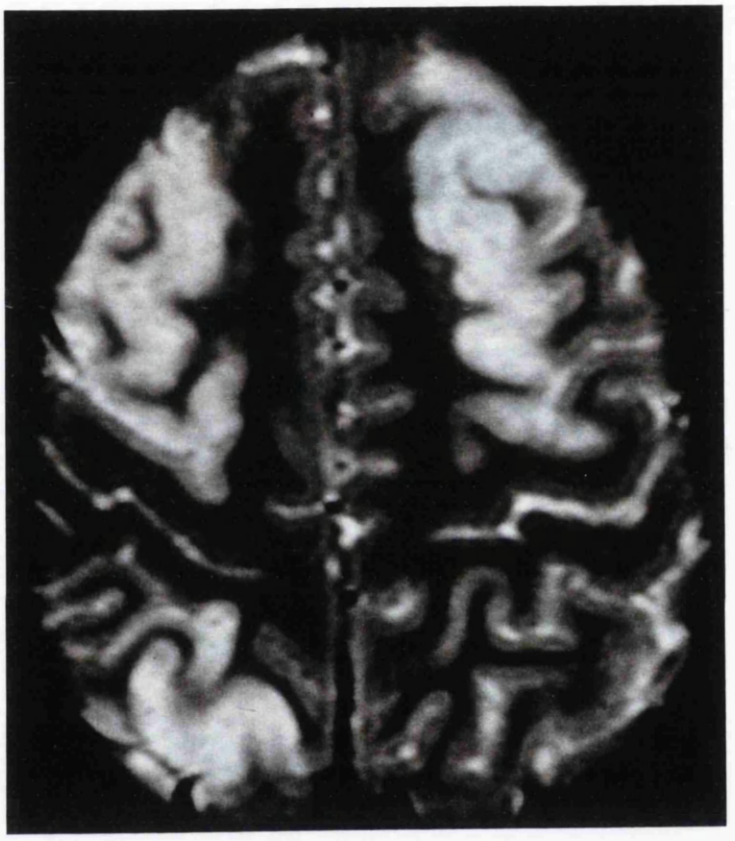


Figure1(8): Posterior circulation infarction.

T2-weighted MRI from patient 63 showing bilateral pontine lesions secondary to R VA dissection

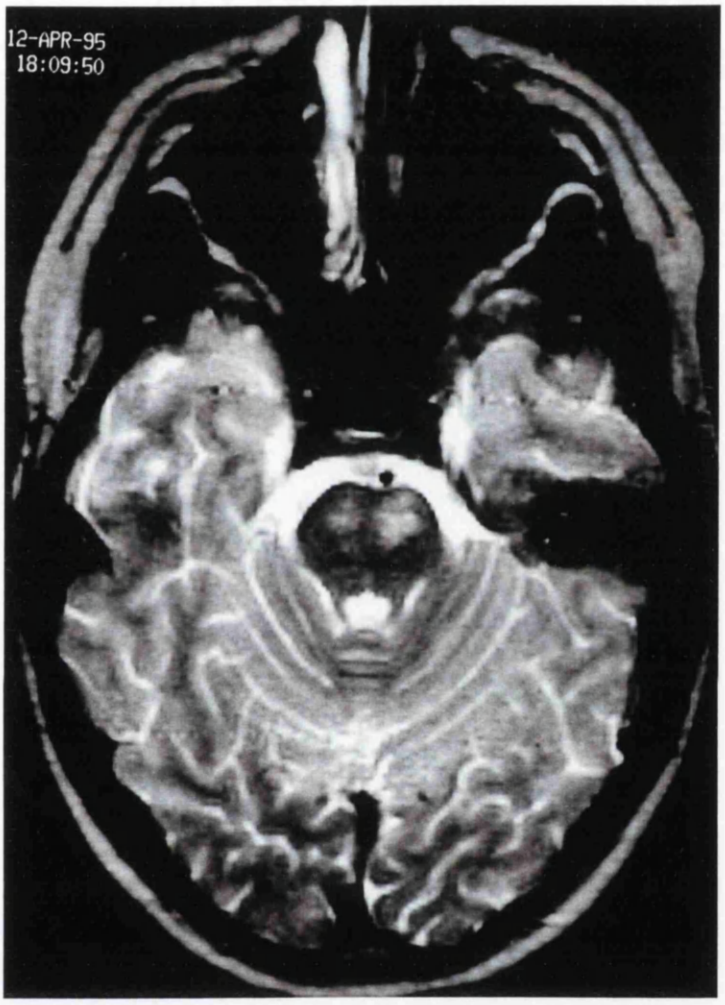
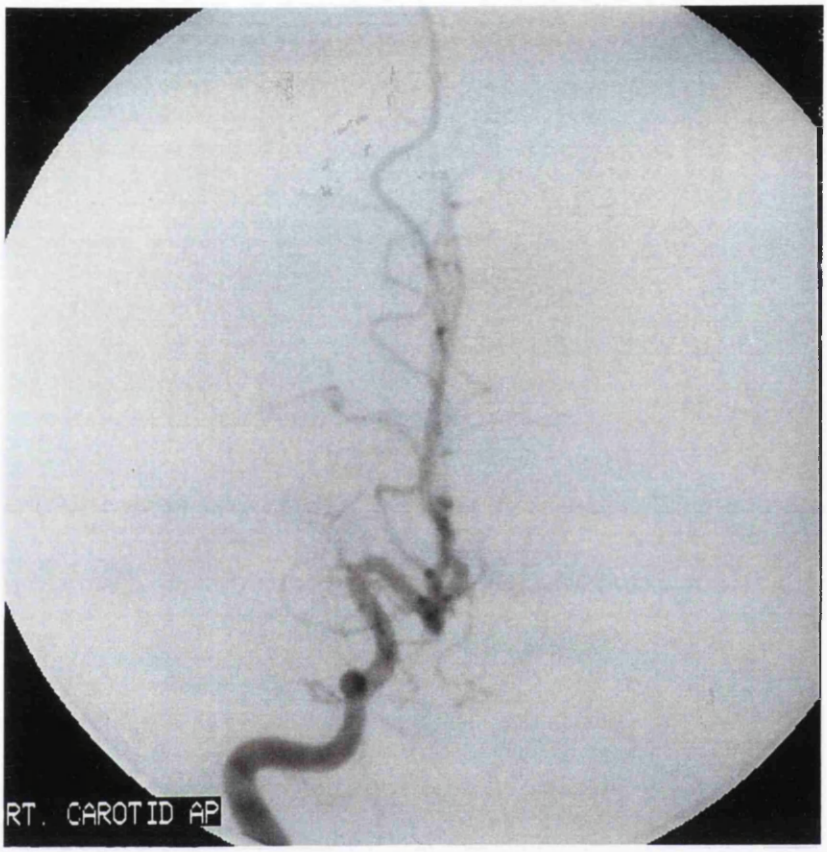


Figure 1(9): MCA occlusion

1(9(i)) Conventional cerebral arteriogram

R carotid injection showing occlusion of the proximal R MCA



1(9(ii)) MRA

3D time of flight MRA of the circle of Willis showing proximal L MCA occlusion

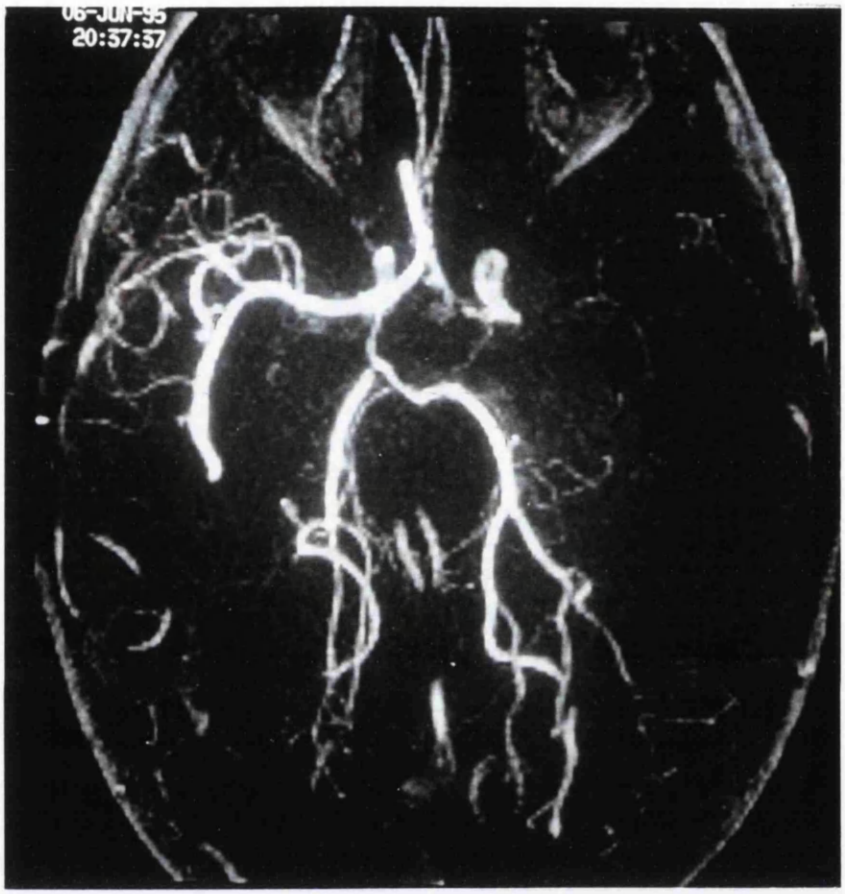
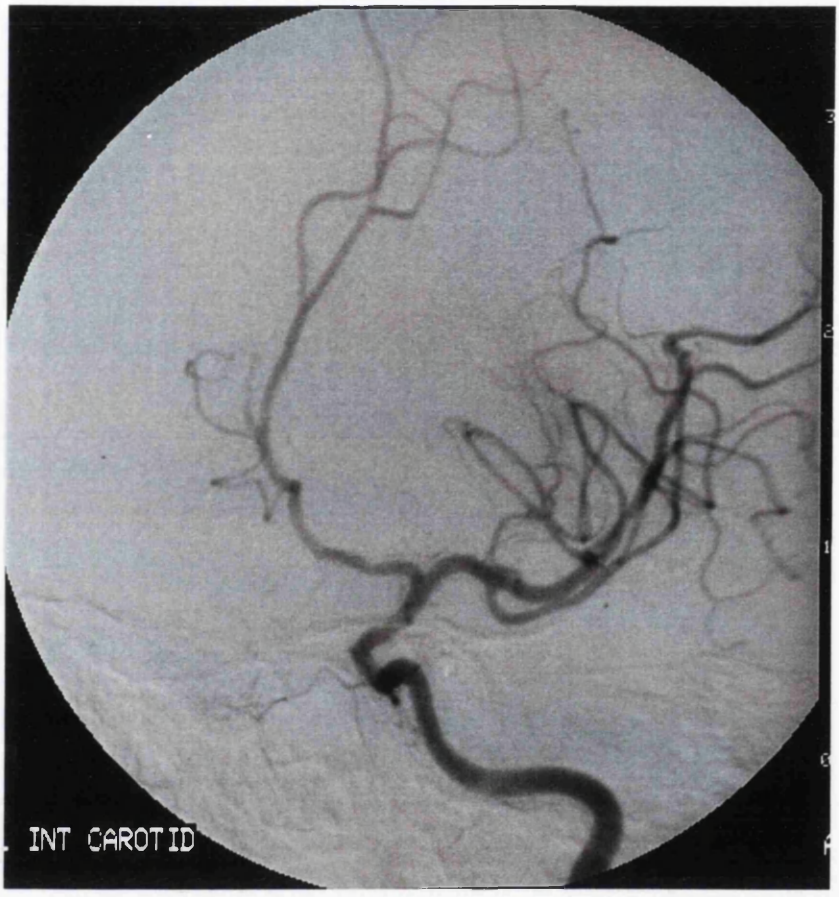


Figure 1(10): MCA stenosis

1(10(i)) Conventional cerebral arteriogram

L carotid injection showing an area of narrowing in the L MCA, just distal to its 1st major bifurcation.



1(10(ii)) MRA

3D time of flight MRA of the circle of Willis showing an area of signal drop-out in the proximal R MCA, suggestive of R MCA stenosis

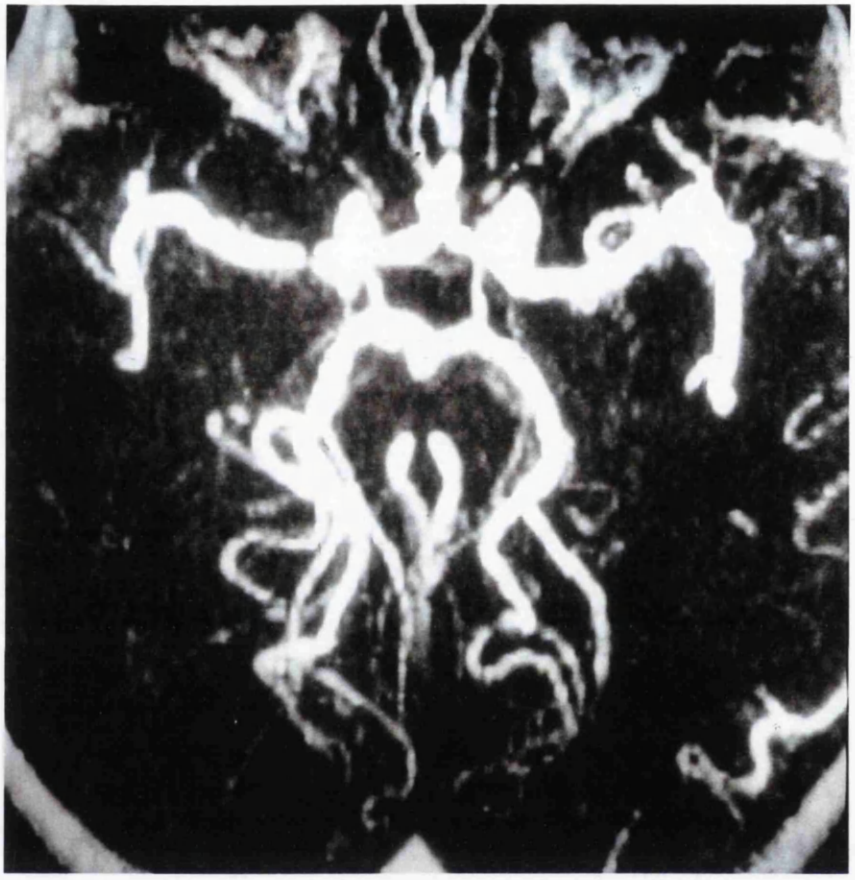
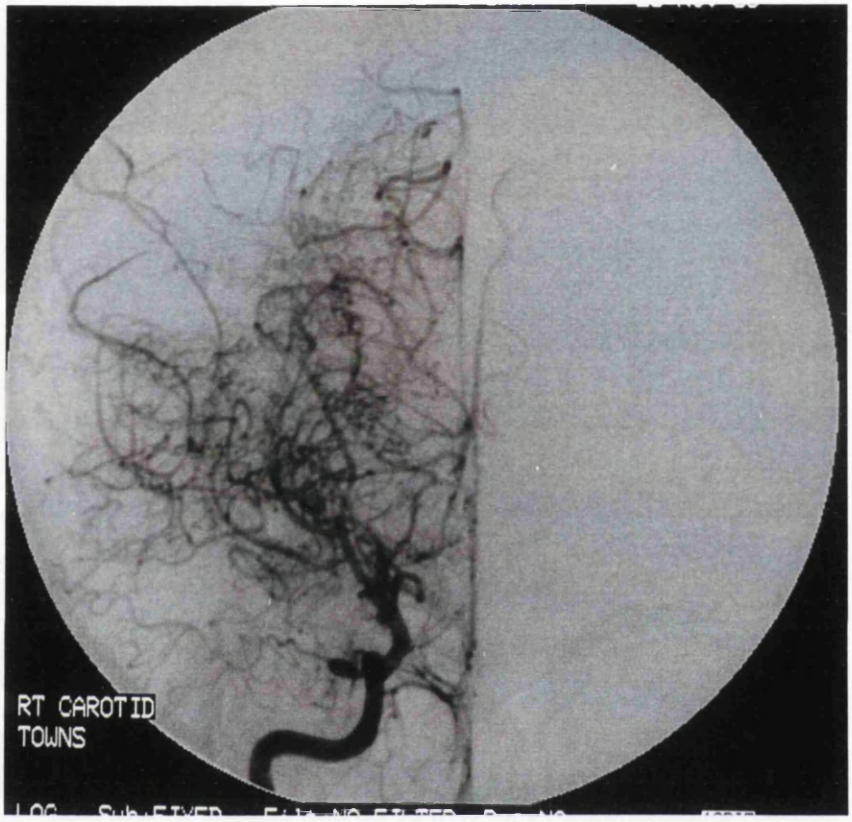


Figure 1(11): Moyamoya syndrome

1(11(i)) Conventional cerebral arteriogram

R carotid injection showing occlusion of the supraclinoid portion of the R ICA with profuse "moyamoya" collaterals



1(11(ii)) MRA

3D time of flight MRA of the circle of Willis showing bilateral terminal ICA occlusion with bilateral "moyamoya" collaterals

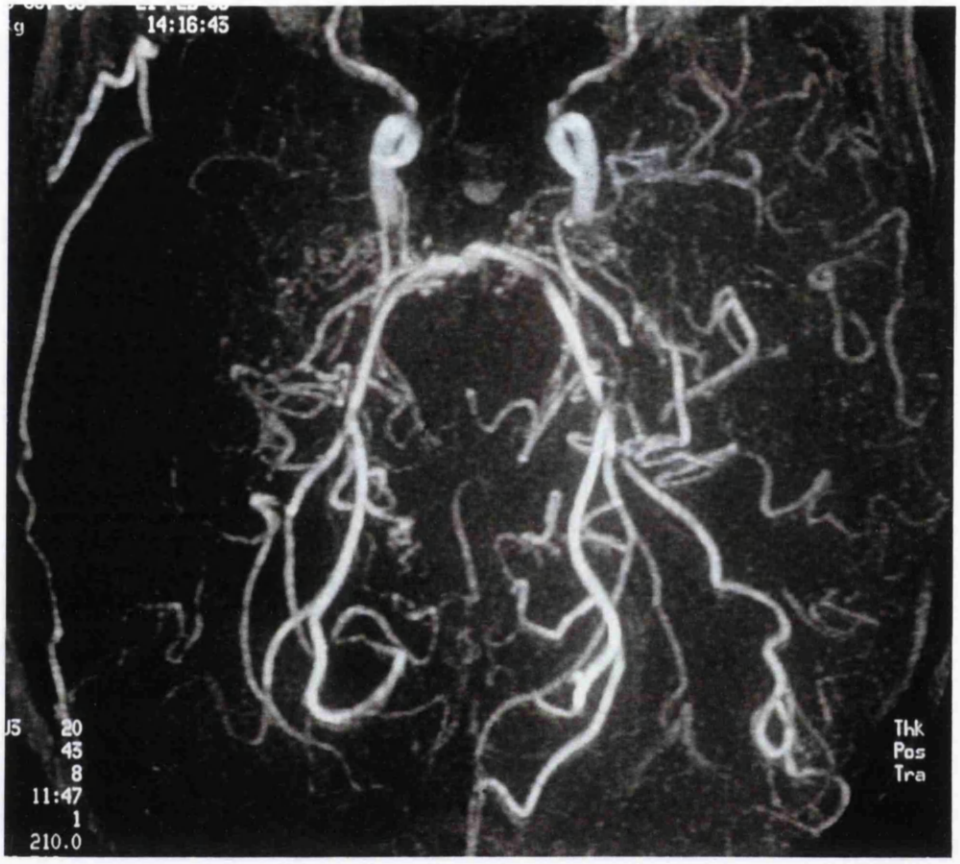


Figure 1(12): ICA dissection

Conventional cerebral arteriogram, L carotid injection showing smooth tapering of the L ICA ("string sign")

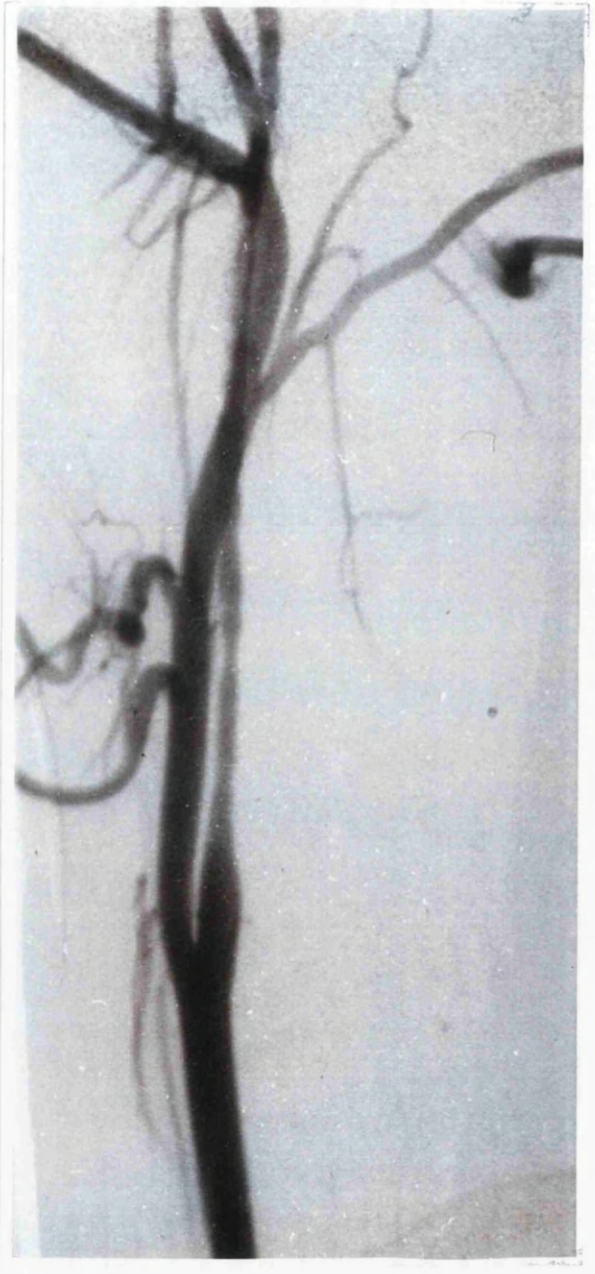


Figure 1(13): Cerebral vasculitis.

Conventional cerebral arteriogram, L ICA injection showing beading, tortuosity and narrowing of the L ICA, ACA and MCA; the child (patient) had had multiple strokes. There were no peripheral inflammatory markers; a brain biopsy was non-diagnostic. The final diagnosis was of isolated angiitis of the central nervous system.

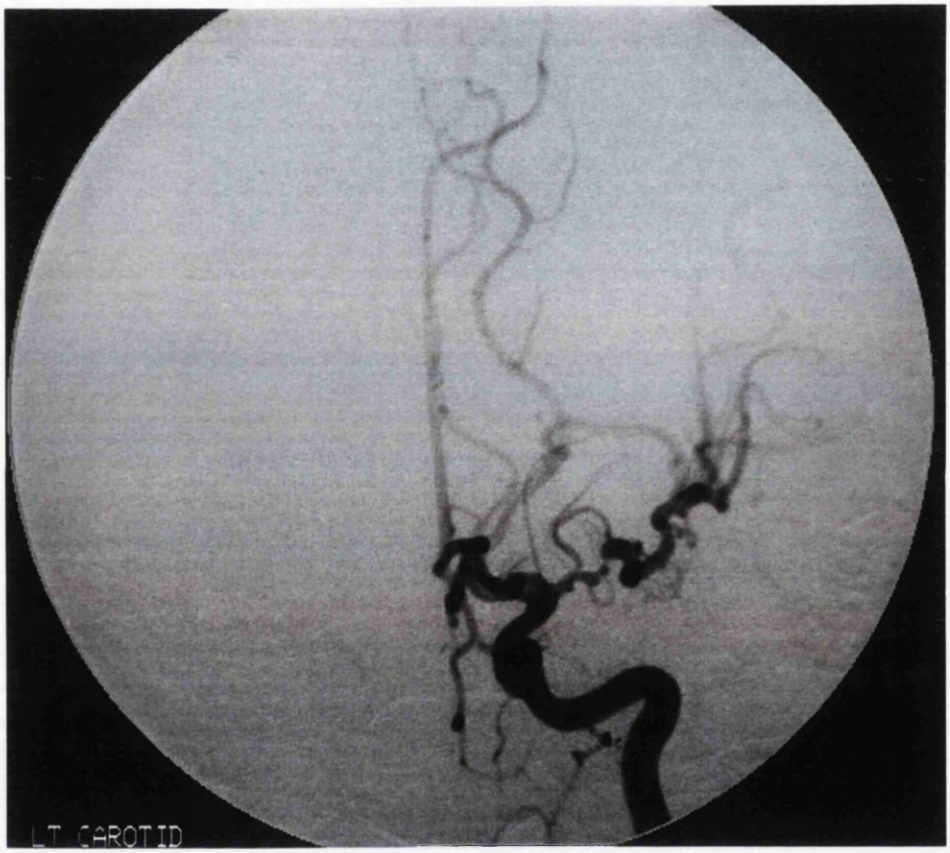
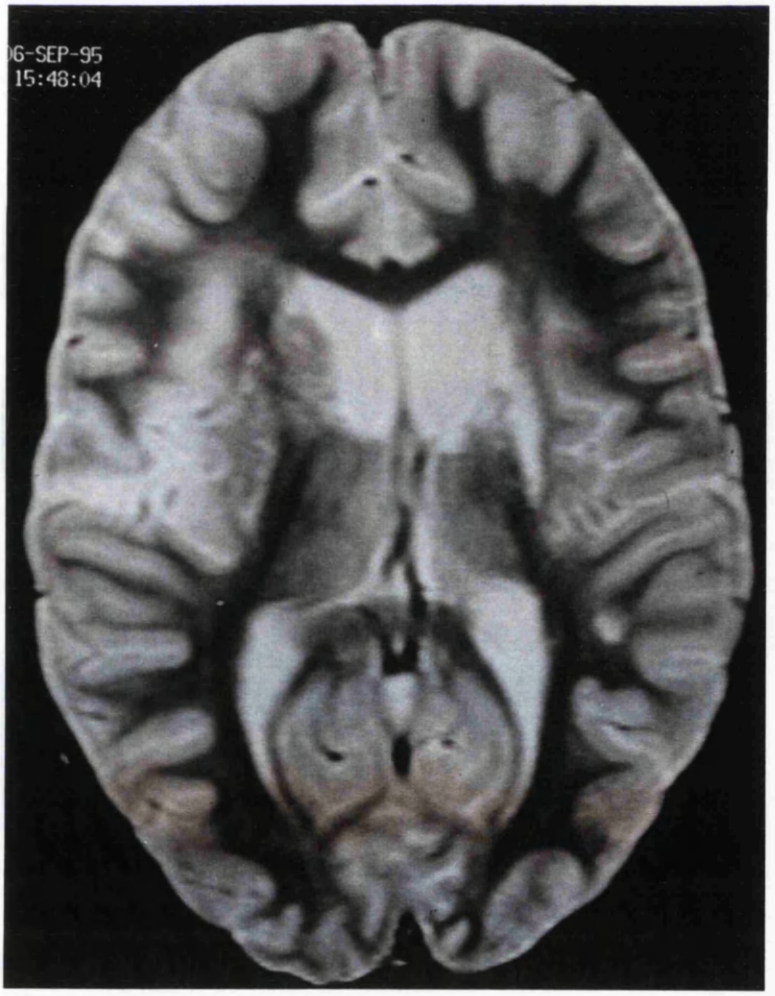


Figure 1(14): Recurrent stroke due to progressive cerebrovascular disease.

T2-weighted MRI showing taken within 24 hours after onset of L hemiparesis (patient 109). The patient had had a previous L MCA territory infarct from which she recovered well and presented with a L hemiparesis 1 year later. The scan shows an acute infarct in the territory of the R MCA and signal change and atrophy in the region of the previous L MCA territory lesion. The initial conventional arteriogram showed L ICA and MCA occlusion; conventional arteriography at this time was suggestive of cerebral vasculitis



2. Aims, patients and methods

2.1. Aims

The specific questions which this study set out to answer were:

1. What are the risk factors associated with ischaemic stroke in childhood?
2. How should ischaemic stroke in childhood be investigated?
3. Do inherited prothrombotic states cause ischaemic stroke in childhood?
4. What is the role of conventional cerebral angiography in the investigation of the child with ischaemic stroke?
5. What is the outcome after ischaemic stroke in childhood?
6. Is outcome predictable at the acute stage?
7. What are the influences of lesion volume and lesion location on outcome after ischaemic stroke in childhood?
8. What is the incidence of recurrent stroke and TIA after ischaemic stroke in childhood?

2.2. Ethical approval

The study was approved by the North Thames regional research ethics committee.

2.3. Setting

This study was conducted in the Department of Paediatric Neurology at Great Ormond Street Hospital for Children NHS Trust, London. This Unit serves as a tertiary level Paediatric Neurology centre for the North Thames region of the United Kingdom which

has a paediatric population of around 500 000. In addition, 38 patients were referred after the acute event from other regions to the paediatric stroke clinic at this institution. Some children with moyamoya syndrome were referred specifically because of the recognised interests of this unit in paediatric cerebrovascular disease.

2.4. Patients

Figure 2(1) shows the source referral of patients included in this study. The patients are numbered according to the details given in table 3(2) and the numbering is consistent throughout the text.

Full ascertainment of all cases of ischaemic stroke seen at Great Ormond Street Hospital for Children was attempted by searching the hospital discharge database for diagnostic codes ICD 434 - 437 and ICD10 codes 160 - 169 between 1990 and 1996.

All patients had had ischaemic stroke as previously defined. However, there were two children who were known to have cerebrovascular disease without cerebral infarction; one (patient 11) had moyamoya syndrome and recurrent TIA's and the other (patient 9) had an axillary artery thrombus and transient dysphasia; CT scan of the brain was carried out very shortly after the onset of the deficit. This was normal and was never repeated. One child (patient 6) had a previously asymptomatic cerebral infarction which was discovered while he was being investigated for hypertension.

Patients in whom stroke occurred within the neonatal period and those with primary haemorrhagic stroke were excluded.

The age distribution of the patients is shown in figure 2(2). The median age was 6 years. There were 74 males and 54 females.

Although all the patients were drawn from this group of 128 children, not all patients were included in every section. Each section will, therefore, briefly outline the patients included.

2.5. Methods

2.5.1. Clinical features and aetiology of ischaemic stroke (chapter 3)

The 128 children were considered in 2 groups according to whether or not they had a previously recognised condition predisposing to stroke. These groups will be referred to as "symptomatic" and "idiopathic" stroke groups, as previously defined.

2.5.1.1. Methods

The history and clinical details of the patients were recorded on a proforma and subsequently entered on to a computerised database. Blood was taken on admission and analysed by the hospital's haematology and biochemistry laboratories as described below.

Prior to 1994, patients were investigated according to the wishes of the supervising clinician. In 1994 a protocol for the investigation of children with acute ischaemic stroke

was constructed (Appendix 3[1]) and from then on it was recommended that patients were investigated according to this. No investigations were carried out specifically for the purposes of this study; rather, the aim of using this protocol was to attempt uniform and consistent investigation of all patients. In particular, MRI and MRA studies were carried out in all patients seen after 1994.

Invasive investigations such as conventional angiography and transoesophageal echocardiography were carried out for clinical indications and were requested by the consultants responsible for the care of individual patients.

2.5.1.2. Imaging studies

The patients were scanned on a 1.5T Magnetom SP4000 (Siemens, Erlangen, Germany) using a standard quadrature head coil. Turbo-spin echo T2-weighted (TE = 90ms, TR = 4600ms) or double echo short tau inversion recovery (DESTIR) (TE = 85ms, TR = 3500ms, TI = 145ms) images throughout the whole head were acquired with 5mm slice thicknesses and a 2.5mm slice gap. A ¾ field of view was used in all cases, together with matrix sizes of 135x256 for the DESTIR and 192x256 for the turbospin echo images.

Magnetic resonance angiograms were acquired using a three dimensional time-of-flight technique centred on the circle of Willis, with a short echo time (less than 8ms) and high spatial resolution (256 or 512 matrix in a field of view of between 18 and 22cm). All scans were reported by a neuroradiologist.

Contrast cerebral angiography was only carried out for clinical indications. Studies were carried out by a neuroradiologist via the femoral arterial route. The decision on the number of vessels to inject was made by the neuroradiologist carrying out the procedure.

2.5.1.3. Haematological investigations

A full blood count (haemoglobin, total and differential white cell count and platelet count) was carried out by the haematology department as part of the routine service.

Blood samples for coagulation studies were anticoagulated with 0.109 M trisodium citrate (9 parts blood, 1 part anticoagulant). They were double centrifuged to remove all residual platelet matter and aliquots of plasma were stored at -40^{0}C until analysis. The prothrombin and activated partial thromboplastin times (PT and APTT) and fibrinogen were performed by standard automated procedures at 37^{0}C and the thrombin time was obtained by manual techniques. Protein C activity was measured by an automatic amidolytic assay using protein C activator (Unicorn Diagnostics) and a chromogenic substrate (Unicorn Diagnostics). Total and free protein S antigen levels were obtained by an ELISA method performed in microtitre plates using polyethylene glycol precipitation (antibodies supplied by Dako). Antithrombin III, heparin cofactor II and plasminogen activities were determined by automated amidolytic assays (Immuno for antithrombin III, Rho for heparin cofactor II, Behring for plasminogen). Tests for the presence of a lupus anticoagulant were carried out according to published guidelines[406]. Anticardiolipin IgG and IgM were detected using an ELISA based method[407]. The APC resistance ratio was measured using the standard APTT based method (Coatest, Chromogenix, Sweden). An APC resistance ratio < 2.7 was considered abnormal. Genomic DNA was extracted from

peripheral blood leukocytes by standard procedures for detection of the factor V Leiden mutation which was performed using a modification of the original method[408].

All assays were controlled using normal control plasma (Instrumentation Laboratories) and/or standard reference plasma (Immuno) and all automated procedures were performed on the ACL 3000 research coagulometer.

2.5.1.4. Biochemical investigations

Plasma ammonia, lactate, urinary amino and organic acids, serum urea, electrolytes, creatinine, serum cholesterol, plasma triglycerides and CSF lactate were measured in the biochemistry laboratory as part of the clinical service.

2.5.1.5.Cardiac investigations

Twelve lead electrocardiograms were carried out in the cardiology department.

Conventional transthoracic echocardiography and transoesophageal echocardiography were carried out by members of the cardiology department. Transoesophageal echocardiography was only carried out in patients if they were having a general anaesthetic for another procedure, usually cerebral angiography, and if no other risk factors for ischaemic stroke were identified.

2.5.2. Inherited prothrombotic states and ischaemic stroke (chapter 4)

2.5.2.1. Investigations

All patients in this section of the study had a full blood count (which included a platelet count) and a routine screen of coagulation function (which included measurement of PT, APTT, TT and fibrinogen). Investigations were carried out as described previously in section 2.5.1.4. in order to detect the following prothrombotic tendencies:

1. Activated protein C resistance
2. Factor V Leiden mutation
3. Protein C deficiency
4. Protein S deficiency
5. Antithrombin III deficiency
6. Heparin cofactor II deficiency
7. Plasminogen deficiency
8. Presence of antiphospholipid antibodies

2.5.2.2. Timing of samples

Patients had blood taken at presentation to the unit. Where abnormalities were detected, repeat samples were obtained 1-3 months after the stroke in order to confirm that they were significant.

2.5.2.3. Normal values

As it is recognised that normal levels of the anticoagulant proteins in the blood are dependant on age, the paediatric normative ranges defined by Andrew[283]were used for reference.

2.5.2.4. Prevalence in asymptomatic population

In the case of protein C, protein S, antithrombin III, heparin cofactor II and plasminogen, the prevalence in the asymptomatic population was taken from published values[287].

In order to estimate the prevalence of the factor V Leiden mutation, 77 specimens of stored DNA from patients at the hospital who were known not to have any history of thrombosis were randomly selected. These specimens were tested anonymously in the Haematology laboratory in order to overcome the ethical problems associated with testing for a common, usually asymptomatic, abnormality. Other characteristics of the control population (e.g. ethnicity) were therefore unknown.

2.5.2.5. Statistical analysis

Fisher's exact test was used to investigate whether there was a significant difference between the prevalence of the prothrombotic states under consideration in children with ischaemic stroke and the control population.

2.5.3. The role of conventional cerebral angiography after ischaemic stroke in childhood (chapter 5)

2.5.3.1. Review of conventional cerebral arteriograms

The conventional angiograms were reviewed retrospectively on separate occasions by two neuroradiologists (WK Chong and L Savvy) who were unaware of the patients' clinical details. The results were recorded on a standardised proforma.

The images were initially inspected for evidence of any of the following abnormalities:

1. vascular occlusion
2. vessel stenosis
3. abnormal vessel tortuosity
4. variation in vessel calibre
5. filling defects

The calibre of abnormal vessels was noted and classified as small (the smallest arterioles seen before the capillary phase), medium (beyond the first division but proximal to the 3rd division of a major artery) or large (proximal to the first division of a large artery).

If possible a radiological diagnosis was given (e.g. arterial dissection, moyamoya syndrome).

2.5.3.2. Results of magnetic resonance angiography studies

All MRA studies had been reported at the time of the study by a neuroradiologist.

2.5.3.3. Comparison of the contribution to patient management of conventional versus magnetic resonance angiography

In the case of patients who had had both conventional angiography and MRA, the specific contribution of conventional angiography to the management of the patient was evaluated by case note review.

2.5.4. Outcome after ischaemic stroke (chapter 6)

2.5.4.1. Ascertainment of outcome - parental questionnaire

In order to ascertain functional outcome after ischaemic stroke in childhood, a simple questionnaire was designed (Appendix 4) to investigate whether the child experienced dependence or disability in activities of daily living at home, at school, with speech and language, behaviour and motor function. There was also a question about the child's requirement for special educational provision. Parents were asked to report if the child had epilepsy requiring anticonvulsant therapy.

The main question (question 4 - see Appendix 4), relating to whether the child required any additional assistance at home or at school, was based on similar simple questions

used to investigate outcome after stroke in adults[380], which have been shown to correlate well with objective scales of functional outcome after stroke such as the Barthel score. Most of the questions required simple "yes" or "no" answers and so the result was a qualitative rather than an quantitative measure of deficit. The only items requiring quantification were questions 5 and 6, relating to the severity of residual motor deficit in the upper and the lower limbs. In these instances, structured guidelines were given to assist with the scoring (see Appendix 4).

The responses to the questions were scored and a composite "outcome score" was calculated for each child. The "outcome score" was an ordinal rather than an interval scale; the individual scores reflected the cumulative burden of residual deficits in individual cases. A score of 0 indicated no residual sequelae and a score of 13 indicated the maximal level of deficit or disability. The patients were divided into two groups according to the "outcome score" with an arbitrary cut-off of 4. Patients with scores of 0 - 4 were categorised as having "good" outcome while those with scores of 5 or more were categorised as "poor" outcome. Such categorisation enabled examination of whether any clinical or radiological parameters were predictive of the eventual outcome.

2.5.4.2. Ascertainment of outcome - assessment by therapists/neuropsychologist

In order to validate parental report as a measure of outcome. the same questions were answered by a paediatric Occupational Therapist (A Gordon) and a paediatric Physiotherapist (N Shack) about any patients whom they had assessed. Neuropsychological evaluation was carried out by Ms A Hogan. For infants, the Bayley's Scales of Infant Development[409] was used to establish age equivalents for motor,

language, behavioural and cognitive functioning. Assessment of IQ was carried out using the Wechsler Pre-school and Primary Scale of Intelligence - Revised (WPPSI-R)[410], the Wechsler Intelligence scale for Children-3rd Edition (WISC-III)[411] or the Wechsler Adult Intelligence Scale-Revised (WAIS-R)[412], according to the chronological age of the child at the time of assessment. Wechsler Scales were administered as part of a large battery of neuropsychological tests, however, only IQ and language results were included in this analysis. Receptive and Expressive language were formally assessed using the Clinical Evaluation of Language Fundamentals-Revised (CELF-R[413], CELF-Preschool[414]). There are no common criteria between local authorities for establishing which children should have a statement of educational needs on the basis of level of IQ so for the purposes of this analysis, those children who scored below the average range (IQ equal to or lower than 79) were considered to be at risk of generalised learning difficulties. Children were also considered to have a residual language disorder if their CELF scores were greater than one standard deviation below the mean of 100 (standard score less than 85).

2.5.4.3. Statistical analysis

In order to examine the agreement between parental report and therapists' or neuropsychological assessments, Cohen's kappa (KC) was calculated. The accepted guidelines for the interpretation of kappa statistics are that 0 - 0.2 implies poor agreement, 0.21 - 0.4 fair agreement, 0.41 - 0.6 moderate agreement, 0.61 - 0.8 good agreement and 0.81 or more very good agreement[415].

A logistic regression analysis was used to examine the independent effects of age at time of stroke, time since stroke, previously recognised risk factor for stroke (present or

absent), seizures during the acute presentation (present or absent) and infarct location (cortical or subcortical and unilateral or bilateral) on outcome (good or poor). The analysis was performed using both forward and backward stepwise (Wald) methods, with $p<0.1$ as a criterion for removal of variables from the model. The backward method yielded the better fit and therefore the results reported here relate to this method of analysis. The required two-tailed significance value was set at 0.05.

2.5.5. Lesion volume, lesion location and outcome after middle cerebral artery territory infarction (Chapter 7)

2.6.5.1. MRI studies

The patients were scanned on a 1.5T Magnetom SP4000 (Siemens, Erlangen, Germany) using the imaging parameters described in section 2.5.1.3.

2.5.5.2. Measurement of infarct and intracranial volumes

Axial T2-weighted MR images were imported to a SUN workstation. Infarct volume was measured by drawing a region of interest around the area judged to be abnormal on the T2-weighted images using the image analysis package Xdispim[416]. Infarcted tissue was defined as tissue having abnormal high signal on T2-weighted images.

The variation of brain volume with age had to be taken into consideration when comparing lesion volumes between patients of different ages. Lesion volumes were

therefore expressed as a percentage of supratentorial intracranial volume (ICV) (including the supratentorial CSF). ICV was measured by drawing a region of interest was drawn around the whole brain, using the method described above, on serial axial T2-weighted images acquired at the highest level of the brain down to the level of the midbrain.

Measurements of area were corrected for the size of the field of view and matrix size. The areas obtained on each slice were multiplied by the slice thickness and summated to give values for lesion or intracranial volume. Finally, the lesion volume was expressed as a percentage of the supratentorial intracranial volume (%ICV infarcted).

The reproducibility of this method of measurement was investigated by comparing lesion volume and intracranial volume measurements determined on two separate occasions by two independent observers. The mean percent difference and 95% confidence intervals were calculated within and between observers for the measurements of intracranial volume and infarct volume.

2.5.5.3. Infarct volume and infarct size category

Infarct size was expressed as a percentage of the ICV i.e. as %ICV infarcted. Lesions were assigned into 1 of three categories called "large" , "medium" and "small" . Definition of these categories was based on the 33rd and 67th percentiles for the mean values of infarct volume (%ICV infarcted) for the whole group.

In the case of the 4 patients with bilateral infarcts, the total infarct volumes for both hemispheres was summated in order to compare reproducibility between the 2 observers.

These patients were not, however, included in the statistical analysis examining the relationship between lesion volume and outcome as the small numbers of patients in this group meant that the effects of bilateral lesions could not be examined separately.

2.5.5.4. Infarct location

In order to investigate whether cortical involvement was an important determinant of outcome in this group of patients, the lesions were divided into those which involved cortical structures and those which were confined to subcortical structures. "Cortex" referred solely to the superficial grey matter; subcortical structures were taken to include the subcortical white matter and deep grey matter. Although this categorisation was crude, subdivision of patients into more specific clinico-pathological groups was not possible due to the small number of patients in the study.

2.5.5.5. Outcome

Outcome was determined by parental questionnaire as described in previously in section 2.5.4. In the case of parents who did not respond, the questionnaire was filled out either at a clinic visit or from case note review. Outcome was considered in terms of the "outcome score" calculated form the responses to the parental questionnaire. Patients were divided into "good" and "poor" outcome groups according to the criteria described in section 2.5.4.1. Patients who died as a direct result of the stroke were included in the "poor" outcome group.

2.5.5.6. Statistical analysis

A logistic regression analysis was used to examine the independent contributions of infarct size (small, medium or large), infarct location (cortical or subcortical), previous risk factor for stroke (present or absent) and age at the time of stroke on outcome (good or poor). The analysis was performed using both forward and backward stepwise (Wald) methods, with $p<0.1$ as a criterion for removal of variables from the model. The backward method yielded the better fit and therefore the results reported here relate to this method of analysis. The required two-tailed significance value was set at 0.05. In view of the findings reported by Saunders[417] of a relationship between lesion volume and outcome in adults with cortical MCA territory infarcts, a separate analysis was performed for this subgroup using similar methods.

2.5.6. Recurrence after ischaemic stroke in childhood (chapter 8)

2.5.6.1. Ascertainment of recurrent events

Recurrent events were considered as recurrent stroke (acute focal neurological deficit lasting for more than 24 hours with evidence of cerebral infarction on brain imaging) or TIA (acute focal neurological deficit resolving within 24 hours). Patients with TIA were not imaged after the event and therefore it was not known whether any of them had had recurrent cerebral infarction. The incidence of recurrent events was ascertained directly from the clinical history or from case note review. In addition, as part of the questionnaire described in section 2.5.4., parents were asked to report whether or not their child had had any recurrent events (see Appendix 4) Reports of recurrent neurological symptoms were

only categorised as recurrent stroke or TIA if this could be directly confirmed by a clinician or by case note review.

2.5.6.2. Statistical analysis

The cumulative survival probabilities and 95% confidence limits of being free from either recurrent stroke or TIA and for being free from recurrent stroke were calculated using life tables. These values were used to construct survival curves.

The cumulative survival probabilities of being free from recurrent stroke or TIA and specifically for being free from recurrent stroke were also calculated according to whether patients had "symptomatic" or "idiopathic" stroke and according to previously identified risk factors for stroke using similar methods. Survival curves were constructed for all these analyses.

Biases encountered in sample population

The population studied here has several inherent biases which should be considered when interpreting the results. Firstly, any hospital based sample is susceptible to sampling bias. Secondly, due to the nature of referral patterns to Great Ormond Street Hospital as a whole (which functions both as a tertiary and supra-regional referral centre for children), there is likely to have been a higher level of co-morbidity in the patients reported here than in the general population of children with ischaemic stroke. Finally, the Paediatric Neurology unit at Great Ormond Street Hospital, has had a long-standing interest in paediatric moyamoya syndrome and a number of patients with this syndrome were referred to the unit specifically for this reason. These factors are particularly relevant in considering the data relating to outcome and recurrence.

Other possible sources of bias also relate to local referral patterns. As stated on page 139, children with "metabolic" stroke were usually managed by another department within the hospital. Children with sickle cell anaemia were predominantly cared for by Paediatric Haematologists and were referred usually after they had had a definite acute stroke. It is therefore possible that children with sickle cell anaemia who had minor strokes were not referred to the Paediatric Neurology Department.

This study focused on ischaemic stroke, rather than including children with haemorrhagic stroke, for two reasons. Firstly, this was done to try and improve homogeneity in the patient population. Secondly, children with haemorrhagic stroke usually presented to the Paediatric Neurosurgeons.

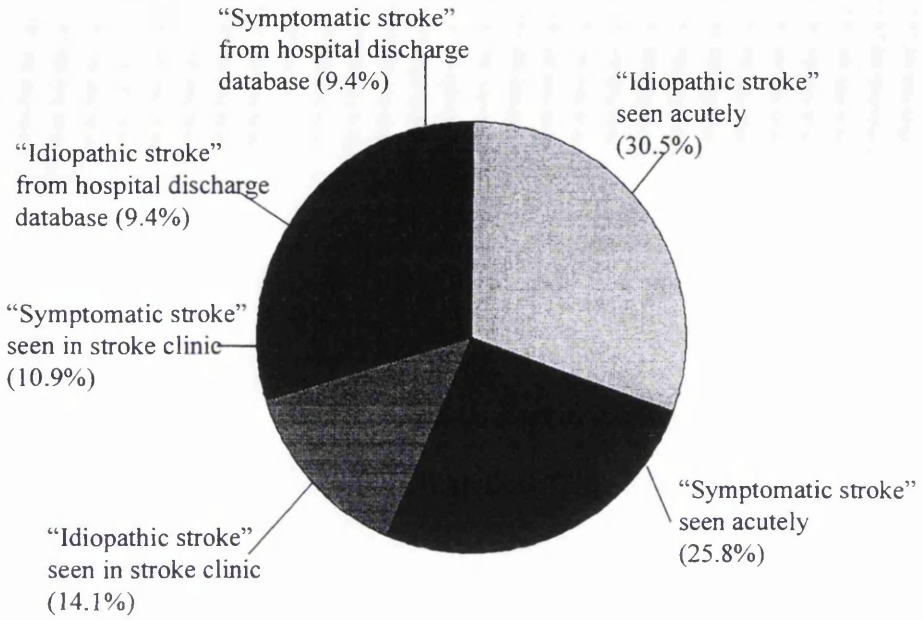


Figure 2(1) Source of referral of patients included in study

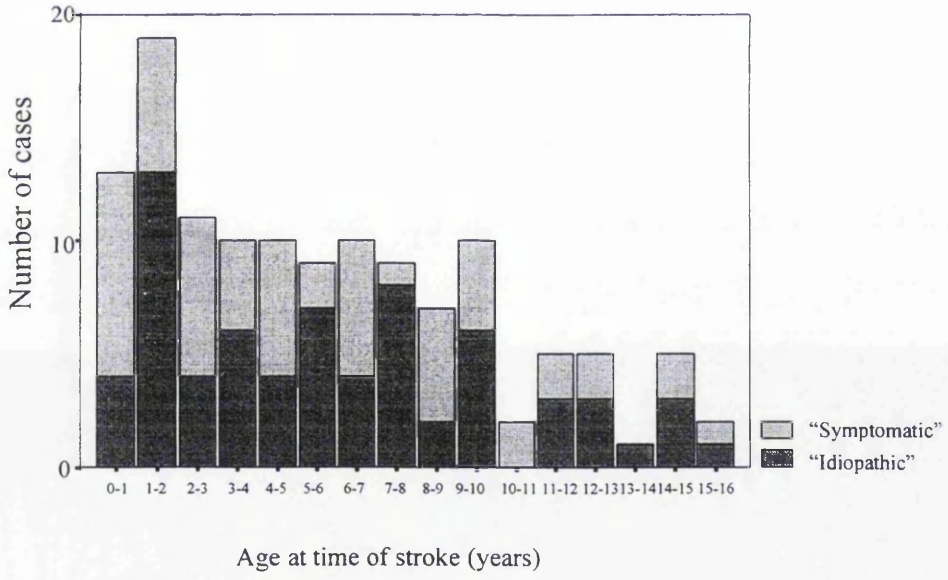


Figure 2(2) Age distribution of patients

Ascertainment and recruitment of patients

The patients were identified and recruited by the candidate during 1995 and 1996. As detailed in figure 2(1), 19% of the patients were identified retrospectively, from lists kept within the unit (dating back to 1990) and by searching the hospital discharge database by discharge diagnostic code.

The majority of the patients were identified prospectively, either at presentation (56%) or at their first visit to the paediatric stroke clinic (25%). Patients presenting acutely were under the care of the duty Paediatric Neurologist at Great Ormond Street Hospital. The candidate was contacted by the clinical team and informed of the patient's admission. The patient was seen by the candidate during the acute admission. Data regarding presentation and aetiology were collected by the candidate at this time, supplemented by case note review and review of laboratory and radiological results. Patients presenting for the first time to the Paediatric Stroke clinic were seen by the candidate and the relevant data collected at that time.

3. Clinical characteristics and aetiology of ischaemic stroke

3.1. Patients

All the patients (n = 128) were included in this section. Fifty-nine children (46%) were known to have medical conditions predisposing to stroke and will be referred to as the "symptomatic stroke" group. Table 3(1) summarises the previous diagnoses in these patients. Sixty-nine children (54%) were previously well and will be referred to as the "idiopathic stroke" group. Possible associations with stroke were noted in 19 children in this group; these were chickenpox within the preceding 6 months in 8 cases, mild cranio-cervical trauma in 6 cases and a preceding febrile illness in 11 cases. The patient characteristics including clinical presentation, infarct location, vascular and non-vascular risk factors for ischaemic stroke are summarised in table 3(2).

3.2. Clinical presentation

One hundred and twenty children (79%) presented with acute focal deficits lasting for more than 24 hours (clinical stroke), while the remainder presented with transient ischaemic attacks (TIA). Fifty-two children (41%) had seizures at acute presentation.

One hundred and one children presented with hemiparesis. This affected the right side in 47 cases. Of the rest, 4 presented with cerebellar signs, 9 presented with bilateral pyramidal signs, 5 with seizures only and 4 presented in coma. Five children had unusual presentations; 1 presented with recurrent attacks of transient visual loss, 1 with chorea, 1

with recurrent transient hemiparesis affecting either side, 1 with dysphasia and a cold, pulseless arm. One child (patient 6) was found to have had an asymptomatic cerebral infarct while being investigated for hypertension.

3.3. Investigations

All the patients had neuro-imaging. Ninety-six children were imaged with MRI of whom 22 had also had CT. Thirty children had CT only. All but two of the patients had evidence of cerebral infarction; the exceptions were patients 9 and 11 who were discussed in section 2.4.

One hundred and seven patients (85%) had imaging of the cerebral circulation. This was with MRA in 92 cases and conventional cerebral angiography in 69; 54 children had both investigations (see table 3(3)).

3.4. Distribution of ischaemic lesions

The distribution of ischaemic lesions is summarised in figure 3(1). Forty-two children had infarcts involving the right side of the brain, 44 had left sided infarcts and 40 children had bilateral lesions. One hundred and twenty one children had lesions in an arterial distribution. Sixty-two children had lesions in the territory of the MCA, 6 in the territory of the ICA, 2 in the territory of the ACA, 3 confined to the internal borderzone in the subcortical white matter and 16 in the distribution of the posterior circulation.

Twenty-four children had bilateral lesions in the distribution of the anterior cerebral circulation. Eight children had lesions in the distribution of both anterior and posterior circulations. Fifteen of the children with multiple lesions had moyamoya syndrome.

Seventy patients had lesions which involved cortical tissue. The patients with lesions in a single vascular territory were further subdivided according to lesion topography as described in section 1.7. Of the 62 children with MCA territory lesions, 26 children had infarcted the whole territory supplied by the MCA, 4 had purely cortical lesions while 32 children had purely subcortical lesions. All the children with ICA and ACA territory lesions had involvement of cortical and subcortical structures. Of the 16 children with posterior circulation lesions, 11 had involvement of the occipital cortex while the remainder had lesions confined to the brainstem or cerebellum.

Five children had cerebral infarction secondary to cerebral venous thrombosis. This was cerebral venous sinus thrombosis in 2 cases and cortical venous thrombosis in the remainder.

3.5. Cerebrovascular abnormalities

Table 3(3) summarises the cerebrovascular abnormalities detected.

Of the 107 children who had cerebrovascular imaging, 91 (85%) had abnormalities. Seventy-two of the 92 children (78%) who had MRA had abnormal studies while 59 of the 69 conventional angiograms (85%) were abnormal.

It is apparent from table 3(3) that the prevalence of cerebrovascular abnormalities not significantly different in the "symptomatic" and "idiopathic" stroke groups (68% and 75%, χ^2, $p = 0.34$). However, the "idiopathic stroke" group were more likely to have had cerebrovascular imaging and particularly cerebral angiography.

A similar range of abnormalities was present in both groups and mainly involved large cerebral vessels. It is of note that 8 children without previous risk factors for stroke had evidence of arterial dissection on vascular imaging. Five of the 6 children with preceding cranio-cervical trauma fell into this group. The prevalence of moyamoya syndrome was similar in both groups; this may partly reflect the referral pattern of patients included in this study (see section 2.4.).

3.6. Non-vascular risk factors for stroke

Table 3(4) summarises the investigations for non-vascular risk factors; table 3(5) summarises the non-vascular abnormalities identified in these patients. Despite the institution of a protocol for investigation (see Appendix 3), many children were not investigated for non-vascular risk factors. Non-vascular abnormalities were identified in 40 patients, 21 in the "idiopathic stroke" group and 19 in the "symptomatic stroke" group.

Cardiac risk factors

One hundred and twenty of the children were investigated with transthoracic echocardiography. Eighteen children in the "idiopathic stroke" group had

transoesophageal echocardiography. Apart from the 25 children already known to have cardiac disease, abnormalities were detected on transthoracic echocardiography in 3 cases; these were PFO in 2 cases, and a cardiomyopathy the final case. Of the children who had transoesophageal echocardiography, 17 studies were normal while 1 child had evidence of a secundum ASD.

Of the 25 children known to have cardiac disease, 20 had cerebrovascular imaging and abnormalities were found in 18 cases. These included large vessel occlusion and stenosis, moyamoya syndrome and arterial dissection. Cerebrovascular abnormalities were also observed in the 4 children with previously undetected cardiac abnormalities.

All of the 25 children known to have cardiac abnormalities had transthoracic echocardiography when they presented acutely with stroke. Intracardiac thrombus was apparent in 5 children (20%).

Prothrombotic abnormalities

Sixty percent of the patients were investigated for the presence of a prothrombotic tendency. These investigations are reported in detail in chapter 4. Of the 10 children with previously unrecognised prothrombotic tendencies, 7 were heterozygous for the factor V Leiden mutation, 1 had activated protein C resistance without the factor V Leiden mutation, 1 had type 1 protein S deficiency, and 1 child had acute thrombocytosis in the context of pneumococcal meningitis.

Lipid abnormalities

Twenty-seven percent of the patients had measurement of random serum cholesterol and plasma triglycerides during the acute admission. Patient 35, who had APC resistance and previous craniopharyngioma, also had familial hypercholesterolaemia with high fasting levels of total and LDL cholesterol and high plasma triglycerides. There was a strong family history of both abnormalities; her father and brother had APC resistance and her mother had familial hypercholesterolaemia. Despite having recurrent strokes, her conventional cerebral arteriogram was normal. Patient 123 had high fasting levels of plasma triglycerides on 3 separate occasions; the most recent measurement was some years after the stroke. There was no family history. He did not have a cerebrovascular imaging study.

Patient 65 who had high random plasma triglycerides at the time of the stroke had VA dissection. Patient 127, who had high random serum cholesterol and plasma triglycerides at the time of the stroke had had recent chickenpox; he did not have a vascular imaging study. Neither of these two patients had repeat measurements after the stroke.

Infection

Twenty-five children had evidence of an infective illness prior to the stroke. Two children with haemolytic uraemic syndrome secondary to infection with *Escherischia Coli* 0157, a child with facial *Herpes zoster* infection and a child with sickle cell anaemia and a facial abscess were included in this group. One child with otherwise unexplained stroke had high titres of anti-*mycoplasma pneumoniae* IgM, suggesting recent infection. Four

children had meningitis at the time of the stroke; another 2 had recovered from meningitis at least 1 year before the stroke. Of the remaining children, one had a diarrhoeal illness (patient 65), one had pneumonia (patient 4) and a third had had otitis media (patient 83). The remaining patients in this group had febrile illnesses with no clinical focus.

Fourteen children had had chickenpox within 6 months of the stroke; one of them (patient 56) had a stroke during the acute illness which was complicated by *purpura fulminans*. Six of the fourteen children (including patient 56) were in the "symptomatic stroke" group. The previous diagnoses in the other patients were cardiac abnormalities in 2 cases, previous cranial irradiation in 1 case, acute tuberculous meningitis in 1 case and a facial naevus in the remaining case. Cerebrovascular abnormalities were detected in all 9 children who had cerebrovascular imaging. Three of the 9 children (patients 56, 104 and 127) who were investigated for a possible prothrombotic tendency had transient abnormalities which resolved in all cases.

Frequency of non-vascular risk factors

As the investigations for non-vascular risk factors were not consistently carried out in the entire population, it is difficult to comment on the relative frequency of these in the "symptomatic" and "idiopathic" stroke groups. A further inconsistency is that the risk factors for which patients were investigated varied over the period of the study as new potential risk factors (e.g. the factor V Leiden mutation) were described. However, from the available data it is apparent that inherited prothrombotic tendencies and asymptomatic cardiac disease were detected in both the "idiopathic" and "symptomatic" stroke groups. In contrast, investigation for metabolic abnormalities predisposing to stroke was

unrewarding in both groups. Although lipid abnormalities were identified in 4 patients, they were only definite in 2 cases. Antecedent cranio-cervical trauma was more frequent in the "idiopathic" stroke group. The frequency of preceding infection, including chickenpox, was similar in both groups.

3.7. Unexplained stroke

Unexplained stroke was defined as stroke in patients with no identified cerebrovascular or non-vascular abnormalities. Clearly, none of the patients who were in the "symptomatic stroke" group fell into this category. Of the "idiopathic stroke" group, only 8 children had ischaemic stroke with apparently normal cerebral vessels and no identified non-vascular risk factors.

3.8. Discussion

As previously discussed, the early studies of ischaemic stroke considered the clinical syndrome of "acute infantile hemiparesis"[6,7,9,10,153]. This term serves to emphasise some of the important clinical features of ischaemic stroke in children i.e. that pre-school children are commonly affected and that acute hemiparesis is a common presenting clinical syndrome. Both these observations have been supported by subsequent studies of children with radiologically confirmed ischaemic stroke[70,75] and by the present study. It is clear from the patients studied here however, that the age distribution encompasses all the childhood years and the spectrum of clinical deficits is very wide.

One striking finding was that many children had lesions in several vascular territories. This was usually due to bilateral cerebrovascular disease, with or without collateral but was also observed in some children with demonstrably normal vessels (e.g. patient 29). All but one child, however, had a recognised risk factor for stroke (either cardiac disease or sickle cell anaemia) and this, together with the lesion distribution, would support either multiple embolic events or perfusion failure as possible mechanisms in these cases.

Despite the now extensive literature on ischaemic stroke in childhood there is little practical guidance on how to investigate patients. Many studies report that investigation is unrewarding and the incidence of "idiopathic" stroke has been reported to be as high as 50%[70]. Many conditions are associated with ischaemic stroke in childhood but it is unclear which of these should be specifically sought. The question of whether children known to be at risk of stroke should be approached differently to those in whom stroke has occurred "out of the blue" also remains unanswered. Finally, the impact of new techniques, such as MRI, in this group of children has not been considered in detail. The rest of this section will focus on the general approach to the investigation of children with ischaemic stroke; specific questions relating to investigation for cerebrovascular disease and prothrombotic states are addressed in other sections.

Computerised tomography is a sensitive imaging modality for ischaemic stroke and has the additional advantage of easily identifying cerebral haemorrhage which may need definitive urgent treatment. T2-weighted MRI is superior to CT in the investigation of ischaemic stroke. Ischaemic lesions may be identified within 6-8 hours of the onset of the clinical deficit and the extent of abnormal tissue is better appreciated[85,87,88,93]; intracranial haemorrhage can also be detected. Magnetic resonance imaging may enable identification

of alternative pathologies such as acute disseminated encephalomyelitis which may present with acute focal neurological deficits. Either CT or MRI should, therefore, be the first line in the investigation of patients presenting in this way. Even in children who have had evidence of cerebral infarction on CT, MRI has a role in improving definition of ischaemic lesions, as well as enabling cerebrovascular examination, and is therefore the imaging modality of choice.

It is clear from the data presented here and from the previous literature that cerebrovascular abnormalities are evident in the majority of children with ischaemic stroke. From the data summarised in table 3(4) it is apparent that cerebrovascular abnormalities, and in particular abnormalities with specific therapeutic implications (e.g. moyamoya syndrome or arterial dissection), were observed with similar frequency in the "idiopathic stroke" and "symptomatic stroke" groups. This observation argues for imaging of the cerebral circulation in both groups. The modalities for investigation of the cerebral circulation are considered in more detail in chapter 5.

In contrast, non-vascular abnormalities were less common. Despite the use of a standardised protocol, however, many non-vascular investigations were omitted in a significant proportion of patients. From the available data, the prevalence of non-vascular abnormalities was similar in children with "symptomatic" and "idiopathic" stroke, suggesting that it would be reasonable to adopt a similar approach to the investigation of both these groups of patients.

Although stroke in children with cardiac disease is frequently assumed to be embolic, in common with previous reports[418], only a minority of patients in this group with previously

recognised cardiac lesions had detectable intracardiac thrombus at the time of the stroke. Furthermore, cerebrovascular abnormalities other than occlusion or stenosis of large vessels which could be attributed to embolism were identified in these children, including arterial dissection and moyamoya syndrome. Children with structural abnormalities of the heart may also have structural abnormalities of the cerebral vessels, including cervicocephalic arterial dissection and intracranial aneurysms[36,228], and particular care should be taken to exclude treatable cerebrovascular pathologies in this group.

Although the literature suggests an association between minor structural cardiac abnormalities (e.g. PFO, atrial septal aneurysm and mitral valve prolapse) and stroke in young adults[238,239,240,241], these did not emerge as important risk factors in the patients studied here. A recent study has suggested that while minor cardiac lesions are important risk factors for stroke in young adults, they are less important in the paediatric age group[21]. Some minor cardiac abnormalities may have been missed in the present study, given that PFO is very common in the young (up to 33% of the background population)[249] and the fact that most of the children in this study were investigated with conventional transthoracic echocardiography. The literature suggests that in young adults with stroke more detailed techniques, such as the use of contrast and a Valsalva strain during conventional or transoesophageal echocardiography, and/or the simultaneous use of transcranial Doppler ultrasound to detect paradoxical emboli in the intracranial circulation significantly increases the detection and characterisation of such lesions[246,249]. Transoesophageal echocardiography has also been shown to be superior to transthoracic echocardiography in the detection of intracardiac sources of potential embolism in patients with stroke[248]. However, transoesophageal echocardiography in childhood requires a general anaesthetic and it may be difficult to incorporate manoeuvres which

increase right heart pressure and thus promote intracardiac shunting. The requirement for an anaesthetic may also influence the timing of the investigation which is important as delays in investigation may cause intracardiac thrombus to be missed. Nonetheless, the detection of either intracardiac thrombus or minor structural lesions could potentially alter treatment. Given the low yield of transthoracic echocardiography in this context, the potential of the more detailed techniques in the investigation of ischaemic stroke during the acute phase should be explored further. A longitudinal study investigating the risk of stroke and stroke recurrence in children with "minor" lesions is required before any firm conclusions can be drawn about whether or not definitive intervention, e.g. surgical closure of PFO, is justified in the paediatric age group.

Investigation for metabolic abnormalities predisposing to stroke was relatively unrewarding in this group of patients. This was partly related to referral bias as patients suspected to have metabolic disorders on clinical grounds were managed in a separate unit within the hospital. The definition of stroke used and the fact that the distribution of lesions was in a clear vascular territory in most cases makes it unlikely that cases of "metabolic stroke"[419], due to mitochondrial disease or organic acidaemias, were missed. Although most patients were screened for homocystinuria, recent evidence that heterozygosity for homocystinuria may be a significant risk factor for vascular disease (see section 1.8.3.2.) suggests that measurement of total plasma homocysteine or urinary homocysteine after methionine loading, as well as investigation for the common genotypes underlying homocystinuria (e.g. methylenetetrahyrofolate reductase deficiency) should be studied in this group of patients.

The relationship between lipid abnormalities and stroke in children has previously been considered in section 1.8.5.3. The data from the present study are inconclusive as relatively few patients in the population had measurement of lipid levels. The timing of the samples were also not optimal as most patients had blood taken at presentation, without prior fasting. There did not appear to be a clear correlation between elevated lipid levels and cerebrovascular abnormalities. The association between ischaemic stroke in childhood and levels of total cholesterol, triglycerides or lipoproteins cannot be established without a large, population based case-control study, ideally including detailed imaging of the cerebral circulation. Without such data it is unclear what approach should be adopted in clinical practice to the measurement of lipids in the child presenting with ischaemic stroke. The current recommendations for screening for hyperlipidaemia in childhood from the British Hyperlipidaemia Association[319] recommend selective screening by measuring the non-fasting total cholesterol in children with a family history of familial hypercholesterolaemia or premature coronary disease. Although no recommendations are made about children with ischaemic stroke, as lipid abnormalities are potentially modifiable, it would be reasonable, on the basis of the evidence discussed previously, to extend similar screening to children with cerebral arterial disease. The aim of this would be to detect cases of familial hypercholesterolaemia; the significance and management of other lipid abnormalities in childhood remain unclear[319].

The initial observation that infection often preceded stroke in children was made over 100 years ago[5]. In the 1960's interest in this association was renewed and several recent studies have found that preceding infection is a significant risk factor for ischaemic stroke[33,129,147,328]. Overall, 20% of the children in this study had preceding or concurrent infection. These observations could be criticised in that markers of infection were not

specifically measured and the prevalence of infection was not compared to a control population. Given the frequency of intercurrent infection in childhood, especially in the pre-school years, a case-control study would be needed to establish whether or not this association was genuine. Even if this was the case, the factors which select out individual children to suffer stroke deserve further consideration.

Preceding infection with *Varicella zoster* was noted in 8 of the children in the "idiopathic stroke" group. The association between *Varicella zoster* and ischaemic stroke in children is now well documented; the underlying mechanisms have previously been considered in section 1.8.6.3 but, in summary, both cerebrovascular abnormalities and transient prothrombotic abnormalities are implicated. The time course of ischaemic stroke as a complication of *Varicella zoster* in relation to the preceding infection is not clear and the limit of 6 months used in this study was intentionally generous. Although stroke is recognised in the acute phase of chickenpox, it is not clear how long the cerebrovascular abnormalities associated with *Varicella zoster* may persist and whether preceding infection is causative in children with otherwise unexplained cerebrovascular abnormalities. The potential for prevention of this complication by mass immunisation against *Varicella zoster* suggests that this association should be further investigated.

Unexplained stroke was relatively rare in this group of patients, affecting 6% of the whole group and 12% of those with apparently "idiopathic stroke". The wide variability in the reported incidence of idiopathic stroke in the literature seems to be related to lack of detailed investigation (see Appendix 1). However, it is important to recognise that while cerebrovascular abnormalities will be identified in most patients, the aetiology of these abnormalities remains unknown in most cases.

On the basis of the data presented here some broad recommendations can be made about the investigation of ischaemic stroke in childhood. Magnetic resonance imaging is the imaging modality of choice; the choice of cerebrovascular investigations is discussed in detail in chapter 5 but it is worth considering that MRA can easily be incorporated into the same examination. It is clear that all children should be investigated for the presence of cerebrovascular abnormalities, cardiac abnormalities and prothrombotic tendencies since these may have implications for acute and long-term management. Although the relevance of hyperlipidaemia to the pathogenesis of ischaemic stroke in children is uncertain, children with arterial disease should be screened for familial hypercholesterolaemia, as described above. The timing of investigations is also important, especially in terms of cardiac evaluation. In the current state of knowledge, transoesophageal echocardiography would be the optimal modality for this. Needless to say, the clinical evaluation should include exclusion of a concurrent infective illness. This approach would exclude treatable risk factors; other investigations should be based on the clinical picture in individual cases. The importance of more recently described modifiable risk factors in this population, such as mild hyperhomocysteinaemia, remains to be determined.

Previous diagnosis	Number of patients
Cardiac disease	25*
Sickle cell anaemia	9 (7 HbSS, 1 HbSβthalassaemia, 1 HbSC)
Malignancy	5
Meningitis	5
Hypertension	3
Nephrotic syndrome	2
Haemolytic uraemic syndrome	2
Systemic vasculitis	2
Other	8**

Table 3(1): Previous diagnoses in "symptomatic stroke" group

*including 1 child with HbSS and 1 child with hypertension

**"other diagnoses" include 2 children with facial naevi (without intracranial angioma), 1 child with neurofibromatosis, 1 child with direct ICA trauma, 2 children who were immunosuppressed, 1 child with *purpura fulminans* and 1 child with facial herpes zoster.

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
1	M	11	R hemiparesis, seizures	ASD; cardiac surgery	L MCA territory	L MCA occlusion	None discovered
2	M	0.85	L hemiparesis	Tetralogy of Fallot; cardiac surgery	L ICA territory	L ICA occlusion	None discovered
3	M	13	Coma, focal seizures	Tetralogy of Fallot; cardiac surgery	R MCA territory, old left sided infarct	R MCA occlusion	None discovered
4	F	6.5	L hemiparesis	Cardiac transplant for congenital heart block, cardiomyopathy; hypertension; preceding pneumonia	R basal ganglia/corpus striatum	R ICA occlusion	None discovered
5	M	9	L hemiparesis and seizures	Double inlet, univentricular heart; cardiac surgery	R MCA territory	R MCA occlusion	None discovered
6	M	13	Asymptomatic infarction	Linear sebaceous naevus syndrome; aortic coarctation; renal artery stenosis; hypertension	L occipital region	Occluded supraclinoid L ICA; narrow L subclavian artery	None discovered
7	F	2.3	L hemiparesis	AVSD; mitral stenosis; cardiac surgery, cardiac failure	R caudate and lentiform nuclei	R MCA stenosis	Intracardiac thrombus at time of stroke
8	M	10	L hemiparesis	Hypertension, aortic coarctation	R caudate nucleus, internal capsule	R MCA stenosis, L MCA aneurysm	None discovered
9	F	15	Expressive dysphasia	Mitral valve regurgitation, dilated cardiomyopathy, previous Wilms tumour-nephrectomy, radiotherapy and chemotherapy	None on early CT scan	Peripheral occlusion of angular branch of L MCA; (R axillary artery occluded at its origin)	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
10	F	7	Transient R sided weakness	VSD (closed spontaneously during early childhood); hypertension	Multiple infarcts in L internal borderzone	Bilateral moyamoya syndrome	None discovered
11	M	9	Recurrent hemiparesis on either side	Noonan syndrome, supravalvular aortic stenosis	Normal	Bilateral moyamoya syndrome	Heterozygous for the factor V Leiden mutation
12	F	1	R hemiparesis	Pulmonary atresia, intact ventricular septum	L MCA territory	L ICA dissection	None discovered
13	F	1.5	Decerebrate posturing, seizures coma then R hemiparesis	Dilated cardiomyopathy	L caudate nucleus, R putamen and external capsule	Normal MRA	Intracardiac thrombus at time of stroke
14	M	15	L hemiparesis	Previous chemotherapy for ALL, cardiomyopathy, cardiac failure	Bilateral scattered infarcts in grey and white matter	Normal MRA	None discovered
15	F	2	L hemiparesis, seizures	Complex cyanotic congenital cardiac disease; cardiac surgery	R MCA territory	Not known	None discovered
16	M	11	L hemiparesis	Coxsackie B myocarditis, congestive cardiomyopathy; atrial tachyarrhythmia	R lentiform nucleus, posterior limb of internal capsule	Not known	Intracardiac thrombus at time of stroke
17	M	16	R hemiparesis	Transposition of the great arteries	L fronto-temporal	Not known	Intracardiac thrombus at time of stroke
18	M	4	R hemiparesis	Tricuspid atresia, VSD, PDA, coarctation	L internal capsule, caudate nucleus, putamen	Not known	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
19	M	2	R hemiparesis, seizures	Univentricular heart; pulmonary and tricuspid atresia; ASD; cardiac surgery; chickenpox within previous 6 months	Bilateral parieto-occipital infarction	Not known	None discovered
20	M	9	L hemiparesis, seizures	None	R occipital region	Not known	None discovered
21	M	2	L focal seizures	Subaortic stenosis, supravalvular mitral membrane, aortic coarctation	R parieto-occipital & head of R caudate nucleus	Not known	None discovered
22	M	1	R hemiparesis, R focal seizures	Double outlet right ventricle, VSD, pulmonary infundibular stenosis; cardiac catherisation; chickenpox within previous 6 months	L ACA territory	Not known	None discovered
23	M	10	L hemiparesis, , seizures, coma	Cardiomyopathy, Friedreichs ataxia	R sylvian region & L hemisphere	Not known	Intracardiac thrombus at time of stroke
24	F	7	L hemiparesis	HbSS	Bilateral frontal infarction	Bilateral moyamoya syndrome	None discovered
25	F	5	R hemiparesis	HbSS	Bilateral scattered infarcts in grey and white matter	Bilateral moyamoya syndrome	None discovered
26	F	5	L hemiparesis	HbSS	Bilateral white matter infarcts	Bilateral moyamoya syndrome	None discovered
27	F	6.7	R hemiparesis	HbSS, end stage cardiac failure	Bilateral frontal and R temporo-occipital regions	Bilateral moyamoya syndrome	None discovered
28	F	7	R hemiparesis and seizures	HbSS, preceding febrile illness	L MCA territory	L MCA occlusion	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
29	M	8.5	Seizures, bilateral pyramidal signs, depressed level of consciousness	HbSS, facial abscess	Bilateral anterior and posterior borderzone infarcts	None (normal 4 vessel cerebral arteriogram)	None discovered
30	M	12	L focal seizures, L hemiparesis	HbSS	R lentiform nucleus	Normal MRA	None discovered
31	M	12	L hemiparesis	HbSβthalassaemia	R frontoparietal white matter	R ICA/MCA stenosis	None discovered
32	M	8.5	Coma, seizures	HbSC, shunted hydrocephalus	Generalised cortical and cerebellar infarction	Absent flow in all vessels on MRA	None discovered
33	F	2.3	L hemiparesis	Cranial irradiation for optic nerve glioma; chickenpox within previous 6 months; preceding febrile illness	R frontal infarct; bilateral basal ganglia calcification	Bilateral moyamoya syndrome	None discovered
34	M	5	L hemiparesis, seizures	Radiotherapy for hypothalamic tumour	L frontal white matter	Bilateral moyamoya syndrome	None discovered
35	F	10	L hemiparesis	Previous surgery for craniopharyngioma	R ACA territory	None (normal 4 vessels cerebral arteriogram)	Activated protein C resistance without the factor V Leiden mutation ; familial hypercholesterolaemia
36	F	7	L hemiparesis	Previous surgery for pinealoma	R frontal white matter	Small R MCA on MRA	None discovered
37	M	9	Transient R hemiparesis, seizures	Chemotherapy for lymphoma	Bilateral occipital infarcts	Irregular small vessels in fronto-parietal region consistent with small vessel disease ?secondary to chemotherapy	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
38	F	1.8	Quadriparesis, seizures, depressed level of consciousness	Streptococcus pneumoniae meningitis	R frontoparietal, L lentiform nucleus and cerebral peduncle, both thalami, several scattered lesions in deep white matter bilaterally	Normal MRA	Thrombocytosis (platelet count = $999x10^9$/L)
39	F	2.5	R hemiparesis and seizures	TB meningitis; chickenpox within previous 6 months	L thalamus	Not known	None discovered
40	M	1.2	L hemiparesis and seizures	Haemophilus influenzae type B meningitis	R caudate & lentiform nuclei and internal capsule	Occlusion of proximal R MCA	None discovered
41	F	2	Transient L hemiparesis	Dermal sinus; previous meningitis	R frontal white matter	Normal	None discovered
42	M	10	R hemiparesis, seizures	Meningitis aged 3 months	L cortical infarct; scattered areas of intracranial calcification and ventricular dilatation bilaterally	Not known	None discovered
43	M	5	R hemiparesis, R homonymous hemianopia, seizures	Polyarteritis nodosa, chronic renal failure	L occipital region	L PCA stenosis	None discovered
44	F	6.5	Generalised seizures	Renal failure secondary to systemic vasculitis	L frontal subcortical white matter infarct	Diffuse intracranial vasculitis	None discovered
45	F	1.7	R hemiparesis	Haemolytic uraemic syndrome, renal failure	L MCA and ACA territory	L MCA occlusion	None discovered
46	F	3	R hemiparesis, aphasia	Haemolytic uraemic syndrome, renal failure	L MCA territory	Not known	None discovered
47	M	5	Seizures, quadriparesis	Nephrotic syndrome	R parietal, posterior frontal	Normal MRA; MRI suggested cortical venous thrombosis	None discovered
48	M	2.5	R hemiparesis, seizures	Nephrotic syndrome	Bilateral parietal infarcts	Superior sagittal sinus thrombosis	Heterozygous for the factor V Leiden mutation; transiently low ATIII and protein S

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
49	M	6	R hemiparesis	Hypertension	L corona radiata	Occlusion of L MCA at origin	None discovered
50	M	11	Coma, L hemiparesis, seizures	Hypertension	L MCA territory	L MCA occlusion	Low protein C, free protein S and heparin cofactor II acutely
51	M	4	R hemiparesis, seizures	Renal artery stenosis,; hypertension; hypertensive cardiomyopathy; cardiac failure	L corona radiata, R cerebellar hemisphere	Generalised attenuation of all vessels probably secondary to chronic hypertension	None discovered
52	M	0.1	Quadriparesis, seizures	Immunodeficiency, meningitis	Cortical MCA territory bilaterally	Neither ICA visualised on MRA	None discovered
53	M	0.5	R hemiparesis and seizures	Bone marrow transplant for Omenn syndrome; L ventricular hypertrophy, hypertension	L MCA territory	Flow void in proximal MCA	Antiphospholipid antibodies
54	F	0.9	R hemiparesis and seizures	Facial naevus (no intracranial angioma)	L posterior frontal infarct; atrophic R hemisphere	Bilateral moyamoya syndrome	None discovered
55	M	2.8	L hemiparesis	Facial naevus (no intracranial angioma), chickenpox 3 months previously, preceding febrile illness	R basal ganglia	R MCA stenosis	None discovered
56	F	0.7	L hemiparesis	Chickenpox Staphylococcus aureus septicaemia, *purpura fulminans*	R PCA territory	R PCA occlusion	Low protein C, protein s & ATIII acutely.
57	F	5	L hemiparesis and seizures	Herpes zoster ophtalmicus	L temporal, parietal and inferior frontal	Not known	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
58	F	6.3	L hemiparesis	Cranial irradiation for optic nerve glioma, neurofibromatosis, preceding febrile illness	L posterior temporal region; atrophic R hemisphere	Bilateral moyamoya syndrome	None discovered
59	M	0.1	Seizures	Osteopetrosis, R ICA traumatised during surgery for decompression of optic nerves	R hemisphere infarction	R ICA damaged during surgery	None discovered
60	F	14	R hemiparesis	Recent mild cranial trauma (fell off bunk bed)	L caudate & lentiform nuclei, internal capsule, corona radiata	L ICA dissection	None discovered
61	F	12	R hemiparesis	Diving into water immediately before	L ICA territory	L ICA dissection	None discovered
62	M	15	L hemiparesis	Fell off skateboard and hit his head	R MCA territory	R ICA dissection	None discovered
63	M	13	Bilateral weakness, brainstem signs	Hit head on a tree while swinging on a rope swing	Pons/ponto-medullary junction	R VA dissection	None discovered
64	M	2	R hemiparesis	Minor head trauma	Pons, thalamus, L PCA territory, L cerebellum	R VA dissection	None discovered
65	M	4	R hemiparesis	Preceding diarrhoeal illness	L cerebellar, R occipital	R VA dissection	Ostium secundum ASD, high plasma triglycerides acutely
66	M	5.5	R hemiparesis	None	L thalamus and occipital cortex	L VA dissection	None discovered
67	M	7.4	Ataxia	None	Bilateral cerebellar L pons, R occipital cortex; bilateral MCA distribution	L VA dissection	None discovered
68	F	1.5	Transient R hemiparesis; then L hemiparesis and seizures	Aplasia cutis congenita	Diffuse low density throughout R hemisphere on CT	Bilateral moyamoya syndrome	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
69	M	12	Recurrent transient R hemiparesis; L hemiparesis, seizures	None	Bilateral temporo-parietal	Bilateral moyamoya syndrome	None discovered
70	F	0.7	Seizures	None	Bilateral diffuse white matter	Bilateral moyamoya syndrome	None discovered
71	F	8	R hemiparesis, coma, seizures	None	Diffuse cerebral and cerebellar atrophy, more marked in fronto-temporal regions	Bilateral moyamoya syndrome	None discovered
72	F	13	Recurrent bilateral hemiparesis	None	Basal ganglia and white matter bilaterally	Bilateral moyamoya syndrome	None discovered
73	F	2.5	L hemiparesis and seizures	None	Bilateral frontal white matter	Bilateral moyamoya syndrome	None discovered
74	M	4	Initial L hemiparesis, then R hemiparesis	Chickenpox prior to second episode	Bilateral cortical MCA territory infarction with cerebral atrophy	Bilateral moyamoya syndrome	None discovered
75	M	2	L hemiparesis	Chickenpox one week previously	R fronto-parietal	Bilateral moyamoya syndrome	None discovered
76	F	8	Recurrent L hemiparesis	None	Bilateral white matter	Bilateral moyamoya syndrome	Type 1 protein S deficiency (mother also affected)
77	M	13	Recurrent transient visual loss in R eye; recurrent L leg weakness	None	L frontal region	L moyamoya syndrome	None discovered
78	F	4	R hemiparesis	Recent head trauma	L basal ganglia and corona radiatia	L moyamoya syndrome	None discovered
79	M	6	L hemiparesis	Preceding febrile illness	R lentiform nucleus	R moyamoya syndrome	None discovered
80	M	6	R hemipareses, seizures, aphasia	None	L basal ganglia and frontal cortex	L MCA occlusion	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
81	F	14	R hemiparesis	None	L fronto parietal deep white matter infarct	L MCA occlusion	None discovered
82	M	9.7	R hemiparesis	None	L MCA territory	L MCA occlusion	Heterozygous for the factor V Leiden mutation
83	F	2	Coma, seizures	Otitis media	Extensive infarction on R, L internal capsule	L ICA occlusion, reduced flow R MCA	None discovered
84	M	15	L hemiparesis	None	R MCA territory	R MCA occlusion	Heterozygous for the factor V Leiden mutation
85	F	10	R hemiparesis	None	L insula & internal capsule	Reduced flow L ICA	Heterozygous for the factor V Leiden mutation
86	M	3.5	L hemiparesis	Preceding febrile illness	R MCA territory	R MCA occlusion	None discovered
87	F	6	R hemiparesis	Chickenpox 4 months previously	L basal ganglia	L MCA occlusion	None discovered
88	M	9	R hemiparesis	None	Multiple lacunar infarcts in the cerebellum	Clot in L VA; irregular basilar tip	None discovered
89	F	5	Headache, visual disturbance, loss of consciousness	None	L cerebellar hemisphere	Occlusion of L PICA	None discovered
90	F	9.5	L hemiparesis, seizures	Preceding febrile illness	R basal ganglia/parietal lobe	Irregular narrowing of R terminal ICA and proximal MCA	None discovered
91	F	4.2	L hemiparesis	None	R basal ganglia	Distal R MCA stenosis	None discovered
92	M	3	L hemiparesis	None	R caudate & lentiform nuclei, corona radiata, insula	R MCA stenosis	None discovered
93	F	7.5	R hemiparesis	None	L lentiform nucleus and corona radiata	L MCA stenosis	None discovered
94	F	6.3	L hemiparesis, headache	None	R basal ganglia, internal capsule, corona radiata	Long stenosis of R terminal ICA and MCA	None discovered
95	F	8	L hemiparesis and seizures	None	L lentiform, internal capsule and corona radiata	Hypoplastic proximal R ACA segment	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
96	F	1.8	R hemiparesis, seizures	Cystinuria; preceding febrile illness	L ICA territory	Stenosis L ICA	None discovered
97	M	5	L hemiparesis	None	R MCA territory	R ICA stenosis	None discovered
98	M	8.5	L hemiparesis and seizures	None	R MCA territory and scattered white matter lesions; L peritrigonal	Proximal R MCA stenosis; R A1 occlusion	None discovered
99	F	15	L hemiparesis	None	R caudate, lentiform nucleus	Stenosis of R ICA/MCA	None discovered
100	M	3.5	Transient L hemiparesis, seizures	None	R caudate nucleus	Focal irregular stenosis L ICA/M1 segment of L MCA	Heterozygous for the factor V Leiden mutation
101	F	6.5	R hemiparesis, aphasia, depressed conscious level	None	L caudate, putamen and external capsule	Irregular stenosis of L ICA and L MCA ?fibromuscular hyperplasia	None discovered
102	M	6	R hemiparesis	Chickenpox 6 weeks previously	L basal ganglia	L MCA stenosis	None discovered
103	F	1.5	L hemiparesis and seizures	Chickenpox 2 months previously	R lentiform nucleus	R ICA and proximal RMCA stenosis	None discovered
104	M	5	R hemiparesis	Chickenpox 2 months previously	L basal ganglia and internal capsule	L MCA stenosis	Low total protein S acutely
105	M	3	L hemiparesis, seizures	Non-specific febrile illness	R caudate, lentiform nucleus, precentral sulcus	Partial occlusion & filling defect in R MCA -?embolic occlusion	None discovered
106	M	6	L hemiparesis, L focal seizures	None	R basal ganglia, corona radiata, anterior limb internal capsule	Minimal stenosis of R ICA/MCA	High titre of anti-mycoplasma pneumoniae IgM
107	M	6.5	Coma	None	Bilateral cerebellar/occipital infarction	Small L PCA	Heterozygous for the factor V Leiden mutation

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
108	M	16	Ataxia	None	L thalamus, cerebellar hemisphere	Irregular basilar tip - ?previous occlusion with recanalisation	None discovered
109	F	7.5	Bilateral pyramidal signs, depressed conscious level	Previous L basal ganglia infarction	R basal ganglia, insula cortex, corona rdiata; old L basal ganglia infarct	Cerebral vasculitis	Mildly elevated serum cholesterol acutely
110	M	1.3	Coma	None	L parieto-occipital infarction	Thrombosis of superior sagittal and R transverse sinus	None discovered
111	M	4	R hemiparesis, seizures	Non-specific febrile illness	L parietal	Cortical venous thrombosis	None discovered
112	M	7	L hemiparesis	None	R putamen	Normal MRA	None
113	F	1.5	L hemiparesis	None	L lentiform, internal capsule	Normal L ICA and VA on conventional arteriogram	None discovered
114	M	5	L hemiparesis	None	R lentiform	Normal MRA	None discovered
115	M	1.5	L hemiparesis and seizures	None	R putamen, head of caudate nucleus	Normal 4 vessel cerebral arteriogram	None discovered
116	F	0.9	L hemiparesis	None	R lentiform nucleus	Normal R ICA on conventional arteriogram	None discovered
117	M	10	R hemiparesis	None	L lentiform nucleus and internal capsule	Normal L ICA and L VA on conventional arteriogram	None discovered
118	M	3	L hemiparesis and L focal seizures	None	R caudate, lentiform, anterior limb of internal capsule, L frontal, R parietal	Normal 4 vessel cerebral arteriogram	None discovered
119	M	8	R hemiparesis	None	L MCA territory	Normal MRA	None discovered
120	M	2.7	L hemiparesis	Non-specific febrile illness	R caudate nucleus and internal capsule	Normal MRA	None discovered

Patient no.	Sex	Age (years)	Presentation	Previously recognised risk factor	Location of cerebral infarct	Vascular abnormality	Non-vascular abnormality
121	M	1.1	L hemiparesis	None	R corona radiata and lentiform nucleus	Not known	None discovered
122	M	1.5	R hemiparesis	None	L lentiform nucleus, internal capsule, corona radiata	Not known	None discovered
123	M	10	Ataxia	None	R cerebellar and occipital	Not known	High serum cholesterol and plasma triglycerides on 3 occasions
124	F	0.2	R hemiparesis, R focal seizures	None	L MCA territory	Not known	None discovered
125	F	10	R hemiparesis	None	L internal capsule & occipital cortex	Not known	None discovered
126	F	7.8	R hemiparesis, seizures	Recent chickenpox	L caudate, lentiform and adjacent cortex	Not known	None discovered
127	M	6	Visual disturbance, R focal seizures	Chickenpox one week previously	R occipital region	Not known	Low free protein S acutely, high serum cholesterol and plasma triglycerides acutely
128	F	1.2	R hemiparesis	Non-specific febrile illness	R lentiform nucleus and corona radiata	Not known	None discovered

Table3(2): Clinical details and results of investigations.

The number allocated to each patient is used consistently throughout the rest of the text.

	Symptomatic stroke (n = 59)	Idiopathic stroke (n = 69)
Cerebrovascular imaging	46 (78%)	61 (88%)
MRA	41 (69%)	51 (74%)
Cerebral angiography	19 (32%)	50 (72%)
Cerebrovascular abnormality	40 (68%)	52 (75%)
Normal cerebral vessels	7	9
Large vessel occlusion	14	9
Large vessel stenosis	5	19
Moyamoya syndrome**	11	13
Arterial dissection	1	8
Cerebral vasculitis	1	1
Diffuse small vessel disease	2	0
Cerebral venous thrombosis	3	2
Other abnormalities*	3	0

*other abnormalities = 1 MCA aneurysm, 1 direct ICA trauma at surgery, 1 MCA branch occlusion

**Moyamoya syndrome is defined as large vessel stenosis or occlusion with collateral formation

Table 3(3): Cerebrovascular abnormalities

Investigation	Number of patients investigated
Prothrombotic screen (see chapter 4 for more detail)	77 (60%)
Plasma [CSF] lactate	59 [25] (46%[20%])
Plasma/urinary amino acids	72 (56%)
Urinary organic acids	48 (38%)
Cholesterol/triglycerides	35 (27%)
Transthoracic echocardiogram	120 (94%)
Transoesophageal echocardiogram	18 (14%)

Table 3(4): Number of children investigated for non-vascular risk factors

	Symptomatic stroke (n = 59)	Idiopathic stroke (n = 69)
Prothrombotic state	1	6
Asymptomatic cardiac abnormalities	2	2
Infection	15	11
Lipid abnormalities	1	3
Chickenpox within 6 months of stroke	3	8
Preceding cranio-cervical trauma	0	6

Table 3(5): Non-vascular risk factors detected

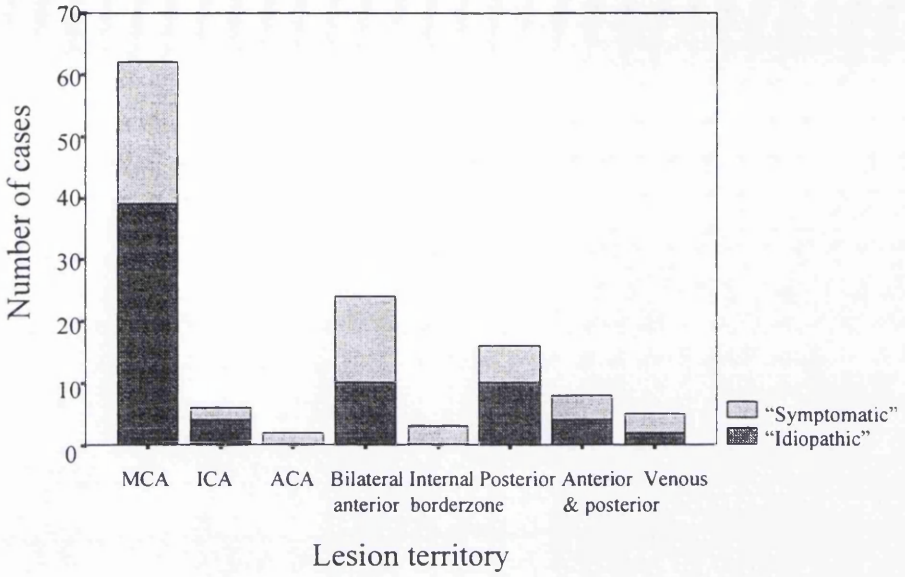


Figure 3(1): Distribution of cerebral infarcts in "idiopathic stroke" and "symptomatic stroke" groups

4. Prothrombotic tendencies and ischaemic stroke

4.1. Patients

Seventy-seven children were investigated for the presence of an inherited prothrombotic tendency. Their ages ranged from 2 months to 15 years (median age 5.5 years). Fifty-nine were investigated at acute presentation; the remaining children were referred after the acute stroke and were investigated at this time. Four patients in this group (patients 47, 48, 110 and 111) had cerebral infarction secondary to cerebral venous thrombosis.

4.2. Prevalence of inherited prothrombotic states

Table 4(1) summarises the number of patients undergoing each investigation and the prevalence of abnormalities.

Abnormalities of one or more parameters were identified on initial investigation in 17 patients. However, on re-investigation after an interval of 3 months, the abnormalities in 8 cases had resolved. Table 4(2) gives the details of the patients in whom transient abnormalities were identified. Patient 50 died and therefore could not be tested again; however, the presence of multiple abnormalities would suggest that the results in this case reflect a generalised consumptive process as a result of acute thrombosis.

Nine patients had persistent abnormalities with evidence of an inherited prothrombotic tendency, as summarised in table 4(3). Of these, 8 had had stroke in an arterial

distribution while 1 (patient 48) had cerebral infarction secondary to superior sagittal sinus thrombosis. There was no history of previous thrombosis either in the children or in their immediate families.

Patient 76 who had moyamoya disease and cerebral infarction had inherited type 1 protein S deficiency (low free and total protein S). Her mother was known to be affected but was asymptomatic.

Eight children had activated protein C resistance. Seven were heterozygous for the FVL mutation; two families were available for testing and in each case another family member was also shown to be heterozygous for the FVL mutation. A further child (patient 35) had a significantly low APC resistance ratio on three separate occasions (2.3, 2.4, 2.3) and was negative for the FVL mutation. Her father and brother also had similar abnormalities. The family have not been screened for any of the more recently described genetic abnormalities which result in APC resistance[291,293].

4.3. Prevalence of FVL mutation in control population

Of the control population of 77 children, 4 were heterozygous for the FVL mutation, giving an estimate of the prevalence of the FVL mutation in the control group of 5.2%.

4.4. Statistical analysis

The prevalence of the FVL mutation in children with arterial territory stroke was 6/50 (12%) which was not significantly different from the prevalence in the control group (Fisher's exact test, $p = 0.19$).

Taking the prevalence of asymptomatic heterozygous protein S deficiency to be in the order of 1:500[287] the finding of a single patient with protein S deficiency is explicable by chance alone. No other inherited prothrombotic tendencies were identified.

4.5. Antiphospholipid antibodies

None of the patients had evidence of a circulating lupus anticoagulant.

Forty one children were investigated for the presence of anticardiolipin antibodies. Ten children had abnormal results as summarised in table 4(4). Nine children had titres of anticardiolipin IgG >7 AEU (NR <7 AEU) acutely; 2 of them (patients 46 and 98) had titres of >20 AEU (NR >20AEU). In 5 cases no further measurements were carried out. Of the remaining 4 cases, 2 children had rising titres over a period of 6 months and 1 year while the levels fell in the remaining 2 patients.

Four children had high titres of anticardiolipin IgM (>10 AEU units); in 3 cases no further measurements were carried out. The titres fell in the remaining case.

4.6. Discussion

While the association between inherited prothrombotic states and cerebral venous thrombosis is well recognised[279], the reported prevalence in series of young adults with arterial stroke ranges from 0% to 25%[279,420,421]. The evidence that such conditions cause arterial stroke in childhood is almost purely anecdotal. Despite this, a "prothrombotic screen" is often one of the first investigations requested by clinicians managing children with ischaemic stroke. Factors which are of importance when making a diagnosis of an inherited prothrombotic state, such as age appropriate normative values, the timing of the blood sample in relation to acute thrombosis and investigation of other family members, are often disregarded. The high prevalence of asymptomatic heterozygosity for many of the inherited prothrombotic states in the background population also casts doubt on the hypothesis that there is a simple "cause and effect" relationship with stroke.

It is attractive to suppose that the association between prothrombotic tendencies and arterial stroke in children is a real one. A mechanism to explain this link is readily available and there may be potential for prevention of further events by use of anticoagulants. However, without establishing whether or not there is a cause and effect relationship, such treatment exposes the patient to the risks of long term anticoagulant therapy and may prevent the clinician from seeking other explanations for the stroke. The results presented above suggest that in a group of children with arterial stroke, inherited prothrombotic tendencies were rare and transient deficiencies of the anticoagulant proteins were observed equally often. These findings are supported by a recent study in a smaller group of children which failed to show an association between protein C

deficiency, protein S deficiency and antithrombin III deficiency and ischaemic stroke in childhood[147].

The FVL mutation is known to increase the risk of venous thrombosis including cerebral venous thrombosis[294,296,297,298,299]. Although a possible association between the FVL mutation and stroke in young adults[306,307], children[278] and neonates[422] has been described, a large prospective study failed to show an association with arterial stroke in adults[305]. The prevalence of this mutation in background populations varies according to the population's composition, a factor which was not considered in any of the previously published accounts of the FVL mutation in juvenile stroke. Ethnicity has been shown to influence the background prevalence[300] and the age of the population may also be important[301] and should be considered. Although a control population in the paediatric age group was used in this study, it comprised children without any thrombotic problems seen at the institution where this study was carried out and were not therefore perfectly matched to the patients. As the controls were anonymous, it was not possible to determine the ethnicity of this population. It should be noted that the numbers in the patient and control groups are relatively small and that a much larger study would be required in order to increase the reliability of the observations made here.

Although the FVL mutation on its own may not confer a significant risk of arterial thrombosis, it may do so in conjunction with other risk factor for thrombosis (e.g. mild to moderate hyperhomocysteinaemia[423]). There is some evidence for this position as Nowak Gottl[278] concluded that the association between APC resistance, the FVL mutation and ischaemic stroke usually occurred in the context of another risk factor for thrombosis. The present study did not confirm these observations as only 3 patients with APC resistance

had other risk factors for ischaemic stroke though this population was not screened for hyperhomocysteinaemia.

APC resistance in patients without the FVL mutation has recently been reported to be associated with stroke in some populations of adults[308]. However, the data presented here does not support an association between the APC resistant phenotype and ischaemic stroke in childhood. This is consistent with the findings of a previous study by Riikonen[424]. Although other mutations in the factor V gene which result in APC resistance have been recently described[291,293], their importance in children with ischaemic stroke has not been determined.

Deficiencies of protein C, protein S and antithrombin III are the most common of the other inherited prothrombotic states. Although there have been numerous descriptions of apparent protein C deficiency in association with stroke in childhood, few authors have considered values of protein C in relation to the child's age[425,426], the timing of thrombotic episode[427,428] and family studies[426,427,429]. Kennedy found that levels of protein C may be depressed in association with active thrombosis after acute stroke in children and may not normalise for up to 18 months later[281]. Low levels may therefore be epiphenomena of the stroke rather than having any pathogenic significance, as has previously been suggested[427]. This observation further calls into question some of the previous accounts of protein C deficiency in relation to childhood stroke, as few authors have reported serial data beyond the acute period[427,429,430].

Even where longitudinal assessment is suggestive of protein C deficiency, it is important that age-appropriate norms are used. At birth, protein C levels are significantly lower than

in adulthood, and remain so until late teenage years. One of the patients in this study (patient 113) was initially thought to have symptomatic protein C deficiency after a stroke and was anticoagulated for this for many years but was reclassified as normal following the publication of a paediatric reference range[283].

Kennedy's study also showed that the prevalence of primary protein C deficiency in children with stroke was not significantly different from that found in age-matched controls[281]. These findings are supported by the results presented here and suggest that any association is probably coincidental.

Primary protein S deficiency results in an increased risk of venous thrombosis[431,432] but, as with the other inherited prothrombotic states, the relationship with arterial thrombosis is less clear. Reports of an association between primary protein S deficiency and stroke in children are scanty and are largely anecdotal[426,433,434]; no case control studies have been carried out.

Although secondary protein S deficiency may result from many inflammatory illnesses, the pathogenetic significance of this with regard to stroke is uncertain. Sacco demonstrated that levels in adults with stroke were not significantly different from those of age-matched controls[435]. Infection with *Varicella zoster* may result in production of antibodies to protein S, resulting in a widespread coagulopathy, usually clinically manifesting as *purpura fulminans* (e.g. patient 56), although there is some evidence to suggest that although the manifestations may be less severe[339] there may be an association with ischaemic stroke[297]. In this context it seems likely that the antibody mediated destruction of protein S and the coagulopathy are related.

As with the other anticoagulant proteins, transient deficiencies of antithrombin III in the context of acute stroke have been described. The evidence for an association with ischaemic stroke in either childhood[289,436] or young adults[279,421,437] is scanty.

Although there are several reports of antiphospholipid antibodies in association with stroke in childhood[312,434,438,439,440,441,442], the importance of the primary antiphospholipid syndrome as a cause of ischaemic stroke in children is not clear. In particular, the pathological significance of anticardiolipin antibodies in ischaemic stroke has been controversial. Although some studies have found an association with stroke and recurrent stroke in young adults[313,443], it has also been suggested that anticardiolipin antibodies are a non-specific accompaniment of vascular disease[444]. The titres at which anticardiolipin antibodies assume pathological significance is also controversial. A high IgM titre is of dubious significance; the IgG titre has to be at least 20 GPL units before it is definitely abnormal[311]. The Antiphospholipid Antibodies and Stroke study did not find a significant increase in recurrent thrombo-occlusive events and death in patients with anticardiolipin antibody titres of >10GPL; however patients with titres of >40GPL were more likely to experience such events than patients with levels <40GPL[445]. Levels may fluctuate, especially in the context of acute illness and as with other prothrombotic states, serial evaluation is important[311].

In a case-control study, Angelini[314] found that 10/13 children with ischaemic stroke (and 0/20 age matched controls) had evidence of antiphospholipid antibodies persisting for 6 months. The levels used in that study (corresponding to 8 arbitrary units for IgG and 6 arbitrary units for IgM) corresponded to 5 standard deviations of paediatric normal

values. Six had had multiple strokes. Although this high incidence of recurrence has also been found in adults with antiphospholipid antibodies and stroke[313], most of the literature examining the association between antiphospholipid antibodies and stroke has focused on the young adult stroke population. This is of importance as other risk factors for cerebrovascular disease in the adult population such as smoking and hypertension interact with the risk conferred by the antiphospholipid antibodies[311]. A recent review by Biller comparing their experience of ischaemic stroke in children and young adults emphasises that, in contrast to young adults, antiphospholipid antibodies are not an important cause of stroke in children[21].

The number of patients with for anticardiolipin antibodies in the present group is difficult to interpret given that in many cases serial data were not available. Most of the single measurements were carried out during the acute phase of illness. None of these patients had other features of the antiphospholipid syndrome (evidence of a circulating lupus anticoagulant, thrombocytopaenia) and only 3 of the patients were entirely well before the stroke (see table 4(4)). One child (patient 98) with rising titres of anticardiolipin IgG has had recurrent strokes; however, he had angiographic evidence of cerebral vasculitis and the presence of an anticardiolipin antibody may well have reflected an inflammatory response. In summary, the data presented here confirms the previously reported high prevalence of positivity for anticardiolipin antibodies in children with ischaemic stroke[446] but it is not sufficient to establish a causal relationship. Data on the prevalence of anticardiolipin antibodies in healthy children and children with non-thrombotic illness as well as further clarification about pathological levels will be required to definitively establish such a relationship.

The data presented here reinforces the importance of longitudinal evaluation, with use of age appropriate normal values, when identifying inherited prothrombotic states in children. It is also important to recognise that, with the exception of DNA analysis for the factor V Leiden mutation, the diagnosis of the inherited abnormalities discussed above can only be made after serial evaluation, once the effects of the acute thrombotic event have resolved. Investigation of the child's parents may be of use in clarifying whether abnormalities identified in the acute phase represent an inherited abnormality.

While, for the reasons discussed above, it is unlikely that a single prothrombotic abnormality will entirely account for stroke in an individual child, the interaction between multiple genetic and acquired risk factors for stroke may be important[280,447]. This provides a rationale for continuing to investigate children with stroke for prothrombotic states in the acute period as intervention may be possible in certain situations. For example, patient 56 developed a stroke in the context of *purpura fulminans* with widespread cutaneous and digital thrombosis after chickenpox, associated with profound protein C, free and total protein S and antithrombin III deficiencies. She was treated with fresh frozen plasma and protein C and antithrombin III concentrates; all the coagulation abnormalities resolved within 1 month. In a patient with an inherited abnormality, acute anticoagulant therapy may be warranted in the presence of other risk factors for thrombosis (e.g. dehydration, infection).

The role of anticoagulant therapy for secondary prevention of stroke in patients with inherited prothrombotic states is unclear. In a recent review on the role of haematological factors in the pathogenesis of ischaemic stroke, Markus concluded that the published data on the importance of natural anticoagulant deficiencies in ischaemic stroke was

conflicting and inconclusive[37]. However, despite this he advocates anticoagulation in "young patients, including children, with stroke associated with hereditary deficiencies and a strong family history of stroke in the presence of anticoagulation abnormalities" . No recommendations are made about the duration of anticoagulation for secondary prevention and in most cases the situation is less clear cut. Firm guidelines on optimal management of such cases must await the results of large scale controlled trials; in the meantime treatment should be considered after evaluation of the combination of risk factors in individual cases.

Further work will be needed to investigate the importance of newly described hereditary prothrombotic states such as mild to moderate hyperhomocysteinaemia[316,317] and the prothrombin 20210 genotype[448] and their interaction with currently recognised risk factors in the pathogenesis of ischaemic stroke in childhood.

Parameter measured	Number of patients tested	Number of abnormal results acutely	Number of persistently abnormal results
Protein C	77	2 (2.6%)	0
Total protein S	75	7 (9%)	1*
Free protein S	67	4 (6%)	1*
Antithrombin III	73	3 (4%)	0
Heparin Cofactor II	64	1	0
Plasminogen	63	0	0
Activated protein C resistance	55	8 (15%)	8 (15%)
Factor V Leiden mutation	55	7 (13%)	7 (13%)
Anticardiolipin IgG	41	9 (22%)	2/4 which were repeated
Anticardiolipin IgM	41	4 (10%)	Not repeated

Table 4(1): Results

*in the same patient

Patient number	Transient abnormality identified	Cerebrovascular abnormalities	Other risk factors for stroke
104	Low total protein S	MCA stenosis	Chickenpox 2 months previously
127	Low free protein S	No vascular imaging	Chickenpox 1 week previously
53	Low free and total protein S	MCA stenosis	Omenn syndrome; bone marrow transplant 1 month previously
109	Low free and total protein S	Cerebral vasculitis	None
83	Low protein C	L ICA occlusion; R MCA stenosis	Non-specific febrile illness
56	Low protein C, free and total protein S and antithrombin III	PCA occlusion	Chickenpox 1 month previously; *purpura fulminans*
50	Low protein C, free protein S and heparin cofactor II	MCA occlusion	None
47	Low antithrombin III	Cerebral venous thrombosis	Nephrotic syndrome

Table 4(2): Transient prothrombotic abnormalities identified

Patient no.	Prothrombotic abnormality	Cerebrovascular abnormalities	Other risk factors for stroke	Other family members affected	Recurrent events
11	FVL heterozygote	Moyamoya	Supravalvular aortic stenosis	Not known	TIA
82	FVL heterozygote	MCA occlusion	None	Brother	None
84	FVL heterozygote	MCA stenosis	None	Not known (father died after stroke)	None
85	FVL heterozygote	ICA occlusion	None	Not known	None
100	FVL heterozygote	L ICA stenosis	None	Not known	TIA
48	FVL heterozygote	Sagittal sinus thrombosis	Nephrotic syndrome; low antithrombin III and total protein S acutely	Not known	None
107	FVL heterozygote	None	None	Father	TIA
35	APC resistance; FVL negative	None	Familial hypercholesterolaemia	Father and brother	Cerebral infarction x 3
76	Type 1 protein S deficiency	Moyamoya	None	Mother	TIA

Table 4(3): Children with inherited prothrombotic abnormalities

Patient number	Anticardiolipin IgG (normal = <7 AEU)	Anticardiolipin IgM (normal = < 10 AEU)	Other risk factors for stroke	Serial studies
2	16.9	Normal	Tetralogy of Fallot	Persistently high IgG over 1 year
46	34.4	Normal	Haemolytic uraemic syndrome	Not repeated
53	16.4	Normal	Omenn syndrome, bone marrow transplant (also had transiently low protein S)	Normal
55	12.7	Normal	Facial naevus	Not repeated
71	11.6	Normal	None	Persistently high IgG over 9 months
75	19.3	Normal	Preceding chickenpox	Not repeated
87	Normal	19.3	Preceding chickenpox	Not repeated
104	9.4	11.8	Preceding chickenpox	Not repeated
91	11.1	19.3	None	Persistently high IgG after 1 year; IgM normal
98	33.1	11.7	Developed cerebral vasculitis; went on to have recurrent strokes	Normal

Table 4(4): patients with elevated titres of anticardiolipin antibodies

5. The role of cerebral angiography in the investigation of ischaemic stroke in childhood

5.1. Introduction

The role of conventional cerebral angiography in the investigation of the child with ischaemic stroke is unclear. With the increasing availability of MRA it has been difficult to ascertain whether this alone is sufficient or whether there is a risk of missing significant pathology requiring alternative management strategies. The aims of this section were to characterise the angiographic findings in a group of children with ischaemic stroke and to compare them, where possible, with findings on MRA. These data were used to construct a clinical algorithm to guide the use of conventional cerebral angiography in the investigation of the child presenting with ischaemic stroke.

5.2. Patient characteristics

Of the 128 children, 69 (54%) had conventional cerebral angiography. Patient selection for conventional angiography was entirely at the discretion of the clinician in charge, without any predefined guidelines; similarly the patients' management was also determined by individual clinicians. In all cases the conventional angiogram and MRA study were carried out during the acute admission though patients who were investigated with both studies usually had MRA prior to conventional angiography. Magnetic resonance angiography became widely available within the unit in 1994 but this does not seem to have had much impact on the use of cerebral angiography. The proportions of

children with ischaemic stroke who had conventional angiography before and after 1994 were 51% and 54% respectively.

Twenty-one studies, of which 19 were known to be abnormal, could not be traced. This left 48 conventional cerebral angiograms available for review. There were 27 boys. The patients' ages ranged from 9 months to 17 years (median age 6.6 years). Fourteen children (29%) had "symptomatic stroke". The clinical details of these patients and results of their radiological investigations are summarised in table 5(1). A possible complication of conventional angiography was noted in one case (patient 82), a child with MCA stenosis who developed occlusion of this vessel and extended his infarct within hours of the procedure.

5.3. Review of conventional cerebral angiograms

Seven patients had normal cerebral angiograms. Forty-one of the 48 children had abnormal studies. Abnormalities predominantly affected the anterior cerebral circulation. Large vessel abnormalities were identified in 36 cases; 6 patients had abnormalities of smaller vessels, which were confined to these vessels in 5 cases (patients 38, 46, 53, 58 and 59).

The radiological diagnoses in the patients with abnormal studies were moyamoya syndrome in 11 cases, arterial dissection in 6 cases, large vessel occlusion in 8 cases, large vessel stenosis in 9 cases, cerebral vasculitis in 3 cases, focal arteritis in 1 case, diffuse small vessel disease in 2 cases, and branch arterial occlusion in 1 case.

5.4. MRA studies

Thirty-seven patients (77%) had MRA in addition to conventional angiography during the acute admission. Large vessel abnormalities were identified on MRA in all 11 children with an angiographic diagnosis of large vessel stenosis or occlusion.

Nine of the 11 children with an angiographic diagnosis of moyamoya syndrome were investigated with MRA. The diagnosis was made on the non-invasive study in all 6 children with bilateral disease but only 1 of 3 children with unilateral disease. Although large vessel abnormalities were identified on MRA in the remaining 2 children (patients 34 and 79), the collateral vessels were not apparent on the non-invasive study.

MRA was considered abnormal but not diagnostic in 4/6 cases of arterial dissection; patient 96 who had arterial dissection in the posterior circulation had normal MRA. Patient 67 had normal MRA at presentation when the conventional angiogram showed irregularity in the left PCA and occlusion of the right SCA. On subsequent angiography, in particular with improved visualisation of the proximal VA's, it was apparent that he had had L VA dissection.

Of the 6 patients with abnormalities of smaller vessels, 1 child (patient 109) also had large vessel abnormalities which were identified on MRA. However, the identification of small vessel disease in this case implied more diffuse pathology and altered clinical management. Patient 51 had evidence of turbulent flow in both proximal MCA's on MRA

but had evidence of diffuse small vessel disease with normal large vessels on conventional angiography.

Of 9 children with normal MRA, 4 (patients 43, 37, 66, 67) had abnormalities detected on conventional angiography. None of the patients with normal conventional arteriograms had abnormal MRA.

5.5. Comparison of findings on cerebral angiography and magnetic resonance angiography

Conventional angiography identified abnormalities not apparent on the MRA in 14 cases; in 11 of these, the additional findings on conventional angiography altered subsequent clinical management.

In 6 patients where the final diagnosis was arterial dissection (involving the ICA in two cases (nos. 61 and 62) and VA in the other 4 cases (nos. 63, 64, 66, 67) anticoagulant therapy was initiated as a result of the angiographic findings. Two children (nos. 37 and 51) had evidence of diffuse vasculopathy of the intracranial vessels secondary to chemotherapy and chronic hypertension respectively and were treated with long-term aspirin. Patient 109 with a final diagnosis of IAC was treated with steroids and Cyclophosphamide; patient 44, who was known to have a systemic vasculitis was immunosuppressed with steroids and Azathioprine following a stroke on the basis of angiographic appearances which were suggestive of cerebral vasculitis. Patient 108 had irregularity in the basilar tip, suggesting previous occlusion and recanalisation, where the

MRA showed only a small basilar artery. He was anticoagulated for 2 years on the basis of the findings of the conventional angiogram.

5.6. Discussion

This study suggests that even if MRA is available, contrast cerebral angiography has a continuing role in the identification of potentially treatable cerebrovascular abnormalities in children with ischaemic stroke.

The frequency and distribution of cerebrovascular abnormalities in this study is similar to that reported in earlier studies of children, predominantly in populations of children with acute hemiplegia i.e. predominantly affecting the terminal ICA and proximal MCA (see table 5(2))[6,7,10,11,30,153,157,323,449,450]. Shillito[153] reviewed the literature on the causes of cerebral arterial occlusion in such children in 1964 and concluded that it could be due to the following mechanisms:

1. Embolism
2. Thrombosis- with intimal ulceration
   - with medial calcification
   - with dissecting aneurysms
3. Trauma (e.g. pharyngeal)
4. Localised arteritis (with proximal extension of thrombus)

As mortality after ischaemic stroke in childhood is low, data on cerebrovascular histology in such cases is scanty. Moreover, the relevance of data derived from the subgroup of

children with an ultimately fatal course to other children with ischaemic stroke is unclear[451]. The available histological data indicates that there may be a variety of abnormalities including congenital vascular anomalies[323] degenerative vascular disease (with atrophy of the elastic lamina and fibrocalcific plaques in the media)[8,324], atheroma[6,323]and venous thrombosis[452]. However, unlike ischaemic stroke in adults, where atheroma is an extremely frequent pathological finding, there is no similar "final common pathway" in children with stroke.

Although improvement in occlusive and stenotic lesions over time has been documented[157,158], they may equally be persistent or progressive[30]. Proposed mechanisms for this "transient cerebral arteriopathy" include transient inflammation[7,11,153,326], possibly related to recent infection with *Varicella zoster*[158], and transient vasospasm, although the trigger for this is unclear. Thrombosis with subsequent recanalisation could result in focal vascular irregularity and this could account for some of the cases where the region of infarction suggests compromise of proximal vessels. However, in some cases with large vessel stenosis, the morphology of the infarcts suggests distal occlusion, possibly due to emboli; it is unclear whether in these cases proximal thrombosis has occurred on a normal vessel with distal propagation of emboli or whether thrombosis has occurred on an already stenotic vessel. The mechanisms leading to intravascular thrombosis are poorly understood; some recognised mechanisms are vascular trauma, structural abnormalities of the vessel wall, inflammation in the vessel, a coagulopathy and systemic illness[323]. However, many cases occur in otherwise healthy children, "out of the blue" and none of these mechanisms can be readily implicated. Embolic vascular occlusion is frequently assumed in such cases but, as discussed in chapter 3, objective evidence for this, even in patients with a potential source of emboli, is often lacking.

Although focal stenosis or occlusion of proximal large vessels in the anterior circulation are the commonest abnormalities seen in children with ischaemic stroke, treatment options in such patients are, at present, limited. The primary aim of cerebrovascular imaging in children with ischaemic stroke should be the detection of potentially treatable cerebrovascular abnormalities, namely arterial dissection[177], moyamoya syndrome[174,402] and cerebral vasculitis[215].

Magnetic resonance angiography is a sensitive imaging modality for moyamoya syndrome, especially in the detection of large vessel stenosis and occlusion. However, collateral circulation is poorly visualised and the degree of large vessel stenosis tends to be overestimated[168]. Cerebral angiography therefore remains mandatory in pre-surgical evaluation. Angiographic technique is important as there is a risk of precipitating ischaemic events. The child should be well hydrated, hypocapnia should be avoided and contrast dosage should be minimised[107]. Magnetic resonance angiography may be of particular value in screening patients "at risk" such as family members[167,168,169], and for serial monitoring in patients who are known to be affected, or after surgery[162].

In the group of patients studied here the diagnosis of moyamoya syndrome was made on MRA in all the bilateral cases, but in only 1 of the 3 unilateral cases. It could be argued that unilateral moyamoya syndrome is relatively rare. However, distinction from unilateral large vessel disease without collateral is important as the natural history may be different and surgical revascularisation may be a therapeutic option for patients with collateral vessels. Of note, 2 of the 3 children with unilateral disease had no identified risk factors, either for ischaemic stroke or, more specifically, for moyamoya syndrome.

Clinical screening may not, therefore, be useful in selecting patients at risk and a high index of suspicion is important. The possibility of moyamoya syndrome should be considered in children with suggestive clinical features such as recurrent ischaemic events or unexplained cognitive decline. Although, as discussed above, collateral vessels may be poorly visualised even in patients in bilateral disease, the presence of bilateral cerebrovascular involvement should also lead to consideration of this diagnosis.

Conventional cerebral angiography remains the gold standard for diagnosing arterial dissection; it has the additional advantage of enabling evaluation of the cerebral circulation for the presence of an associated abnormality such as fibromuscular dysplasia[177,179]. The angiographic features of ICA dissection are occlusion of the artery adjacent to, or just distal to, the dissection; if the vessel is not completely occluded, luminal irregularity and narrowing over a variable distance results in a classical "string" sign (see figure1(12)), double barrel lumen or visualisation of an intimal flap; in some cases a pseudoaneurysm may be apparent[176,178,179,453]. On serial angiography, most stenotic lesions resolve or improve[177,179]; however, occlusions are unlikely to recanalise and aneurysms may develop in previously stenotic areas[178,179,454]. Although VA dissection may also result in a classical "string sign", other features include distal branch occlusion and basilar tip occlusion due to embolus[178,180,455].

More recently MRI, MRA and Duplex ultrasound have proved to be effective methods of detecting arterial dissection. Diagnostic findings of arterial dissection on MRI are an eccentric flow void surrounded by a crescent shaped hyperintensity (due to the intramural haematoma) on T1- and T2-weighted images. The diagnostic sensitivity of MRI can be improved by taking fine cuts in the axial and coronal planes and by use of T1-weighted

images with fat suppression[177,189]. Although ICA stenosis or occlusion can also be detected by MRI, this lacks specificity for the diagnosis of dissection; similarly, an apparent reduction in flow may be artefactual and should not be over-interpreted. The overall diameter of the affected vessel is usually larger than on the unaffected side[189]. Magnetic resonance angiography may be useful in serial evaluation of lesions and can demonstrate evidence of vascular healing[453].

Overall, the sensitivity of MRI and MRA for the diagnosis of VA dissection is less than for ICA dissection[241,455]. This is due to the anatomical location of the VA's and the greater potential for artefact from surrounding structures, making MRI and MRA difficult to interpret in this area. Angiography may, therefore, be necessary to exclude dissection in the posterior circulation[201]. Patient 67 who had recurrent strokes in the distribution of the posterior circulation had 2 arteriograms showing stenosis of the L PCA and occlusion of the R SCA. A third study was carried out in view of the child's recurrent symptoms which was suggestive of dissection of the V3 segment of the L VA. Following review, it was apparent that the 2 earlier studies had not imaged the proximal VA's; this point should be considered when excluding this diagnosis in patients with posterior circulation ischaemia.

Ultrasound (either Doppler or Duplex ultrasound of the cervical vessels or transcranial Doppler ultrasound of the basal vessels) may be a valuable adjunct to diagnosis. The sensitivity for ICA dissection is just over 90% and is especially high in cases with vascular occlusion[177,199]. Ultrasound is less sensitive in VA dissection with a sensitivity of just over 70%[200].

Although specific MRI sequences may improve detection of arterial dissection, as discussed above, these are not always available yet on a routine basis in clinical practice. This may partly account for the relative lack of sensitivity of MRI and MRA for arterial dissection in the patients discussed here. Four of the 6 patients with arterial dissection gave a history of cranial trauma within 48 hours of the stroke but this was minor in most cases (e.g. hitting the head on a door frame, falling off a skateboard, diving). However, all the patients who gave a history of cranio-cervical trauma were subsequently shown to have arterial dissection. Patient 67 had a choreo-athetoid cerebral palsy and may have had recurrent mild trauma to the VA. It would, therefore, be reasonable to suggest that dissection should be excluded in all children with ischaemic stroke who had preceding cranio-cervical trauma; movement disorders or conditions associated with cervical vertebral anomalies. Clinical features such as head or neck pain or Horner's syndrome may provide additional clinical clues to the diagnosis. Given the relatively poor sensitivity of non-invasive techniques in the detection of VA dissection, the threshold for proceeding to cerebral angiography should be lower in patients with infarction in the distribution of the posterior circulation.

Although large vessel involvement in cerebral vasculitis may be apparent on MRA, the distinction from focal vascular disease may be impossible without examination of smaller vessels. Angiographic features suggestive of vasculitis are alteration in vessel calibre, usually resulting in constriction, irregularity or dilatation of vessels, beading, vascular occlusion and the presence of collateral pathways[209]. The process may be contiguous within a vessel or multifocal involving many vessels. Angiography is abnormal in over half of cases but these abnormalities may be non-specific[217]. The size of vessel involved varies according to the underlying process. Ten percent of patients will have disease in the

pre-capillary arterioles which are beyond the resolution of angiography[208,456]. The appearances of IAC and a secondary vasculitis (e.g. due to infection) may be radiologically indistinguishable; an underlying process should therefore be sought in all cases[209].

In addition to the 4 children with angiographic appearances of cerebral vasculitis described here (patients 27, 44, 90 and 109), an additional patient (patient 98) who had isolated MCA stenosis at the time of this study has gone on to develop angiographic evidence of a diffuse cerebral vasculitis. Patients 27 and 44 were known to have a systemic vasculitis. Patient 90 had angiographic evidence of a focal vasculitis with beading of the affected segment, without any underlying process. Patients 98 and 109 have had progressive cerebrovascular disease without evidence of a systemic vasculitis and fall into the diagnostic category of IAC. Both have had recurrent strokes (see figure 1(14)) resulting in severe neurological disability. The aggressive course of the cerebrovascular disease was not predictable on the basis of the initial conventional angiogram in either case. The diagnosis of cerebral vasculitis should be considered in patients with recurrent or progressive symptoms or in those with a vasculitic process elsewhere. A normal conventional angiogram does not exclude a diagnosis of cerebral vasculitis and cerebrovascular imaging may need to be repeated before the diagnosis is apparent.

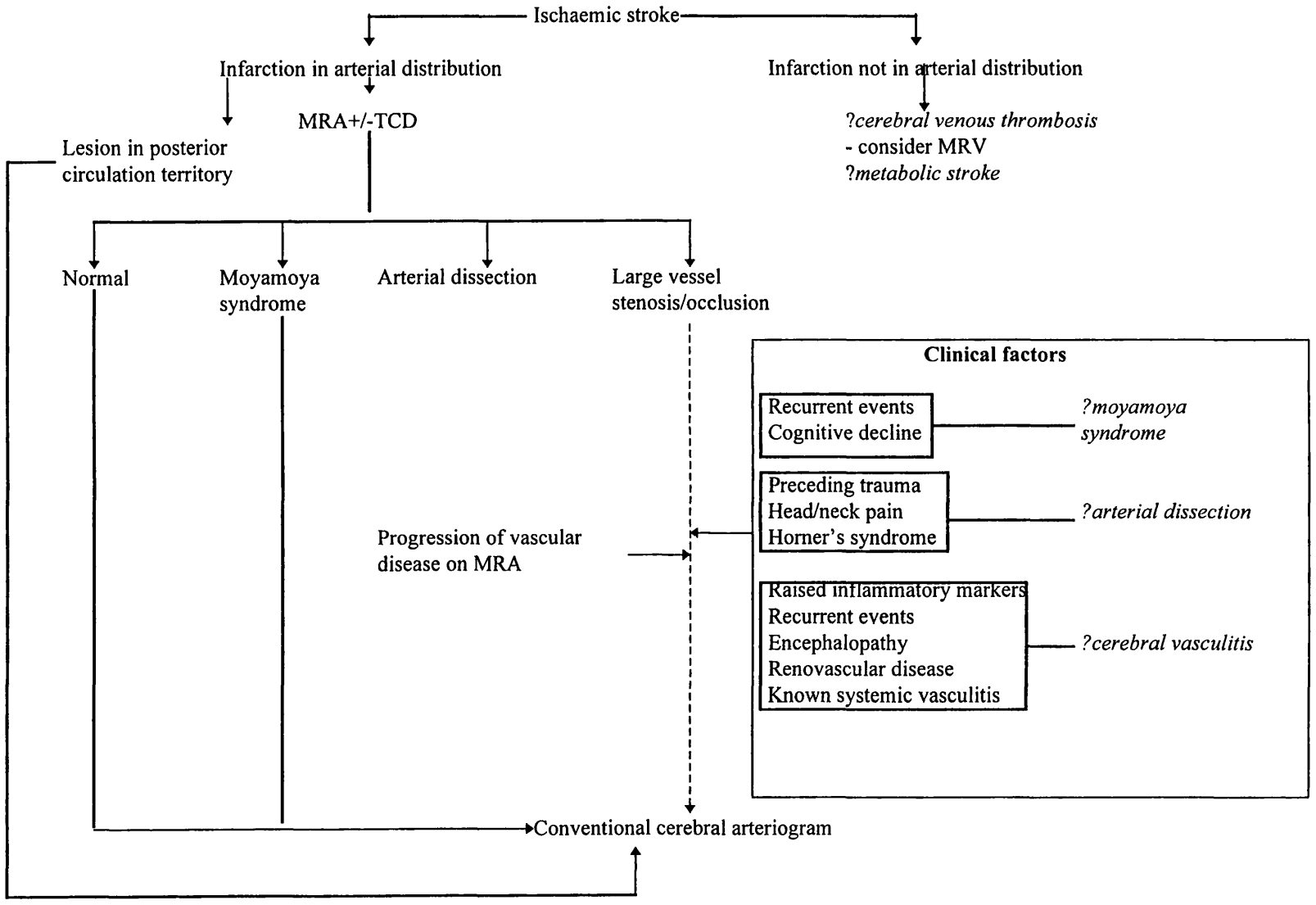
The diagnosis of fibromuscular dysplasia was not made in any of the patients included in this study. It is tempting to speculate that at least some cases of long segment ICA or MCA stenosis represent areas of fibromuscular dysplasia but in the absence of other supportive evidence (e.g. extracranial vessel involvement)[221] this would require

histological confirmation. Although the "string of beads" appearance on angiography is said to be typical, there may be variety of other angiographic appearances such as smooth tubular stenosis, webs or diverticulae[160,222]. The "string of beads" appearance may be mimicked by focal arteritis and is therefore not pathognomonic[86]. Angiography remains necessary for diagnosis as MRA is of insufficient resolution at present.

In practical terms, what approach should be adopted in investigating the child with acute ischaemic stroke for the presence of cerebrovascular disease? Magnetic resonance angiography and TCD have both been shown to have high sensitivity compared to conventional angiography in the detection of large vessel disease in children with sickle cell anaemia[115,124]. Could a similar approach be extended to all children presenting with ischaemic stroke? Although detection of large vessel disease determines management in children with sickle cell anaemia, as discussed previously, the spectrum of treatable cerebrovascular abnormalities in other children is much wider. The resolution of MRA only permits examination of vessels of more than 1mm in diameter[106]. The sensitivity of MRA for lesions in the posterior circulation is relatively poor[115], as was evident in the present group of patients. Transcranial Doppler ultrasound, similarly, only permits examination of the large basal vessels. The technique is not widely available to paediatricians and a significant number of patients may not have an ultrasonic window. Both MRA and TCD rely on flow characteristics; neither technique gives true anatomical information and normal studies may not, therefore, exclude vascular disease. Based on these technical factors and the results of the present study a clinical algorithm for the use of contrast angiography in children with ischaemic stroke is outlined in figure 5(1). Although the present study would support the view that all children presenting with ischaemic stroke should be investigated with MRA in the first instance, this algorithm is

intended to assist patient selection for cerebral angiography to maximize detection of potentially treatable cerebrovascular abnormalities (i.e. arterial dissection, moyamoya syndrome and cerebral vasculitis). Conventional angiography remains the gold standard for defining cerebrovascular pathology. As more treatments become available for ischaemic stroke, contrast angiography may assume even greater importance in guiding their use.

Figure 5(1): Algorithm for the use of cerebral angiography in the investigation of ischaemic stroke in childhood



Patient	Risk factor	Angiographic findings	Findings on MRA
9	Ventricular septal defect	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
21	Facial naevus	Bilateral moyamoya syndrome	MRA not done
28	Noonan syndrome, heterozygous for FVL mutation, supravalvular aortic stenosis	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
44	None	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
81	None	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
93	None	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
113	Preceding chickenpox	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
114	Type 1 protein S deficiency	Bilateral moyamoya syndrome	Bilateral moyamoya syndrome
19	Cranial irradiation	L sided moyamoya syndrome	Reduced flow L MCA
65	None	L sided moyamoya syndrome	L sided moyamoya syndrome
77	None	L sided moyamoya syndrome	L MCA stenosis
*88	Cranio-cervical trauma	L ICA dissection	Reduced flow L ICA/MCA/ACA
*99	Cranial trauma	R ICA dissection	Reduced flow R ICA/MCA
*97	Cranial trauma	R VA dissection	Occlusion of distal R VA
*100	None	L VA dissection	Normal
*120	None	Occlusion of R SCA; irregularity of L PCA; evidence of L VA dissection on 3rd arteriogram	Normal
*124	Cranial trauma	R VA dissection	Reduced flow R VA
7	Haemolytic uraemic syndrome	L MCA occlusion	L MCA occlusion
12	Aortic coarctation, hypertension	L ICA occlusion	MRA not done
62	None	LMCA occlusion	MRA not done
64	Non-specific febrile illness	Partial occlusion of R MCA by embolus	R MCA occlusion
66	None	L MCA occlusion	Reduced flow L ICA
85	None	Basilar tip occlusion, filling defect in L VA	MRA not done
94	None	Occlusion of L PICA	MRA not done

Patient	Risk factor	Angiographic findings	Findings on MRA
95	Preceding chickenpox	R MCA occlusion	R MCA occlusion
***83**	None	Irregular basilar tip	Small basilar artery
86	FVL heterozygote	Proximal L MCA stenosis	L MCA stenosis
91	None	Terminal L ICA and MCA stenosis	L MCA stenosis
101	None	R terminal ICA/MCA stenosis	MRA not done
***104**	None	R MCA stenosis; posterior circulation normal	Abnormal flow R MCA and PCA
109	High titre of anti-*mycoplasma pneumoniae* IgM	Stenosis R terminal ICA/MCA	MRA not done
115	FVL heterozygote	Stenosis of R terminal ICA	Reduced flow R ICA, MCA, ACA
117	None (Subsequently had 2 further strokes)	R MCA stenosis	Proximal R MCA occlusion
123	FVL heterozygote	Terminal R ICA and MCA stenosis	Absent flow proximal R MCA and ACA
***38**	Polyarteritis nodosa, hypertension	Attenuated and tortuous small vessels compatible with arteritis	Normal
***59**	Systemic vasculitis	Irregularity/focal stenosis of multiple vessels compatible with cerebral vasculitis	MRA not done
***70**	None (this study carried out after second stroke)	Stenosis and tortuosity of multiple vessels suggestive of cerebral vasculitis	L MCA occlusion
60	None	Focal arteritis of R MCA	Small R ICA/MCA
***46**	Chemotherapy for abdominal lymphoma	Irregularity of small vessels	Normal
***53**	Severe hypertension	Attenuation of all vessels compatible with chronic hypertension	Abnormal flow proximal MCA bilaterally
***58**	Dilated cardiomyopathy; axillary artery thrombosis	Occlusion of L angular branch of MCA	Not done
11	Homozygous sickle cell anaemia	Normal 4 vessel study	Normal

Patient	Risk factor	Angiographic findings	Findings on MRA
14	Previous meningitis	Normal 4 vessel study	Normal
48	Previous surgery for craniopharyngioma, APCr, familial hyper-cholesterolaemia	Normal 4 vessel study	Normal
72	None	Normal R carotid study	Normal
73	None	Normal 4 vessel study	Normal
110	None	Normal L carotid and vertebral study	MRA not done
112	None	Normal 4 vessel study	MRA not done

Table 5(1) Clinical details and radiological findings

* = patients in whom findings on conventional cerebral angiography altered clinical management

6. Outcome after ischaemic stroke

6.1. Patients who died

Of the whole group, 15 children had died at the time of the study. Six children had died in the acute period following the stroke. Two children (patients 3 and 50) had died of intractable intracranial hypertension secondary to massive MCA territory infarction. Patient 32 died secondary to massive cerebral venous thrombosis. Patient 7 had a secondary intracranial haemorrhage while on heparin and died following this. Patient 59 suffered infarction as a result of direct ICA trauma during surgery for a craniopharyngioma and died in the post operative period. Patient 15,who had complex cyanotic congenital cardiac disease, died as a result of cardiac disease in the acute period following the stroke.

Nine children died some time after the stroke. Seven of them were known to have cardiac disease and died as a consequence of this. The cause of death was unknown to us in the two remaining cases (patients 47 and 52).

6.2. Patients whose parents responded to the questionnaire

The parents of 90 children responded to the questionnaire survey and these children will be discussed in detail. They were aged 3 months to 16 years (median age 5 years) at the time of stroke. Thirty-six of the 90 children (42%) were in the "symptomatic" stroke group. The interval between the stroke and collection of outcome data was between 3

months and 13 years (median 3 years). Of those who did not respond, 14 families had moved and could not be contacted by post or telephone.

Seventy-five children (83%) presented with acute hemiparesis (involving the right side in 36 cases), 4 presented with cerebellar signs and 2 presented in coma. Six children had bilateral motor signs, one child presented with recurrent transient visual loss and the final child with chorea. Patient 9 presented with dysphasia after developing an axillary artery thrombus, as previously described. Thirty children (33%) had seizures during the acute presentation.

The lesions involved the territory of the anterior cerebral circulation in 65 children (72%), the territory of the posterior circulation in 13 children, both distributions in 6 children and were confined to the internal borderzone in 2 children. Three children had cerebral infarction secondary to cerebral venous thrombosis. Thirty children (34%) had left hemisphere lesions, 31 had right hemisphere lesions and 28 children had bilateral lesions. Fifty-three (59%) children had lesions which involved cortical structures.

6.3. Ascertainment of outcome - results of parental questionnaire

Table 6(1) summarises the results from the parental questionnaires. Seventy-eight of the children were reported to have developed clear handedness before the stroke. Twenty-three of them had changed handedness following the stroke. Four children were not able to walk at the time of follow-up. One of them (patient 109) had bilateral MCA territory infarctions; although she made a good recovery from the first stroke she became quadriplegic after the second event; another child (patient 96) was walking with a frame

after a right hemiparesis at 10 months of age but became quadriplegic after an encephalitic illness. The third child (patient 2) had complex cyanotic congenital cardiac disease and developed left hemiparesis after right ICA occlusion at 10 months of age; he was not able to weight bear through his leg 6 months later, at the time of the questionnaire. However, subsequently, following successful cardiac surgery, his rate of developmental progress has increased and he is cruising. The final child (patient 53) had a bone marrow transplant for Omenn syndrome and developed a right hemiparesis at 6 months of age. He went on to develop intractable epilepsy and at 9 months of age had evidence of a bilateral motor disorder. Following control of his seizures he has also begun to make developmental progress.

Thirty-eight children (42%) were reported to have speech and language difficulties; of them 14 had left hemisphere lesions, 8 had right hemisphere lesions and the remaining 16 had bilateral lesions.

The outcome scores for the whole group are shown in figure 6(1). Overall, 13 children (14%) were reported to have no residual deficits. Thirty-seven children (41%) had a "good" outcome and fifty-three children (59%) had a "poor" outcome as previously defined in section 2.5.4.1.

6.4. Ascertainment of outcome - therapists' assessment and neuropsychological evaluation

Twenty-two children (24%) had been seen by the paediatric therapists. Neuropsychological assessments were carried out in 19 children, 15 of whom had also been seen by the therapists. Four children were assessed using the BSID. IQ was measured using the WPPSI-R in 2 children, the WISC-III in 9 children and the WAIS-R in 3 children. Language was assessed in 19 children using the Clinical Evaluation of Language Fundamentals-Revised (CELF-R, CELF-Preschool).

Three of the 4 pre-school children assessed using the BSID were significantly delayed i.e. functioning at an age-equivalent level that was more than 20% below their chronological age. Of the others, 5 children had IQ in the average range (90 to 109); 8 were low average (80 to 89), 2 were extremely low (<69) and 2 were high average range (110 to 119). Nine children had a significant discrepancy between verbal and performance IQ. On the basis of the criteria previously discussed, the 10 children with an IQ of equal to or less than 89 were deemed to be at risk of learning difficulties; 7 of them (including both the children with IQ<69) had had a formal assessment of their educational needs within the educational system. Two of the children with IQ in the low average range were in mainstream education without any additional help.

Eight children were significantly impaired on tests of expressive and receptive language function (total CELF score <85 or functioning at >20% below chronological age for language function in BSID). Seven of them had evidence of cognitive impairment; 4 had

IQ in the low average range, 1 had IQ in the exceptionally low average range and 2 infants showed evidence of significant cognitive delay in the BSID.

6.5. Agreement between parental report and therapists'/neuropsychological assessment

Table 6(2) summarises the agreement between parental report and professionals' assessment. Agreement was good or very good for the questions which required a qualitative assessment, with the exception of the assessment of speech and language. For this measure, agreement was moderate between the parents and the therapists but only fair between parental assessment and neuropsychological assessment. Parents tended to under-report deficits in language function which were apparent on neuropsychological assessment. Agreement was only moderate for the two questions which required quantitation (questions 5 and 6) although agreement was very good as to whether or not a motor deficit was present in either the upper or the lower limb. This is not surprising as it has previously been shown that increasing the number of possible responses reduces the inter-observer agreement[457]. Where there was a discrepancy in the scoring of the motor deficits, the parents rated upper and lower limb function as being worse than the therapists in all except 1 case.

6.6. The effect of clinical factors on outcome

A logistic regression model was used to examine the effect of clinical factors on outcome (see table 6(3)). R^2 for the model was 0.15. Age at the time of stroke emerged as a

significant predictor of outcome: the age of the patients with poor outcome was significantly lower (see figure 6(2)). None of the other variables examined (time since stroke, presence of a previous risk factor for stroke, infarct location (cortical vs. subcortical and unilateral vs. bilateral) and seizures at acute presentation) was significantly predictive of outcome.

6.7. Discussion

The findings of the present study indicate that although some children with ischaemic stroke are left with few neurological deficits, the majority have residual difficulties which encompass a wide range of functions and lead to difficulties both in the home and in the educational environment. Younger children appear to have a worse prognosis that older children; however, other clinical variables do not appear to clearly influence outcome.

It is important to acknowledge the deficiencies of the present study. The questionnaire used here was intentionally simple in design and had the disadvantage of relying on reported accounts of the level of the child's disability. Such reports may both over- and under-estimate residual deficits, as was evident in the questions relating to quantitation of motor function. There are two potential sources of bias to explain parental over-reporting of the severity of motor deficits. The first is that parental perception of the severity of a deficit will be in relation to the unimpaired population while therapists will tend to rate deficits in relation to the whole spectrum of motor deficits which they experience in their professional capacity. Secondly, clinical experience suggests that as physical impairment is more readily apparent in daily life, parental attention is frequently focused on this area.

The poor agreement between the parents, therapists and neuropsychological assessment as to whether or not language impairment was present reflects some of the difficulties in assessing this complex area of function. Parents and therapists were asked for a qualitative judgement which may be a better reflection of mechanical difficulties with speech production such as oro-motor dyspraxia. Neuropsychological assessment may, on the other hand, detect deficits in the area of higher language function which may go unrecognised in day to day life, where language is used more automatically. This is reflected in the relatively poor agreement between parental perception and psychometric assessment.

Although formal measures of independence used to assess adult stroke patients such as the Barthel scale[458] have been used in a paediatric population[387], these do not touch on many of the activities of daily living relevant to a child's life (e.g. education, behaviour and play). Such scales have been shown to correspond well to the responses to simple questions about recovery and dependence in the investigation of outcome after stroke in adults[380]. Although the design of our questionnaire attempted to modify simple outcome questions to explore areas of function more specifically relevant to children, it is important to acknowledge that it has not been validated against any alternative stroke outcome scale. However, overall, there was good or very good agreement between parental and professional assessment about the areas in which the children was experiencing difficulties.

The population in this study was, of necessity, determined by parental willingness to return the questionnaire. Although this was independent of any clinical intervention, it

could be argued that parents whose children have relatively major deficits are more motivated to participate in research, and that parents who deny the severity of residual impairments may not have wished to explore these questions. However, there was a good response to the survey and the majority of the cases who were failed to respond were subsequently found to have changed address, so the data is likely to be representative. Even if this is the extreme end of a spectrum, it suggests that there are significant sequelae after stroke in childhood.

The contribution of neuronal plasticity to recovery after focal brain injury in childhood and the influence of therapeutic interventions on this process are areas of active research. The immaturity of both the brain and neuromuscular system mean that there is significant potential for physical, cognitive and behavioural deficits as well as secondary epilepsy[68]. The reported rates of disability after ischaemic stroke in childhood vary between series, determined by the populations studied and the methods used for follow-up. Appendix 2 summarises the previous studies which reported outcome after stroke in childhood. Overall, previous studies have reported that around 75% of children have residual sequelae after ischaemic stroke, similar to the rate reported in the present study.

Earlier studies of acute hemiplegia indicated that outcome was particularly poor in children presenting before the age of two, with seizures at onset[9,10,459]. The present data would suggest that a younger age at the time of the insult is predictive of a poorer outcome. It has previously been noted that the cognitive sequelae (as measured by IQ) of hemiplegia are particularly severe if brain lesions are acquired between 1 month and 5 years of age[460,461]. The data presented here would suggest that global outcome is also related to the age of lesion acquisition.

The reported mortality after acute ischaemic stroke in childhood varies widely between series and is influenced by the population characteristics[24,70,71,75,76,351]. It had been reported that the mortality within the first month is between 5 and 15% and that there is a steady mortality in the next 2 years[24]. Although some older series reported late death, usually related to prolonged seizures, this has not been reported in the more recent literature. Many children succumb to their underlying condition rather than as a result of the stroke[25,26,76], a tendency that was evident in the present group of patients.

Some studies have suggested that the presence of an underlying risk factor was an important determinant of outcome and that children with "symptomatic" stroke fared worse than those with "idiopathic" stroke[70,75,76]. This was not the case in the present group of patients, perhaps because of improved management of some chronic medical conditions in recent years.

It has been suggested that subcortical infarction in childhood carries a relatively favourable prognosis[67,70]. In the present group there was a trend towards worse outcome among those with cortical infarction rather than purely subcortical lesions, though this did not reach statistical significance. The present data differs from that reported by previous authors in that it concentrated on functional impairment rather than relying on medical assessment. This may be more revealing about significant residual functional deficits from what may be, in neurological terms, a relatively minor deficit.

Two studies, by Higgins[18] and Keidan[19], have specifically investigated the factors influencing outcome after stroke in children; unfortunately both included children with

both ischaemic and haemorrhagic stroke and did not clearly distinguish between these groups when discussing outcome. Higgins investigated outcome in terms of survival and death and suggested that cerebral haemorrhage and depression of conscious level were significant risk factors for death[18]. Age was not a predictor of survival or death, in contrast to the findings of the present study. Keidan[19] was unable to show any relationship between age, gender, aetiology and outcome in their group of 45 children. In this study, however, outcome was categorised in terms of specific deficits (e.g. motor deficit, seizures) whereas the present study investigated the effect of clinical variables on global outcome.

Overall, residual motor deficits are common after ischaemic stroke in childhood and may affect up to 90% of children[10,24,26,70,381,382]. Given than acute hemiparesis is the commonest presentation of acute ischaemic stroke in childhood[70,76], it is not surprising that motor deficit takes this form in most children. As lesions most commonly affect the MCA territory, a common pattern of deficit is for the upper limb to be more severely affected than the lower limb, both at onset and in terms of subsequent recovery[17]. Hemiparesis of early onset may be associated with reduction of growth in the affected limb[462]; in functional terms, a leg length discrepancy may further impair gait.

Children with striatocapsular infarcts may experience significant residual dystonia of the hemiparetic hand[70]; this appears to be a sequel of basal ganglia injury which is unique to childhood[26,463] and may affect around 60% of children[68,70]. Dystonia appears to be more common in children with no underlying disorder (i.e. "idiopathic" stroke)[70,76]. Lanska[82] noted that children who had not regained useful hand function within the first fortnight after stroke were unlikely to do so and were more likely to change handedness. Clinical

experience suggests that motor recovery occurs most slowly and incompletely in the area of hand function. It may, therefore, be useful to target hand function specifically in early rehabilitation therapy. Although it has been observed that dystonia may be progressive[70], this was not observed in the patients studied here. However, it is important to acknowledge that we did not specifically try to identify dystonia and no conclusions can therefore be drawn about this area.

In contrast to this, although difficulties were reported as commonly with leg function as with hand function, all but 4 children in the present group were able to walk after their stroke. These exceptions had had more than one neurological insult in 2 cases and had had very severe early insults, complicated by hypoxia and seizures, in the other 2 instances. Following treatment of the cardiac disease and control of seizures respectively, the rate of developmental progress in the latter 2 children suggests that they will eventually learn to walk. It is, in fact, the norm for children to regain ambulation after ischaemic stroke, unless they have secondary insults[82]. In children who are going to make a good motor recovery, the maximal improvement usually occurs within the first fortnight[82]; recovery of function tends to be faster in the lower limb compared to the upper limb and proximally rather than distally. Persistence of hemiparesis beyond 1 month predicts a poor motor outcome[67].

No attempt was made to evaluate other deficits such as cortical sensory deficits and visual field defects. These have previously been noted[68,76,77,462] but are probably under-reported due the difficulties of identifying such problems in young children. Visual field defects may affect up to ¼ of children who have had stroke[76,462] and ascertainment of such deficits in young infants may require detailed neurophysiological investigations. Cortical sensory

deficits may significantly impede rehabilitation due to difficulties with orientation of body parts in space[68,77]. Mirror movements are also frequently seen in children with residual hemiparesis and are thought to be related to reorganisation of central motor pathways[68].

The reported incidence of secondary epilepsy after ischaemic stroke varies widely. The Joint Committee for Stroke Facilities[68] reported an incidence of 50% but did not distinguish between haemorrhagic and ischaemic stroke. Isler[351] reported an incidence of 50% in 87 children with cerebral arterial occlusion. However, in more recent series[70], residual epilepsy occurred less frequently, affecting 12/44 (27%) of children with radiologically confirmed ischaemic stroke and only 2/22 children in whom no aetiology could be identified. The exclusion of patients with syndromes such as HHE from later studies probably at least partly accounts for this. Overall, the prevalence of epilepsy after stroke seems to be higher than in children compared to adults, in whom it is around 5%[130]. The short period of follow-up in this study may have resulted in a falsely low impression of the prevalence of secondary epilepsy. Cortical involvement and persistence of seizures beyond 2 weeks have been shown to be risk factors for persistent seizures[67,83]. As unrecognised epilepsy may be a cause of cognitive impairment, a high index of clinical suspicion should be maintained.

It is notable that none of the studies of paediatric stroke summarised in Appendix 2 included any information about language outcome. The effect of brain injury on language function is complex. Although early clinical observations suggested that language function is usually spared after early brain injury, this has been refuted by subsequent investigations[464] though relative preservation of verbal skills may occur at the expense of

visuospatial skills or reduction in overall IQ[461,464]. Lees and Neville showed that recovery after acquired aphasia proceeded in two phases; there is a rapid recovery phase and then a slower phase which may continue for 1-2 years. They also found that children functioning within the "normal range" could have qualitative deficits in speech and language function[465]. It is apparent from the data presented here that significant speech and language problems, recognisable by the child's parents, are relatively common. As parents were not asked to distinguish between the mechanical and cognitive aspects of speech and language, the prevalence of deficits in higher language function may be higher than reported here. It was apparent from the small subgroup of children who underwent formal evaluation of language that significant language impairment can go unrecognised by lay observers and this area should be specifically targeted for formal evaluation.

In a previous study, Abram[67] found that most children who had had stroke could be educated in a mainstream school environment. Although most of the children in this study were in mainstream education, 56% were in primary school at the time of data collection; secondary education may prove more challenging to this group. Detailed psychometry may reveal subtle cognitive deficits in this population, evident in the high frequency of children with significant discrepancies between verbal and performance IQ's. In particular, the cognitive sequelae of striatocapsular infarction deserve further investigation in the paediatric stroke population where such lesions are common[131,139].

The relatively high prevalence of behavioural difficulties in our patients is similar to that previously noted in a study of children with hemiplegia[460]. While behavioural sequelae may be a direct consequence of lesions of the frontal lobes or basal ganglia[140], secondary behavioural problems may also arise as a result of functional disability. Hyperkinesis,

impulsivity, reduced attention and unrecognised cognitive deficits may impede function within a mainstream school environment[68]; difficulties with peer group relationships may compound this. Anxiety may also be an important factor underlying behavioural difficulties[460].

One of the frequent comments made by parents surveyed in this study related to the lack of awareness and information about the spectrum of difficulties experienced by children after stroke; the lack of information and rehabilitative facilities for children with stroke has also received some recent attention in the media[383]. The personal and economic sequelae of stroke in childhood in adult life remains unexplored. Although more detailed studies will be required in order to better characterise these deficits, this preliminary survey has identified some of the areas in which children who have suffered ischaemic stroke experience difficulties and may serve as a guide for professionals involved in the rehabilitation of children who have had ischaemic stroke. This data also suggests that acute stroke therapies merit formal evaluation in the paediatric stroke population as there is potential for prevention of long-term disability.

Parental questionnaire investigating outcome

The questionnaire investigating outcome was designed by the candidate and was given to parents either at a clinic visit or sent to them in the post. The questionnaire was usually completed by the parents at home.

The main disadvantage of the questionnaire as a clinical tool for investigating outcome is lack of validation in relation to a recognised paediatric functional outcome measure. A further weakness is that it provides little information about cognitive or psychological outcome. There was overall a bias towards identifying disabilities associated with motor impairments. Another potential source of bias was reliance on reported rather than objective responses to the questions. Although the therapists completed the questionnaire in the same manner at the parents, the study could have been strengthened by asking them to complete the questionnaire prospectively.

Despite these limitations, the strengths of the questionnaire are that it comprises simple questions about very broad, global areas of function and there was, in general, good inter-rater agreement. Although biased, it provides some insight into parental perception of outcome, which may be more informative than a professional's perspective.

Area investigated	Number of children (%)
Child needs additional help in some areas more than other children of comparable age	58 (64%)
Child needs help at home	54 (60%)
Child needs help at school	53 (59%)
Child has motor impairment	66 (74%)
Child has difficulty using hemiparetic hand	59 (66%)
Child has difficulty using hemiparetic leg	59 (66%)
Child has difficulty with speech and language	38 (43%)
Parents concerned about child's behaviour	33 (37%)
Child is on anticonvulsants for epilepsy	13 (15%)
Child attends mainstream school (with help)	73 (81%) (30 (33%))
Child attends special school	17 (19%)
Child has had statement of educational needs	43 (48%)
No residual deficit	13 (14%)
Good outcome	37 (41%)
Poor outcome	53 (59%)

Table 6(1): Outcome reported by parents

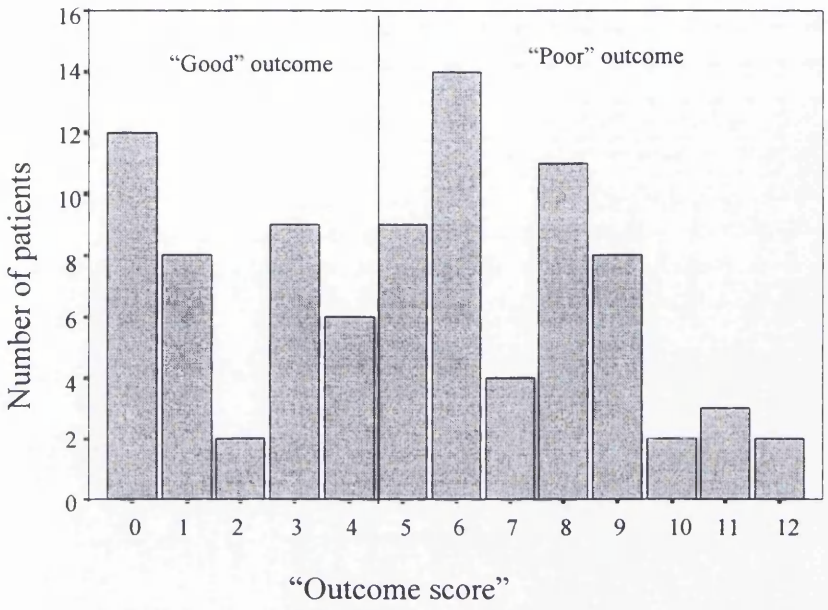


Figure 6(1):" Outcome scores" for patients who responded to questionnaire

Question	Number of children who had parental and professional assessment	Number in whom both assessments agreed	Agreement - KC (95% confidence intervals)
Does the child need additional help in any areas (more than you would expect for his/her age?)	18	17 (94%)	0.82 (0.49 - 1.15)
Does the child need help at home?	14	13(93%)	0.76 (0.31 - 1.21)
Does the child need help at school?	13	13 (100%)	1.00
Does the child have difficulties with speech and language? (parental response compared to therapists response)	18	12 (67%)	0.60 (0.15 - 1.05)
Does the child have difficulties with speech and language? (parental response compared to neuropsychological assessment)	21	13 (62%)	0.22 (-0.17 - 61)
Does the child have a residual motor deficit in the upper limb?	10	10 (100%)	1.00
How well can the child use his/her weaker hand ? (score 0-3)	18	11 (61%)	0.47 (0.18 - 76)
Does the child have a residual motor deficit in the lower limb?	20	19 (95%)	0.83 (0.5 - 1.16)
How well can the child use his/her weaker leg ? (score 0-3)	20	11 (55%)	0.42 (0.17 - 0.67)

Table 6(2): Comparison of parental report and functional/neuropsychological assessments

Variable	Regression coefficient (b)	SE (b)	Odds ratio (Exp b)	95% CI for odds ratio	p
Age at time of stroke	-0.12	0.06	0.89	0.79 - 0.99	0.04
Time since stroke	-0.02	0.07	0.98	0.85 - 1.12	0.76
Lesion location 1. cortical vs. subcortical	-0.73	0.48	0.48	0.19 - 1.23	0.13
2. unilateral vs. bilateral	0.24	0.59	1.28	0.40 - 4.07	0.68
Previous risk factor for stroke ("symptomatic vs. "idiopathic" stroke)	-0.73	0.53	0.48	0.17 - 1.36	0.17
Seizures at time of stroke (present or absent)	-0.12	0.51	0.89	0.79 - 1.00	0.82

Table 6(3): Results of logistic regression analysis examining the effect of clinical factors on outcome

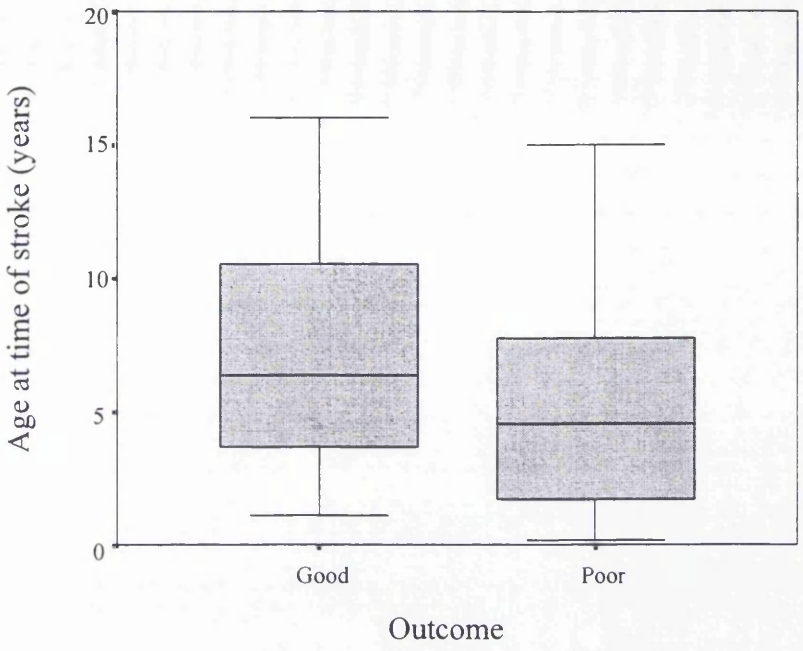


Figure 6(2): Relationship between age at time of stroke and outcome

On the box-and-whisker plot, the horizontal line indicates the median value, the shaded box indicates the quartiles and the "whiskers" indicate the extreme values.

7. Lesion volume, lesion location and outcome after middle cerebral artery territory infarction

7.1. Patient characteristics

The territory of the middle cerebral artery is the most frequently affected arterial territory in children with ischaemic stroke[17] and the clinical features of lesions in this area are well characterised. In order to examine the influence of lesion characteristics on outcome in as homogenous a group of patients as possible, this section of the study was limited to children with lesions in the MCA territory. Children with lesions in this territory who had moyamoya syndrome were excluded because firstly, many had multiple infarcts, and secondly, neurological dysfunction in this group may be secondary to cerebral hypoperfusion as well as to infarction.

Thirty-eight children were studied. They ranged in age from 6 months to 15 years (median age 6 years). There were 22 boys. In 24 cases MRI studies were available from the first week after the acute stroke; 6 patients were imaged within 1 month and 5 within a year of the stroke. Three patients were imaged much later (after 5, 6 and 8 years). One child (patient 82) had an acute deterioration after making an initial recovery; in this instance the scan obtained after the second event was analysed.

Eleven children fell into the "symptomatic stroke" group. Risk factors for ischaemic stroke in these patients were congenital cardiac disease in 7 cases, haemolytic uraemic syndrome in 1 case, meningitis in 1 case, sickle cell anaemia in 1 case and recent bone marrow transplantation for immunodeficiency in the remaining case.

Four children had had previous strokes and bilateral lesions (patients 3, 13, 28, 112); in two of these cases (patient 13 and patient 3) areas of infarction which had occurred "silently" (i.e. without any corresponding clinical event) were apparent on T2-weighted MRI at the time of a second, clinical stroke. Although the lesion volumes were measured in these patients and the data used in the section on reproducibility of volume measurements, the data from these children was not included in the statistical analysis of the effect of lesion volume on outcome as, due to the small numbers, the effect of having bilateral lesions could not be examined separately.

7.2. Reproducibility of volume measurements

Table 7(1) summarises the reproducibility of the measurements of intracranial and infarct volume within and between the 2 observers. The reproducibility of volume measurements for small lesions was much poorer than for large lesions as is evident in figures 7(1(a)), 7(1(b)) and table 7(1); the frequency of relatively small lesions in this study tended to increase the mean percentage difference between observers for values of lesion volume.

7.3. Infarct volumes and infarct size category

The lesion volumes ranged from $1cm^3$ to $244cm^3$. Figure 7(1(a)) shows the allocation of lesions into "large" "medium" and "small" categories (defined according to the 33^{rd} and 67^{th} percentiles for mean values of %ICV infarcted (1.03%ICV and 5.29%ICV)) by each observer. Figure 7(1(b)) depicts mean %ICV infarcted plotted on a logarithmic scale to

allow better visualisation of the comparison between measurements of small lesions made by each observer.

The measurements of the 2 observers resulted in assignment to the same lesion volume category in 33/38 cases. In the 5 cases where lesion volumes were assigned to different categories, the differences in the %ICV infarcted between the two observers was 1.29%, 1.44%, 0.18%, 0.14%, 0.13%; i.e. the differences in the %ICV infarcted between the observers were very small. This suggests that these values lay around the cut-off points for the categories, as apparent in figures 7(1(a)) and 7(1(b)) The final allocation of individual patients into the categories was based on the mean value for %ICV infarcted.

7.4. Infarct location

Figure 7(2) indicates the location of the lesions. Twenty-one of the lesions involved cortex while the remaining 17 lesions were confined to subcortical structures. All but one of the lesions which involved cortex also involved subcortical structures (i.e. there was only 1 purely cortical lesion - patient 98).

7.5. Outcome

Twelve children had a "good" outcome while 26 children with significant residual deficits had a "poor" outcome. Two children died as a result of intractable intracranial hypertension in the acute period after the stroke; they were included in the "poor" outcome category.

7.6. Relationship between infarct size category, infarct location and outcome

R^2 for the logistic regression model was 0.30. None of the variables examined (infarct size, infarct location, previous risk factor or age) emerged as significant predictors of outcome for the group as a whole (see table 7(2)). In the analysis of the subgroup of children with cortical lesions (n= 21), R^2 was 0.41. Again, none of the variables examined (infarct size, previous risk factor or age) significantly predicted outcome (see table 7(3)).

Inspection of figure 7(4), however, reveals that the subset of patients with lesion volumes greater than around 10%ICV appear to have a uniformly poor outcome. Separate comparison of this subgroup with the group of patients with smaller lesions (<10%ICV) revealed a significant difference in outcome between the 2 groups (Fisher's exact test, p = 0.036). In all these cases the lesions involved cortical tissue. No similar size threshold was apparent for the subgroup of children with subcortical lesions (see figure7(4)).

All the children who had bilateral lesions (patients 3, 13, 28 and 112) fell into the poor outcome category. One (patient 70) was in the "small" lesion category, one (patient 112) in the "medium" lesion category and two (patients 3 and 28) were in the "large" lesion category. Both the children who died (patients 3 and 28) had "large" lesions.

All of the 7 children with "small" lesions and poor outcome had lesions which involved the basal ganglia (patients 40, 99, 101, 102, 112, 114 and 115). Five of them had lesions confined to these structures.

7.7. Discussion

The findings of this study indicate that, in children with MCA territory infarcts, although the functional sequelae of small lesions may be variable, infarction of more than 10% of intracranial volume is associated with significant residual deficits.

There are methodological constraints inherent in measuring infarct volumes in the manner described in this study. The reproducibility of measuring individual volumes in the present study was compromised by the subjectivity of defining the lesion boundaries, both in the acute and chronic stages. This was especially difficult for small lesions, as apparent from the data presented in table 7(1), where relatively small absolute differences in measurement resulted in large percentage differences in repeated measurements. In contrast, the reproducibility of the ICV measurements was good.

The natural history of cerebral infarction on MRI is for signal hyperintensity and swelling on T2-weighted images to be apparent around 6 - 12 hours after symptom onset[90]. Chronic infarcts show signal hyperintensity and tissue atrophy on T2-weighted imaging. In the early stages of evolution of a cerebral infarct, tissue swelling makes definition of lesion boundaries difficult; in more chronic lesions, atrophy may cause similar problems. Although automated or semi-automated image analysis techniques may improve reproducibility[104,417] the accuracy with which such techniques measure the true volume of damaged tissue could be questioned. Moreover, absolute values for infarct volume at any stage in the lesion's evolution must be viewed with some scepticism as early

measurement may overestimate and late measurement underestimate the actual volume of damaged tissue. As swelling is more apparent around large lesions than small ones, lesion size may also be an important factor in determining the variation in individual lesion volumes during evolution. The patients investigated here comprised a heterogeneous group in terms of the timing of imaging in relation to the neurological insult. Although most of them were imaged acutely, in some cases there was an interval of several years between the event and the MR study. However, the relative rather than the absolute effects of lesion volume on outcome were under consideration (by categorising lesions into "small", "medium" and "large" lesion groups), inclusion of all the patients was considered valid.

In a recent study examining the relationship between lesion volume and outcome in adults with cortical MCA territory stroke in adults, Saunders[417] showed a significant relationship between lesion volume on T2-weighted MRI obtained within 72 hours of the onset of symptoms and outcome. The population in this study was relatively elderly (mean age 66.5 years) and of the 9 patients who died, this was not a direct result of the stroke (although at least 2 died of secondary illnesses e.g. pulmonary embolism). Compared to this group, the patients described here were more heterogeneous, including patients with purely subcortical infarction, and death or disability were more directly attributable to the acute stroke.

Lovbald[104] found that in adults with MCA territory infarction, the volume of lesions on T2-weighted MRI at a chronic time point correlated well with indices of stroke severity and functional outcome. Although this study included some patients with purely subcortical lesions, these relationships were stronger in the subgroup of patients with

cortical MCA lesions. It was noted that the correlation between lesion size and clinical status was less for smaller lesions than large ones. The relative frequency of small, subcortical lesions in the present study may partly account for the discrepancies between our findings and those of Lovbald . The methodological difficulties previously discussed may also have some bearing on this. However, an additional factor to consider when comparing the present results with those of both these studies is the differing consequences of basal ganglia injury between adults and children, as discussed below.

Unlike adult stroke patients in whom the profile of risk factors is relatively homogenous, children who suffer ischaemic stroke are a heterogeneous group. "Symptomatic " stroke or stroke in children with a pre-existing medical condition (e.g. congenital heart disease) has previously been reported to be a risk factor for a poor outcome[70,75,76]. Although this may be related to factors relating to the underlying diagnosis (e.g. chronic hypoxia) it is noteworthy that these children tended to have larger lesions. Compensatory mechanisms may be less efficient in children whose cerebral perfusion is under chronic stress. In children with cardiac disease, emboli may result in occlusion of arterial trunks, resulting in larger lesions. However, as apparent from the data presented here, the relationship between the presence of a risk factor for stroke and lesion size, lesion location and outcome is not a simple one. Neurological co-morbidity from the pre-existing risk factor needs to be considered; however given the small numbers of patients in this study , these questions could not be examined in further detail.

"Idiopathic" ischaemic stroke in childhood has previously been reported to be involve mainly to basal ganglia structures[70]. In the present group 15 of the 27 patients without previous medical diagnoses had lesions confined to the basal ganglia, without cortical

involvement. Five of them had had chickenpox within 6 months of the stroke; the relationship between preceding chickenpox and basal ganglia infarction in childhood has been discussed previously[133].

Some children with relatively small lesions confined to the basal ganglia had significant residual deficits. Unlike adult patients, children have been shown to develop significant residual dystonia after basal ganglia infarction[26,70,130,134,347]. Although the cognitive and behavioural sequelae of subcortical infarction in childhood have not been characterised in detail, there is some evidence to suggest that language function[80], behaviour and attention[140] may be affected in these children.

Although anecdotally outcome after stroke in childhood is thought to be good, it is clear from the previous literature that most children have residual deficits and that there is an appreciable mortality[24,25,466]. This would argue for a role for acute stroke therapies in the prevention of long term disability in the paediatric stroke population. The recent trials of acute stroke treatments in adults have shown that very large numbers of patients are required in order to evaluate therapies which have a finely balanced risk-to-benefit ratio. Although the estimated incidence of ischaemic stroke in childhood varies widely from 0.6 to 8 per 100 000 children per year[24,26], compared to ischaemic stroke in adults (which has an incidence of 180/100 000 per year[27]), patients numbers are small. Some means of categorisation of patients into prognostic groups would facilitate evaluation of treatment efficacy in smaller groups of patients.

In the present group of patients, infarction of more than 10% of ICV was associated with significant disability or death in all cases. This suggests that a size threshold exists for

lesion size, above which outcome is universally poor. The clinico-pathological stroke syndrome of "malignant MCA infarction" is characterised by large MCA territory infarcts. This has been shown to have a very poor prognosis in adult patients[125,126]. It would appear from this study that a similar clinico-pathological syndrome is identifiable in children. The data presented here suggest that, by combining information from lesion volume and topography, a group of children with ischaemic stroke who would be predicted to have poor outcome could be identified and enrolled in future therapeutic trials.

	Mean (95% confidence limits)
Intraobserver difference in ICV as % of mean ICV (Observer 1)	1.83 (0.99 - 2.67)
Intraobserver difference in ICV as % of mean ICV (Observer 2)	0.78 (0.53 - 1.03)
Intraobserver difference in infarct volume as % of mean infarct volume (Observer 1)	20.17 (12.59 - 27.66)
Intraobserver difference in infarct volume as % of mean infarct volume (Observer 2)	7.39 (5.29 - 9.49)
Inter-observer difference in ICV as % of mean ICV	1.96 (1.07 - 2.85)
Inter-observer difference in infarct volume as % of mean infarct volume	22.02 (12.21- 31.82)
Inter-observer difference in %ICV infarcted as % of mean %ICV infarcted	22.63 (12.99 - 32.26)
Inter-observer difference in %ICV infarcted as % of mean %ICV infarcted for "small" lesions (≤ 1.03%ICV)	43.83 (18.73 - 68.93)
Inter-observer difference in %ICV infarcted as % of mean %ICV infarcted for "medium" lesions (>1.03 & ≤ 5.29% ICV)	15.19 (7.86 - 22.52)
Inter-observer difference in infarct volume as % of mean infarct volume for "large" lesions (>5.29%ICV)	8.28 (4.76 - 11.8)

Table 7(1): Inter- and intra-observer reproducibility of ICV and infarct volume measurements.

Intra- and inter- observer differences refer to the absolute values of the differences in either infarct volume or ICV.

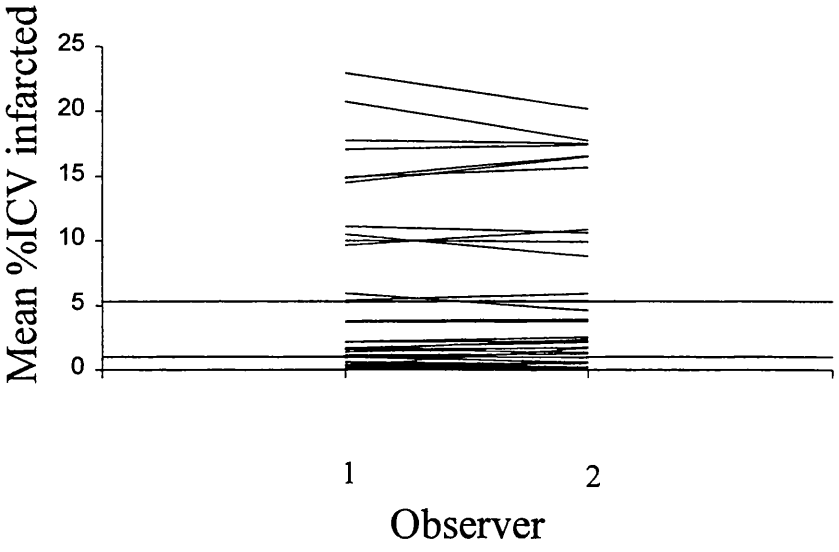


Figure 7(1(a)): %ICV infarcted measured by observers 1 and 2.

The solid horizontal lines indicate the 33rd and 67th percentiles for the values of %ICV infarcted according to which lesions were allocated into "small", "medium" and "large" categories.

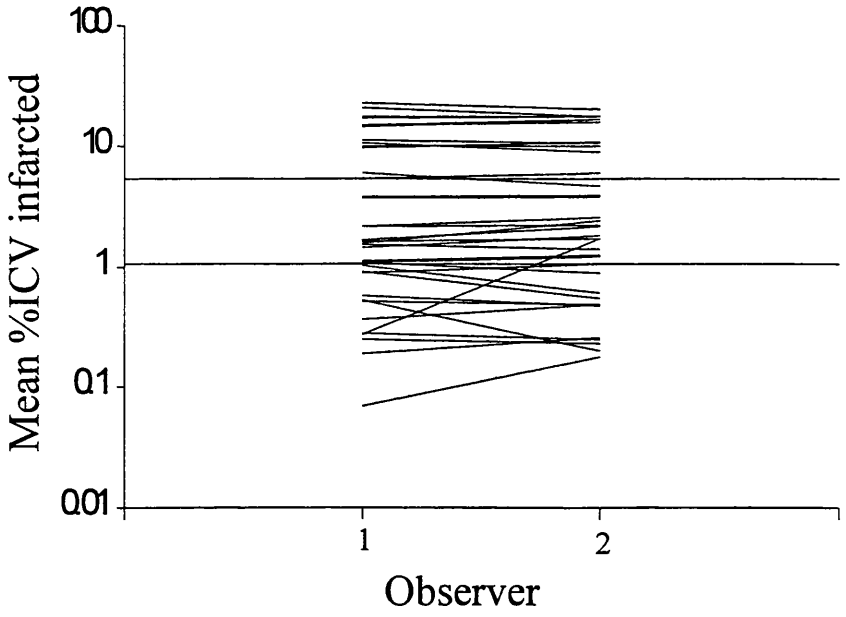
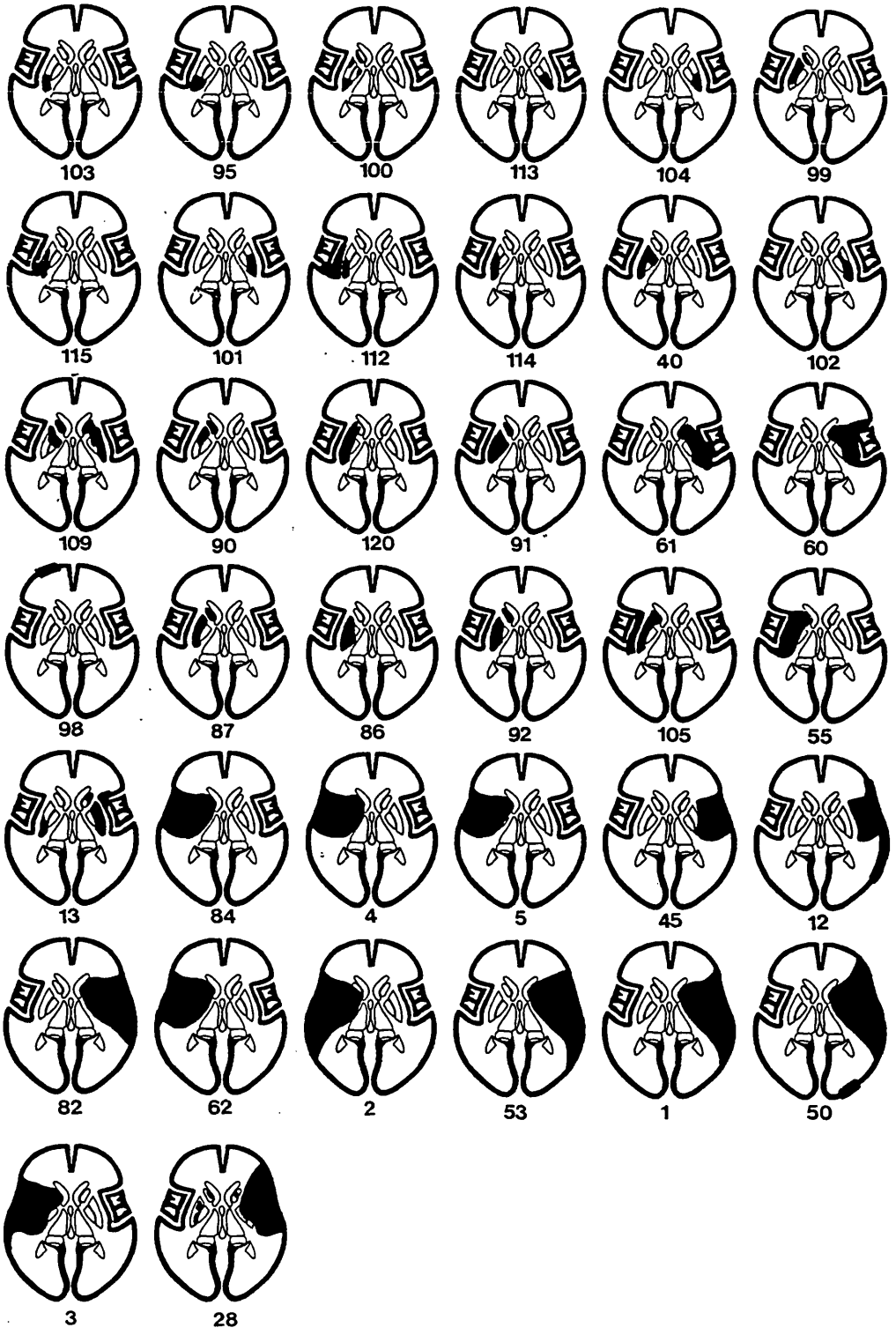


Figure 7(1(b)): %ICV infarcted measured by observers 1 and 2 plotted on a logarithmic scale.

This has been done to better illustrate the allocation of the small lesions. The solid horizontal lines indicate the 33rd and 67th percentiles for the values of (mean %ICV) infarcted according to which lesions were allocated into "small", "medium" and "large" categories.

Figure 7(2): Lesion locations depicted on line drawings of an axial section through the brain taken at the level of the IIIrd ventricle, ordered by lesion size.

The lesion location at this level is shown for each patient. Some patients had more extensive lesions at other levels. The first 13 patients have lesions which were in the "small" category, the next 12 have lesions in the "medium" category and the final 13 have lesions in the "large" category.



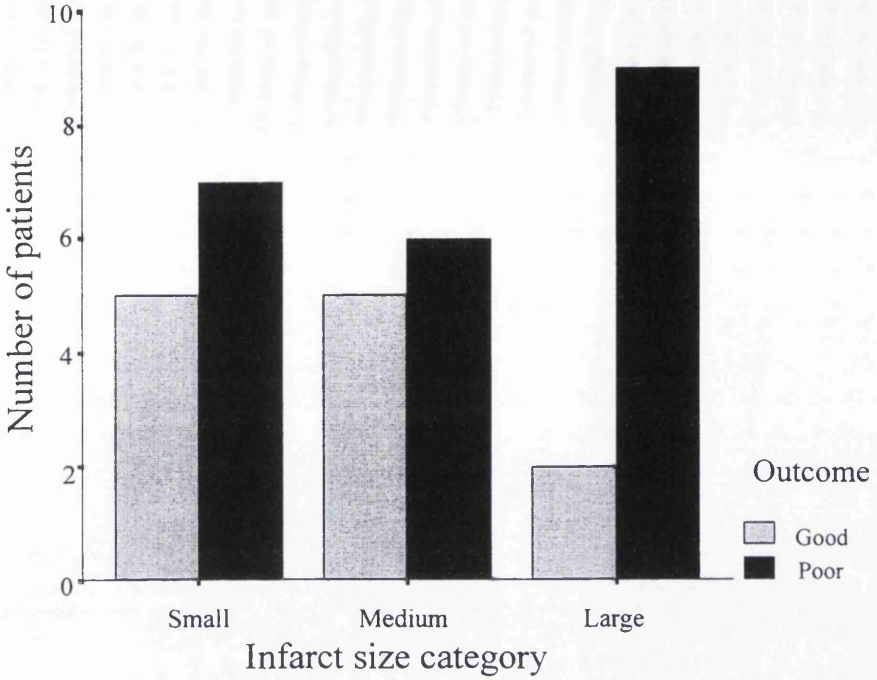


Figure 7(3): Outcome related to infarct size category.

Variable	Regression coefficient (b)	SE (b)	Odds ratio (Exp b)	95% CI for odds ratio	p
Lesion size 1. small vs. medium and large	-0.42	1.48	0.66	0.4 - 11.9	0.78
2. medium vs. small and large	-0.62	1.38	0.54	0.04 - 8.1	0.66
Lesion location (cortical vs. subcortical)	-0.40	0.92	0.67	0.11 - 4.08	0.66
Previous risk factor ("symptomatic" vs. "idiopathic" stroke)	-1.37	1.41	0.25	0.02 - 4.00	0.33
Age at time of stroke	-0.05	0.10	0.95	0.78 - 1.16	0.61

Table 7(2) Results of a logistic regression analysis examining the effects of lesion volume, lesion location, presence of a previous risk factor and age on outcome for all patients

Variable	Regression coefficient (b)	SE (b)	Odds ratio (Exp b)	95% CI for odds ratio	p
Lesion size 1. small vs. medium and large	6.70	56.62	820.64	$0 - 1.28x10^{51}$	0.91
2. medium vs. small and large	-2.62	1.90	0.07	0 - 3.04	0.17
Previous risk factor ("symptomatic" vs. "idiopathic" stroke)	0.15	1.83	1.16	0.03 - 42.28	0.93
Age at time of stroke	-0.19	0.19	0.82	0.57 - 1.18	0.29

Table 7(3): Results of logistic regression analysis examining the effects of lesion volume, presence of a previous risk factor and age on outcome for patients with cortical MCA territory lesions

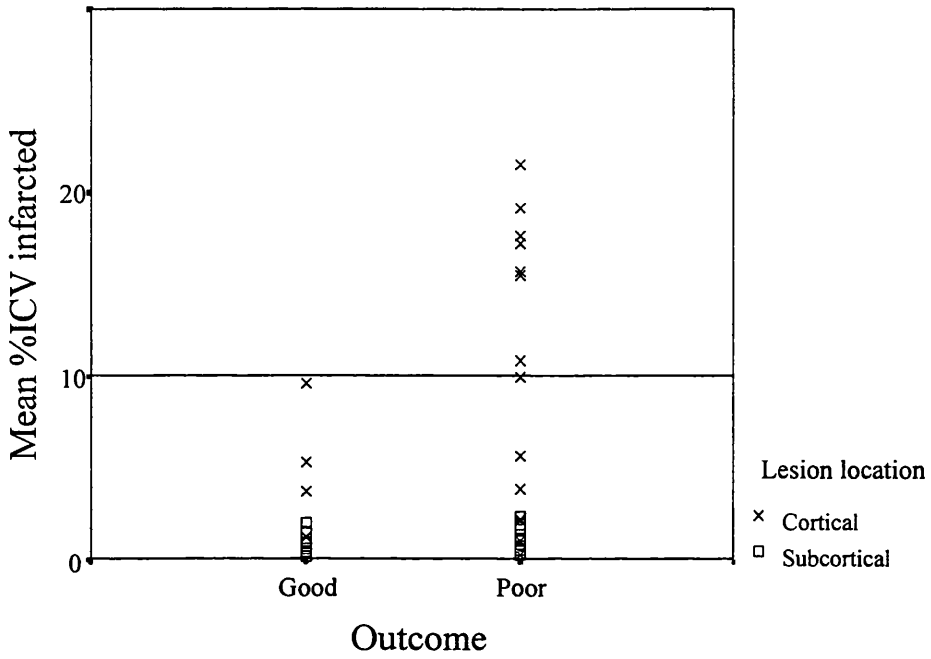


Figure 7(4): Outcome related to mean %ICV infarcted and lesion location.

8. Recurrence

8.1. Patients

Six children had died as a result of the acute stroke; one of them (patient 3) as a result of his second stroke. Information about recurrent TIA or stroke was available for 113 of the 122 children who survived the acute stroke. Transient ischaemic attacks immediately preceding stroke or extension of cerebral infarction during the acute phase of stroke were not considered as recurrent events. Figure 8(1) shows the duration for which patients were followed up. The duration of follow-up ranged from 3 months to 13 years (median 3 years).

8.2. Incidence of recurrent stroke and TIA

The incidence of recurrent events and risk factors identified in patients with recurrence are summarised in table 8(1). The clinical details of the patients who had recurrent events are summarised in table 8(2).

In total, 38 patients (32%) had recurrent events; 14 patients (11.7%) had recurrent stroke with new areas of cerebral infarction on brain imaging and 24 had recurrent TIA. Although many of the children with recurrent TIA had more than one event, none of them went on to develop stroke during the time of the study. Children who had TIA were not usually imaged after the event and the imaging correlates of the clinical events were not

known. Figure 8(2a) shows the cumulative probability of being free from recurrent stroke or TIA against time. Figure 8(2b) shows the cumulative probability of being free from recurrent cerebral infarction against time. The 95% confidence limits for the cumulative survival probabilities on which these survival curves are based are shown in the tables 8(3a) and 8(3b) respectively. For the group as a whole, the cumulative probability of being free from either recurrent stroke or TIA was 0.13 over 13 years (95% confidence limits -0.07 - 0.33); the cumulative probability of being free from recurrent stroke, with new areas of cerebral infarction, was 0.30 over 13 years (95%confidence limits -0.13 - 0.73).

It is not surprising, given that only around 30% of patients were followed-up for more than 5 years (see figure 8(1)), that the confidence intervals for the cumulative survival proportion (proportion free from recurrence) at 13 years are extremely wide. If the data over 5 years are considered, the proportion of patients free from any recurrent event at 5 years was 0.68 (95% confidence limits 0.57 - 0.79) whereas the proportion free from recurrent stroke was 0.86 (95% confidence limits 0.78 - 0.94).

8.2.1. Patients with more than one recurrent stroke

Two children had more than 2 strokes. Patient 98 had 2 strokes within a short period and then had 2 further strokes despite being anticoagulated. His initial arteriogram showed focal large vessel stenosis but subsequent studies went on to show more diffuse cerebrovascular disease. Despite a negative brain biopsy the clinical picture and angiographic findings were felt to be compatible with a diagnosis of isolated angiitis of

the central nervous system; following immunosuppression he has had no further events. Patients 67 had choreo-athetoid cerebral palsy and 3 strokes; the second and third strokes occurred despite aspirin prophylaxis. As his third cerebral angiogram showed evidence of VA dissection (as discussed in chapter 5), the multiple strokes were probably related to recurrent trauma to the VA.

8.2.2. Recurrence on prophylactic treatment

Of the 3 children with sickle cell anaemia and 1 child with HbSßthalassaemia who had recurrent strokes, 3 were on transfusion therapy at the time of recurrence. However, the percentage of HbS was below 20% in only one case. The remaining child had recently discontinued transfusion therapy. Five children had recurrent events whilst they were anticoagulated with warfarin. All 5 children had cerebrovascular abnormalities. In addition to having bilateral moyamoya syndrome, patient 11 was heterozygous for the factor V Leiden mutation. His symptom control was critically dependent on the level of anticoagulation (INR of 2 - 3). Five children had recurrent events whilst on low-dose aspirin. All had cerebrovascular disease. One child (patient109) had a recurrent stroke two weeks after her parents discontinued low dose aspirin against medical advice. She was subsequently found to have isolated angiitis of the central nervous system.

8.3. Risk factors for recurrent stroke and TIA

The incidence of recurrence in the "symptomatic stroke" and "idiopathic stroke" groups were similar. (see figures 8(3a) and 8(3b)). The proportion of patients with recurrence in each diagnostic category is shown in figure 8(4).

8.3.1. Cerebrovascular abnormalities

Cerebrovascular abnormalities, especially moyamoya syndrome, were frequently observed in children with recurrent TIA or stroke. Five of the children with moyamoya syndrome were having recurrent TIA at presentation. The diagnosis of isolated angiitis of the central nervous system was made in 2 children (patients 98 and 109) only after they had had at least 2 strokes. Two children with arterial dissection had recurrent strokes; one was on low dose aspirin and the other was anticoagulated at the time when the recurrent stroke occurred.

Of the children with cerebrovascular abnormalities, 4 had sickle cell anaemia, 3 had prothrombotic tendencies (1 with protein S deficiency and 2 who were heterozygous for the factor V Leiden mutation), 2 had a structural cardiac abnormality and another had hypertension. One child (patient 11) who had moyamoya syndrome and the factor V Leiden mutation also had a structural cardiac abnormality and one of the children with sickle cell anaemia and moyamoya syndrome also had a cardiomyopathy.

8.3.2. Non-vascular risk factors and recurrence

Only 2 children (patients 35 and 41) had non-vascular risk factors for stroke without any evidence of cerebrovascular disease.

A high incidence of recurrent events was observed in the children with sickle cell anaemia; four of the eight children with sickle cell anaemia in the study population had recurrent events despite prophylactic transfusion. However, all 4 also had moyamoya syndrome; of the 4 without recurrent events, 2 had normal cerebral vasculature, 1 had moyamoya syndrome and the other had MCA occlusion at the time of her stroke.

8.3.3. Patients with unexplained recurrence

Three children (patients 114, 115 and 119) had no apparent basis for recurrent stroke as they had normal cerebrovascular imaging (on conventional angiography in one case and MRA in the other 2) and no identified non-vascular risk factors.

8.3.4. Risk of recurrence according to identified risk factors for ischaemic stroke

The cumulative probability of being free from recurrent stroke or TIA and specifically for recurrent stroke according to identified risk factors are shown in figures 8(5a) and 8(5b) respectively. The confidence limits for the cumulative survival proportions (proportions free from recurrence) on which the survival curve shown in figure 8(5a) is based are given in table 8(4). It is apparent from the extremely wide confidence intervals for the cumulative survival proportions that the subgroups of patients in each category of risk

factor is too small to enable firm conclusions to be drawn. Given that if recurrent stroke alone is considered, the numbers of patients in each category is even smaller, the confidence limits for the cumulative survival proportions for the values on which figure 8(5b) are based are likely to be even wider and have not been shown.

However, inspection of the survival curves shows some interesting trends. Patients with moyamoya syndrome and cardiac disease appear to be at highest risk of recurrence. Comparing figures 8(5a) and 8(5b), patients with moyamoya appear to have recurrent TIA more frequently than other groups of patients. Patients with cardiac disease appear to be risk of both early and late recurrence. Although these data suggest that there is a low probability of recurrence for patients with sickle cell anaemia, 5 of the 8 patients with sickle cell anaemia in this study had moyamoya syndrome and were classified accordingly. Reallocating the 4 children with sickle cell anaemia and moyamoya syndrome to the "sickle cell anaemia" group gives quite a different picture (see figure8(6)).

8.4. Discussion

Although some children e.g. those with moyamoya syndrome or sickle cell anaemia are known to be at high risk of recurrent stroke[78], the risk of recurrence after ischaemic stroke in other children has not been systematically investigated. Although it has been stated that recurrence does not occur, especially after apparently "idiopathic" cases of ischaemic stroke[70,86], this is clearly not the case[67,76,147].

The incidence of recurrent stroke and TIA is higher in the present study than in those discussed previously. However, the incidence of recurrent stroke specifically is also higher than that in previous studies. Furthermore, it was not known whether any of the children with TIA had had recurrent cerebral infarction. There may be several reasons to account for the differences between previous reports and the findings of the present study. Firstly, for the reasons previously discussed, the study population included relatively large numbers of children with moyamoya syndrome. Although the population studied here were a relatively large cohort, a hospital based study is necessarily influenced by referral bias. The parents of patients were specifically asked to report recurrent events, both as part of the questionnaire relating to outcome and in the clinical situation. This was to ensure high ascertainment and may have resulted in reporting of deficits which may have otherwise passed unnoticed. As is evident in figure 8(1), patients follow-up was terminated relatively early for a large number of patients. This is apparent in tables 8(2a) and 8(2b) where the confidence intervals for the cumulative survival proportions become progressively wider as the duration of follow-up increases. However, within the first 5 years of follow-up, the confidence limits are less wide and would support the assertion that there is a significant incidence of recurrent stroke and TIA after a first ischaemic stroke in childhood.

In a recent study, Mancini[76] reported that 11% of the 35 patients studied had had recurrent strokes; all had well recognised risk factors for stroke, namely, sickle cell anaemia, homocystinuria, Williams syndrome and HIV infection. Riikonen[147] reported an incidence of recurrent events of 25%; this included patients with migrainous infarction (according to

International Headache Society criteria) as well as patients with focal cerebrovascular abnormalities and some with unexplained stroke. Of note, 3 children died as a direct result of recurrent stroke. DeVivo[22]reported that 21% of 54 children followed for a period of 5 years had a recurrent event; however, although the majority of patients had ischaemic stroke, this group also included 12 children with haemorrhagic stroke. Cardiac disease, sickle cell anaemia and systemic lupus erythematosis were factors associated with recurrence in this group. Abram[67] found that 17% of children included in his study had recurrent stroke; 3 had moyamoya syndrome and no details are given about the other 4 patients. Dusser[70] noted recurrent stroke in 4 out of 41 patients; three had moyamoya syndrome and the remaining child had cyanotic congenital cardiac disease. No recurrence was observed in children with apparently idiopathic stroke in this group.

Recurrent TIA or stroke is one of the well recognised clinical features of both primary and secondary moyamoya syndrome in Japanese children. The frequency of such events is directly related to the level of cognitive impairment[120]. Recurrent ischaemic events also characterise moyamoya syndrome in non-Japanese populations[402]. Surgical revascularisation appears to be effective in preventing recurrent attacks and in stabilising cognitive function, both in children with idiopathic and secondary moyamoya syndrome[395,396,402]. Given the high frequency of recurrent events both in this and in previous studies, there would appear to be a strong case for considering assessment of cerebrovascular reserve and surgical referral at the time of diagnosis in order to prevent further disability.

Patients with cerebrovascular abnormalities other than moyamoya syndrome also appear to be at significant risk of recurrence. A high index of vigilance for recurrence as well as exclusion of other risk factors is important in this group. There appears to be a good case for serial cerebrovascular monitoring in order to try and detect progressive cerebrovascular disease, such as diffuse cerebral vasculitis, before it becomes symptomatic. However, such disease may affect vessels which are beyond the resolution of MRA. Although in the context of recurrent strokes more invasive imaging (i.e. conventional angiography) may be justified, this is clearly not a reasonable approach to adopt in all cases. The optimal strategy in patients with focal large vessel abnormalities remains unclear; although low dose aspirin has been advocated by some in such cases, the risk-to-benefit ratio of this strategy is not known.

Although recurrent arterial dissection is well recognised, recurrent stroke in patients with previous dissection more unusual. Both such patients described here had evidence of persistent VA irregularity; such areas could act as foci for thrombosis and distal embolisation. It has been suggested that anticoagulation should be continued in patients with dissection until there is evidence of vascular healing[453] but the management of patients with persistent arterial abnormalities is less clear. The importance of trauma in precipitating posterior circulation stroke is well recognised[146,149,150] and it would be prudent to screen patients for structural abnormalities or instability of the cervical spine which may be amenable to surgical intervention.

Cardiac disease is known to be associated with a high risk of recurrent stroke[78]and was noted in 15% of the children with reported here. The risk of recurrent stroke is further

augmented by the risks associated with cardiac catheterisation and cardiac surgery. The data from this study would suggest that there is a significant incidence of late recurrence in this group, probably related to long-standing structural abnormalities, as well as secondary complications such as cardiac failure. Although minor cardiac lesions, such as PFO, have been reported as risk factors for recurrent stroke in young adults with stroke, the importance of such lesions seems to be less in children with stroke[21]. Although such lesions were not detected in any of the patients with recurrence reported here, for the reasons previously discussed in chapter 3, a more detailed transoesophageal echocardiographic study would be required in order to reliably determine the incidence of PFO in children with stroke and stroke recurrence. Although surgical closure of such lesions is possible, given the frequency of such lesions in the paediatric population, there is currently no evidence to support this strategy as a means of preventing recurrent strokes in children.

Prevention of recurrent stroke in children with structural cardiac abnormalities has not been systematically examined. Given the high risk in the peri-operative period anticoagulation may be justified at this time[233]; however, the case for long term anticoagulation for the prevention of stroke recurrence remains unexplored. Some children with cardiac abnormalities may have cerebrovascular abnormalities (e.g. moyamoya syndrome) which may be amenable to specific treatment and these should be specifically sought.

Two thirds of children with sickle cell anaemia who have stroke will experience a recurrent event. Identification of cerebrovascular abnormalities is predictive of stroke[123].

The risk of recurrence in patients without cerebrovascular disease has not been reported; although the data from this study would suggest that it is lower than in those with cerebrovascular disease, the numbers involved are to small to enable any firm conclusions to be drawn. The efficacy of blood transfusion in markedly reducing the risk of recurrent stroke in children with sickle cell anaemia has previously been discussed in detail. However, it should be recognised that transfusion is not totally effective and reduces the risks from over 60% to around 10%[253]. The optimal level of transfusion is unclear and practical difficulties may make maintenance of HbS below 20 - 30% difficult. Although bone marrow transplantation effectively cures sickle cell anaemia, the availability of suitable donors and the facilities for carrying out the treatment means that this treatment is only be available to relatively few children. Treatments such as hydroxyurea appear to be unacceptably hazardous. The role of prophylactic adeno-tonsillectomy in children with evidence of obstructive upper airways disease and nocturnal desaturation has not been formally evaluated. For children with sickle cell anaemia who have moyamoya syndrome, surgical revascularisation may be effective in improving cerebral perfusion as well as in preventing recurrent events[395,467]. The findings of the present study, that recurrence was highest in children with moyamoya syndrome, would suggest that transfusion alone is not likely to prevent further stroke in such cases. However, the efficacy of surgical revascularisation and the implications for future transfusion requirements have not been formally evaluated.

The relationship between prothrombotic tendencies and ischaemic stroke has been considered in detail in chapter 4. It is noteworthy that 3 of the children with recurrent events had APC resistance and that 2 were heterozygous for the factor V Leiden mutation;

all had other risk factors for stroke. The response of recurrent ischaemic symptoms to anticoagulation was striking in the case of patient 11, whose symptom control was strongly linked to his level of anticoagulation. Although, as discussed in chapter 4, the relationship between activated protein C resistance, the factor V Leiden mutation and ischaemic stroke in children is unproven, a combination of risk factors may be important in individual patients[291,424]. In the absence of definitive guidelines, the question of prophylactic anticoagulation may need to be considered in light of co-existent risk factors in individual cases.

It could be argued that all avenues of investigation had not been exhausted in the 3 children with unexplained stroke who experienced recurrence. The results of transoesophageal echocardiography, for example, in these patients may be of interest. However, patients investigated to a similar extent have been classified in the literature as having idiopathic stroke and, in contrast to previous reports, recurrence does seem to be a risk in such patients. The magnitude of risk in this and other patient groups requires quantification, both for the purposes of counselling and for consideration in the risk-to-benefit ratio of potential preventative therapies.

It is unclear whether the risk of recurrence increases into adult life and whether this is influenced in any way by the risk factors for vascular disease (e.g. smoking) more frequently encountered in adults. These issues are of importance as often patients are lost to follow-up between the adult and paediatric services and the long term natural history is not readily appreciated. The interaction of risk factors for cerebrovascular disease in childhood and adult life is likely to be complex and remains unexplored.

	Symptomatic stroke (n = 59)	**Idiopathic stroke (n = 69)**
Information about recurrent events	53	66
Died as a result of acute stroke	6*	0
Recurrent TIA	9	15
Recurrent stroke	7	7
Moyamoya syndrome	10 (9)	12 (9)
Large vessel occlusion	12 (1)	10 (1)
Large vessel stenosis	4 (0)	16 (4)
Cerebral vasculitis	0	2 (2)
Arterial dissection	1 (0)	8 (2)
Other cerebrovascular abnormalities	5 (5)	2 (0)
Normal cerebral vessels	6 (2)	9 (3)
Cardiac abnormality	21 (5)	2 (1)
Sickle cell anaemia	8 (4)	0
Prothrombotic abnormality	4 (2)	6 (2)
Malignancy	5 (4)	0
Hypertension	2 (1)	0
Infection	12 (3)	9 (2)
Other	5 (1)	0
Unexplained stroke	-	9 (3)

Table 8(1) Prevalence of cerebrovascular and non-vascular risk factors in children for whom data on recurrent stroke or TIA were available.

Numbers in brackets indicate the numbers in each diagnostic category who had a recurrent event.

*including 1 child who died of recurrent stroke

Patient number	Recurrent event	Time after initial stroke (years)	Cerebrovascular abnormality	Other risk factors	Other relevant factors/treatment at time of recurrence	Further recurrent events/ treatment after recurrence
24	Stroke	1	Moyamoya syndrome	HbSS	On transfusion programme but HbS not <20%	
27	Stroke	4.1	Moyamoya syndrome	HbSS, cardiomyopathy	Recently discontinued transfusion therapy	
58	Stroke	5	Moyamoya syndrome	Cranial irradiation for optic nerve glioma, Neurofibromatosis	None	
74	Stroke	1	Moyamoya syndrome	None known	None	
109	Stroke	1	Cerebral vasculitis	None known	Recently discontinued aspirin	
98	Stroke	0.2	Cerebral vasculitis	None	None at time of initial recurrence	2 further strokes 2 years later while anticoagulated; treated with prednisolone & cyclophosphamide
66	Stroke	1	VA dissection	None	Anticoagulated at time of recurrence	

Patient number	Recurrent event	Time from initial stroke (years)	Cerebrovascular abnormality	Other risk factors	Other relevant factors/treatment at time of recurrence	Further recurrent events/ treatment after recurrence
67	Stroke	1.1	Initially thought to have occlusion of R SCA and irregularity of L PCA; third arteriogram suggested diagnosis of L VA dissection	Choreo-athetoid cerebral palsy - ?recurrent cervical trauma	On aspirin at time of recurrence	Further recurrent stroke
8	Stroke	2	R ICA stenosis, L MCA aneurysm	Hypertension, aortic coarctation	Second stroke following L MCA aneurysm repair	
3	Stroke	12	R MCA occlusion	Tetralogy of Fallot	Died as a result of second stroke	
92	Silent infarction	1.5	MCA stenosis	None	Anticoagulated at time of recurrence	
37	Stroke	1	Diffuse small vessel disease	Chemotherapy for B cell lymphoma		Aspirin started after 2nd stroke but has had several recurrent TIA's
35	Stroke	1.5	None	Resection of craniopharyngioma, activated protein C resistance, familial hypercholesterolaemia		Anticoagulated after 2nd stroke; no further recurrence

Patient number	Recurrent event	Time from initial stroke (years)	Cerebrovascular abnormality	Other risk factors	Other relevant factors/treatment at time of recurrence	Further recurrent events/ treatment after recurrence
114	Stroke	4	None	None known		
33	TIA	0.1	Moyamoya syndrome	Cranial irradiation		Had surgical revascularisation
10	TIA	0	Moyamoya syndrome	VSD (spontaneously closed)		Had surgical revascularisation
31	TIA	3.2	Moyamoya syndrome	HbSβthalassaemia	On transfusion regime at the time of recurrence; HbS% <20%	Further TIA on transfusion programme
34	TIA	0	Moyamoya syndrome	Cranial irradiation		Had surgical revascularisation
25	TIA	1.7	Moyamoya syndrome	HbSS	On transfusion programme but HbS >20%	
11	TIA	0	Moyamoya syndrome	Supravalvular aortic stenosis, heterozygous for the factor V Leiden mutation	TIA's abolished with warfarin if INR maintained between 2 and 3	
68	TIA	0.1	Moyamoya syndrome	None		
70	TIA	0	Moyamoya syndrome	None		Had surgical revascularisation
72	TIA	0	Moyamoya syndrome	None		Had surgical revascularisation

Patient number	Recurrent event	Time from initial stroke (years)	Cerebrovascular abnormality	Other risk factors	Other relevant factors/treatment at time of recurrence	Further recurrent events/ treatment after recurrence
73	TIA	8	Moyamoya syndrome	None		Started on aspirin after recurrent event
75	TIA	1	Moyamoya syndrome	Chickenpox preceding initial stroke	On aspirin at time of recurrence	
76	TIA	0	Moyamoya syndrome	Type 1 protein S deficiency		Had surgical revascularisation
77	TIA	0	L moyamoya syndrome	None		Had surgical revascularisation
78	TIA	2.5	Moyamoya syndrome	None	Preceding intercurrent illness	
9	TIA	5	Embolic occlusion of MCA branch acutely	Thick, regurgitant mitral valve, dilated cardiomyopathy, previous Wilms tumour- nephrectomy, radiotherapy and chemotherapy		
100	TIA	1.5	L ICA/MCA stenosis	Heterozygous for the factor V Leiden mutation		
102	TIA	0.2	L MCA stenosis	Chickenpox preceding initial stroke	On aspirin at time of recurrence	

Patient number	Recurrent event	Time from initial stroke (years)	Cerebrovascular abnormality	Other risk factors	Other relevant factors/treatment at time of recurrence	Further recurrent events/ treatment after recurrence
87	TIA	1.7	L MCA occlusion	Chickenpox preceding initial stroke	Anticoagulated at time of recurrence	
90	TIA	6	R ICA/MCA stenosis	None		
51	TIA	2	Diffuse small vessel disease	Hypertension with cardiomyopathy	On aspirin at time of recurrence	
41	TIA	0.3	None	Dermal sinus, previous meningitis		
115	TIA	0.5	None	None		
119	TIA	0.1	None	None		Further TIA 3 years later
121	TIA	1.3	Not known	None		

Table 8(2) Clinical details of patients with recurrent stroke and TIA

Where time to recurrence = 0, patients presented with recurrent TIA

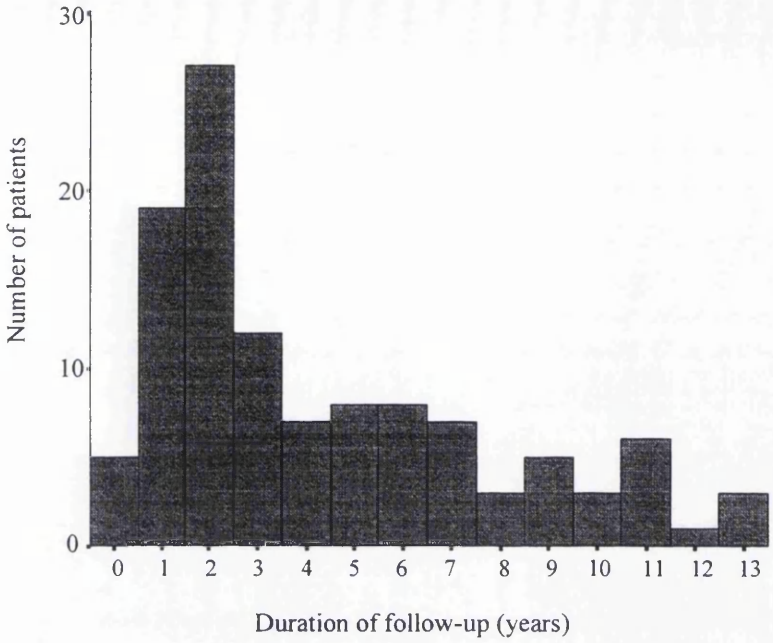


Figure 8(1): Duration of follow-up

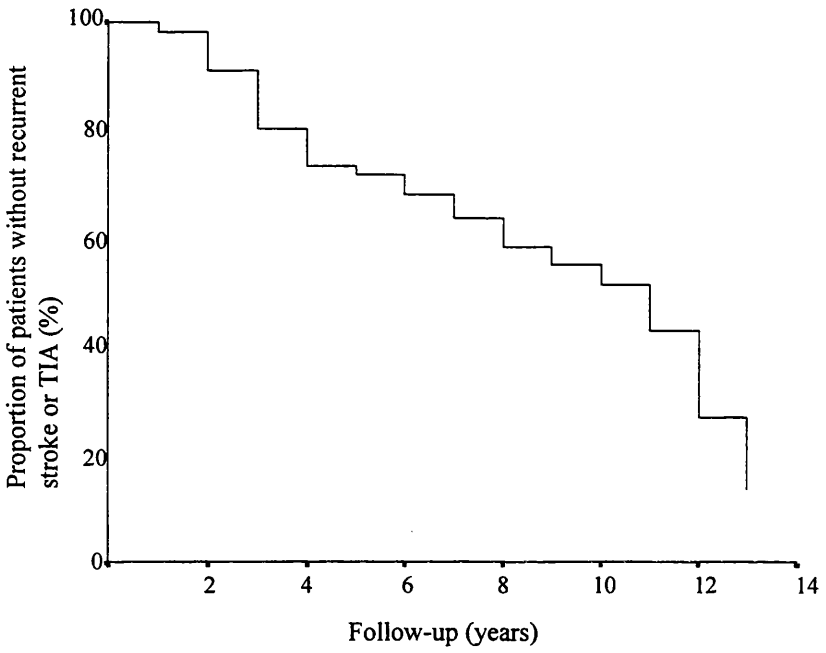


Figure 8(2a): Cumulative survival proportion free from recurrent stroke or TIA

Interval (years)	Number entering interval	Number of recurrent events during interval	Cumulative survival proportion	95% confidence limits
0	114	2	0.98	0.96 - 1.00
1	100	7	0.91	0.85 - 0.97
2	83	9	0.80	0.72 - 0.88
3	61	5	0.73	0.63 - 0.83
4	48	1	0.72	0.62 - 0.82
5	42	2	0.68	0.57 - 0.79
6	34	2	0.64	0.52 - 0.76
7	26	2	0.58	0.45 - 0.71
8	19	1	0.55	0.41 - 0.69
9	16	1	0.51	0.38 - 0.65
10	13	2	0.43	0.23 - 0.59
11	9	3	0.27	0.10 - 0.44
12	4	0	0.27	0.10 - 0.44
13	3	1	0.13	-0.07 - 0.33

Table 8(3a): Confidence limits for cumulative survival proportions free from recurrent stroke or TIA from which the survival curve shown in figure 8(2a) has been constructed

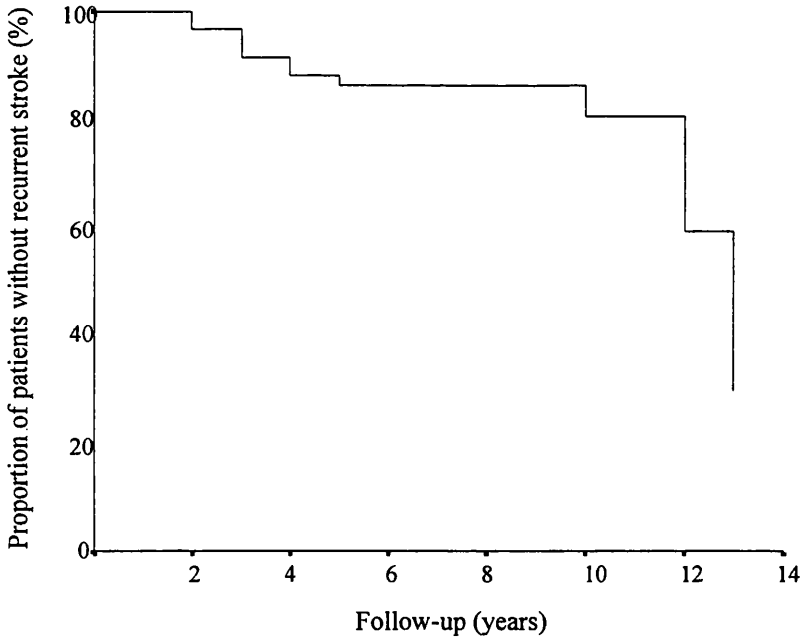


Figure 8(2b): Cumulative survival proportion free from recurrent stroke

Interval (years)	Number entering interval	Number of recurrent strokes during interval	Cumulative survival proportion	95% confidence limits
0.00	114	0	1	
1.00	100	3	0.97	0.93 - 1.00
2.00	83	4	0.92	0.86 - 0.98
3.00	61	2	0.88	0.81 - 0.95
4.00	48	1	0.86	0.78 - 0.94
5.00	42	0	0.86	0.78 - 0.94
6.00	34	0	0.86	0.78 - 0.94
7.00	26	0	0.86	0.78 - 0.94
8.00	19	0	0.86	0.78 - 0.94
9.00	16	1	0.81	0.68 - 0.94
10.00	13	0	0.81	0.68 - 0.94
11.00	9	2	0.59	0.32 - 0.86
12.00	4	0	0.59	0.32 - 0.86
13.00	3	1	0.30	-0.13 - 0.73

Table 8(3b): Confidence limits for cumulative survival proportions free from recurrent stroke from which the survival curve shown in figure 8(2b) has been constructed

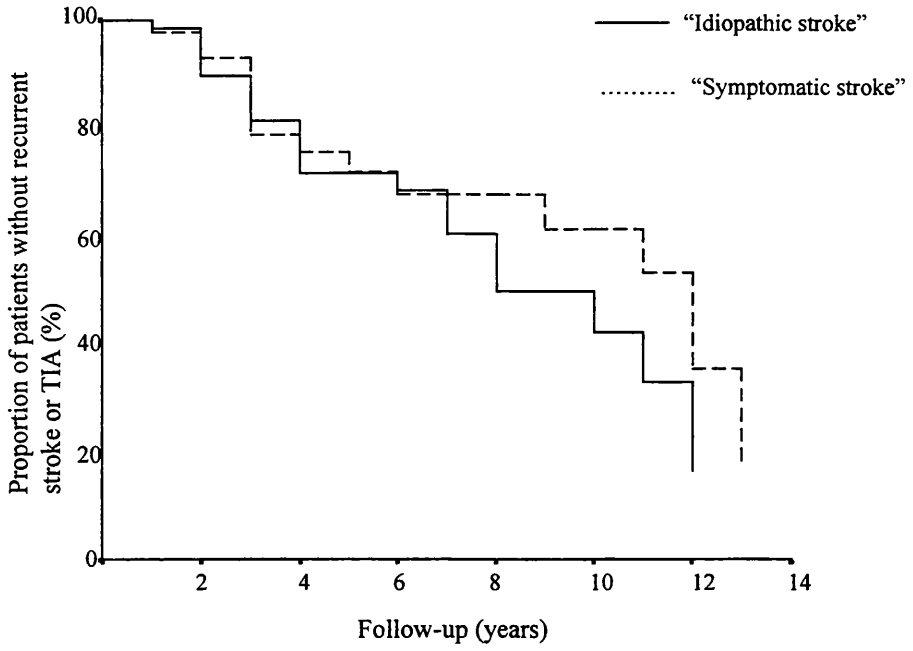


Figure 8(3a): Cumulative survival proportion free from recurrent stroke or TIA in "symptomatic" and "idiopathic" stroke groups

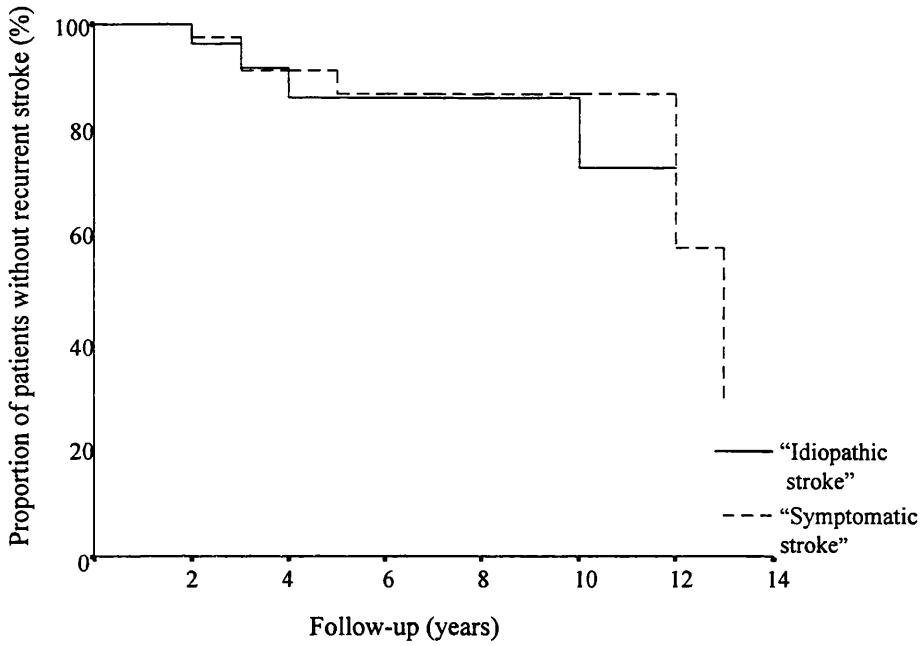


Figure 8(3b): Cumulative survival proportion free from recurrent stroke in "symptomatic" and "idiopathic" stroke groups

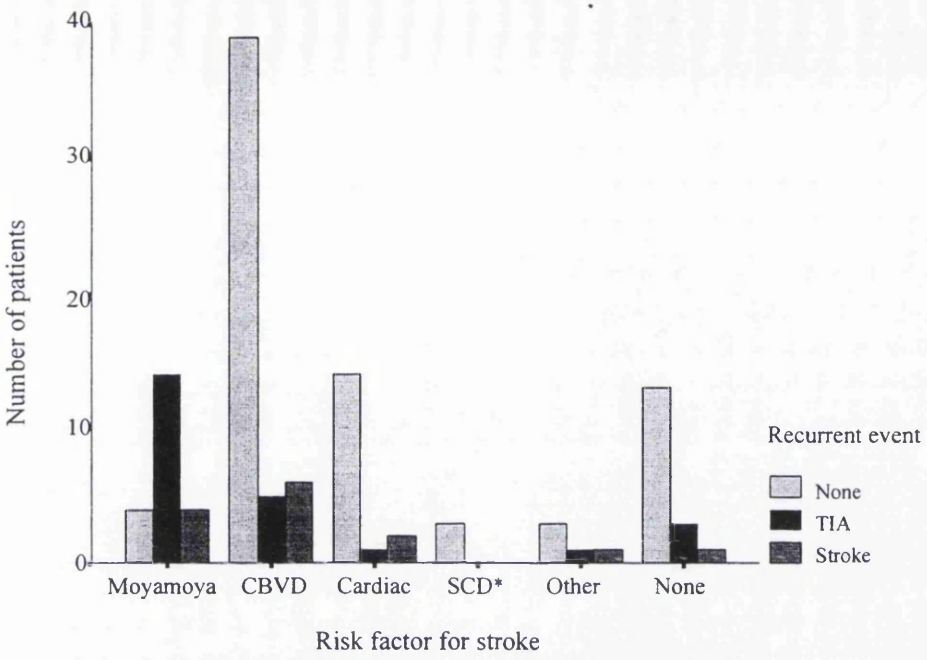


Figure 8(4): Incidence of recurrence according to risk factors

CBVD = cerebrovascular abnormalities other then moyamoya syndrome

SCD* = sickle cell disease, excluding patients with moyamoya syndrome

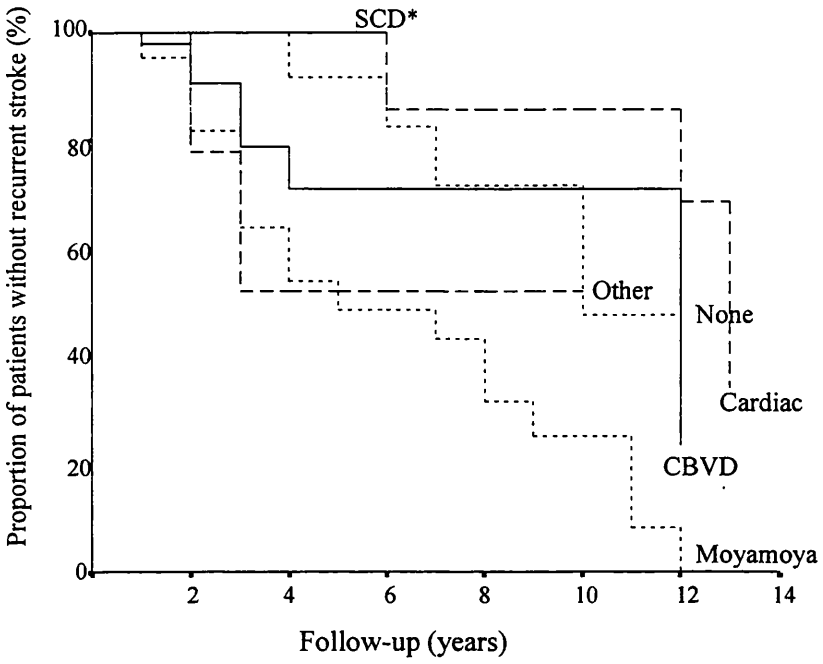


Figure 8(5a): Cumulative survival proportion free from recurrent stroke or TIA according to risk factor

SCD* = patients with sickle cell anaemia without moyamoya syndrome

Cardiac = structural cardiac abnormalities

CBVD = cerebrovascular abnormalities other than moyamoya syndrome

Other = other risk factors for stroke (e.g. prothrombotic states, hypertension)

None = no identified risk factors for stroke

See table 8(4) for confidence limits for cumulative survival proportions

Table 8(4)

Risk factor	None				Moyamoya syndrome				other vascular disease			
Interval (years)	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits
0.00	17	0	1	-	22	1	0.95	0.86 - 1.03	50	1	0.98	0.93 - 1.02
1.00	15	0	1	-	21	3	0.81	0.65 - 0.97	43	3	0.91	0.82 - 1.00
2.00	13	0	1	-	18	4	0.64	0.44 - 0.84	35	4	0.79	0.66 - 0.92
3.00	12	1	0.92	0.76 - 1.07	14	2	0.54	0.33 - 0.75	22	2	0.71	0.55 - 0.87
4.00	11	0	0.92	0.76 - 1.07	10	1	0.48	0.27 - 0.69	16	0	0.71	0.55 - 0.87
5.00	10	1	0.83	0.61 - 1.05	9	0	0.48	0.27 - 0.69	13	0	0.71	0.55 - 0.87
6.00	9	1	0.72	0.44 - 0.99	9	1	0.43	0.21 - 0.65	8	0	0.71	0.55 - 0.87
7.00	5	0	0.72	0.44 - 0.99	8	2	0.32	0.11 - 0.53	5	0	0.71	0.55 - 0.87
8.00	4	0	0.72	0.44 - 0.99	5	1	0.25	0.05 - 0.45	3	0	0.71	0.55 - 0.87
9.00	3	1	0.48	0.06 - 0.90	4	0	0.25	0.05 - 0.45	2	0	0.71	0.55 - 0.87
10.00	2	0	0.48	0.06 - 0.90	3	2	0.08	-0.07 - 0.23	2	0	0.71	0.55 - 0.87
11.00	1	0	0.48	0.06 - 0.90	1	1	0	-	2	1	0.24	-0.30 - 0.78

Table 8(4) (continued)

Risk factor	Sickle cell anaemia				Cardiac disease				Other risk factor			
Interval (years)	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits	Number entering interval	Number with recurrence during interval	Cumulative survival proportion	95% confidence limits
0.00	3	0	1	-	17	0	1	-	5	0	1	-
1.00	3	0	1	-	13	0	1	-	5	1	0.78	0.40 - 1.16
2.00	3	0	1	-	11	0	1	-	3	1	0.52	0.03 - 1.01
3.00	2	0	1	-	9	0	1	-	2	0	0.52	0.03 - 1.01
4.00	1	0	1	-	8	0	1	-	2	0	0.52	0.03 - 1.01
5.00	1	0	1	-	7	1	0.86	0.61 - 1.11	2	0	0.52	0.03 - 1.01
6.00					6	0	0.86	0.61 - 1.11	2	0	0.52	0.03 - 1.01
7.00					6	0	0.86	0.61 - 1.11	2	0	0.52	0.03 - 1.01
8.00					6	0	0.86	0.61 - 1.11	1	0	0.52	0.03 - 1.01
9.00					6	0	0.86	0.61 - 1.11	1	0	0.52	0.03 - 1.01
10.00					6	0	0.86	0.61 - 1.11				
11.00					5	1	0.69	0.32 - 1.06				
12.00					4	0	0.69	0.32 - 1.06				
13.00					3	1	0.34	-0.17 - 0.85				

Table 8(4): Confidence limits for cumulative survival proportions free from recurrent stroke or TIA according to risk factor for stroke from which the survival curves in figure 8(5a) has been constructed

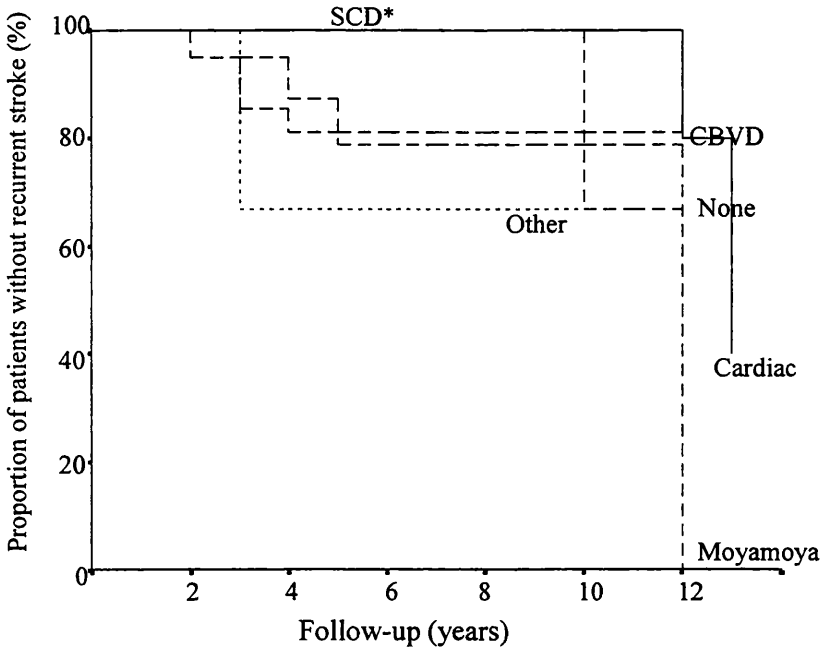


Figure 8(5b): Cumulative survival proportion free from recurrent stroke according to risk factor

SCD* = patients with sickle cell anaemia without moyamoya syndrome

Cardiac = structural cardiac abnormalities

CBVD = cerebrovascular abnormalities other than moyamoya syndrome

Other = other risk factors for stroke (e.g. prothrombotic states, hypertension)

None = no identified risk factors for stroke

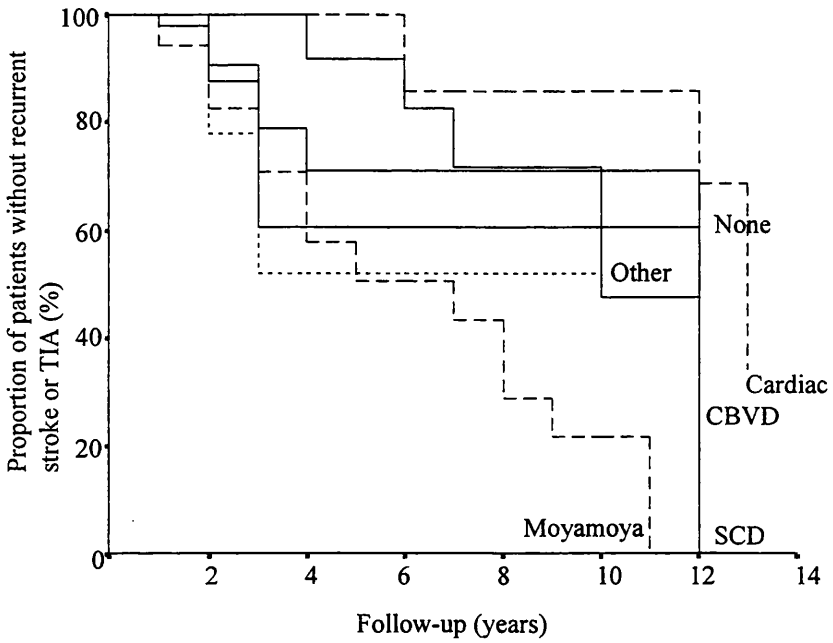


Figure 8(6): Cumulative survival proportion free from recurrent stroke or TIA according to risk factor

(*patients with sickle cell anaemia and moyamoya categorised as "sickle cell anaemia")

SCD = patients with sickle cell anaemia

Cardiac = structural cardiac abnormalities

CBVD= cerebrovascular abnormalities other than moyamoya syndrome

Other = other risk factors for stroke (e.g. prothrombotic states, hypertension)

None = no identified risk factors for stroke

9. General discussion and conclusions

This study has examined the natural history of ischaemic stroke in a large group of children. The size of the cohort made it possible to investigate the importance of specific risk factors such as cerebrovascular abnormalities and prothrombotic tendencies, as well as to examine questions relating to outcome.

The influence of CT and MRI on the study of ischaemic stroke is apparent insofar as patient inclusion was defined on the basis of radiologically apparent abnormality. Magnetic resonance imaging was particularly useful in allowing detailed analysis of lesion characteristics.

The observation that cerebrovascular abnormalities occur in the majority of children with ischaemic stroke is not new but has been neglected with the waning popularity of conventional angiography. The availability of MRA, in particular, has provided the clinician with a non-invasive tool with which to assess the cerebral circulation, both acutely and over a longer time. Despite this, conventional angiography appears to have a definite and definable role in the investigation and management of children with ischaemic stroke, as outlined in chapter 5.

Although the pathophysiological basis for some vascular abnormalities are at least partly understood, the basis of focal large vessel occlusion or stenosis remains obscure. It seems unreasonable to assume that all these cases represent embolic vascular occlusion with or without recanalisation. Evidence for an embolic source in the arterial circulation is lacking in many patients with structural cardiac abnormalities and the incidence of potential connections between the right and left sides of the heart was surprisingly low.

The previous literature and the location of lesions provides little evidence that atheroma may be responsible. A meticulous search for cardiac emboli or PFO using transoesophageal echocardiography in the acute phase of stroke will be useful in quantifying the true incidence of embolic events. Ultimately a systematic histological study is needed, although given the low mortality related to acute stroke in childhood, such a study is likely to be difficult.

The previous literature has made a distinction between stroke in children at risk and stroke which occurs apparently "out of the blue". Although patients were divided in this way during this study, it is clear that a similar approach to investigation should be adopted in all patients. Although hundreds of associations with ischaemic stroke are described, indiscriminate trawling for a cause is clearly impractical. All children should have cerebrovascular and cardiac imaging; the timing and nature of imaging may vary in individual cases. Investigation for prothrombotic states and lipid abnormalities is justified in all cases as they are potentially modifiable factors, even if the association with ischaemic stroke remains unproven. Other than the investigations discussed above, the clinical context and the findings on cerebral imaging should guide investigation.

The relationship between inherited prothrombotic states and ischaemic stroke is often quoted but has not previously been systematically examined. Although the data from this group of patients suggested that there was no direct cause and effect relationship, the issue is not completely clear cut. Firstly, as discussed in chapter 8, the presence of a prothrombotic tendency may influence the incidence of recurrent events in patients with other risk factors. Secondly, the importance of some of the most recently described prothrombotic tendencies, such as mild to moderate hyperhomocysteinaemia in particular,

were not examined. In population terms this has emerged as a very important risk factor for vascular disease and merits future attention. Finally, it is likely that a combination of genetic and environmental risk factors for thrombosis is more likely to be important in the pathogenesis of stroke than an isolated abnormality. The relationship between antiphospholipid antibodies and ischaemic stroke could not be examined in detail due to lack of serial data and a control population.

In contrast to adults with ischaemic stroke, there is no recognised measure of outcome after stroke in children. The questionnaire used to evaluate outcome in this study was able to address some simple questions relating to outcome. At present it seems that the prevalence of residual deficits is significant but unpredictable on the basis of clinical factors other than age. The data obtained from analysis of lesion volumes suggests, that in general lesion size and lesion location cannot be used in a simple way to predict outcome. However, lesion volume analysis was useful in defining a group with universally poor outcome. The role of newer MRI techniques such as diffusion-weighted imaging or perfusion-weighted imaging in predicting outcome in children will require further investigation.

The high prevalence of residual deficits in this population argues for evaluation of acute stroke therapies in the paediatric stroke population. Although many of these therapies are, at present, dangerous, the potential for preventing disability is significant. This is not only important to individual children but also to society as a whole, if the costs of rehabilitation and education after such disability is considered. However, the lesson from the adult stroke therapy trials should be heeded i.e. that at present drug effects are small and large numbers of patients are required before robust conclusions can be drawn.

This is a further area in which MRI may, in the future, contribute to the study of ischaemic stroke in children. Improved characterisation of lesions on conventional or newer MRI techniques may enable patients to be divided into relatively homogenous groups for therapeutic trials. Given the apparent 3 hour therapeutic time window for thrombolytic therapy in adults, there is pressure to accurately identify ischaemic stroke as early possible after the onset of a clinical deficit. This will be possible once new MRI techniques such as diffusion-weighted imaging and perfusion-weighted imaging become widely available for clinical use. For most children however, the rate limiting step will be at the stage of diagnosis. The differential diagnosis of acute focal neurological deficits in childhood is wide but a high index of clinical suspicion and use of appropriate imaging is necessary to make the diagnosis early enough for acute therapies to even possibly have a role. This is especially true in populations of children at risk where, in some cases (e.g. sickle cell anaemia), therapy is already available.

There was a relatively high incidence of recurrent stroke and TIA in the present study compared to previous reports, partly due to the characteristics of the population under consideration. However, there was a significant rate of unexpected recurrence which could not be readily explained. At present this data is anecdotal but it suggests that further evaluation of this is warranted. Without accurate information about the relative risks in individual groups it is impossible to counsel patients and to evaluate the potential benefits of preventative therapy. Furthermore, the optimal duration and level of surveillance in children who have had one stroke is uncertain, even in populations at high risk.

This work has characterised some aspects the aetiology and natural history of ischaemic stroke in childhood, with a particular focus on issues of relevance to clinical patient

management. Although the availability of modern techniques and improved knowledge about the pathogenesis of cerebrovascular disease may form the basis of future work, there are still many fundamental questions relating to patient management which can only be answered by collaborative clinical studies in large cohorts of patients.

Further studies

This work has suggested several areas for future studies.

Aetiology

1. Role of acute infections (especially *varicella)* preceding stroke. A case-control study is needed, ideally also investigating cerebrovascular correlates.
2. Importance of "minor" cardiac anomalies e.g. PFO.
3. The importance of hyperhomocysteinaemia and newly described prothrombotic abnormalities e.g. mutations in the prothrombin gene.

Investigation

1. Validation of the protocol for cerebral angiography proposed in chapter 5 in a prospectively studied cohort.
2. Role of diffusion and perfusion weighted MRI in exploring pathophysiology and guiding clinical management.

Outcome

1. Further development of an outcome measure for paediatric stroke.
2. Characterization of the correlates of subcortical infarcts.
3. Investigation of neuropsychological outcome.

Treatment

1. Safety and efficacy of anticoagulation in the treatment of arterial dissection
2. Indications for surgical revascularisation for paediatric moyamoya syndrome in non-Japanese patients.

Future work will be considerably strengthened by taking a multi-centre or population based approach.

10. Abbreviations

ACA	anterior cerebral artery
ADC	apparent diffusion coefficient
ADP	adenosine diphosphate
ALL	acute lymphoblastic leukaemia
APC	activated protein C
APTT	activated partial thromboplastin time
ASD	atrial septal defect
ATIII	antithrombin III
ATP	adenosine triphosphate
AVM	arteriovenous malformation
AVSD	atrio-ventricular septal defect
BSID	Bayley's Scales of Infant Development
CA	conventional cerebral angiography
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy
CAST	Chinese Acute Stroke Trial
CELF-R	Clinical Evaluation of Language Fundamentals-Revised
CI	confidence intervals
CNS	central nervous system
CSF	cerebrospinal fluid
CT	computerised tomography
CXR	chest x-ray
DESTIR	double echo short tau inversion recovery
DIC	disseminated intravascular coagulation

DNA	deoxyribonucleic acid
DRVVT	dilute Russell's viper venom time
EBV	Epstein Barr virus
ECASS	European Collaborative Acute Stroke Study
ECG	electrocardiogram
ECHO	echocardiogram
EC-IC	extracranial-intracranial
ECMO	extracorporeal membrane oxygenation
EDAS	encephaloarteriodurosynangiosis
EEG	electroencephalogram
ELISA	enzyme linked immunosorbent assay
EMS	encephalo-myosynangiosis
excl.	excluded
FBC	full blood count
FMD	fibromuscular dysplasia
FVL	factor V Leiden mutation
Hb	haemoglobin
HbF	fetal haemoglobin
HbSS	homozygous sickle cell anaemia
HDL	high density lipoprotein
HHE	hemiplegia, hemiconvulsions, epilepsy
HIV	human immunodeficiency virus
HUS	haemolytic uraemic syndrome
IAC	isolated angiitis of the central nervous system
ICA	internal carotid artery

ICAM	intercellular cell adhesion molecule
ICV	intracranial volume
IHS	International Headache Society
IL	interleukin
INR	International Normalised Ratio
IQ	intelligence quotient
IST	International Stroke Trial
KC	Cohen's Kappa
LDL	low density lipoprotein
LVF	left ventricular failure
MCA	middle cerebral artery
MELAS	mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes
MR	magnetic resonance
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRV	magnetic resonance venogram
NR	normal range
OTC	ornithine transcarbamylase
PCA	posterior cerebral artery
PDA	patent ductus arteriosus
PET	positron emission tomography
PFO	patent foramen ovale
PICA	posterior inferior cerebellar artery
PT	prothrombin time

RIND	reversible ischaemic neurologic deficit
rTPA	recombinant tissue plasminogen activator
SCA	superior cerebellar artery
SE	standard error
SPECT	single photon emission computerised tomography
TB	tuberculosis
TCD	transcranial Doppler ultrasound
TE	time to echo
TIA	transient ischaemic attack
TNF	tumour necrosis factor
TOE	transoesophageal echocardiogram
TR	time to repeat
TT	thrombin time
TTP	thrombotic thrombocytopaenic purpura
UK	United Kingdom
VA	vertebral artery
VSD	ventricular septal defect
WAIS-R	Weschler Adult Intelligence Scale-Revised
WISC-III	Weschler Intelligence Scale for Children-3rd edition
WPPSI-R	Weschler Pre-school and Primary Scale of Intelligence

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12. Appendices

Appendix 1: Summary of previous studies reporting aetiology of ischaemic stroke in childhood, 1927 - 1998

Authors	*Population*	*Number of patients*	*Age*	*Cerebrovascular abnormalities*	*Cardiac disease*	*Sickle cell anaemia*	*Procoagulant abnormality*	*Infection (CNS)*	*Trauma*	*Idiopathic*	*Other*
Schaffer 1927[8]	Acquired infantile hemiplegia	43			excl.			23 (excl.)		19	
Bickerstaff 1964[7]	Acute hemiplegia	15		15	excl.						
Greer 1965[13]	Acute neurologic disorders of infancy and childhood	23	Under 18 years	3	excl.			3 (excl.)	9 out of 23		
Aicardi 1969[9]	Acute hemiplegia	122	Under 15 years	8							
Solomon 1970[10]	Acute hemiplegia	86		16	10	5		11(11)	11	25	AVM = 4; craniometaphyseal dysplasia = 1; smallpox vaccination = 1; ulcerative colitis = 1; perioperative hypoxia = 1.

Authors	*Population*	*Number of patients*	*Age*	*Cerebrovascular abnormalities*	*Cardiac disease*	*Sickle cell anaemia*	*Procoagulant abnormality*	*Infection (CNS)*	*Trauma*	*Idiopathic*	*Other*
Abraham 1971[468]	Stroke	20	11-20 years	7							9 "acute infantile hemiplegia", 1 aortic arch syndrome
Hilal 1971[152]	Acute acquired hemiplegia	87	1 - 9 years	17	10	5		11	11	25	AVM = 4
Tibbles 1975[12]	Acute hemiplegia	28	0.5 - 12 years	5				(excl.)			
Schoenber 1978[24]	Ischaemic stroke	38	up to 15 years	3 (all moyamoya)	18			(excl.)	excl.	13	4
Blennow 1978[326]	Ischaemic stroke	14	Under 20 years	13/14 (9 embolic, 3 arteritis, 1 FMD)	excl. children with known cardiac disease; 1 had myocard itis		?in 3	4 (1)			2 high cholesterol, normal triglycerides
Eeg-Olofsson 1983[25]	Ischaemic stroke	11	15 years or under		5			55%, usually URTI		4	
Isler 1984[351]	Acquired cerebral arterial occlusion	87		4				9	7	2/3of cases	11 (described as "varia")

Authors	*Population*	*Number of patients*	*Age*	*Cerebrovascular abnormalities*	*Cardiac disease*	*Sickle cell anaemia*	*Procoagulant abnormality*	*Infection (CNS)*	*Trauma*	*Idiopathic*	*Other*
Dusser 1986[70]	Ischaemic stroke	44	6 weeks - 15 years	31/35	8			5 (4)	1	22	Migraine = 1; Klippel-Trenauny syndrome 1; Post radiotherapy = 1.
Wanifuchi 1988[75]	Ischaemic stroke	23	up to 15 years	17/21	8			1	3	11	
Higgins 1990[18]	Cerebrovas-cular disease	95 (41 with cerebral infarctio n)	1 month to 22 years	10	12	12	1	20 (7)	8	11 out of 95	Malignancies = 2, migraine = 3,drugs, = 2, prior surgery = 4, dehydration = 1, lipoproteinaemia = 1, thrombocytopaenia = 8, factor IX deficiency = 1, AVM = 7
Lanska 1991[82]	Unilateral ischaemic stroke	30	neonate to 15 years		21					6	post-mastiodectomy = 1, water intoxication = 1, migraine = 1
Satoh 1991[17]	Ischaemic stroke	54	under 16 years	40	2			10	10	31	Renal hypertension = 1; Hyperlipidaemia = 7
Inagaki 1992[133]	Ischaemic basal ganglia stroke	16	11 months to 9 years	5	1			9 had preceding chickenpox		5	
Kerr 1993[469]	Ischaemic stroke	22	6 months - 18 years	5	1			6 (6)		8	Kawasaki disease = 1

Authors	*Population*	*Number of patients*	*Age*	*Cerebrovascular abnormalities*	*Cardiac disease*	*Sickle cell anaemia*	*Procoagulant abnormality*	*Infection (CNS)*	*Trauma*	*Idiopathic*	*Other*
Broderick 1993[382]	Ischaemic stroke	7	15 years or under		2		1 protein C deficiency	1(1)		2	Sagittal sinus thrombosis = 1
Riikonen 1994[147]	Ischaemic stroke	44	1 month to 16 years	3	4	0	0	15; EBV = 1, Yersinina = 1, adenovirus = 1, chickenpox = 2, borrelliosis = 2		24/44	Mitochondrial disease = 2; migraine = 6 (IHS criteria); ALL = 1; Wiskott Aldrich syndrome = 1; hypogammaglobulinaemia = 1
Nagaraja 1994[129]	Ischaemic stroke	43	1 - 16 years	15	3 mitral valve prolapse	0		(excl.)	excl.	24/43	Scorpion sting = 2
Keidan 1994[19]	Cerbrovascular disease	45 (29 isch. stroke)	Older than 4 weeks	5 out of 45	13	1		(excl.)	excl.	9 out of 45	renal hypertension = 4, shock = 7, AVM = 3, haemophilia - 1, thrombocytopaenia = 1
Giroud 1995[26]	Ischaemic stroke		16 years or under	3	6	0	0	4	4	2	Leukaemia = 1
Barinagar-remente-ria, 1996[470]	Ischaemic stroke	47	11 - 20 years	16	3		9			18	Migraine = 1
Abram 1996[67]	Ischaemic stroke	42	9 months to 18 years		excl.		excl.	(excl.)			

Authors	*Population*	*Number of patients*	*Age*	*Cerebrovascular abnormalities*	*Cardiac disease*	*Sickle cell anaemia*	*Procoagulant abnormality*	*Infection (CNS)*	*Trauma*	*Idiopathic*	*Other*
Brower 1996[138]	Basal ganglia and thalamic infarction	36	neonate to 13 years	4	3	3	1	8 (6)	7	9	dehydration = 2, previous hypoxic event = 1
Andrew 1997[466]	Ischaemic stroke	165	neonate to 13 years		36		15	8		52	Dehydration = 5, cancer = 3, "other" = 47
Mancini 1997[76]	Ischemic cerebrovascular disease	35	2 months - 15 years	2	1	7	1 protein C deficiency; 1 lupus anticoagulant	1 Coxsackie A type 9; 2 HIV		7	Williams syndrome = 3; Homocystinuria = 2; migraine = 1; MELAS = 1; phaeochromocytoma = 1.
Giroud 1998[130]	Ischaemic stroke	31	mean age 10.4 years	4	9	0	0	0	7 mild trauma	4 (13%)	ALL = 2; HUS = 1; 7 mild prodromal; infection

Appendix 2. Summary of previous studies reporting outcome after ischaemic stroke in childhood, 1965 - 1998

Authors	Population	Number of patients	Motor deficit	Cognitive impairment	Epilepsy	Death	No sequelae	Other outcomes
Greer[13]	Acute neurologic disorders of infancy and childhood	12		4 (33%)			1	Disability graded as "minimal" in 5 cases and "moderate" in 6 cases
Aicardi[9]	Acute hemiplegia	122		68 (56%)	60 (49%)	4 (3.2%)		
Solomon[10]	Acute hemiplegia	41	30 (73%)	17 (41%)	20 (49%)	3 (7%)		14/41 hyperkinetic behaviour
Tibbles[12]	Acute hemiplegia	10	6	0	0			
Schoenberg[24]	Ischaemic stroke	34	31 (91%)	8 (24%)	5 (15%)	4 (12%)	6%	94% had "residual disability"
Blennow[326]	Ischaemic stroke	14			3	1	4	Minor deficit in 4 cases, moderate deficit in 4 cases.
Eeg-Olofsson[25]	Ischaemic stroke	11				2 (18%)	25%	75% had residual disabilities
Isler[351]	Acquired cerebral arterial occlusion	87	70%	55%	50%	11%		
Dusser[70]	Ischaemic stroke	41	31 (76%)	11 (27%)	12 (29%)			2/41 hemianopia
Wanifuchi[75]	Ischaemic stroke	23				8.70%	5 (22%)	18/23 (78%) had residual deficits
Higgins[18]	Cerbrovascular disease	88				20 (23%)	20 (23%)	
Lanska[82]	Unilateral ischaemic stroke	42	32 (76%)		8 (19%)	0		

Authors	Population	Number of patients	Motor deficit	Cognitive impairment	Epilepsy	Death	No sequelae	Other outcomes
Satoh[17]	Ischaemic stroke	54						44% had residual neurological deficits at 6 months, especially motor deficit
Inagaki[133]	Ischaemic basal ganglia stroke	16	5 (31%)		1		5 (31%)	
Broderick[382]	Ischaemic stroke	7	6 (86%)	1	0	0		
Keidan[19]	Cerebrovascular disease	45(37 followed up)	23 (62%)	13 (35%)	13 (35%)	18%	11 (30%)	
Giroud[26]	Ischaemic stroke	17	11 (65%)		2	1		
Abram [67]	Ischaemic stroke	42	20 (48%)	16 (38%)	7 (17%)	1	15 (36%)	18 had "poor" outcome, 24 had "good outocme"; 15 developed behaviour problems
Brower[138]	Basal ganglia and thalamic infarction	36	15 (42%)		1	0	4 (11%)	Mild disability in 16, moderate in 1 and severe in 5.
Andrew[466]	Ischaemic stroke	165			16	10	35	Neurological deficit = 94
Mancini[76]	Ischemic cerebrovascular disease	35	10 (29%)	3 (9%)	4 (11%)	1 (3%)	17 (49%)	2/45 visually impaired

Appendix 3: Protocol used for investigation of acute ischaemic stroke in childhood[1]

1. T2-weighted brain MRI

2. MRA of circle of Willis

3. Haematology

PT/APTT/TT/Fibrinogen	
Procoagulant screen	Protein C Protein S Antithrombin III APCr ratio FVL status Plasminogen Heparin cofactor II dRVVT Anticardiolipin antibodies

4. Biochemistry

plasma lactate
plasma amino acids
urinary amino acids
urinary organic acids
random serum cholesterol
random plasma triglycerides

5. Cardiac

12 lead ECG
transthoracic echocardiogram

Other investigations performed according to clinical indications

e.g. conventional angiography

transoesophageal echocardiography

CSF lactate

infection screen

Appendix 4: Questionnaire used to investigate parent-reported outcome after ischaemic stroke

(scoring given in italics)

Name:
Date of birth:
Age at time of stroke:
Time since stroke:
Side of the body affected by the stroke: Left ☐ Right ☐
Before stroke was your child: L handed ☐ R handed ☐
Is your child now: L handed ☐ R handed ☐

1. Have there been any further episodes similar to the initial stroke?

No	☐
Yes, but they resolved fully	☐
Yes, my child has had more than one stroke	☐

2. Is your child on any medication/treatment

	Currently	Previously
Aspirin	☐	☐
Warfarin	☐	☐
Heparin	☐	☐
Other		

3. What type of school does your child go to?

Mainstream school	*Score 0*	☐
Mainstream school with help	*Score 1*	☐
Other	*Score 2 if not in mainstream education*	

Has your child had a statement of educational needs? Yes☐ No☐

4. Does your child need help in any areas (more than you would expect at his/her age)? Yes☐ No☐

If yes, is this	at school	*Score 1 if "yes"*	Yes☐	No☐
	at home	*Score 1 if "yes"*	Yes☐	No☐
	with feeding		Yes☐	No☐
	with dressing		Yes☐	No☐
	with toiletting		Yes☐	No☐

5. In your view, does your child have any difficulties with speech or language?

Score 1 if "yes" Yes☐ No☐

6. How well is your child able to use his/her weaker hand?

Without any difficulty	*Score 0*	☐
Has some difficulties but could use it to hold a jar while taking the lid off with the other and	*Score 1*	☐
Has significant difficulties but can use it as a prop or support e.g. to hold down paper when writing	*Score 2*	☐
Is unable to use it at all	*Score 3*	☐

7. How well is your child able to use his/her weaker leg?

Without any difficulty	*Score 0*	☐
Minimal difficulty - e.g. has difficulty running and may drag leg when tired	*Score 1*	☐
Has significant difficulties e.g. can only walk short distances	*Score 2*	☐
Unable to walk	*Score 3*	☐

Does your child ever require an aid e.g. splint/wheelchair? Yes☐ No☐

If yes, what sort

How and when is it used?

8. Do you have any concerns about your child's behaviour

Score 1 if "yes" Yes☐ No☐

If so what are they?

9. .Is your child under regular follow-up by

Paediatric neurologist	Yes☐	No☐
Hospital paediatrician	Yes☐	No☐
Community paediatrician	Yes☐	No☐
GP	Yes☐	No☐

10. Has your child ever had a seizure (fit)? Yes☐ No☐

If so when was this?

Does your child still have seizures? Yes☐ No☐

Score 1 if "yes" and on an anticonvulsant

11. When did your child have chickenpox?

12. Is there anyone in your family who suffers from migraine?

13. Has anyone in your family ever suffered a thrombosis (blood clot) e.g. in the legs or lungs?

Yes☐ No☐

Please feel free to make any additional comments:-

Thank you for your assistance.

"Outcome score" = sum of scores of responses to scored questions

Minimum score = 0 (no residual deficit)

Maximum score = 13 (maximum residual deficit)

13. Declaration

The candidate was responsible for the design of the study and for collection and analysis of the data.

Dr WK Chong and Dr Lloyd Savvy reported the cerebral angiograms in the study discussed in chapter 5.

Ms A Hogan, Ms N Shack and Ms A Gordon provided the therapists' assessments for the study discussed in chapter 6.

Dr V Ng was the second observer for the lesion volume measurements reported in chapter 7.

Some of the data reported here has previously been published by the candidate in peer reviewed journals. These publications on the next page.

Peer-reviewed publications

1. Ganesan V, Kelsey H, Cookson J, Osborn A, Kirkham FJ. Activated protein C resistance in childhood stroke. *Lancet* 1996; **347**: 260

2. Ganesan V, Kirkham FJ. Mechanisms of ischaemic stroke after chickenpox. *Archives of Disease in Childhood* 1997; **76**: 522-525.

3. Ganesan V, Kirkham FJ. Noonan syndrome and moyamoya. *Pediatric Neurology* 1997; **16**: 256

4. Ganesan V, Kirkham FJ. Carotid dissection causing stroke in a child with migraine. *British Medical Journal* 1997; **314**: 291-292.

5. Ganesan V, Kirkham FJ. Stroke due to arterial disease in a child with congenital heart disease. *Archives of Disease in Childhood* 1997; **76**: 175

6. Connelly A, Chong WK, Johnson CL, Ganesan V, Gadian DG, Kirkham FJ. Diffusion-weighted magnetic resonance imaging of compromised tissue in stroke. ***Archives of Disease in Childhood*** 1997; **77**: 38-41.

7. Ganesan V, Isaacs E, Kirkham FJ. Variable presentation of cerebrovascular disease in monovular twins. *Developmental Medicine and Child Neurology* 1997; **39**: 628-631

8. Ganesan V, McShane MA, Liesner R, Cookson J, Hann I, Kirkham FJ. Inherited prothrombotic states and ischaemic stroke in childhood. *Journal of Neurology, Neurosurgery and Psychiatry* 1998 (in press).

9. Ganesan V, Savvy L, Chong WK, Kirkham FJ. The role of conventional cerebral angiography in the investigation of children with ischemic stroke. *Pediatric Neurology* (in press).

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Supervision

Dr FJ Kirkham, Senior Lecturer in Paediatric Neurology, Institute of Child Health, University College London supervised the candidate in conducting the work described in this thesis.