

I

**THE DURBAN STROKE DATA BANK WITH
SPECIAL EMPHASIS ON HIGHER CORTICAL
FUNCTION DEFICITS**

by

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Table of Contents

Chapters	Page
1.0	Introduction 1
2.0	Literature review 4
2.1	Rationale for emphasis of higher cortical function impairment in stroke 4
2.2	Rationale for using stroke to study cognitive deficits 5
2.3	Overview of stroke data bank design 5
2.4	Uses of stroke data banks and the issue of population based versus hospital based registries 6
2.5	Clinical and cost factors 7
2.6	The concepts of impairment, disability and handicap their measurement 8
2.7	Overview of neurological scales and rationale for inclusion in the DSDB 9
2.8	Cognitive issues 13
2.8.1	The challenge of cognitive assessment 13
2.8.2	Important points about cognitive testing 15
2.8.3	Reasons for adopting a clinical (bedside) cognitive screening test 18
2.8.4	Cognition - what is human intelligence and what are we measuring? 20
2.8.5	Disorders of intelligence and disorders of the forces which modulate intelligence 20
2.8.6	Disorders of forces which modulate intelligence 21

2.9	Using the syndrome of stroke as a means of studying cognitive disorders	21
2.10	There are several major problems with cognitive testing that necessitate discussion	23
2.10.1	Rationale of clinical bedside testing as opposed to standardised mental test schedules. Qualitative versus quantitative testing	23
2.10.2	Theoretical considerations of qualitative versus quantitative assessment	24
3.0	Aim	27
4.0	Methods	28
4.1	Data collection	28
4.2	Stroke protocols	28
4.2.1	The minimum work up included (1st tier)	29
4.2.2	Additional work up when appropriate (2nd tier)	30
4.2.3	A category of seldom required tests (3rd tier)	31
4.3	Diagnostic classification	31
4.4	Clinical stroke diagnosis	34
4.5	Clinicoinvestigative aetiopathogenetic diagnosis according to the modified TOAST (expanded) classification	34
4.6	The Barthel Index of activities of daily living	35
4.7	The Rankin Scale	36
4.8	Cognitive Testing	36

4.9	Single Photon Emission Computed Tomography (SPECT) brain scanning	39
4.10	Final diagnosis	40
4.11	Statistical analysis	52
4.11.1	Descriptive statistics	52
4.11.2	Computational statistics	52
4.12	Stroke data bank software and design	53
4.12.1	Multimodality digitised storage	53
4.12.2	Multiple data base layouts	53
4.12.3	Flexibility with database fields, back up storage and portability of data bank	54
4.13	Statistical software	55
4.14	Exclusions	55
5.0	Results	56
5.1	Stroke data bank results	56
5.1.1	Descriptive statistical analyses	56
5.1.1.1	Demographics	56
5.1.1.2	Timing of initial examination and initiation of investigations	58
5.1.1.3	Symptoms	58
5.1.1.4	Risk factors	60
5.1.1.5	Examination findings	61

5.1.1.6	Initial clinical stroke classification (OCSP) and intracerebral haemorrhage	63
5.1.1.7	Anatomical brain scans	64
5.1.1.8	Laboratory investigations	65
5.1.1.9	Aetiologies - TOAST categories and “Other” subgroups	70
5.1.1.10	Causes of stroke in black patients	79
5.1.1.11	The young stroke population (8-49 years)	80
5.1.1.12	Cerebral perfusion index - early prognostication	81
5.1.1.13	Complications	83
5.1.1.14	Follow up	84
5.1.1.15	Treatment	85
5.1.2	Stroke data bank - computational analytical statistics	86
5.1.2.1	Clinical subtype on admission versus final aetiopathogenetic classification for ischaemic patients	86
5.1.2.2	Age analysis (young and old) and aetiopathogenetic diagnosis	87
5.1.2.3	Neurological admission deficit versus disability - CNS versus Rankin scales	88
5.1.3	Treatable stroke mechanisms - examples	89
5.2	Cognitive testing results	107
5.2.1	Descriptive statistics	107
5.2.2	Cognitive computational statistics	110
5.2.2.1	Higher cortical function screening test sensitivity and specificity compared to the gold standard - neuropsychological testing	110

5.2.2.2	Risk factors for higher cortical function deficits: univariate and multivariate analyses	111
5.2.2.3	Results of multivariate logistic regression	115
5.2.2.4	Overall incidence of HCFD in younger (<49y) and older (>49y) patients with stroke (Table 12)	117
5.2.2.5	Incidence of HCFD subgroups in younger(<49y) and older (>49y) patients with stroke (Table 13)	118
5.2.2.6	Frontal lobe syndromes - cerebral lesion site as determined by functional brain scanning (Table 14)	119
5.2.2.7	Frontal lobe syndromes in young and old patients (Table 15)	120
6.0	Discussion of results	121
6.1	Stroke Data Bank Issues	121
6.1.1	Symptoms	121
6.1.2	Risk factors	122
6.1.3	Signs	122
6.1.4	The importance of determining stroke mechanism	123
6.1.5	Subtypes of ischaemic stroke. Clinical versus aetiological classification	124
6.1.6	Black stroke issues	124
6.1.7	Vasculitis	125
6.1.8	Dissection	126
6.1.9	Prothrombotic states	127
6.1.10	Young stroke population results	128
6.1.11	Cardioembolic stroke	132

6.1.12	Patent foramen ovale	133
6.1.13	Dolichoectasia	134
6.1.14	Infection related stroke	137
6.1.15	Impairment, disability and handicap and their measurement	137
6.1.16	Complications after stroke	138
6.2	Cognitive Issues	141
6.2.1	General - early evaluation and wide spectrum of deficits	142
6.2.2	Subcortical and subtentorial stroke and cognitive impairment - frontal system syndrome impairment	143
6.2.3	DSDB contributions to frontal systems syndromes	146
6.2.4	Frontal lobe syndromes in stroke - relation to lesion site	147
7.0	Conclusions	150
8.0	Concluding remarks	152
9.0	The Future	154
10.0	Appendices	155
10.1	Appendix 1: Definitions	155
10.2	Appendix 2: Higher cortical function screening test manual	174
10.3	Appendix 3: Digitised score sheet of the DSDB	186
10.4	Appendix 4: Peer reviewed articles published	227

11.0	References	187
11.1	Introduction	187
11.2	Review of the literature	190
11.3	Disability and handicap	193
11.4	Cognitive issues - overview	194
11.5	Methods	197
11.6	Results	200
11.7	Discussion - general	201
11.8	Discussion - vasculitides	205
11.9	Discussion - dissection	206
11.10	Discussion - prothrombotic states	210
11.11	Discussion - young stroke data bank issues	211
11.12	Discussion - cardiac embolism	216
11.13	Discussion - patent foramen ovale	216
11.14	Discussion - dolichoectasia	218
11.15	Discussion - infection	219
11.16	Discussion - complication post stroke	219
11.17	Discussion - general on cognitive issues	221
11.18	Discussion - frontal lobes	223
11.19	Conclusion and future	224
11.20	Appendix 1	224
11.21	Appendix 2	226

Tables

Table 1.	Prospectively defined symptoms	59
Table 2.	Risk factors - frequencies	60
Table 3.	Brain scan, laboratory, Doppler investigations	66
Table 4.	Cardiac abnormalities	68
Table 5.	Cerebral perfusion index in acute young strokes	82
Table 6.	Clinical subtypes vs final aetiological diagnosis	86
Table 7.	Young vs old stroke patients - aetiology	87
Table 8.	Neurological admission deficit vs disability	88
Table 9.	HCFD screening test sensitivity and specificity compared to Neuropsychological testing	110
Table 10.	Risk factors for higher cortical function deficits: univariate and multivariate associations	111
Table 11.	Results of multivariate logistic regression	115
Table 12.	Overall incidence of HCFD in younger and older patients with stroke	117
Table 13.	Incidence of HCFD subgroups in younger and older patients with stroke	118
Table 14.	Frontal lobe syndromes - cerebral lesion site as determined by functional brain scanning	119
Table 15.	Frontal lobe syndromes in young and old patients	120

Figures**Page**

Figure 1	56a
Figure 2	56b
Figure 3	56c
Figure 4	63a
Figure 5	70a
Figure 6	89a
Figure 7a	90a
Figure 7b	90b
Figure 7c	90c
Figure 7d	90d
Figure 8	91a
Figure 9	92a
Figure 10a	93a
Figure 10b	93b
Figure 11a	94a
Figure 11b	94b
Figure 12a	95a
Figure 12b	95b
Figure 13	96a
Figure 14	97a
Figure 15	98a
Figure 16	99a
Figure 17	100a
Figure 18	101a
Figure 19a+b	102a
Figure 20a+b	103a
Figure 21a+b	104a
Figure 22	105a
Figure 23	106a

Ethics

This serves to state that the University of Natal Ethics committee approved the methodology of this thesis on the 26 May 1992 and found it to be ethically acceptable.

Abstract

Background: Stroke is a leading cause of death and morbidity in all countries, yet treatment options are few. Numerous agents that were successful in animal models, failed in humans. Establishing the cause of stroke in the individual patient from the heterogeneous stroke mechanisms and measurement of clinical deficit including cognitive impairment in stroke are pivotal in successful treatment. An indigenous stroke data bank was established with specific emphasis on aetiology of stroke and higher cortical function measurement.

Aim:

1. Establishment of an indigenous stroke data bank using contemporary neuroinvestigative modalities to determine stroke mechanism as precisely as possible.
2. To determine in this population, the frequency and extent of cognitive disorders in the acute and subacute stroke period, using a battery of predefined higher cortical function tests applied to all patients.
3. Collation of a comprehensive array of epidemiological, clinical, investigative and prognostic variables in complete digitised storage form.

Methods: The patient population was a hospital based consecutive case series with an inpatient and outpatient stroke service in association with an acute stroke unit. A three tier investigative protocol was devised to incorporate contemporary neuroinvestigative modalities. All patients had mandatory investigations of stroke relevant blood tests, electrocardiogram, chest radiograph and brain scan. All patients were evaluated with a comprehensive

battery of predefined, bedside higher cortical function tests. Standardised neurological deficit, clinical stroke scales, aetiological scales and disability scales were incorporated to quantitate deficit, stroke subtype and handicap at presentation. All patients were evaluated by the author and all information digitised by the author into the computerised registry - Durban Stroke Data Bank (DSDB).

Results

1. Stroke Data Bank Issues: The first 1000 patients evaluated comprised of 561 men, 439 women, 781 Whites, 103 Asian Indians, 100 Blacks, 14 of Mixed Race and 2 other race groups. All patients had either a CT brain scan (698;69.8%), MRI brain scan (426;42.6%) or both (124;12.4%). Single Photon Emission Computed Tomography scans were performed in 104 (10.4%). Among the 23 different symptoms coded for, long tract signs, vision abnormalities and speech impairment predominated but 150 (15%) had additional other symptoms not coded for. Among the 29 different risk factors coded for, hypertension (42.1%), smoking (26.7%), cardiac illness (17.7%), Diabetes Mellitus (10.4%) and carotid stenosis (25.1%) were the most numerous. Approximately 96 different causes and possible causes of stroke were identified. The clinical ischaemic stroke classification (OCSP) revealed partial anterior circulation strokes in 447 (44.7%), posterior circulation in 258 (25.8%), total anterior circulation in 185 (18.5%) and lacunar in 82 (8.2%). The aetiological classification identified a large proportion of strokes due to "other" (253;25.3%) causes as opposed to large (264;26.4%) and small vessel disease (262;26.2%) or cardioembolism (122;12.2%). In 99 (9.9%) patients no cause could be established. The haemorrhage group was small (48;4.8%). Comparison of the clinical and aetiological classifications showed a significant difference overall (Chi square p-value=0.001). Black race had relatively higher other causes (39%) and unknown (20%) causes as did the young stroke (8-49 years) population; other (46.5%) and unknown (19.1%). Final aetiological classification differed significantly in young versus old in all

categories ($p=0.001$) except cardioembolism ($p=0.884$). Admission neurological deficit (CNS) score compared to admission disability score (Rankin) showed moderate correlation with a Kappa value of 0.543.

2. Cognitive issues: One or more higher cortical function abnormalities was detected in 60.7% of non drowsy (drowsy, coma or delirious $n=45$) patients. The most numerous categories were aphasias (25.2%), apraxias (14.5%), amnesias (11.6%) and frontal systems syndromes (9.2%). In 76 patients, neuropsychological testing, (used as the gold standard) was performed and comparison to the HCFD test revealed a sensitivity of 80.2% (CI: 72-88%) and specificity of 100%. Cognitive impairment occurred without elementary neurological deficits (motor, sensory or visual impairment) in 137/608 (22.5%). Univariate and multivariate analyses of risk factors and likelihood of developing a HCFD revealed that increasing age, black race, being overweight and recent infection were independent variables at a p value of 0.05. HCFD did not differ significantly in younger versus older patients ($p=0.194$). Frontal system syndromes were more common in subcortical (32.3%) versus cortical (23.5%) lesions and more common in younger versus older patients ($p=0.001$)

Conclusions:

1. Cognitive disturbance is present in the majority of all types of stroke. This necessitates a reliable appraisal of this form of neurological deficit in all stroke patients in order to measure the true extent of deficit and monitor treatment and rehabilitation. This has important consequences for acute treatment trials that depend on changes in quantifiable deficit.

2. At times cognitive disturbance may be the sole presentation of stroke, unaccompanied by long tract signs. Therefore inadequate HCFD assessment may miss the deficit altogether.

3. Subcortical stroke is commonly associated with cognitive impairment - usually of a frontal system impairment. Such deficits are best correlated with functional brain scanning and not anatomical brain scanning. This is consistent with the network theory of brain functioning.
4. Risk factors for developing cognitive impairment in the indigenous stroke population included increasing age, black race, overweight body habitus and recent infection. This is an important message for the local population as the latter two are amenable to preventative measures.
5. In the young stroke population, although causes of stroke were numerous, prothrombotic states, infection associated strokes and dissection were the most numerous. All are amenable to primary preventative measures and treatable in the acute phase of stroke.
6. The Durban Stroke Data Bank showed that at least two dozen symptoms in stroke are important. In some instances, the diagnosis of stroke may be missed altogether if a wide array of symptoms are not entertained on presentation.
7. There were important black white differences in stroke with black people being younger with an increasing rate of HIV associated stroke being documented.
8. Clinical and aetiological post investigative classification is useful in the management of stroke patients with significant differences found in all subgroups. This guides early, emergent stroke investigations and management.

1.0 INTRODUCTION

Stroke is a major cause of death and morbidity with few treatment options at the present time. Having to date suffered from therapeutic nihilism and consequently unenthusiastic diagnostic, stroke as a disease entity, is moving towards medical emergency status. Numerous therapies have been shown to work in animal models [1,2] but their application thus far to humans has been fraught with difficulty and largely negative results [3]. The few successes have been possible only with the identification of specific subgroups of stroke populations; anti coagulation in nonvalvular atrial fibrillation [4], carotid endarterectomy in greater than 70% symptomatic carotid stenosis [5] and nimodipine in acute stroke of less than 12 hours of onset of symptoms [6]. More recently, the thrombolytic agent tissue plasminogen activator has been heralded as the first real acute stroke therapy albeit in a strictly defined subgroup of patients [7]. Because both presentation and the aetiology of stroke is protean and heterogeneous, a large number of variables need to be collated for each patient.

Higher function deficits in particular need to be carefully assessed together with the more traditional and elementary neurological deficits such as long tract signs. So called silent infarcts are being increasingly recognised. This may be due to the patient not having reported the event or the attending doctor dismissing such a deficit or not identifying it. It may be said that a "limping brain is more difficult to identify than a limping leg" [8]. Many silent infarcts occur in the frontal and parietal lobes, areas that need specific testing for higher function deficits. Patients tend not to volunteer such deficits.

Traditional testing, using a battery of higher cortical function is time consuming and impractical. In depth neuropsychological testing is not suited to bed side assessment that often needs to be done rapidly in order to diagnose stroke or an evolving stroke. The assessment therefore needs to be done in a hierarchical manner from high sensitivity to high specificity with progressively more in depth assessment only as required [8].

Several stroke data banks have been designed and have each contributed the most valuable data on stroke populations because of systematic uniform compilation of data, power in numbers and by virtue of being population based [9-31]. This has often led to the establishment of stroke units at such centres. Others have also shown improved outcome to patients in terms of morbidity and mortality when admitted to such a unit without the application of specific treatment modalities [32,33].

As treatment of acute stroke seems imminent [1,2,6,7] the value of having a rigorous method of defining the different subgroups of stroke patients by means of a SDB is self evident. This system can subsequently be applied to all patients with stroke.

There are several unique features to the Durban Stroke Data Bank (DSDB)

1. The DSDB is a hospital based, prospective study of first ever stroke patients according to the WHO definition of stroke with a 100% brain scan confirmation of stroke.
2. The DSDB incorporates 6 standardised scales allowing quantitative measurement of impairment, disability, handicap, aetiology and prognostication.
3. It is one of the few stroke data banks using the full complement of contemporary investigative modalities in a tailored protocol [9-31].
4. The DSDB was designed with specific questions in mind, unlike most of the previous stroke data banks in existence [9-29]; namely the extent and variety of cognitive disturbance in acute stroke and the variety of causative stroke mechanisms. As a corollary it also provided a database for cognitive syndromes.

5. A state of the art relational database software program was used to digitise all data collected. This included digitisation of all clinical and investigative information and where appropriate digitisation of radiographic, photographic and acoustic data.

6. A major concern expressed by the investigators of the two largest and also most comprehensive stroke registries (Mohr JP of the NINCDS Stroke Data bank; n=1805 and Bogousslavsky J of the Lausanne Stroke Registry n=>3000) [9,10,16,17] was the reliability of assessment and the recording of information in the registry.

The DSDB represents a personal series (n=1000) with all patients evaluated by the author, all information digitised by the author and more than 90% of patients managed clinically by the author.

7. Adaptable design allowing new data field incorporation such as newer scales, investigations and risk factors to be added.

2.0 REVIEW OF THE LITERATURE

2.1 Rationale for emphasis of Higher cortical function impairment in stroke.

Cognitive impairment in the acute stroke situation may be the sole clinical neurological deficit in a cerebrovascular episode [1,2]. Subtle or covert mentation disturbances, both for practical and traditional reasons, do not have the same import for lesion localisation as do "classic" neurological symptoms or signs [3,4]. The diagnosis and localisation of stroke is facilitated when heralded by elementary neurological deficits such as hemiparesis, hemihypesthesia or hemianopia [5,6], but good clinical acumen is required for the patient without long tract signs who either fails to volunteer or even actively denies the presence of neurological symptoms because of a neglect, agnosic or alexic syndrome.

A high index of suspicion is required for the diagnosis of a higher cortical function deficit (HCFD) in stroke patients, as their affliction may be labelled as "confusion" to the casual observer. The differential of an acute confusional state prominently features metabolic, infectious, toxic or drug etiologies, whereas stroke is rarely placed high on the list [6]. For example, an isolated sensory aphasia may be mistakenly diagnosed as a delirious state [3]. Moreover, the delirious or agitated behaviour of some stroke patients, especially with right hemisphere involvement, may also preclude adequate assessment of sensorimotor deficits, the traditional hallmark of stroke. It is not uncommon for a behavioural neurological syndrome to manifest in the absence of any other abnormality on neurological examination [5].

A variety of neurocognitive deficits need to be considered in evaluating patients with stroke which require specific tests, methods of elicitation and an appreciation of their co-occurrence as predicted by the contemporary "network" theory of brain behaviour function [7]. Specific testing is especially

important as brain imaging may fail to demonstrate the lesion or depict clinically irrelevant lesions [8]. Finally, studies of patients with cerebrovascular disease provide superior clinicoradiologic and clinicopathologic associations, as opposed to either neoplastic or traumatic lesions, since mass effect and contrecoup effects, respectively, detract from correlative precision [5]. The frequency of HCFD, has not been addressed in a large stroke population [9-20]. The DSDB provides an opportunity to investigate the importance of HCFD in a prospectively evaluated stroke patient cohort.

2.2 Rationale for using stroke to study cognitive deficits

Stroke is widely regarded as the best neurological process to study brain behaviour relationships. The disease process is unique in that it is rapid in onset, circumscribed anatomically and mostly presents with relatively stereotyped clinical presentations limited by cerebral vascular territories. In addition the degree of oedema contributing to the clinical deficit is minimal with strokes, multiple lesions are uncommon and mass effect is rare. These characteristics, most notably the discreet, relatively clean lesion process of stroke make it the most ideal cerebral disorder for the study of cognition which is contained in complex widely distributed networks [7].

2.3 Overview of Stroke Data Bank design

Many stroke data banks are in existence, but it has been noted that fewer than 10 such computerised registries fulfil the ten criteria for optimal data bases put forward by the committee at a recent workshop on *Challenging Issues in Stroke Data Bank Research* [20]. The Ten criteria for an optimal SDB used for clinical research are:

1. Diagnostic criteria

2. First ever strokes
3. High rate of CT investigations
4. Detailed autopsies whenever possible
5. Prospective data whenever possible
6. Pilot phase and interrater studies
7. Consistent screening procedures to identify patients enrolled and consistent time frame of examinations
8. Collection of a large spectrum of clinical and investigative data
9. Follow up investigations
10. Baseline report

2.4 Uses of stroke data banks and the issue of population based versus hospital based registries.

Because of the diversity of clinical syndromes and causes of stroke, stroke registries are currently regarded as the best tools to improve our knowledge concerning cerebrovascular diseases [21]. The various types of stroke registries in existence include

1. hospital based studies
2. single centre studies
3. hospital based multicentre studies
4. hospital based community studies
5. community studies.

SDB's are powerful tools for clinical research especially when designed prospectively to answer specific questions in mind. Brainin [22] regarded the place of stroke registries as being intermediate between case series studies and epidemiological studies. The relative strengths of SDB's in general include;

1. Deciphering similar patterns in related items of information
2. Deciphering similar patterns in unrelated items of information
3. Looking for trends in the data collected
4. Generation of research hypotheses, theories and analogies
5. Testing of current and new hypotheses on aetiological and clinical issues in stroke such as acute treatments and interventions.

An advantage that epidemiological or population/community based studies have over hospital based studies are the ability to address incidence and prevalence of disease. In practice such studies are rare and not practical in large metropolitan centres.

2.5 Clinical and cost factors

For several reasons, stroke data banks are important from a clinical and cost containment point of view. Stroke causes are heterogeneous and vary between races, regions and countries - hence the need for local data. Dedicated stroke units which typically arise from a stroke data bank project, improve outcome and reduce hospital stay.

Stroke data banks and trials do not give adequate attention to the incidence of higher cortical function deficits. The true extent of a neurological deficit must be known to ascertain treatment and monitor rehabilitation. Meaningful stroke measurement at the present time may well have been misguided and this may be an important factor in the almost universal stroke treatment failures thus far [23]. We may well be measuring the wrong thing wrt improvement and

outcome when applying the standard stroke scales. It appears more important to weight or emphasise higher cortical function deficits in the acute stroke setting to enable ascertainment of true improvement [23]. Thus far only two stroke scales have achieved this objective - the CNS and NIH scale [23].

2.6 The concepts of impairment, disability and handicap and their measurements.

Perhaps one of the most important functions of a stroke registry is the measure of human suffering, handicap and cost.

Illness may be viewed as incorporating the following components;

Disease

Impairment

Disability

Handicap (WHO).

This allows for decreasing objectivity but increasing relevance. This part of the DSDB was designed to incorporate popular validated scales to measure each of these components. The scales used included the CNS (impairment), Barthel (disability) and Rankin (handicap) scales.

The International classification of disease (ICD) is the official basis for morbidity and mortality of the World Health Organisation (WHO). This classification is mainly based on aetiology which is the primary axis. The model may be depicted as

Aetiology (microorganism, external cause, genetic defect)

pathology - manifestation (syndrome, symptom, disease).

The International Classification of Impairments, Disabilities and Handicaps (ICIDH) is a more sophisticated model that allows for definition by aetiology, pathology, impairments and handicap.

Disease (or disorder)

Impairment (exteriorised)

Disability (objectivised)

Handicap (socialised).

The application of these principles to the DSDB may be presented as follows:

Disease (categorisation of stroke subtype and aetiology DSDB and ICD classifications)

Impairment (analysis of neurological manifestations - CNS)

Disability (measure of ADL and IADL activities - Barthel)

Handicap (assessment of changes/losses in social roles - Rankin)

2.7 Overview of neurological scales and rationale for inclusion in DSDB

Many different scales are in existence and were designed to measure outcome in trials, treatment responses and rehabilitation. Neurorehabilitation

recognises that premorbid status is rarely quantified and the negative connotations of “handicap scales” should rather be replaced by the more positive terms of activities of daily living and instrumental activities of daily living. Overall, measurement of disability and handicap may be categorised into:

1. Activities of daily living (ADL)
2. Instrumental or extended activities of daily living (IADL)
3. Outcome scales mainly used in medical trials
4. Global health [1]

The reason for measuring ADL is that these best measure the basic skills necessary for personal independence. A review of which of the various ADL scales best suited the purposes of the present study suggested the Barthel Index for ADL and Rankin Scale for global health. Due consideration was given to a reliable, valid and above all simple to perform evaluation and the ability to ascertain telephonically for follow up purposes. The telephonic assessment validity has been done in well designed studies for only few of these studies including the Barthel index of ADL scale [1] and Rankin scale much more recently [2]. The choice of the Barthel index of ADL was made after review of the literature indicated that there were 10 essential activities in any ADL assessment. These included:

1. Dressing
2. Bathing
3. Transfers
4. Grooming
5. Managing stairs
6. Walking
7. Feeding
8. Going to the toilet
9. Wheelchair skills

10. Continence

Measuring ADL is essential to guide clinical management especially where various treatments are being used or evaluated, in the initial stages of stroke, the identification of the most important disabilities and making follow up more precise and scientific. Communication between researchers and different centres is facilitated if the same measurement tools are being used. In the current economic climate of rationalisation of medical care, the scored disability assessment will be most important to securing remuneration for rehabilitation services and other supportive services required.

The choice of the Barthel index of ADL is supported in the review by Wade and Collin [3] who proposed that this scale should be the preferred measure of physical disability because it contains all 10 ADL activities, has been used in research studies more than any other scale and has been used to evaluate a wider range of conditions. Gresham et al showed that the Barthel was superior to the Katz ADL Index and the Kenny Self Care evaluation [4]. The aspects looked at were sensitivity to change, completeness of the scale, amenability to statistical evaluation and greater familiarity amongst clinicians because of widespread use. Self report and obtaining the information from nursing staff or care givers was shown also to be quick (less than 5 minutes) and reliable [5]. Reliability and sensitivity studies on the Barthel index were reported and found to be adequate [6-9]. Collin argued for the acceptance of the Barthel scale as the standard index of disability [1].

No scale is perfect and knowledge of the limitations is as important as its advantages so as not to overlook possible meaningful clinical deficits or recovery. The Barthel index suffers from inability to measure communication, cognition and motivation. In the event of requiring testing for such parameters, scales designed to measure these specifically need to be implemented.

The Modified Rankin Scale

The modified form of which (includes death) appears below:

Grade	Description
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Moderate disability; requiring some help, but able to walk without assistance
3	Moderately severe disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention.
6	Death

The Freanchay Activities Index is the best tool to assess return to “normal living” - the only scale that does this [11]. This was not used in the DSDB.

2.8 Cognitive issues

2.8.1 The challenge of cognitive assessment

Overview and inherent constraints - a brief synopsis of problem areas in testing cognition as noted by prominent researchers in the field [1-7].

Traditional cognitive assessment is organised according to discrete mental faculties such as apraxias, amnesias, aphasias. These may reflect abstractions on the part of the clinician rather than correlate with neural organisation [2].

With higher mental function assessment it is important to note the most elementary cognitive disturbance before proceeding with the entire screening or more complex neuropsychological assessment. The tiers of assessment appear in the left column. The right hand column delineates their individual limitations on further cognitive testing [1];

Cognitive domain:

consciousness
attention
language
memory
frontal system syndromes

If impaired limits:

all other cognitive testing
interaction and tasks
communication
tests/past relevant history
interaction eg abulia

Viewed in another way, each mental task basically has the following components:

input channel (consciousness, attention language)

intermediary processing stage (language, memory, frontal systems)

an output channel (language).

Because of the network theory of the brain [2], very similar behavioural deficits may occur due to widely different brain lesions. For example hemispatial neglect may arise with frontal, parietal or thalamic lesions. More precise localisation requires evaluation of neighbourhood signs which accompany the behavioural deficit.

Our available repertoire of mental tests allows us to test only those faculties that are easily testable, such as memory, language and praxis. There are no tests for a wide variety of other equally important human functions such as lateral thinking ability, reasoning, perseverance and judgement [2]

To gain a reasonable overview of mentation, the choice of tests must be individualised and flexible and degrees of difficulty need to be used according to the individual's level of ability.

The requirement of flexibility in cognitive testing is not limited to the level of difficulty. A person may present with complaints for which no specific tests exist let alone a medical description. An example is a report of patients with brainstem stroke either having strange dreams or sudden of lack of dreams.

The history given by the patient may differ considerably from that given by family members. Often the latter is more accurate and revealing.

The particular difficulty the person has also must be related to the deficits in daily living.

Such problems in cognitive testing are challenging and daunting. As Mesulam has put it so aptly;

“ the task should be approached with the spirit of an explorer, the cautious flair of a detective and the training of a neuroscientist” [2].

Flexibility and improvisation are essential.

2.8.2 Important points about cognitive testing

A particularly succinct review of the currently perceived problems with cognitive testing is quoted from Orrin Devinsky [1].

“The mental status examination has an undeservedly bad reputation and should never be omitted from the neurological examination”.

During neurological assessment, it is as inappropriate to omit the mental status examination as it is to ignore the muscle strength or reflexes. It should be the first component of the neurological examination as it is critical to the interpretation of other findings.

“The neurologists law - localise the lesion - also applies to mental function”.

Findings from the mental status examination must be synthesised with each other and with findings from the neurological and general medical examinations.

“The observation and history of the patient’s behaviour are the most important aspects of mental evaluation”.

There are several reasons why behavioural problems are easily overlooked:

1. Most people tend to minimise problems, especially behavioural ones
2. Some patients are not fully aware of their problem
3. The duration of patient contact for most physicians is limited
4. Behavioural problems are often intermittent or situation dependent [1]

“Mental status examination is systematic and hierarchical”.

It is essential to recognise this in cognitive testing as certain functions are critically dependent on the integrity of others. For example, if comprehension is impaired as with Wernicke's aphasia, praxis testing cannot proceed and one cannot test memory before attention.

The following is regarded as the strict test order for mental status examination:

1. Level of consciousness
2. Attention
3. Orientation
4. Language
5. Memory
6. Others [1]

“Neuropsychological testing is an elaboration of the mental status examination”

“Bedside mental status testing is limited by time, environment, qualitative analysis and materials. Neuropsychological evaluation permits a more complete and quantitative assessment of cognitive functions. However neuropsychological testing does not replace bedside screening of mental status” [1].

Note: In the hyperacute setting cognitive evaluation must proceed as accurately and with as much thoroughness as the situation allows. An emergency standby neuropsychologist is neither necessary, nor does the anxious, frightened or alarmed patient make a good candidate for concentrating on neuropsychological testing when emergency treatment and urgent investigations must take priority. What cannot be accomplished in the form of cognitive testing within approximately 15-20 minutes during the acute admission must wait for a more opportune time when the patient's condition

has stabilised and the patient is in a better frame of mind to concentrate on the neuropsychological testing which is demanding even for normal individuals.

There is no practical battery of neuropsychological tests that will be applicable to all patients. Neuropsychologists often use a battery of tests but supplemental tests will often be required to delineate a deficit fully. In the acute stroke setting, indications for neuropsychological testing include the assessment of the extent and degree of cognitive deficit and determining areas of preserved functioning which then become important for rehabilitation.

“Positive symptoms reflect activity of preserved, but often dysfunctional nervous tissue”

“Positive symptoms are abnormal superimposed behaviours that presumably reflect overactivity of neural function”

“Diaschisis is dysfunction in cerebral areas remote from the destructive lesion”.

Subcortical lesions are able to disrupt function at remote sites. Interruption of fibres passing from the brainstem to the diencephalon and cerebral cortex can cause coma and depress cerebral blood flow and oxygen consumption. Failure to activate specific cognitive areas may be the explanation for specific language and other cognitive deficits consequent to thalamic lesions.

The concept of diaschisis may be important not only to explain behavioural deficits observed in clinical neurology but may provide insights into the mechanism of functional recovery and ultimately therapy [8,9]. Future neurological therapy may focus on brain regions that are structurally intact but functionally impaired and restorative neurology may be able to reverse the process of diaschisis.

“Subcortical lesions can produce cortical deficits”

“The neurobehavioural relationship between higher and lower centres is not a one-way street. The anatomy of the cortex and subcortical areas are intricately interwoven. Cortical and subcortical areas that are richly interconnected are associated with strikingly similar clinical findings when either one is damaged” [1].

Examples included

Language

Mutism - cingulate, medial forebrain bundle, diencephalon

Dysarthria - pyramidal and extrapyramidal tracts, cerebellum

Aphasia - subcortical white matter, striatum, thalamus

Short term memory

Hippocampus, fornix, basal forebrain

modified from [1]

2.8.3 Reasons for adopting a clinical (bedside) cognitive screening test

As the method of testing was important, a number of experts from different backgrounds in the field were consulted. These included behavioural neurologists, neuropsychologists and biological psychiatrists [1-12].

1. There is no standardised cognitive test applicable to stroke. Lezak describes specific batteries for Multiple Sclerosis, Parkinsons, Epilepsy and others [10].

2. Stroke is now classified as a medical emergency and treated as such (American Heart Association Stroke Council). There is no time within the first few hours or even days in many patients to conduct neuropsychological testing.

3. A screening battery has the advantage of screening for a wide range of cognitive impairments without becoming too specific and also without standardisation and test scores. This is the value of well conducted predefined clinical tests and they have an important function in this respect. Once the clinical situation has stabilised, the patient feels more comfortable and the family has calmed down better cooperation is usually possible. The testing therefore is done in at least 2 stages and sometimes in several stages. During this time period the emergence of new deficits and disappearance of others may occur, such as Global aphasia to Broca's to dysnomia. The process is dynamic and a more flexible and easily administered battery of cognitive testing has its value. Also, the clinician who sees the patient on a daily basis is best suited to do this testing but is in most instances not the most qualified to do so. By having clear, concise, definitions for the various cognitive deficits, the elicitation of the many and interesting deficits will be better appreciated. Neuropsychologists are not generally found in the emergency room and generally operate and do best on an elective appointment basis. Although there may be merit in involving a neuropsychologist more acutely in stroke, as indeed was done for the Transient Global Amnesia (TGA) patients, this is not practical and requires resources and finances that are scarce especially in developing countries.

Both Lezak [10] and Luria [11] advocate flexible, (double dissociation) qualitative as opposed to quantitative testing. A similar conclusion was also drawn in Watts Runge's PhD thesis [12]. Both have their value.

2.8.4 Cognition - what is human intelligence and what are we measuring.

The dominant view of human intelligence from a psychological point of view was of a unidimensional or monolithic capacity. It is now viewed as a diamond ie multifaceted array of distinct capacities [13]. There is however no universal agreement on how to conceptualise, measure or clinically evaluate these differing entities. Howard Gardner [14, 15] proposed that intelligence can be divided into seven relatively autonomous types

Linguistic

Musical

Logical-mathematical

Spatial

Bodily kinesthetic

Intrapersonal

Interpersonal

Each is conceptualised as a basic unit of intelligence that is not further divisible. These are regarded as the fundamental building blocks of human intelligence which in turn is dependent on the integrated action of these multiple discreet information processing components. Gardner's schema has been noted to be very compatible with the behavioural neurological approach (aphasias, amnesias, apraxias, agnosias etc). The cognitive approach allows for a more fine grained assessment. In addition the clinical disorders of human intelligence can be understood in terms of which facets of intelligence are impaired and which underlying information processing modules are affected [14,15].

2.8.5 Disorders of intelligence and disorders of the forces which modulate intelligence.

Both of these need individual assessment as the latter influence the former. These include;

consciousness

attention

personality

motivation

emotion [13,16]

Only consciousness and attention are assessed by the Cognitive Screening Test used in the DSDB. The lack of assessment of personality, motivation and emotion is a potential criticism of the DSDB screening battery, although it should be recognised that they are complex and difficult to assess at the bedside.

2.8.6 Disorders of forces which modulate intelligence

This concept allows us to readily understand the difference (from a cognitive neurological point of view) between dementia and encephalopathy;

- cognitive disorders occurring with normal level of consciousness and attention are called dementias

- cognitive disorders occurring in the context of a minor or subtle decline in the level of consciousness and attention are termed encephalopathy.

2.9 Using the syndrome of stroke as a means for studying cognitive disorders

As Orrin Devinsky has remarked, stroke has been one of the great teachers of behavioural neurology. Most of the classical neurobehavioural syndromes such as aphasia, apraxia, alexia without agraphia, cortical blindness, left sided neglect, anosognosia and peduncular hallucinosis were originally described in patients with stroke. Tumours, infectious diseases, demyelinating diseases and trauma diffusely injure the brain and are often associated with increased intracranial pressure, oedema and compression of surrounding structures. Stroke produces more circumscribed and “purer” lesions. Four or five days after a stroke is a good time in general for assessment because the oedema and compression in some acute strokes has then subsided [1].

The DSDB was designed with this knowledge in mind and the cognitive testing done in the acute and subacute phase within the first week. Before conclusions about a stroke related cognitive disturbance can be drawn a cautionary note by Devinsky is appropriate here;

“Alterations in behaviour suggest brain dysfunction. Diseases that affect the brain in a multifocal or diffuse manner (vascular, infectious, inflammatory, neoplastic) produce unusual clinical pictures. A common diagnostic pitfall is the assumption that emotional, bizarre and atypical cognitive disorders are psychiatric in nature especially when exaggeration or emotional overlay is superimposed on organic features” [1].

A good example of just how precise the clinico radiological association in stroke syndromes can be is given by the example of left anterior choroidal infarction. This is virtually the only cause when the triad of;

hemiparesis

hemisensory loss

hemianopia

without aphasia is present clinically.

2.10 There are several major problems with cognitive testing that necessitate discussion:

2.10.1 Rationale of clinical bedside testing as opposed to standardised mental test schedules. Qualitative versus quantitative testing.

2.10.2 Theoretical considerations of qualitative versus quantitative assessment.

2.10.1 Rationale of clinical bedside testing as opposed to standardised mental test schedules. Qualitative versus quantitative testing.

Many mental test schedules have been devised ranging in complexity, ease of use and time taken to administer them. Many require specialised test items and training in their administration and are for this reason alone not suited to the practising clinician handling medical emergency patients such as those with stroke.

Three of the more commonly used tests include the Mini Mental State Examination, The Information Memory Concentration Test and the ten item Hodkinson Mental Test [3]. Although having normative data and good interrater reliability there are several major criticisms and shortcomings if applied to the stroke population.

1. These tests tend to sample cognitive areas of attention, concentration, memory, language and visuospatial abilities and a low score may be due to one area of cognitive dysfunction or several. Two entirely different disorders may have the same score.
2. The profile of performance in these tests is not taken into consideration -

only the overall score. A low score may reflect a severe deficit in one domain only or a mild impairment across all the domains evaluated.

3. All schedules were developed for the quantification of cognitive impairment in elderly patients with dementia or delirium and not the more circumscribed impairments of stroke patients.

4. These standardised tests are particularly insensitive to circumscribed cognitive deficits such as amnesia, aphasia, visuospatial, right hemisphere or frontal lobe syndromes [3].

2.10.2 Theoretical considerations of qualitative versus quantitative assessment.

As argued by Watts in her thesis [12] and Lezak [10], both techniques are required for effective assessment.

The psychometric evaluation reflects a persons performance on specific tests relative to age adjusted, educational and other representative criteria.

Psychometric tests therefore focus on a person's performance. Such a model is inadequate for neuropsychological evaluations for several reasons [12];

1. It has been observed in neurology and neuropsychology that the descriptive approach has led to the accurate identification of many of the syndromes recognised today (Gerstmann's, alexia without agraphia) and the development of theories [17].

2. Tests and procedures which involve averaging and comparisons of group performances are bound to miss patients with specific and unique deficits. Descriptions such as alexia without agraphia have contributed to an understanding of brain behaviour relationships [18].

3. The clinical method, as opposed to the psychometric method has the ability to pick up new and unusual syndromes and in the apt words of Anastasi; “is best suited to the processing of rare and idiosyncratic events whose frequency is too low to permit the development of statistical strategies” [19].

4. Every brain injured person is unique and so is the premorbid personality characteristics, reaction to the brain behaviour disturbance, capacity for adaptation and recovery. These factors impact assessment and evaluation [10].

Such views have led authors such as Watts to comment that the use of the psychometrics seems limited to defining whether or not brain damage is present or not [12].

The theme of much of American neuropsychology traditionally has been based on the application of quantitative standardised tests [10,20-25].

Walsh in particular has recommended the application of more flexible, informal batteries of tests [24,25].

The single case study method is a feature of the Lurian approach to neuropsychological assessment and such an approach may in fact be traced back to Hippocrates and was particularly popular in the nineteenth century when many of the neuropsychological syndromes were identified [18,26,27].

In turn, the problem of generalising from the results of a specific case study were highlighted [28,29]. An important aspect of the Lurian approach to neuropsychological assessment is the interpretation of data using syndrome analysis and double dissociation (that all functional systems which involve a disturbed factor will be disrupted whilst those which do not include this factor will remain intact) of function. Syndrome analysis necessitates a detailed qualitative analysis of the symptoms and signs in accordance with this principle of double dissociation [11,12].

3.0 AIM

1. Establishment of an indigenous stroke data bank using contemporary neuroinvestigative modalities to determine stroke mechanism as precisely as possible.
2. To determine in this population, the frequency and extent of cognitive disorders in the acute and subacute stroke period, using a battery of predefined higher cortical function tests applied to all patients.
3. Collation of a comprehensive array of epidemiological, clinical, investigative and prognostic variables in complete digitised storage form.

4.0 METHODS

4.1 Data collection

The DSDB was a prospective, observational, hospital based study with collection of acute care and follow-up clinical and laboratory data on patients with stroke. The study was designed to facilitate research on the characteristics, clinical course and outcome of patients with acute stroke and with particular emphasis on cognitive impairment in the acute and subacute phase. Each patient with acute stroke was examined by the author and all patients underwent initial and subsequent computerised tomographic brain (CT) scanning or magnetic resonance imaging brain (MRI) scanning or both. Information was collected on each patient concerning the details of medical, neurological and social history, general and neurological examinations, cognitive examination, laboratory studies, final diagnosis or diagnoses and complications.

4.2 Stroke protocols

Since patients often have several risk factors and more than one possible cause of stroke (eg atrial fibrillation and carotid artery stenosis), ending the work up at the first positive test may not be the optimal approach. Until various algorithms are compared however, stroke diagnostic plans needed to be individualised. This has recently been supported in a review by Adams [1].

1. Recommended minimum work up
2. Additional work up in selected patients.
3. Rarely used tests but listed as options

The latter two tiers were used as appropriate - tailored to each individual patient's conundrum of clinical details. Hence a 3 tier investigative protocol was used, incorporating a basic minimum workup, tests often used and tests seldom used.

4.2.1 The minimum workup included (1st tier):

Basic stroke relevant blood tests

complete blood count
platelets
serum electrolytes
urea
creatinine
lipogram
Lipoprotein (a)
erythrocyte sedimentation rate (ESR)
serum glucose
International Normalised Ratio (INR)
partial thromboplastin time (PTT)

Neuroimaging

computerised tomography (CT) or
magnetic resonance imaging (MRI) brain scan or
single photon emission computed tomography (SPECT)

Cardiac tests

chest radiograph
electrocardiogram (ECG)

Higher cortical function deficit (HCFD) bedside screening test

4.2.2 Additional work up when appropriate (the 2nd tier) included:

Sonographic studies

transcranial Doppler (TCD) of the intracranial large arteries
duplex Doppler (DD) sonography of the cervicocephalic vessels (common, internal and external carotids, proximal vertebral (origin or V1) and extracranial (V2) vertebral arteries
transcranial Doppler studies of the distal internal carotid arteries
transcranial Doppler of the distal vertebral arteries (V3 and V4) intracranial segments
Transcranial Doppler with 10 ml aerated saline injection in antecubital vein for the detection of right to left shunt (patent foramen ovale, pulmonary shunts)

Angiography noninvasive and invasive

MR angiography
Spiral computerised tomography angiography
Catheter cerebral, extracranial and arch angiography

Additional cardiac

transthoracic (TTE) echocardiography
transoesophageal (TEE) echocardiography
Holter monitoring
Exercise stress testing

Prothrombotic tests

Antithrombin III
Protein C
Protein S
Anticardiolipin antibodies

Plasmin system defects

Autoimmune tests

Antinuclear factor

Rheumatoid factor

Neuropsychological testing

Cerebrospinal fluid analysis (CSF)

4.2.3. A category of seldom required tests (the third tier) for the following:

Fasting plasma homocysteine levels for homocystinuria (heterozygotes)

Coagulation defects - factor VIII, IX, V, afibrinogenaemia

Haemoglobinopathies (Sickle Cell disease, haemoglobin SC)

Lactate levels - mitochondrial cytopathies (MELAS)

Brain biopsy

4.3 Diagnostic classification

The databank was designed according to the four levels of illness in the World Health Organisation model of impairment, disability and handicap (WHO ICDH) [2] model:

pathology (organ or organ system)

impairment (symptoms and signs)

disability (functional limitations - interaction between the organism and environment)

handicap (social consequences of disease) [3].

Several scales were employed in this registry to accommodate these measurements in an objective and quantifiable manner. In addition it facilitated accurate comparison within the registry, with other data banks and stroke trials. These included six classification systems each measuring differing but important aspects of disease;

1. A neurological deficit scale

Canadian Neurological Scale [4] (CNS)

2. A clinical stroke scale

Oxfordshire Community Stroke Project Scale [5] (OCSP)

3. A disability scale

Barthel Index [6] (BI)

4. A handicap scale

Rankin [7] (R)

5. An aetiopathogenetic scale

Trial of Org 10172 in acute stroke [8] (TOAST)

6. The International Classification of Diseases Neurology [9] (ICD-9)

Many scales in use represent simplified versions of a neurological examination focussed more on diagnostic and localisation information rather than functional deficits and prognostic data. Most scales in use have not been validated, are difficult to use and are in some ways inappropriate for the acute stroke patients. The CNS was used because of the following points as outlined by Cote' et al [10]:

detection of clinical noteworthy differences in the neurologic status

testing of relevant modalities most commonly affected in acute stroke and having possible prognostic value

ease of use and interpretation by observers with different medical training

brevity and practicality of its use in the acute stroke period. In addition to the above points, the CNS paid particular attention to the three basic types of validity; content, criterion and construct validity.

The scales were chosen because of their validity according to the following principles for evaluation of clinimetric scales;

Content validity - the extent to which the scale includes all relevant dimensions of what is being measured

Criterion validity - whether a scale can be used to estimate the current clinical status (concurrent validity) or predict the future health status (predictive value) of the acute stroke patient

Construct validation - the behaviour of the scale compared with an index which measures a different type of deficit (discriminant validity) and its responsiveness in identifying change in the neurologic status of stroke patients (convergent validity) [10].

The combination of scales is of great advantage and the CNS and Barthel are amongst the best scales for stroke currently in use. However a glaring deficit with all scales is the paucity of cognitive function testing in stroke patients [12].

The International Classification of Diseases Index for Neurology categories included:

430	Subarachnoid haemorrhage
431	Intracerebral haemorrhage
432	Other haemorrhage for example subdural haemorrhage
433	Occlusion or stenosis of precerebral arteries
434	Occlusion or stenosis of cerebral arteries
434.1	Embolism of the cerebral arteries
435	Transient ischaemic attacks
436	Stroke - ill defined
437.0	Stroke - other cerebral atheromatous
437.6	Cerebral venous thrombosis
437.4	Vasculitis
437.1	Binswangers
437.5	Moya Moya Syndrome
437.7	Transient Global Amnesia
362.34	Amaurosis Fugax

4.4 Clinical stroke diagnosis

Oxfordshire Community stroke Project grading for ischaemic infarction into

1. Total anterior circulation infarct (TAC)
2. Partial anterior circulation infarct (PAC)
3. Lacunar infarct (LAC)
4. Posterior circulation infarct (POC)

Clinical diagnosis of intracerebral haemorrhage

5. Intracerebral haemorrhage

4.5 Clinicoinvestigative aetiopathogenetic diagnosis according to the modified TOAST (expanded) classification:

1. Cardioembolism
2. Large vessel disease
3. Small vessel disease
4. Other

In the “other” category were included probable or presumed causes of stroke after the investigative protocol failed to determine any cause of stroke. The “other” category included strokes in association with or directly as a cause of;

vasculitides
cervicocephalic dissection
aortic arch atheroma
metabolic strokes
drug induced strokes
prothrombotic states
migraine
Moya Moya syndrome
cerebral venous thrombosis
dolichoectasia.

5. Unknown

4.6 The Barthel index of activities of daily living

This choice was made after review of the literature indicated that there were 10 essential activities in any ADL assessment. These included:

1. Dressing
2. Bathing
3. Transfers
4. Grooming
5. Managing stairs
6. Walking
7. Feeding
8. Going to the toilet
9. Wheelchair skills
10. Continence

4.7 The Rankin Scale

This scale incorporated a simple 6 item scale;

- | | |
|---|---|
| 0 | No symptoms at all |
| 1 | No significant disability despite symptoms; able to carry out all usual duties and activities |
| 2 | Moderate disability; requiring some help, but able to walk without assistance |
| 3 | Moderately to severe disability; requiring some help, but able to walk without assistance |
| 4 | Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance |
| 5 | Severe disability; bedridden, incontinent and requiring constant nursing care and attention. |
| 6 | Death |

4.8 Cognitive Testing

Cognitive Testing - Timing

Was deemed to be important so as not to miss the true extent of neurological deficit as this is not reflected adequately in the current neurological scales. A higher cortical function deficit (HCFD) screening examination was applied to all alert patients in the DSDB in the first two weeks of presentation.

Only alert patients were tested cognitively within the first week of presentation. There is no ideal time as initially oedema, diaschisis, and metabolic abnormalities may confuse the clinical picture. A trade off however is unavoidable as some patients have only fleeting or very transient deficits that last hours or days.

Cognitive Testing - Indication for neuropsychological testing.

1. In patients whose deficit was subtle
2. In patients whose brain imaging revealed an appropriate stroke but who on bedside cognitive testing were normal.
3. Where the screening examination suggests but does not decisively delineate a syndrome.

Note that this was in accordance with the recently published recommendations from the report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology that appeared subsequent to the design of the DSDB. This provided Class II evidence and an A grade recommendation for the use of neuropsychological testing in specific neurological disorders including stroke subject to certain stipulated guidelines [12]

Neuropsychological test battery employed included:

Clinical interviews

Trail Making Test [13,14]

Symbol Digit Modalities Test [13,15]

South African Wechsler Adult Intelligence Screen (Digit Span, Block Designs, Object Assembly) [16]

Rey Complex Figure Test [13]

Wechsler Memory Scale [17]

Rey Auditory Verbal Learning Test (RAVLT) [13]

Verbal Fluency Tests (FAS) (adapted from Benton and Hamsher 1976 and cited in Lezak in 1995) [13]

Category Naming (adapted from Newcombe 1969, cited in Lezak in 1995) [13]

Wisconsin Card Sorting Test (WCST) [18]

Luria's Neuropsychological Investigation (South African adaptation) [19,20] including preliminary conversation, motor functions (optic - spatial organisation), writing (letter), reading (text) and arithmetic skills.

The neuropsychological assessment procedure incorporated both a qualitative and quantitative data analysis, the latter according to the norms indicated above. Qualitative analysis proceeded according to a process of hypothetico deduction and was based on the principal of syndrome analysis and double dissociation as per Luria [21].

The rationale of the cognitive testing in this study was that simple bedside higher cortical function testing and not in depth neuropsychological evaluation must remain the mainstay of assessment as these patients are often critically ill,

exhausted and anxious and the latter testing is inappropriate at such times. In addition time constraints do not permit lengthy testing and with the advent of acute stroke therapy an evaluation of HCFD must be made rapidly but as accurately as possible. Neuropsychological testing was regarded as an elaboration of the bedside cognitive assessment in this study.

4.9 Single Photon Emission Computed Tomography (SPECT) brain scanning

Performed in patients with discrepancy of clinical signs and anatomical brain scan despite appropriate timing of CT or MRI brain scanning. Twenty Millicuries ^{99m}Tc Technetium - HMPAO 99 is administered intravenously. Ceretec with Technetium produces a lipophilic complex which crosses the blood brain barrier and is retained in the brain, allowing assessment of regional cerebral blood flow. Imaging commenced 2-3 minutes after the injection of the tracer. The patient is positioned as comfortably as possible with the room slightly darkened and encouraged to be as relaxed as possible. Scans are obtained for 20 seconds, with regular 6 degree rotation of the camera head around the patient, completing a 360 degree rotation with approximately 60 images obtained. This required cooperation from the patient for a period of about 30-40 minutes. A medium to high resolution collimator was used on the gamma camera. Reconstruction was performed with positioning of the patient in the orbitomeatal line, in the transverse, coronal and sagittal planes. Transaxial slices were contiguous, 16 in number and 3.3 mm thick. Three dimensional reconstruction was also performed. Images were interpreted on the computer screen comparing right and left regions of interest. This was done both visually in a qualitative manner by a radiologist blinded to the anatomical scan and semi quantitatively, the latter adapted from methods by Podreka et al [22] and Steinling et al [23]. The transaxial slice with the largest perfusion defect was identified and a circular region of interest traced over that area. These circular regions of interest (ROI) were also obtained for six areas of the gray matter. These included the cerebellum,

thalami, basal nuclei, frontal, parieto occipital and temporal regions. These areas and their mirror images on the homologous region of the other hemisphere were stored on a template and adjusted for surface area when required for a particular scan. The ROI radioactive counts from homologous regions of both hemispheres were taken to compare side to side perfusion differences and expressed as an asymmetry index. An asymmetry index percentage (AI) was calculated according to the formula $A-B/[A+B/2] \times 100$ where A and B represent right and left sides. AI comparison was done with 5 age matched controls (on a case by case basis) and matched on education but not social class. Follow up scans were not routinely performed.

4.10 Final diagnosis

A final diagnosis was made with the benefit of all available clinical and investigative data by the same cerebrovascular neurologist. For a diagnosis to be made within the frame work of the extended TOAST classification, the diagnosis needed to be one of exclusion in which all clinically indicated tests according to the hierarchical protocol were negative save for the factor in question. Comorbidity was also documented. It is acknowledged that some would be definite diagnoses, some probable and some possible by this method.

Clinical, investigative and follow up information documented (definitions in appendix) included;

Demographic factors

Full names

Address

Telephone numbers

Medical Insurance

Gender

Race

Age

Age breakdown into 10 year intervals

Date of birth

Handedness

Number and dates of visitations

Referral source

Symptoms at time of stroke onset

Right sided

Left sided

Weakness

Numbness

Any altered sensation

Headache

Speech difficulty

Memory poor

Dysphagia

Comprehension problem

Confusion

Vision impairment

Imbalance

Incoordination

Involuntary movement

Gait abnormality

Vomiting

Seizures

Dizziness

Loss of consciousness

Tremor

Other

Risk factors (definitions in appendix)

None

Hypertension

Cardiac disease (specify)

Diabetes Mellitus

TIA

Previous stroke

Hyperlipidaemia

Smoking

Alcohol excess

Int. Claudication

Overweight

Migraine

Hypercoagulable state

Drug/Substance abuse

Oral contraceptive

Gout

Sleep apnoea/signif snoring

COAD

Cervical manipulation

Neck trauma

Infection in last month

HIV positive

Tuberculosis

Neurocysticercosis

Collagen vasc disease

Autoimmune disease

Vasculitis

Cancer

Personal emotion/stress

DVT's

Other

Examination timing since stroke onset

0-6	hours
7-12	hours
13-24	hours
25-48	hours
3-7	days
1-4	weeks
1-3	months
3-6	months
7-12	months
>1	year

Level of consciousness (definitions in appendix)

Alert

Drowsy

Light coma

Deep coma

Abulic

Agitated

Delirious

Motor weakness

Grading 0-5 (MRC)

Normal

Abnormal right or left

Bilateral

Hemiparesis

Monoparesis

Quadriparesis

Triparesis

Tongue weakness

Dysphagia

Dysarthria

Digital

Other

Reflex status and tone

Normal

Abnormal right or left

Hyperreflexia

Hyporeflexia

Limb hypotonic

Limb hypertonic

Sensory impairment

Normal

Grading - hypoesthesia

- hyperesthesia

- anaesthesia

Abnormal right or left

Hemi involvement

Face

Distal arm

Whole arm

Distal leg

Whole leg

Truncal level (brainstem strokes)

Digit

Visual, ocular, brainstem signs, incoordination

Amaurosis fugax

Homonymous hemianopia

Quadrantanopia

Sectoranopia

Gaze palsy

Nystagmus

Ophthalmoplegia

Internuclear ophthalmoplegia

Anisocoria

Horner's syndrome

Cervical bruit

Appendicular incoordination

Axial incoordination

Ataxia

Higher cortical function deficits (see subtypes and definitions in appendix)

Normal

Abnormal

Level of consciousness

Attention

Aphasias

Apraxias

Agnosias

Amnesias

Aprosodias

Alexias

Anosognosias and neglect syndromes

Visuospatial impairment

Frontal syndromes

Miscellaneous

Other

Neuropsychological deficits

Normal

Abnormal

Attention/concentration impairment

Speed of information processing

Visuospatial dysfunction

Constructional dyspraxia

Right hemisphere syndrome

Neglect syndrome

Frontal lobe syndrome

Aphasia

Amnesias

Apraxias

Alexias

Aprosodias

Agnosias

Agraphias

Acalculias

Brain scan topographic lesions - brain anatomical scanning (CT and MRI)

Brain anatomical structures and vascular territories of the brain were diagnosed according to the anatomical plates with CT and MRI correlates of Kretschmann with permission for the supratentorial territories. For the brainstem and cerebellar territories this was according to the templates of and since December 1996 according to Bogousslavsky et al with permission.

General

Normal

Right or left hemisphere

Multiple

Subcortical

Territories

MCA

ACA

PCA

Anterior choroidal

Posterior choroidal

Cerebellar arteries

Brainstem medulla

 pons

 midbrain

Regions

frontal

parietal

occipital

temporal

basal nuclei

thalamus

corona radiata

perisylvian/insula

striatocapsular

caudate

internal capsule

external capsule

Other

watershed

Duplex Doppler findings

General

Normal

Abnormal

Carotid unilateral disease

Carotid bilateral disease

Vertebral

Other vessel

Stenosis

minimal <40%

moderate 40-60%

severe 60-80%

preocclusive 80-90%

occlusion

Plaque

smooth

complex

Transcranial Doppler findings

Normal

Abnormal

Stenosis

Occlusion

Collateral flow

Emboli

Other

Angiographic findings

Normal

Abnormal
Catheter angiography
MRA
Spiral CT
Stenosis
Vessel irregularity
Anomaly
Aneurysm
Other

SPECT findings

Normal
Abnormal
Absent
Hypoperfusion
Hyperperfusion
Mixed

Cardiac findings

Normal
Abnormal
Arrhythmia
Ischaemic ECG
Myocardial infarct
Congenital heart disease
Cardiomyopathy
Cardiac failure
Prolapse mitral valve syndrome
Patent foramen ovale
Atrial septal aneurysm

Dyskinetic segment
Intracavity clot
Spontaneous echo contrast
Aortic arch disease

Modalities

Transthoracic echocardiography
Transoesophageal echocardiography
Holter monitor

Laboratory values

Normative values were taken from the three regional laboratories used in the study; Bouwer and Partners, Pillay MacIntosh and Partners, department of Health laboratories based at Addington, Wentworth and King Edward Hospitals.

Treatment modalities

General

Antihypertensives
Hypoglycaemics
Antiarrhythmics
Hypolipaeemics
Anticonvulsants
Beta blockers
Calcium channel blockers
Antidepressants
Antiparkinson's

Specific stroke treatments

Aspirin
Heparin

Dipyridamole
Warfarin
Nimodipine
Tissue plasminogen activator (t-PA)

Surgical

Carotid endarterectomies (CEA)
Extracranial - intracranial bypass

Complications

None
Present
Recurrent stroke
Progressing stroke
Pneumonia
Cardiac (arrhythmia, infarct)
Post CEA stroke
Behavioural abnormality
Depression
Seizures
Deep venous thrombosis
Pulmonary embolism
Brachialgia
Decubitus ulcers
Died
Other

Follow up

one week
one month

2 months to 5 years (see digitised form in appendix)

Grading

Rankin better

Rankin worse

Rankin same

Intervals (with specific Rankin scores)

1 week

2 weeks

3 weeks

4 weeks

2 months

4 months

6 months

1 year

1-2 years

4.11 Statistical analysis:

4.11.1 Descriptive statistics

Frequencies and percentages were calculated for categorical data while means and standard deviations were calculated for continuous data. For skewed distributions (for example CNS score) a median value and range were reported.

4.11.2 Computational statistics

Cross tabulations

Significance of associations between categorical variables were assessed using Chi square or Fisher's Exact Test for 2x2 tables with small cell sizes.

Sensitivity and 95% confidence intervals were calculated for HCFD using neuropsychological testing as the Gold standard.

The CNS score was compared to the Rankin score using a Spearman correlation coefficient. CNS was also categorised as mild (11.5-9.5), moderate (9.0-5.5) or severe (5.0-0). This was compared to the Rankin score graded as independent (0-1), dependent (2-3) and severely affected (4-5). The Kappa statistic was calculated to assess the agreement between these two parameters.

Risk factors related to HCFD

Chi square or Fisher's Exact Test was applied for assessing the univariate associations between an abnormal HCFD and the various recorded risk factors. In addition, the Odds ratio and 95% confidence intervals were reported for these associations.

Risk factors with a p-value of <0.200 on univariate analysis were subsequently entered into a Multivariate Logistic Regression model to determine which of the variables independently associated with an abnormal HCFD. A Maximum Likelihood estimation procedure was applied. A stepwise backward technique was used to eliminate the non significant risk factors with a p-value to stay of <0.05 .

4.12 Data Bank Software and design

The software used was Filemaker Pro 3.0 (Apple Macintosh and Windows 95). The following were unique features exploited with this software.

4.12.1 Multimodality digitised storage

New information needs to be incorporated easily and the various investigations and imaging data are not usually part of the databank. The DSDB design

enabled digitised storage of:

- text (clinical notes, final diagnoses, follow up notes)
- images (brain MRI, CT, SPECT, Doppler, angiographic images)
- sound (aphasia progress monitoring, Doppler embolic sounds)

4.12.2 Multiple database layouts

In addition five different layouts of the databank were designed, the switching from one layout to another easily executed with one “mouse click”. These included:

- layout 1: comprehensive clinical admission, progress, follow up notes
- layout 2: official report to referring doctor or institution
- layout 3: stroke data bank of 50 fields each with 2-76 variables
- layout 4: patient name lists
- layout 5: stroke data bank fields with neuroimaging in selected patients
- layout 6: optional - any combination of fields possible

These special features of the data bank allowed for easy and rapid access to the rough notes, official report to colleagues, patient lists and the prospective input to predetermined fields and variables. The latter is done by means of a check list with variables entered with a “point and click” operation from a computer mouse or touch pad. This expedites data entry and accuracy.

4.12.3 Flexibility with database fields, back up storage and portability of databank.

Additions and reordering of database fields is simple and necessary as new classifications and information becomes available. Data is exported to a statistical package for statistical calculations. Such a data base can be entirely independent from conventional file storage systems and with the aid of

external hard drives. The external drives used were Iomega Zip drive (100 mb discs) and Jaz drives (1000 mb) can be easily transported. The method described saves time and money and obviates delays in obtaining conventional patient charts and radiographic images.

The Modular principle of the Durban Stroke Data Bank

Because certain core features are important and to allow for comparison with other stroke data bank these are always collected. It allows for additional items to be gathered. Also the theme is from general to specific or from areas of high sensitivity (HCFD screening examination) to high specificity (neuropsychological testing).

4.13 Statistical software

Epi Info (Centres for Disease Control package).

Available at; <http://www.cdc.gov/EPO/EPI/EPI.HTML>

4.14 Exclusions

Patients presenting with transient ischaemic attacks were excluded provided they had a normal brain scan. This population as whole were not included as the differential is wide and includes partial seizures, classic, complicated and common migraine, cerebral tumours and other mass lesions such as infectious and inflammatory disorders.

5.0 RESULTS

5.1 Stroke Data Bank Results

5.2 Cognitive Results

5.1. Stroke Data Bank Results

5.1.1 Descriptive statistical analysis

5.1.1.1 Demographics

Patients in DSDB n=1000

Gender

Male 561

Women 439

Race groups

Whites 781

Indian 103

Black 100

Mixed race 14

Burmese 1

Uncertain 1

Figure 1. Age Analysis of patients in 10 year increments.

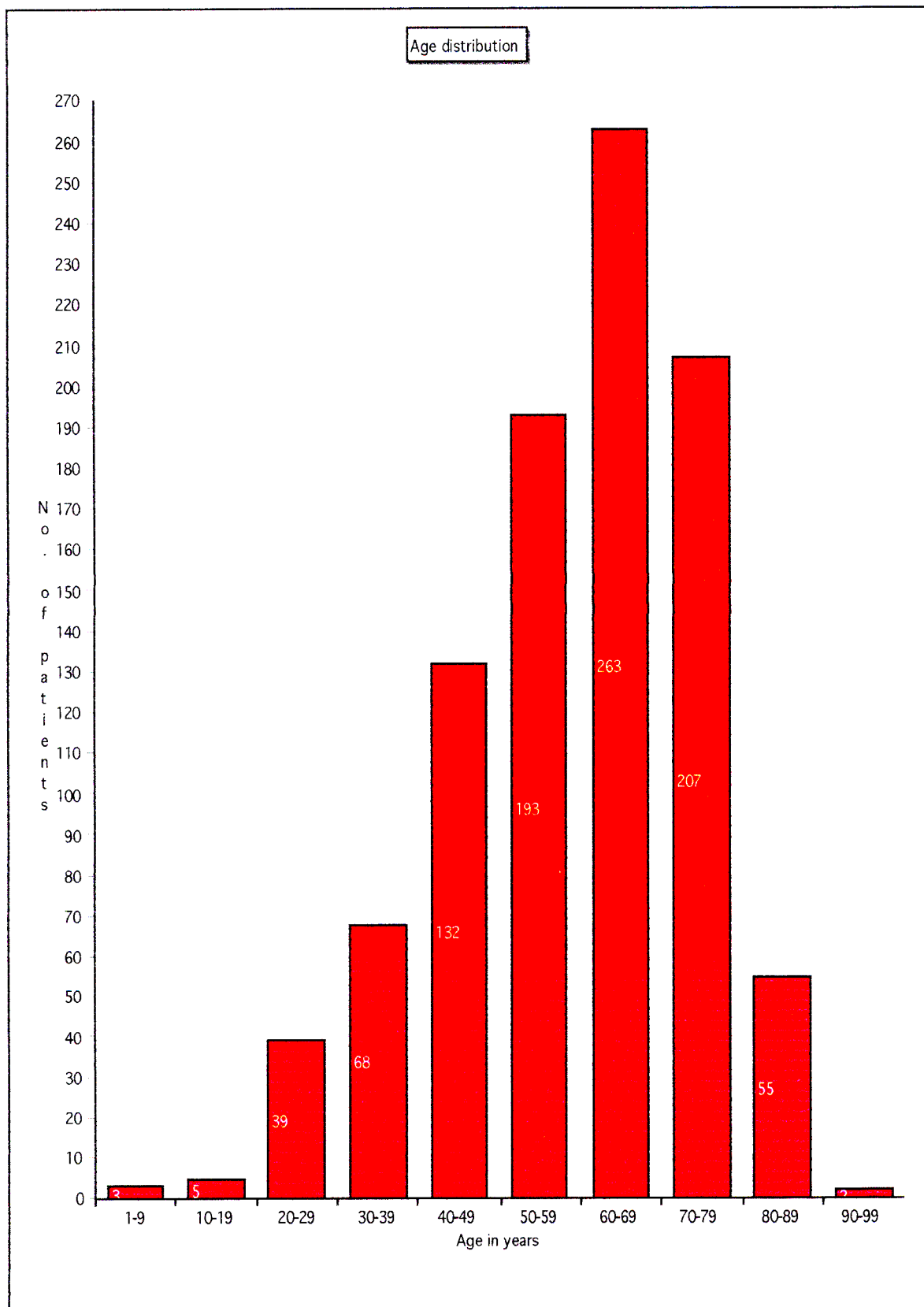


Figure 2. Box and Whisker plot of age analysis

Maximum

90

75% Quartile

70

50% Median

62

25% Quartile

50

Minimum

8

Mean: 59.1
Standard deviation: 15.0
Skewness: -0.61
Kurtosis: 0.025

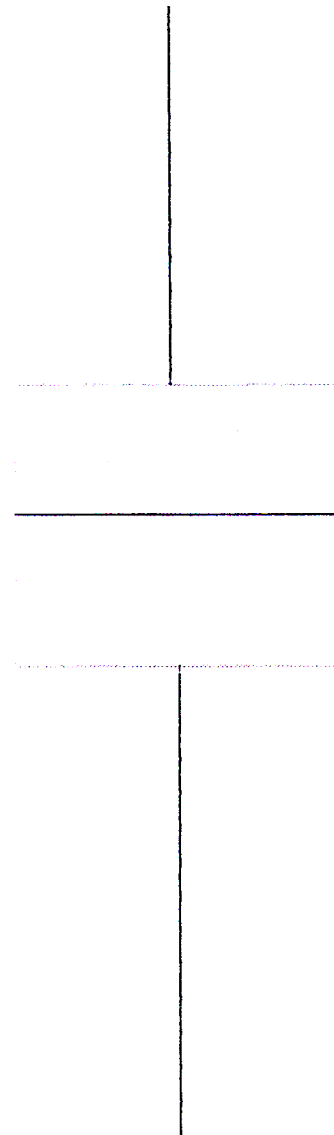
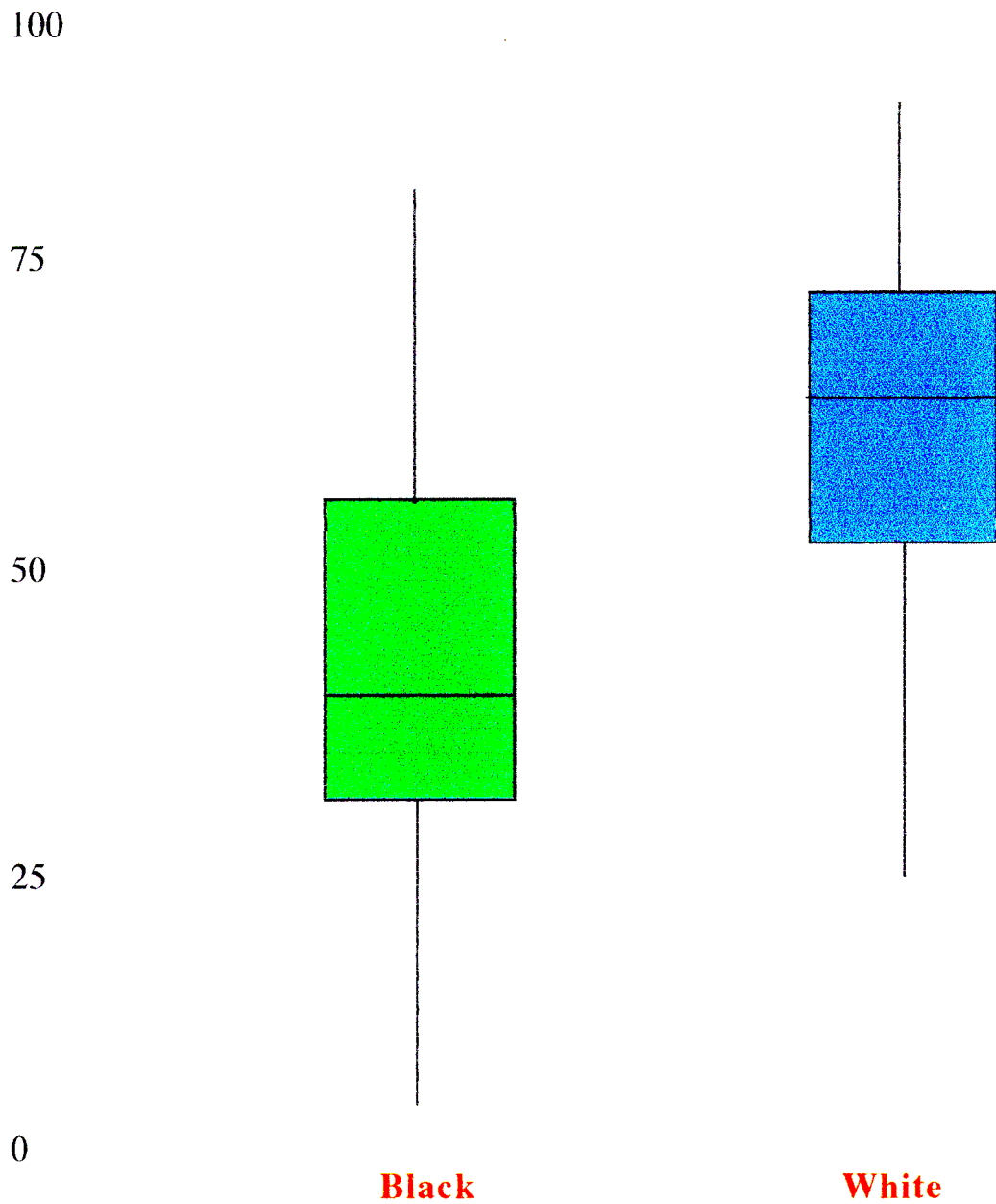


Figure 3. Box and whisker plot of black versus white age group analysis

	Black	White
100% maximum	87	90
75% quartile	54	71
50% median	41.5	64
25% quartile	34	52
0% minimum	8	8
Mean	43.5	61.4
SD	14.40	14.05
Skewness	0.333	-0.713
Kurtosis	0.007	0.38

Years



Age analysis (years). Three basic groups were categorised.

Paediatric	0-14 years
Young	15-49 years
Middle aged and elderly	50-100 years

n %

Paediatric

0-14 4 (0.4)

Young

15-49 243 (25.1)

Middle aged and elderly

50-59 193 (20.0)

60-69 263 (27.2)

70-79 207 (21.4)

80-89 55 (5.7)

90-99 2 (0.2)

Handedness

Right handed 982 (98.2%)

Left handed 13 (1.3%)

Ambidextrous 5 (0.5%)

5.1.1.2 Timing of the initial examination and initiation of investigations

Acute period: This was performed within

0-6 hours in 84 (8.4%)

7-12 hours in 55 (5.5%)

13-24 hours in 88 (8.8%)

25-48 hours in 74 (7.4%).

Subacute period: The examination was performed within

3-7 days in 137 (13.7%)

1-4 weeks in 182 (18.2%)

1 to 3 months in 109 (10.9%).

Delayed: the examination was performed within

3-6 months in 36 (3.6%)

7-12 months in 21 (2.1%).

In 84 (8.4%) patients the initial examination and investigations were performed longer than one year after initial onset of symptoms or the timing or date was uncertain.

5.1.1.3 Symptoms

Although 23 different symptoms were prospectively sought at time of stroke presentation, in 150 patients, some of their symptoms did not fit into one of the categories. Within the category named other, examples of these nonclassifiable symptoms of relatively sudden onset included; subdued behaviour, relatively sudden onset of depression lacking, blunting of emotion, impaired insight into condition, sudden onset of impaired bladder control (not

incontinence but for example micturating in the bedroom), slowed up in work environment (unable to manage well known software programmes), slowness of thinking and talking in general, sensation of a thick and swollen tongue and hearing strange sounds (auditory illusions). In 15 (1.5%) patients this was the only symptom.

Table 1. Prospectively defined symptoms. Frequency.

Weakness	469	(Symptoms: right:319,left:295)
Speech difficulty	305	
Numbness	208	
Vision impairment	168	
Dizziness	147	
Headache	139	
Imbalance	99	
Confusion	95	
Loss of consciousness	79	
Seizures	47	
Memory problem	43	
Vomiting	37	
Involuntary movement	33	
Gait abnormality	24	
Altered sensation	22	
Comprehension	17	
Incoordination	11	
Tremor	11	
Dysphagia	9	
Other	150*	

* Other with no other concomitant symptoms 15/150 (10%)

5.1.1.4 Risk factors - modifiable

These were divided into proven and as yet unproven risk factors. Non modifiable such as age, race, sex and hereditary factors were not analysed apart from within the demographics section.

Table 2. Risk factors. Frequency

Proven Risk factors

Hypertension	421
Smoking	267
Cardiac disease	177
Diabetes Mellitus	104
Alcohol excess	82
Transient ischaemic attack	53
Hyperlipidaemia	47
Carotid stenosis	251

Probable but unproven risk factors

Lipoprotein (a)	195
Infection within the last month	43
Gout	33
Personal stress or emotion	30
Intermittent claudication	20
Sleep apnoea	4
Cervical manipulation	4
Homocystinaemia	3

5.1.1.5 Examination findings

Elementary Neurological signs

Hemiparesis was the most common presentation in 309 (30.9%), followed by tongue weakness in 57 (5.7%), dysphagia in 38 (3.8%) and monoparetic presentations in 35 (3.5%). Unusual patterns such as tri paresis and isolated digital weakness were encountered and typically associated with diagnostic delay. In most patients the degree of (Medical Research Council grading) weakness was normal (53.7%) or mild (34.2%) with 106 (10.6%) patients presenting with plegia.

Motor impairment

Weakness profile

Right sided weakness	169
Left sided weakness	140
Hemiparesis	309
Monoparesis	35
Quadriparesis	20
Triparesis	2
Tongue weakness	57
Dysphagia	38
Digital (isolated)	3
Other	10

Grading (MRC). At time of initial examination and included only the weak limbs strongest and weakest muscle groups.

0	106
1	33
2	31
3	41
4	342
5	537

Sensory impairment

Sensory impairment type was most commonly a hypoesthesia (24.8%) or 86.7% of total instances of sensory deficit types. Sensory impairment topography was most commonly in a hemi distribution (20.6%) with a fragmentation of the deficit involving the face only in 23 (2.3%), distal arm in 21 (2.1%). The leg was less often involved with the distal leg only occurring in 15 (1.5%) and the whole leg in 7 (0.7%) being infrequently encountered and not always volunteered by the patient Interestingly a hand digit alone in 9 (0.9%) was about as commonly involved as the entire leg. Although rare, the DSDB has demonstrated as have other data banks (Lausanne) that stroke may mimic a peripheral nerve sensory pattern (digital only in 9 patients) or myelopathic pattern (truncal level in 2 patients with brainstem stroke).

Sensory deficit topography profile

Hemi involvement	206
Face only	23
Whole arm	25
Distal arm	21
Distal leg	15
Whole leg	7
Digit only	9
Truncal level	2

Sensory deficit type

Hypoaesthesia	248
Hyperaesthesia	7
Anaesthesia	2
Other (nonclassifiable)	29

Vision impairment

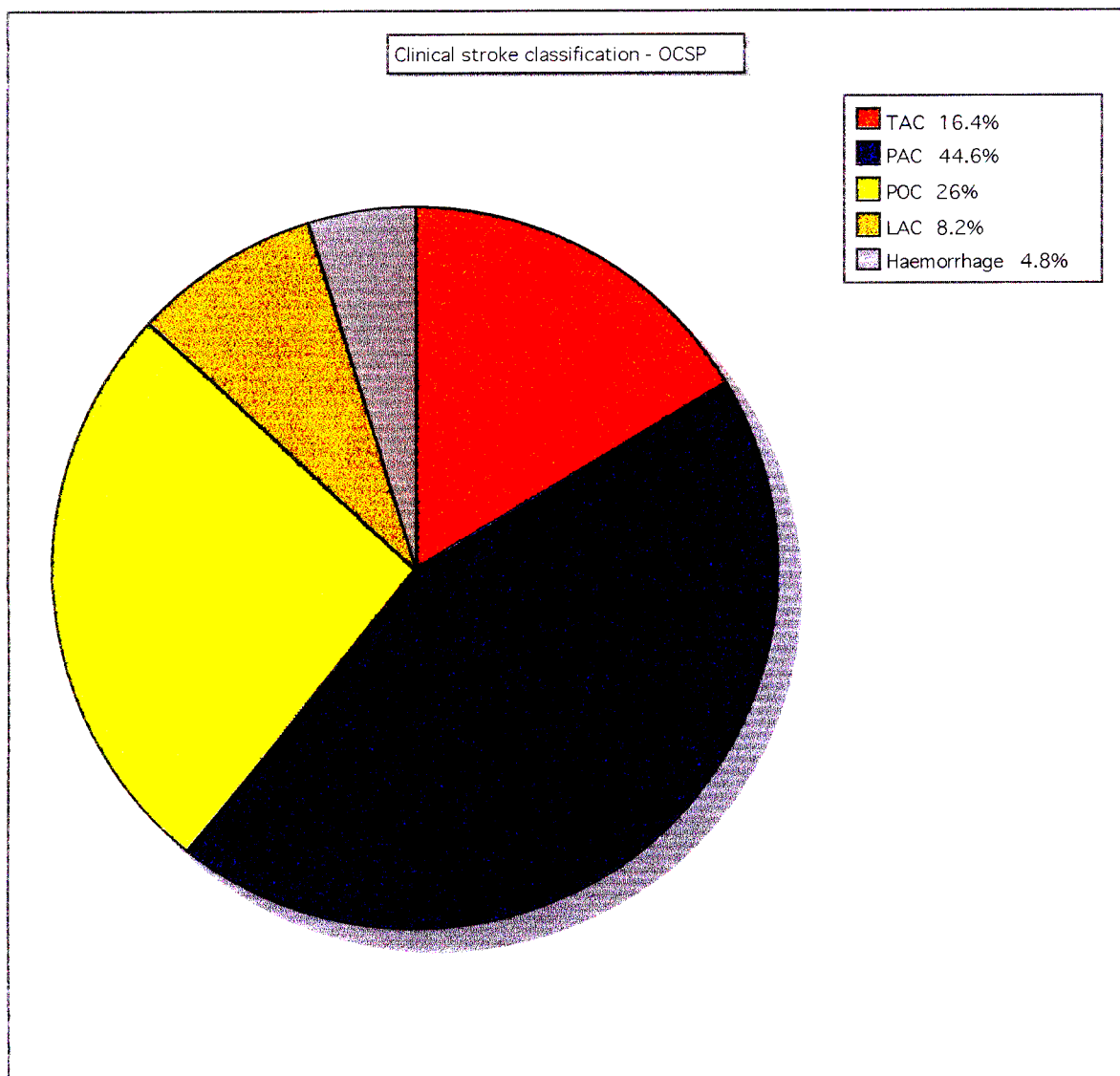
Visual neurological deficits such as homonymous hemianopias, quadrantanopias, sectoranopias (n=80; 8%) and various ophthalmoplegias (n=38;3.8%) were the least common of the so called elementary neurological deficits.

Homonymous hemianopia	47
Quadrantanopia	27
Sectoranopia	6
INO and Ophthalmoplegias	38

5.1.1.6 Initial clinical stroke classification (Oxfordshire Community Stroke Project Classification) and intracerebral haemorrhage.

The most numerous group of stroke patients were in the category of partial anterior circulation infarct numbering 447, followed by posterior circulation infarct numbering 258, followed by total anterior circulation infarct with 185 and the smallest group was the lacunar infarct group with 82. The intracerebral haemorrhage and haemorrhagic infarct group numbered 48.

Figure 4. Clinical Stroke Subtypes - Oxfordshire Community Stroke Project Classification (OCSP)



Legend to clinical types of infarcts as per OCSP

- TAC: Total anterior circulation
- PAC: Partial anterior circulation
- POC: Posterior circulation
- LAC: Lacunar

5.1.1.7 Anatomical brain scans

All 1000 patients had an anatomical brain scan. Either a CT (n=698) or MRI (n=426) brain scan or both 124 (12.4%) were done in all patients. The distribution of lesions consistent with strokes were 411 in the right hemisphere, 426 in the left hemisphere and 296 subcortical. Multiple strokes were seen in 189 people.

The arterial distribution frequencies included 259 in the middle cerebral artery cortical territory, 87 in the brainstem arteries, 61 in the cerebellar cortices, 25 in the anterior cerebral cortical artery territory, 52 in the posterior cerebral cortical territory, 37 in watershed distribution, 2 anterior choroidal and 5 in the venous system.

From an anatomical point of view;

Cortical supratentorial

Frontal	106
Parietal	154
Occipital	82
Temporal	3
Perisylvian/Insula	23

Subcortical supratentorial

Corona radiata	111
Thalamus	60
Basal Nuclei	52
Caudate	17
Internal capsule	50
External capsule	10
Striatocapsular	5

Infratentorial

Brainstem	87
Cerebellum	61
Total	854

5.1.1.8 Laboratory investigations

The frequencies of abnormalities is listed in Table 3. All patients had 1st tier investigations hence the number of abnormalities is a fraction of 1000. For the 2nd and 3rd tier investigations the number is listed as a fraction of the total number of investigations done within that category.

Laboratory findings listed in Table 3 were notable for the high rate of complete blood count (haemoglobin, mean cell volume, haematocrit, white cell count and differential count, platelets) abnormality in 99 patients compared to the relatively few abnormalities for INR (8;0.8%), PTT (7;0.7%) and ESR (35; 3.5%). There were 143 instances of blood count abnormalities including haemoglobin (high in 17, low in 25), MCV (high in 31, low in 8), white cell count (high in 32, low in 3), platelets (high in 7, low in 3), haematocrit (high in 10, low in 2) and MCHC (high in one, low in 3). With respect to the 43 patients reporting an infection in the month prior to their stroke, only 15 of these (32 overall) had raised white cell counts.

Lipogram abnormalities were notable for the relatively high rate of elevated Lipoprotein (a) fractions recorded (195 or 19.5%). Interestingly 345 (34.5%) of patients had either a lipogram abnormality or Lipo(a) abnormality, 168 (16.8%) had both and 150 had a lipogram abnormality without raised Lipo(a). These levels were measured with relatively high reference values that have recently been lowered so in fact may represent a slight underestimate.

Prothrombotic factors such as protein S, C, antithrombin III and anticardiolipin antibodies were not tested in all patients. Together they were thought to be aetiologically causative in only 21 cases.

In 5 patients with clinical and angiographically demonstrated vasculitis there was a clinical indication for brain biopsy of which 2 were negative. The three positive biopsy proven cases were ascribed to temporal arteritis in one, systemic lupus erythematosus (SLE) in one and isolated angiitis in one.

Table 3: Brain scan, laboratory, Doppler sonographic and cardiac investigations - frequency of abnormalities

	n	%
First tier investigative findings		
<u>Anatomical brain scanning</u>	1000	100
CT	698	
MRI	426	
<u>Laboratory abnormality overall</u>	484	48
Complete blood count abnormality	99	
Elevated Lipoprotein (a)	195	
Lipogram abnormality	150	
Lipogram and Lipoprotein (a) abnormality	168	
Erythrocyte sedimentation rate	83	
Glucose	68	
INR	8	
PTT	7	

Second tier investigative findingsFunctional brain scanning

SPECT	78/104	75
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Sonography

Duplex Doppler	325/629	51.6
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Transcranial Doppler	268/575	46.6
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Cardiac

Cardiac echo transthoracic	131
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Cardiac echo transoesophageal	21
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<u>Angiography total</u>	261
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Abnormal	146
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Catheter angiography	135
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MRA	88
-----	----

Spiral CT	38
-----------	----

Laboratory

Anticardiolipin antibody	10
--------------------------	----

Protein S	5
-----------	---

Protein C	3
-----------	---

Antithrombin III	3
------------------	---

Fibrinogen	5
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Third tier investigative findings

Homocysteinaemia	4
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Brain biopsy	3/5
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Transcranial Sonography

Testing for patent foramen ovale was carried out in 16 patients, 7 of which were positive. In 2 patients high intensity transient signals (HITS) were detected over a middle/anterior cerebral artery bifurcation in the setting of prosthetic heart valve and atrial fibrillation in one patient and preocclusive stenosis due to fibromuscular dysplasia in one patient. (See figures)

Cardiac

Significant cardiac abnormalities were present in 122 patients (with 162 cardiac abnormalities) and accounted for a relatively smaller number (12.2%) in comparison to other young stroke data banks [1-23]. High risk and medium risk causes as noted in Table 4 were all diagnosed with the help of echocardiography (131 transthoracic and 21 transoesophageal). Patent foramen ovale as the most likely factor associated with stroke occurred in 7 patients (age range; 25-47 years and mean age; 35.8 years) and accounted for 25% of the cardiac causes in the young stroke population. In one patient this was associated with an atrial septal aneurysm. All patients were diagnosed with transcranial Doppler and the injection of agitated aerated saline in an antecubital vein and all patients had an echocardiogram. However since only 4 patients had TEE the true incidence of other frequently occurring abnormalities such as atrial septal aneurysms cannot be commented on. Other predisposing factors for blood clot formation in the context of PFO included;

Valsalva manoeuvre (vomiting, asthma attack)	2
Atrial septal aneurysm	1
Prothrombotic state (anticardiolipin positivity)	1
Congenital heart disease (Ebstein's anomaly)	1
Concurrent infection (influenza)	1
Significant emotional/personal stress	1

In the dysrhythmia group, atrial fibrillation accounted for 32 (43%).

Table 4. Cardiac abnormalitiesHigh risk cardiac source

Ischaemic heart disease	62
Atrial fibrillation with dilated left atrium	1
Mechanical prosthetic valve and atrial fibrillation	1
Rheumatic mitral stenosis, atrial fibrillation, dilated left atrium	1
Left ventricular thrombus	1
Dilated cardiomyopathy with left ventricular clot	1
Atrial myxoma	1
Infective endocarditis	1
Congenital heart disease - Eisenmenger's complex, infective endocarditis	1
Congenital heart disease - Ebsteins anomaly	1
Congenital heart disease - Atrial septal defect - perioperative repair stroke	1

Medium risk cardiac source

Dysrhythmia	73
Patent foramen ovale	7
Mitral valve prolapse	6
Dyskinetic or hypokinetic left ventricular segment	3
Atrial septal aneurysm and patent foramen ovale	1
Mitral annular calcification	1
Total	162

5.1.1.9 Aetiologies - TOAST categories and 'Other' subgroups.

Within the slightly modified TOAST aetiological classification, the most numerous groups with similar frequencies included; large vessel disease 264 (26.4%), small vessel disease 262 (26.2%) and other 253 (25.3%). Cardiac causes were relatively less frequent, numbering 122 (12.2%) and in 99 (9.9%) the cause of stroke was classified as unknown and not associated with a recognised cerebrovascular risk factor in isolation.

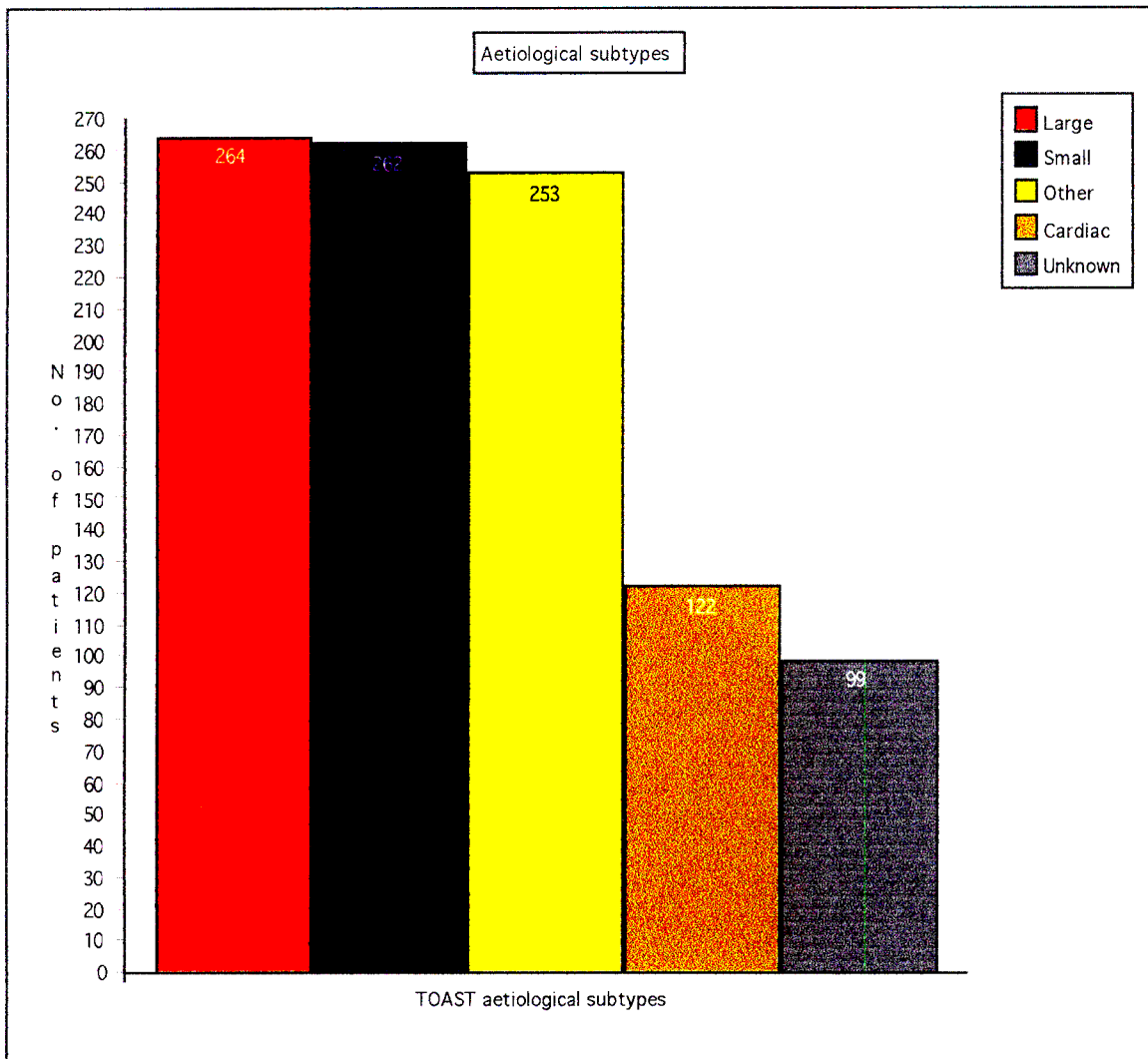
In the subcategories of the 'Other' group the conditions diagnosed were classified into definite, probable and possible causes. The most frequently diagnosed conditions were;

- prothrombotic states
- vasculitides
- dissection
- migraine
- metabolic

In the miscellaneous group the most frequently diagnosed conditions were;

- cerebral haemorrhage
- dolichoectasia with artery to artery embolism or thrombosis
- transient global amnesia (abnormal SPECT, normal MRI scans)
- cerebral venous thrombosis

Figure 5. Aetiological Subtypes of Stroke (TOAST classification)



Subgroup analyses: Frequencies of abnormalities included;

Prothrombotic group 58

Definite - laboratory determined

Anticardiolipin antibody	10
Elevated fibrinogen	5
Protein S deficiency	5
Protein C deficiency	3
Antithrombin III deficiency	3
Plasmin system defect	1

Probable prothrombotic mechanisms. Recognised predisposing causes for hypercoagulable state. Other causes of stroke excluded(probable causes)

Anaemia and raised ESR	9
Polycythaemia	8
Malignancy	5
Oral contraception	3
Connective tissue disease and infection	2
Pregnancy	2
Ulcerative colitis	1
Hepatic failure	1

Four patients had 2 prothrombotic causes.

Vasculitides

41

Biopsies were performed in 5 patients (2 negative). Angiograms were performed in 20 patients. In 18 patients the diagnosis was made on the basis of laboratory evidence together with a known cause of vasculitis with other possible causes of stroke excluded. In the latter group the diagnosis of vasculitis was regarded as probable.

Infections

HIV associated	13
TB vasculitis	2
Neurocysticercosis	3
Neurolues	4
Herpes Zoster	2

Large cell

Takayasu's	5
Giant cell arteritis	1
Kawasaki disease vasculitis	1

Connective tissue disease associated

Rheumatoid arthritis	2
SLE	2

Chronic granulomatous

Sarcoid	1
Crohn's disease	1

Other

Isolated angiitis of the CNS	1
------------------------------	---

Unknown

3

Dissection 20

Diagnosis was based on a typical clinical history of neck pain, stroke with either angiographic evidence (n=14) or duplex Doppler evidence of dissection (n=14).

Spontaneous carotid dissection	7
Blunt cervical trauma	5
Spontaneous vertebral dissection	4
Fibromuscular dysplasia/dissection	2
Temporally related to chiropractic manipulation	1
Spontaneous basilar artery with subarachnoid haemorrhage	1

Migraine 9

Metabolic stroke (hyperhomocysteinaemia) 4

Moya Moya syndrome 1

Due to substance abuse (Cocaine) 1

Other - Miscellaneous category

The following most likely causes were identified after a diagnosis of exclusion (possible causes):

Cerebral haemorrhage	47
Dolichoectasia with artery to artery embolism or thrombosis	28
Transient global amnesia (abnormal SPECT, normal MRI scans)	14
Cerebral venous thrombosis	5
Cerebral aneurysm with distal territorial embolism	3
Sleep apnoea syndrome	2
Anaesthetic complication, cardiac arrest, hypoxic encephalopathy	2
Stroke in association with brain tumours	2
Chemotherapy complicated by stroke	2
Stroke in association with cerebral trauma	2
Eclampsia and stroke	1
Arterial redundancy of a persistent hypoglossal artery	1
Arterial redundancy of a persistent trigeminal artery	1
Carotid coils, kinks and loops (arterial redundancy)	1
Gunshot to the neck with carotid artery with thrombosis	1
Brainstem AVM haemorrhagic infarct, polycystic kidneys	1
Post operative stroke during cervical spondylotic surgery	1
Migril abuse related cerebral haemorrhage	1
Latrodectism (spider bite) haemorrhage	1
Low serum folate level	1
Surgical clip placed over middle cerebral artery	1
Basilar artery fenestration	1
Stroke in association with electrocution	1
Stroke due to vasospasm after aneurysmal clipping in SAH	1

Haemorrhage

The relatively small number of haemorrhagic infarcts and intracerebral haemorrhages (n=47) were due to established and pre existing hypertension in only 25 patients (53.1%). In 15 patients without a history of hypertension other associated conditions known to cause cerebral haemorrhage are listed in Table. These causes were thought to be probable. In 7 patients the diagnosis of the intracerebral bleed could not be established.

Probable causes of cerebral haemorrhage (n=15)

Cardiac valvular disease or atrial fibrillation	2
Arteriovenous malformation	1
Infective endocarditis (mycotic aneurysm)	1
Cerebral amyloidosis	1
Alcoholic liver disease	1
Trauma - assault	1
Trauma - motor vehicle accident	1
Brainstem AVM haemorrhagic infarct, polycystic kidneys	1
Migril abuse related cerebral haemorrhage	1
Latrodectism (spider bite) haemorrhage	1
Aneurysmal bleed	1
Takayasu's arteritis with Moya Moya	1
Congenital - Colpocephaly, absent corpus callosum	1
Luetic vasculitis	1
Total	15

Dolichoectasia

<u>Associated medical and neurological conditions</u>	<u>n</u>
Hypertension	24
Hyperlipidaemia	10
Smoking	8
Alcohol excess	5
Ischaemic heart disease	4
Diabetes	3
<u>Clinical presentations</u>	
i) Syndromes	
Posterior circulation	16
Anterior circulation	6
Frontal lobe syndrome	3
Lateral medullary syndrome	1
ii) Isolated symptom (1 or 2 of the following)	
Facial neuralgias, dysesthesias or parathesias	5
Vertigo	4
“Bell’s palsy”	3
Imbalance/ataxia	3
Diplopia/Polyopia	3
Exertional headache	3
Tinnitus	2
Hemifacial spasms	2
Pulsating neck mass with bruit	1

Investigations

Radiology

i) Brain parenchymal imaging and angiography (MRA, catheter angiography, spiral CT)

Arterial territories	n	%
Basilar artery	32	(100)
Vertebral artery	2	(6)
Anterior circulation - carotid	1	(3)
Anterior circulation - middle cerebral arteries	1	(3)
Aortic arch with "Shaggy aorta syndrome"	1	(3)

Brain parenchymal imaging abnormalities (CT and MRI)

Posterior circulation infarcts	27	(100)
Multiple	18/26	(69)
Ventriculomegaly	4/31	(13)

Sonography - Transcranial Doppler

Low velocity and increased pulsatility	18/25	(72%)
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Clinical neurological scale (OCSP)

	n	(%)
POC	19	(70)
PAC	5	(19)
LAC	2	(7)
TAC	1	(4)
	27	(100)

5.1.1.10 Causes of stroke in black patients

These differed markedly to the White and Indian population group and to the DSDB as a whole. Contrary to the usual atherogenic subgroups of large and small vessel disease being the most numerous, in black patients the “Other” group and those with causes unknown were the most populous. Within this group HIV vasculopathy was the most common cause of the vasculitides accounting for 13 % of all black strokes.

Other	39
Unknown	20
Small vessel disease	17
Cardioembolic	12
Large vessel disease	12

Analysis of the “Other” group

Vasculitides	19
Haemorrhage (ICH)	11
Dissection	4
Prothrombotic states	3
Moya Moya	1
Drug induced	1

Analysis of the largest subfraction - vasculitides

HIV associated vasculitis	13
Takayasu’s arteritis	3
TB associated vasculitis	1
Luetic vaculitis	1
Neurocysticercosis vasculitis	1

5.1.1.11 The young stroke population (8 - 49 years)

A multitude of causes were found consistent with young stroke studies in general (n=245).

Other	114	(46.5%)
Unknown	47	(19.1%)
Small vessel disease	33	(13.4%)
cardiac	29	(11.8%)
Large vessel disease	22	(8.9%)

Other - expanded categories were classified into definite, probable and possible causes. The most frequently diagnosed conditions (and as a percentage of the group other) were;

- vasculitides	29	(25.4%)
- prothrombotic states	26	(22.8%)
- dissection	13	(11.4%)
- migraine	9	(7.8%)
- cerebral venous thrombosis	4	(3.5%)

Two important treatable conditions were common in young stroke patients;

1. Non atherosclerotic vasculopathies:

- cervicocephalic dissections
- fibromuscular dysplasia
- vasculitis
- Moya Moya syndrome
- migraine
- arterial redundancy - coils, loops and kinks
- hypoplasia and agenesis

accounted for 76/245 (31%) causes and probable causes in the young stroke population.

2. Patent foramen ovale

This condition accounted for 7 of the 29 cardioembolic causes.

Aetiologies - racial differences

Differences were most obvious within the large 'Other' group which contained 39/100(39%) blacks and 193/781 (24.7%) whites. The majority of strokes in blacks studied in this limited sample were infection related (HIV, TB, Takayasu's, Syphilis, Neurocysticercosis) vasculitides (n=19; 19%)

Severity of stroke (as assessed by CNS, Barthel and Rankin scales).

Assessment for neurological deficit (by CNS scale), revealed that 47% were normal and a further 40% had a mean score of 9.4. When the Barthel Index was computed, 4% had a normal Barthel index on admission and a further 65% scored 16-19. Measurement by Rankin score, 87% had a score of 0-3, ie ambulant. There was moderate agreement between the CNS and Rankin scales (kappa = 0.58)

5.1.1.12 Cerebral Perfusion Index - early prognostication

Single photon emission computed tomography scanning was performed as per protocol in 104 patients of which 78 (75%) studies were abnormal (graded as hypoperfusion, hyperperfusion, absent, mixed). These were also used to calculate the cerebral perfusion index (CPI) together with transcranial Doppler values in acute stroke patients.

Overall in the DSDB, The CPI was performed in 44 patients in the acute phase

of stroke (within 48 hours of onset of the ictus). Because of the possibility of other neurodegenerative disease only the young patients were considered for analysis. The Rankin scale mean value of these patients showed a significant difference (ANOVA) between the poor and medium, poor and good, but not between good and medium categories.

Table 5. Cerebral perfusion index in the acute phase of stroke in the young stroke patient.

CPI		n	Mean Rankin score (48h)
Good	15-20	5	1.6 (SD 0.6)
Medium	6-12	25	1.8 (SD 0.9)
Poor	1-5	2	3.5 (SD 0.7)

ANOVA $p = 0.029$

5.1.1.13 Complications

Eight specific categories of complications were specifically sought according to predefined criteria. Overall, complications as prospectively sought and recorded over a 4 month follow up period occurred in 347 patients. In order of frequency that they occurred:

Behavioural abnormality	166
Seizures	53
Depression	44
Recurrent stroke	30
Pneumonia	23
Progressing stroke	6
Post carotid endarterectomy stroke	5
Brachialgia	2
Died	53
Sleep apnoea syndrome (post stroke)	4

5.1.1.14 Follow up

Follow up was possible in 824 (82.4%) patients. The frequencies at the itemised intervals included;

1 week	351
2 weeks	147
1 month	266
2 months	153
4 months	91
6 months	88
1 year	544
1-2 years	34
> 2 years	50

Patients that died during the follow up period numbered: 53/824 (6.4%).

Range 1 week to 5 years.

5.1.1.15 Treatment

Specific stroke treatment included:

<u>Antiaggregant therapy</u>	<u>n</u>
Aspirin	745
Dipyridamole	10
 <u>Antithrombotic therapy</u>	
Warfarin	92
Heparin	116
 <u>Antifibrinolytic therapy</u>	
Tissue Plasminogen Activator	1
 <u>Carotid endarterectomy</u>	
	140

5.1.2 Stroke Data Bank - computational analytical statistics

5.1.2.1 Table 6. Clinical subtype on admission (OCSP) vs final aetiopathogenetic classification (TOAST) for ischaemic stroke patients

	Card	Large	Small	Other	Unk	Total
TAC	40	19	38	45	21	163
PAC	49	124	147	86	37	443
LAC	9	41	23	8	1	82
POC	22	78	52	75	31	258
						946

Chi square test ($p=0.001$) showed a significant difference in the overall distribution between the clinical scale (OCSP) and the final aetiopathogenetic scale (TOAST).

Pairwise comparisons: comparing different combinations of OCSP categories with relation to TOAST:

TAC vs PAC	$p=0.001$
TAC vs LAC	$p=0.001$
TAC vs POC	$p=0.001$
PAC vs LAC	$p=0.003$
PAC vs POC	$p=0.001$
LAC vs POC	$p=0.001$

Legend: (OCSP and TOAST scales - see appendix)

TAC - total anterior circulation
 PAC - partial anterior circulation
 LAC - lacunar
 POC - posterior circulation
 Cardiac - cardiogenic stroke
 Large artery
 Small artery
 Unknown
 Other

5.1.2.2 Table 7. Age analysis (young and old) and aetiopathogenetic diagnosis

Age	Small vessel		
	<u>No</u>	<u>Yes</u>	
0-49	214	33	Chi square value: p=0.001
>49	499	221	

Age	Other		
	<u>No</u>	<u>Yes</u>	
0-49	131	116	Chi square value: p=0.001
>49	588	132	

Age	Cardioembolism		
	<u>No</u>	<u>Yes</u>	
0-49	217	30	Chi square value: p=0.884
>49	630	90	

Age	Unknown		
	<u>No</u>	<u>Yes</u>	
0-49	201	46	Chi square value: p=0.001
>49	670	50	

Age	Large artery		
	<u>No</u>	<u>Yes</u>	
0-49	225	22	Chi square value: p=0.001
>49	497	223	

5.1.2.3 Table 8. Neurological admission deficit versus disability - CNS vs Rankin scales

Rankin Score	CNS Score			
	<u>11.5-9.5</u>	<u>9.5-5.5</u>	<u>5.0-0</u>	
<u>0-1</u>	454	13	0	467
<u>2-3</u>	227	110	8	345
<u>4-5</u>	15	81	78	174
	696	204	86	

Kappa = 0.543. There is moderate agreement between CNS and Rankin scores.

5.1.3 Stroke Data Bank: Treatable stroke mechanisms

Noteworthy case reports of stroke mechanisms elucidated by the protocol of neurodiagnostics.

1. Luetic cerebral vasculitis (LW).

Clinical: A 59 year old white man with multiple minor strokes, frontal lobe syndrome and subcortical impairment.

Serology: Positive syphilis serology WR and FTA in the blood and CSF.

Anatomical brain scan: MRI brain scan revealed multiple hyperintense lesions in the subcortical regions and leukoaraiosis.

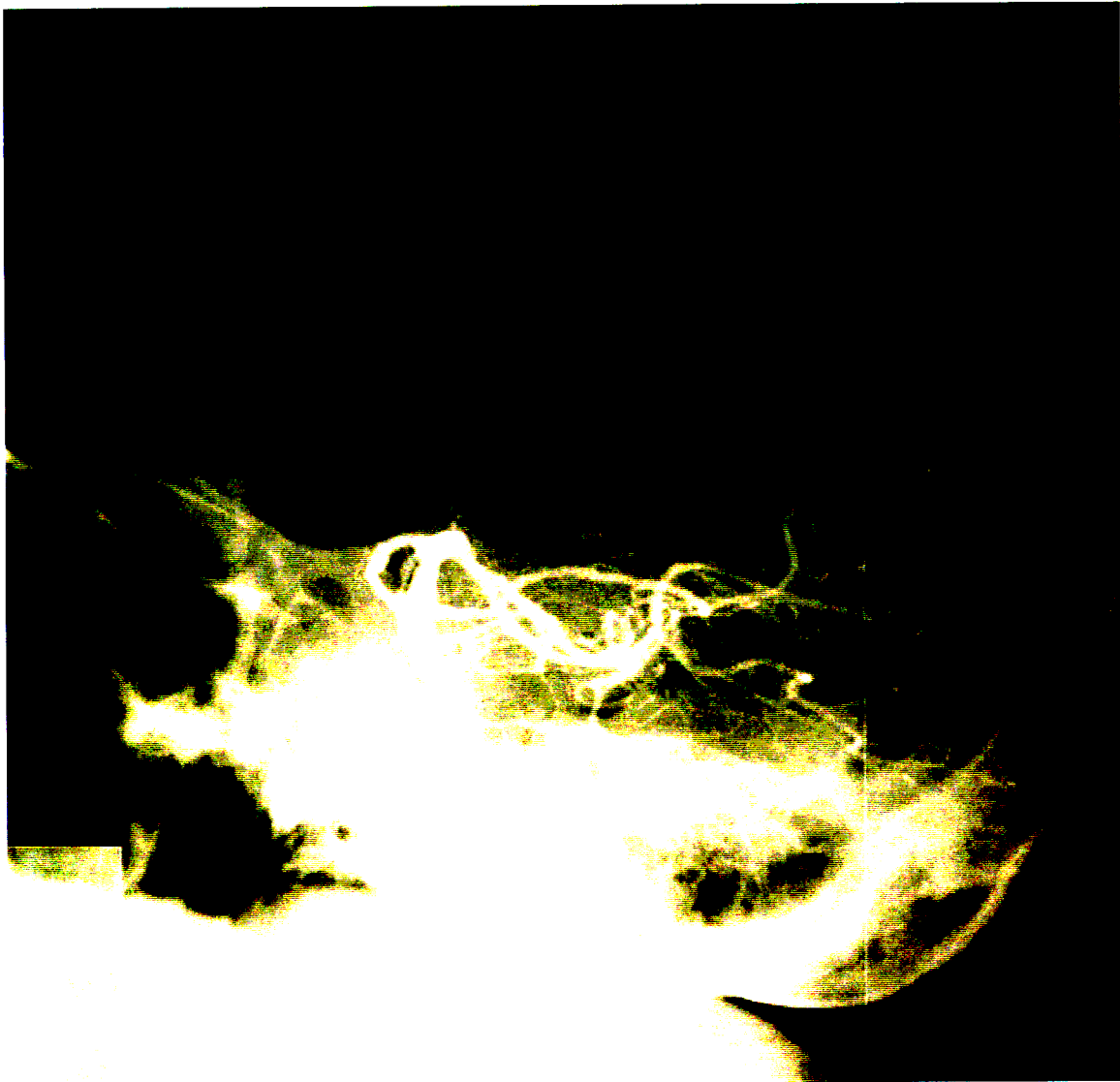
Doppler sonography: Cervicocephalic vessels normal.

Cardiological tests: Normal.

Angiography: Catheter angiography revealed multiple vessel narrowing in the anterior and posterior circulation.

Interpretation: Syphilis angiitis.

Figure 6. Cerebral Luetic Vasculitis. Catheter angiogram showing irregularity of the basilar artery and posterior cerebral arteries.



2. Haemodynamic hemispheric hypoperfusion with haemodynamic transient ischaemic attacks and failing medical therapy - a case for EC/IC bypass? (WR)

Clinical: A 56 year old white man with positive symptoms of left limb shaking TIA's and right altitudinal type amaurosis fugax since an episode of nonfatal strangulation.

Sonography: Duplex Doppler sonography revealed an occluded right internal carotid artery and transcranial Doppler showed preserved and normal flow of the right middle cerebral artery that ceased entirely with digital occlusion of the right common carotid or right external carotid.

Anatomical brain scan: MRI brain scan showed punctate hyperintense lesions in the high cortical region typical of watershed infarcts.

Functional brain scan: SPECT brain scanning revealed marked underperfusion of the right hemisphere which was exacerbated by intravenous Acetazolamide suggesting exhausted cerebrovascular reserve.

Cardiological tests: Normal

Angiography: Catheter and MR angiography revealed pial collateralisation of the left middle cerebral artery territory by the left posterior cerebral artery territory. Both posterior communicating arteries were absent. Collateralisation was also seen through the left ophthalmic artery from the left maxillary artery confirmed by angiography and transcranial Doppler.

Interpretation: Haemodynamic transient ischaemic attacks and established infarcts failing medical therapy. He would satisfy current criteria for extracranial/intracranial bypass surgery [1,2].

Figure 7a. MRI brain scan showing typical watershed infarcts (arrows) consequent to right internal carotid occlusion. This patient had no posterior communicating arteries.

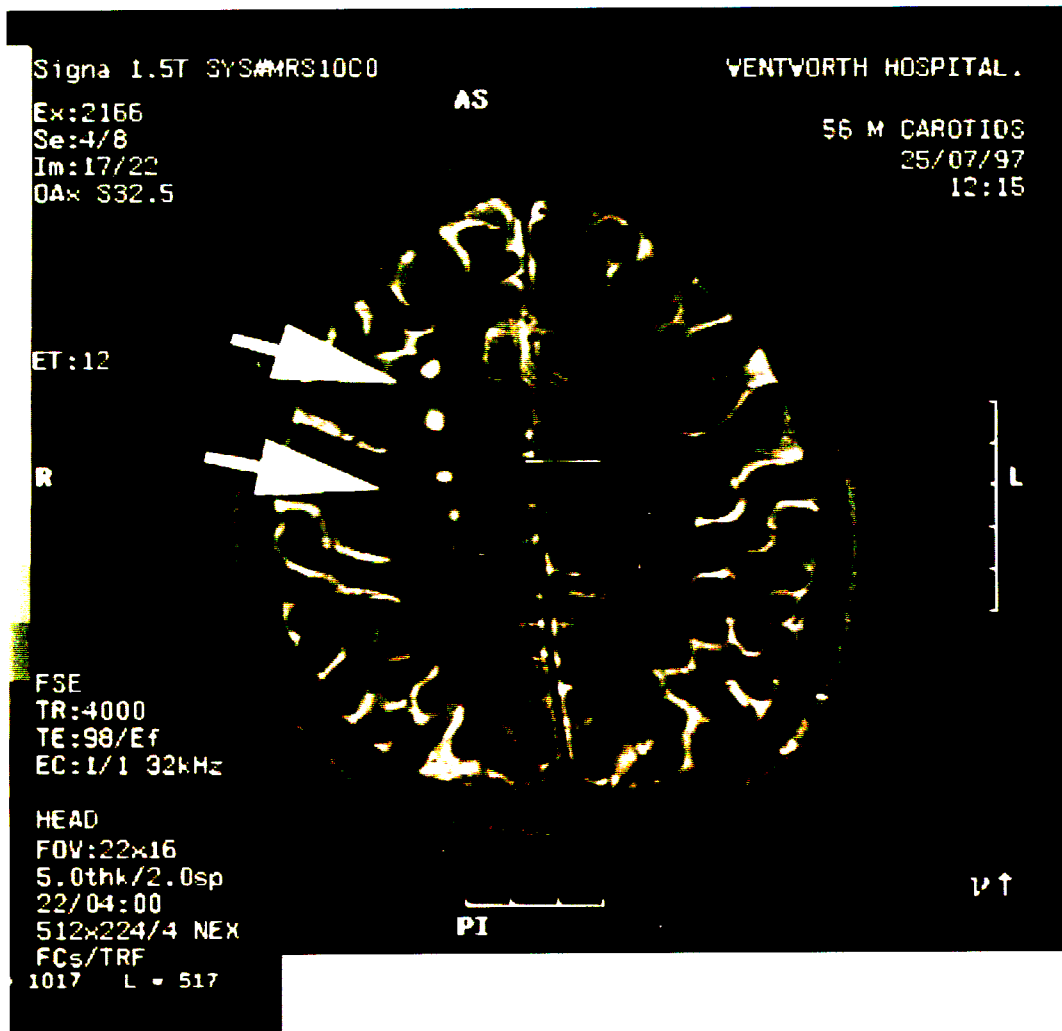


Figure 7b. SPECT scan with Diamox (upper half images) and without Diamox (lower half images) revealing marked right hemisphere hypoperfusion (arrows).

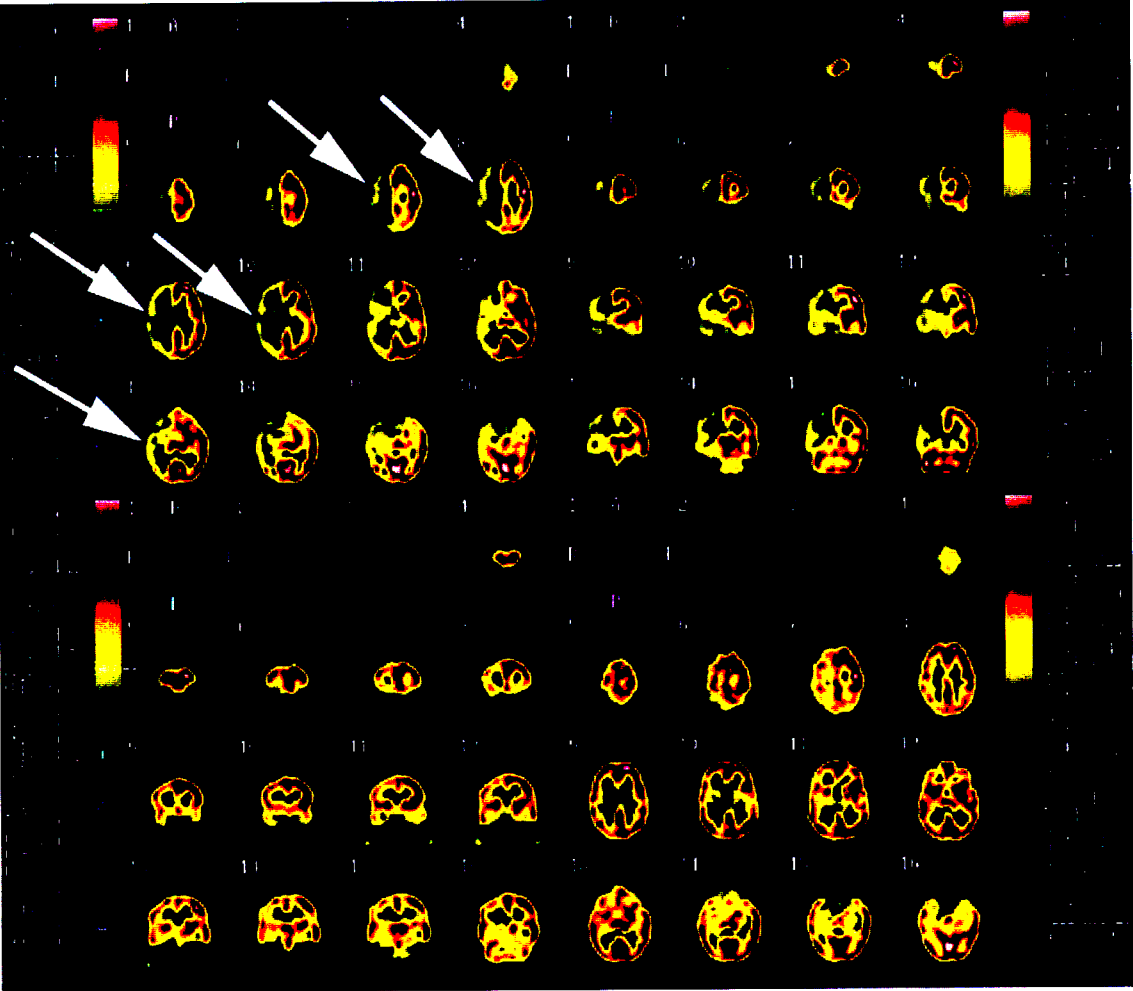


Figure 7c. Magnetic resonance angiogram showing asymmetric right posterior cerebral artery flow indicative of the contribution of the right posterior cerebral artery to pial collateralisation. This patient had bilaterally absent posterior communicating arteries - the most important source of cerebrovascular collateralisation.

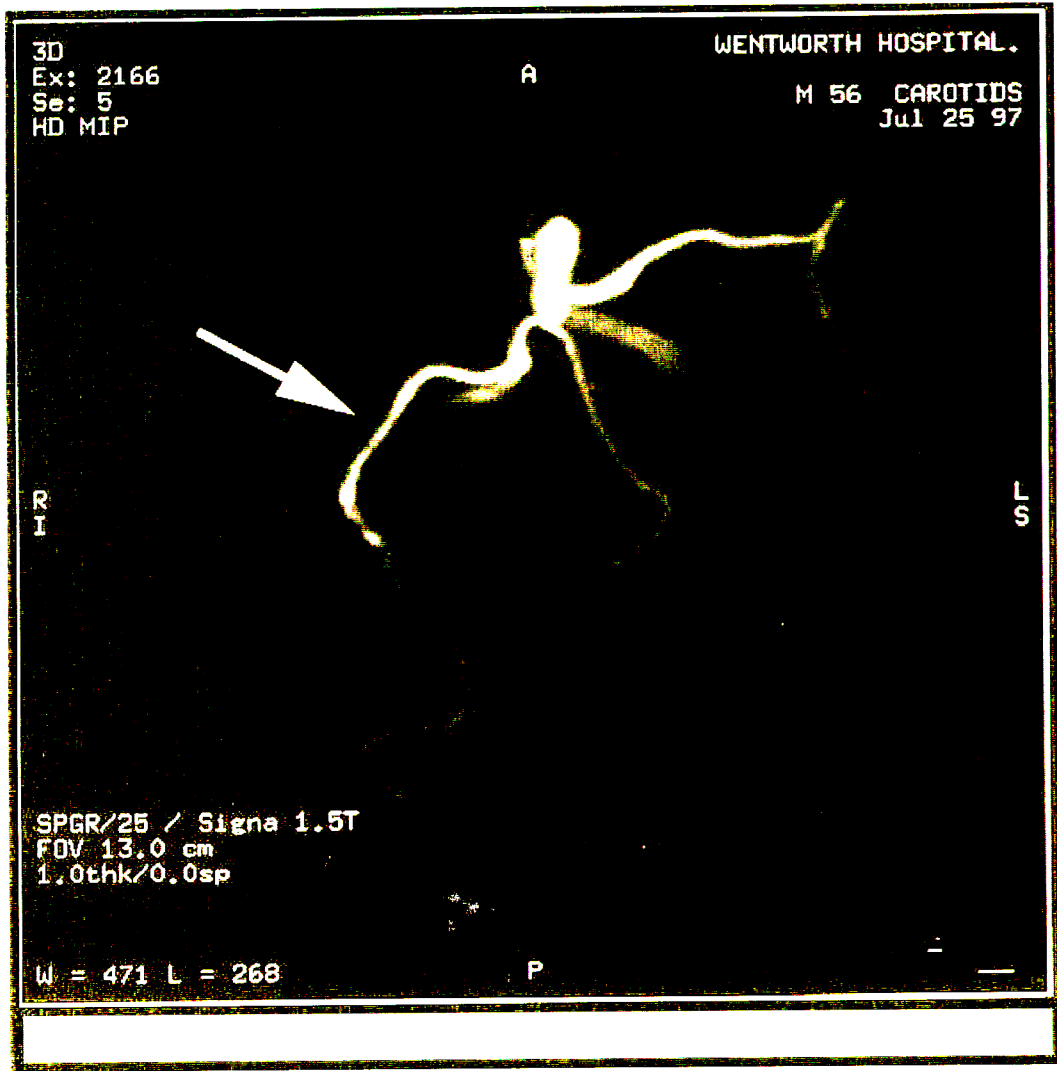


Figure 7 d. Catheter angiogram demonstrating collateralisation via the external carotid artery, maxillary artery, ophthalmic and reconstitution of middle cerebral artery blood flow.



3. Congenital artery abnormality and arterial redundancy - persistent hypoglossal artery and stroke

Clinical: A 48 year old white woman reported a sudden onset of bilateral visual impairment lasting several minutes, followed by intermittent shaking on both sides of her body lasting about 2 hours. Turning her head to the left for more than 1-2 minutes invariably provoked dizziness.

Anatomical brain scan: The magnetic resonance (MRI) brain scan was normal.

Doppler sonography: Transcranial Doppler sonography including dynamic studies with head rotation and flexion was normal. Specifically basilar artery velocity was unchanged with head rotation to the right and left for 2 minutes.

Cardiological tests: Normal

Angiography: Catheter and MR angiography showed an abnormal signal void due to a carotid basilar anastomosis which was confirmed on time of flight magnetic resonance (MR) angiography as a very dilated tortuous hypoglossal artery with an aplastic right vertebral and hypoplastic left vertebral artery. Selective angiography confirmed the MR angiogram findings.

Functional brain scan: The SPECT brain scan showed left hemisphere hypoperfusion to visual inspection and semiquantitative analysis. The asymmetry index was calculated as 22%, significantly different to the normal controls. The cerebral vasomotor response was tested with intravenous Diamox without any further abnormalities noted on the SPECT scan.

Interpretation: A persistent primitive hypoglossal artery was the sole identifiable stroke risk factor for a patient presenting with positional, posterior circulation ischaemic episodes. Redundancy of the primitive hypoglossal artery was the postulated mechanism of cerebral ischaemia on a haemodynamic basis.

Figure 8. MR angiogram of the cervicocephalic vessels showing the hypoglossal artery connecting to the basilar artery (arrow)



4. Comorbidity in stroke - which is the relevant mechanism?

Clinical: A 49 year old white woman presented with symptoms and signs of posterior circulation stroke. She had rheumatic fever, a mitral valve replacement and had triple atherogenic risk factors.

Anatomical brain scan: The CT brain scan showed a superior cerebellar infarct and the MRI minor subcortical infarcts bilaterally.

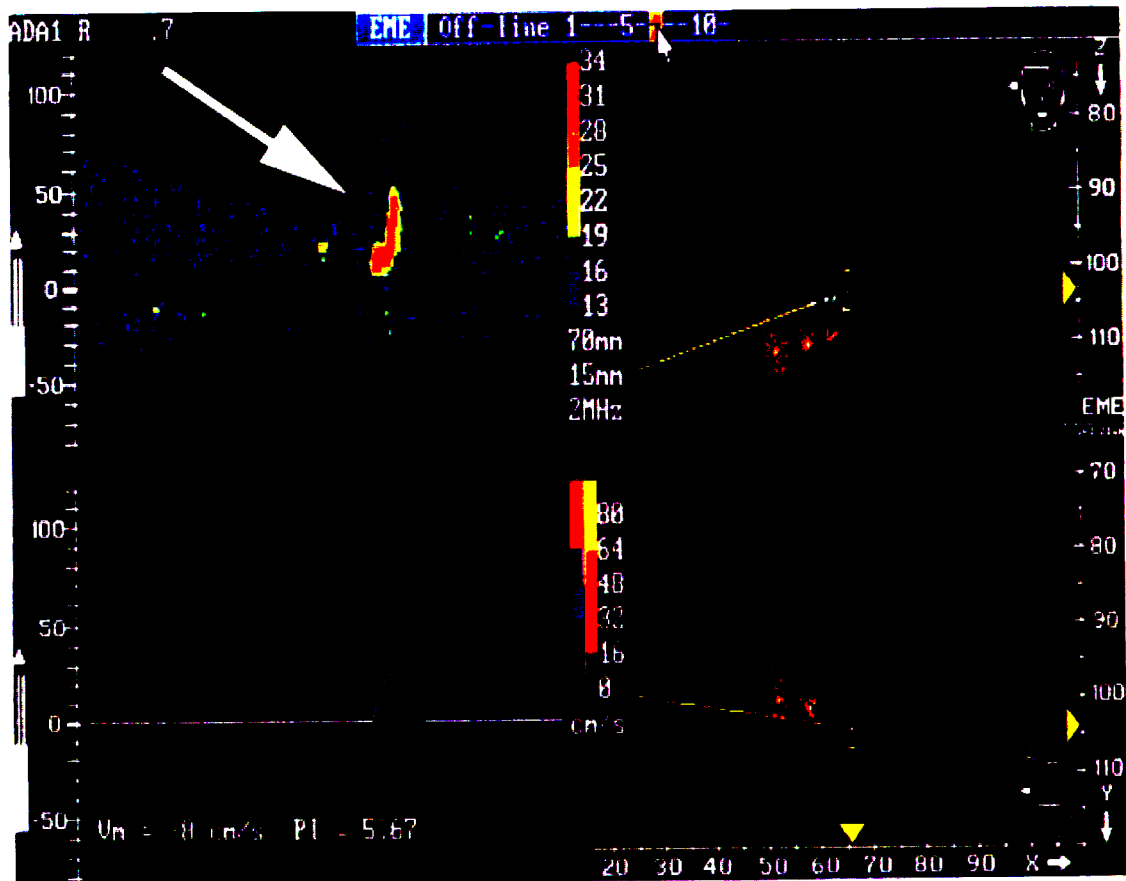
Doppler sonography: Duplex Doppler of the carotid arteries showed bilateral significant carotid stenosis. Transcranial sonography revealed multiple high intensity transient signals (HITS) interpreted as emboli. These occurred in both middle cerebral arteries and the basilar artery.

Functional brain scan: SPECT showed biparieto occipital hypoperfusion.

Cardiological tests: Prosthetic mitral valve, atrial fibrillation.

Comment: It was most likely that the HITS were cardiogenic emboli as they occurred in all vascular territories. An increase in the INR abated the symptoms.

Figure 9. Terminal intracranial internal carotid artery Doppler wave form. High intensity transient signal with all the criteria of an embolus. These occurred with a frequency of several per minute in a patient with atrial fibrillation and mitral valve prosthesis.



5. Patent foramen ovale and stroke. The role of other contributing factors.

Clinical: A 29 year old professional sky diver and scuba diver presented with sudden onset imbalance, dysarthria and diplopia immediately after extensive aerial acrobatics during which he became violently ill and vomited copiously.

Anatomical brain scan: The MRI scan showed a right posterior inferior cerebellar and superior cerebellar branch infarction as well as a right frontoparietal infarct.

Angiography: Catheter four vessel angiography was normal.

Doppler Sonography: Transcranial Doppler with contrast injection showed multiple air embolic signals in the middle cerebral artery.

Cardiological tests: Transoesophageal cardiac echocardiography: In addition to confirming a patent foramen ovale, an atrial septal aneurysm was diagnosed.

Comment: Forceful valsalva manoeuvre (plus other factors?) was required in addition to the patent foramen ovale to cause the stroke. In addition the atrial septal aneurysm could have served as a nidus for clot.

Figure 10 a. Injection of 10 ml of agitated saline and simultaneous recording of the middle cerebral artery Doppler waveform. Multiple air artefactual signals (arrows) indicating a right to left shunt, in this case a patent foramen ovale.

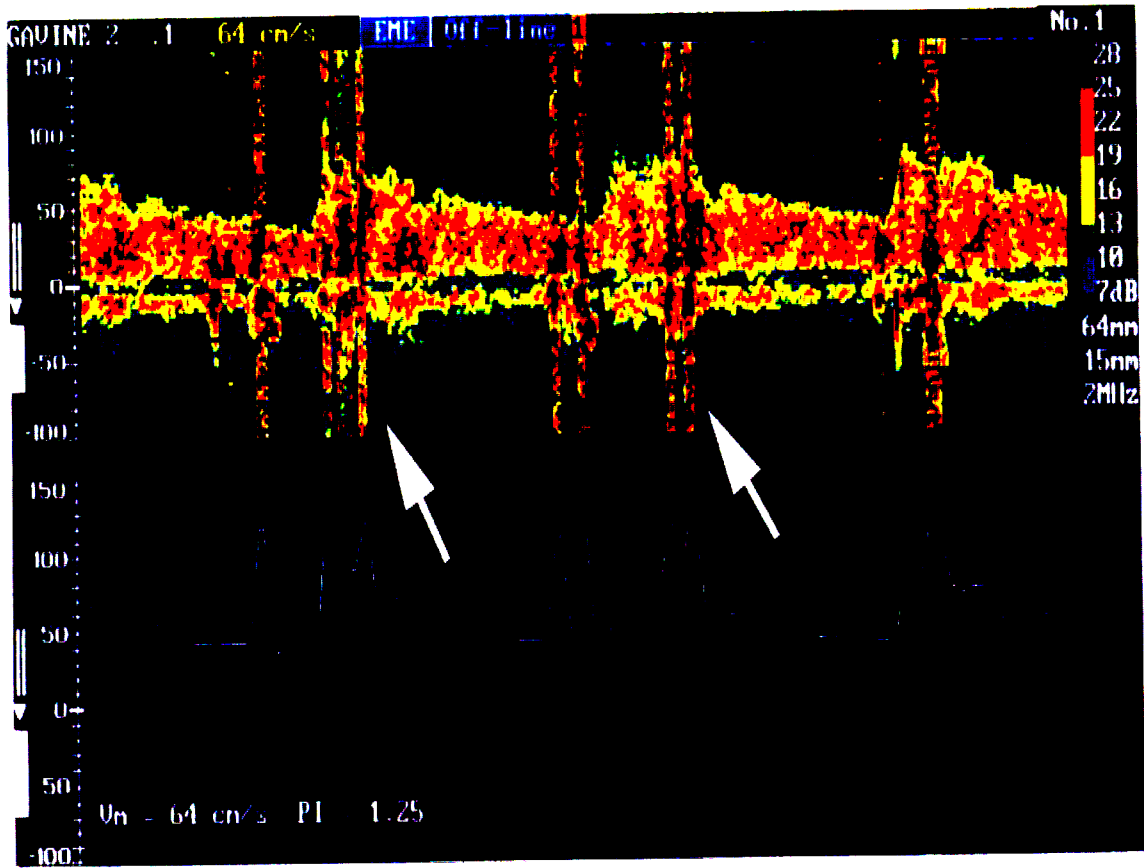
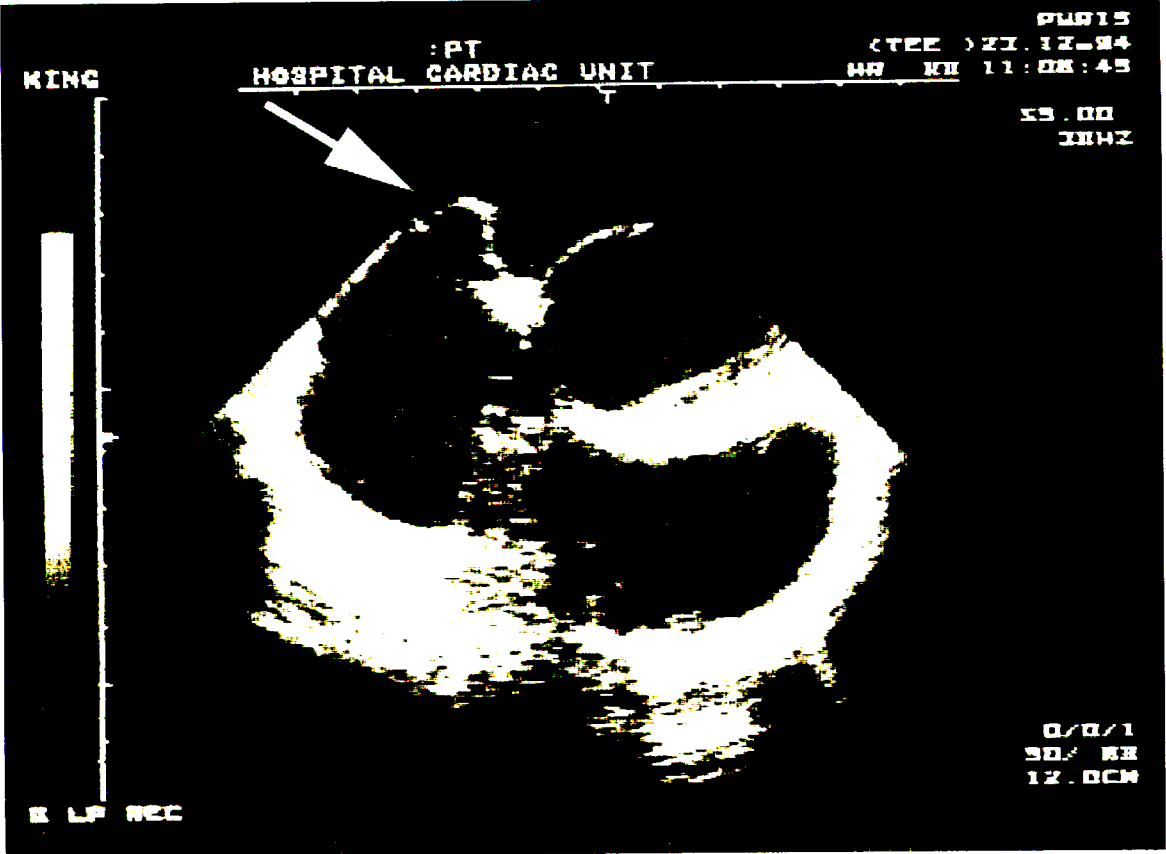


Figure 10 b. This patient also had an atrial septal aneurysm (arrow) in addition to the patent foramen ovale - seen on transoesophageal echocardiography.



6. Basilar artery fenestration causing posterior circulation ischaemia and stroke - an obscure cause.

Clinical: A 71 year old white man suffered progressively more debilitating attacks of dizziness, diplopia, imbalance and incoordination over a 7 year period with several daily attacks present at time of presentation.

Anatomical brain scan: The MRI brain scan revealed no parenchymal lesion.

Functional brain scan: The SPECT brain scan revealed bi occipito parietal hypoperfusion.

Doppler sonography: Cervical and intracranial sonography was normal.

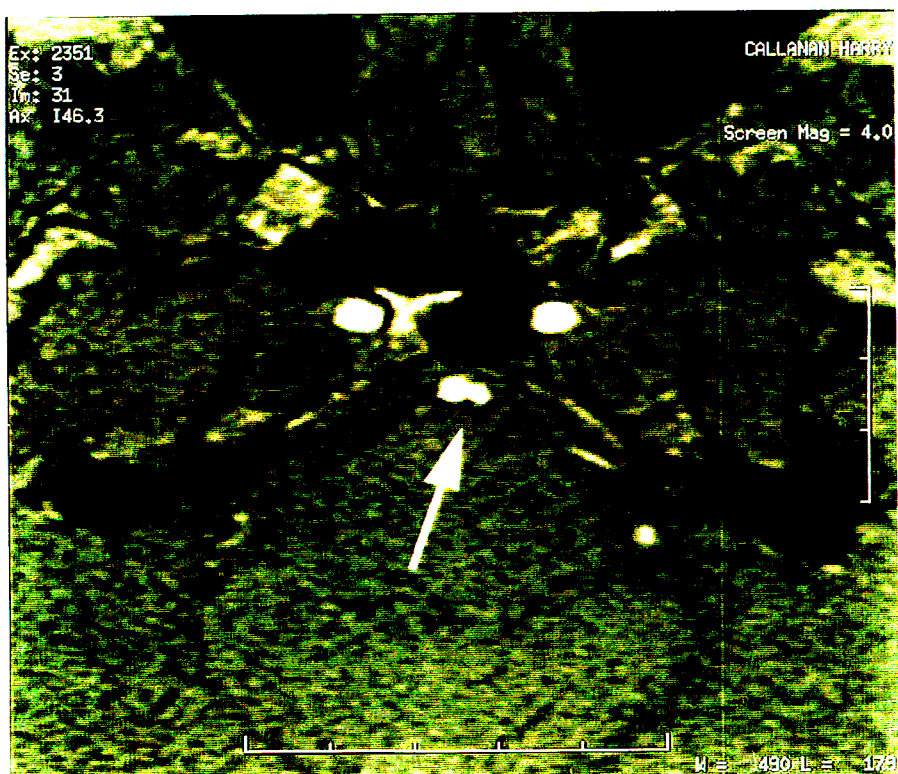
Cardiac echocardiography: Normal.

Angiography: MR angiography revealed basilar artery fenestration.

Comment: Basilar artery fenestration with recurrent artery to artery emboli was the postulated mechanism of stroke/ischaemia. No other causes of stroke were identified and his symptoms improved dramatically with antiaggregant therapy - a combination of Aspirin and Persantin.

Figure 11 a. Above. Magnetic resonance angiogram of the vertebrobasilar arteries. A dilatation of the mid basilar artery with an intravascular hypointense signal (arrow).

Figure 11 b Below. Transaxial magnetic resonance angiogram revealing the biconcave appearance of the basilar artery typical of a fenestration (arrow).



7. Significant carotid stenosis but with symptoms referable to the posterior circulation. Transcranial Doppler detection of relevant intracranial stenosis.

A 76 year old hypertensive man reported sudden onset visual blurring and visual illusions.

Anatomical brain scan: The MRI brain scan revealed a right parieto occipital infarct.

Doppler sonography: Duplex Doppler revealed a >80% stenosis of the right internal carotid origin. Transcranial Doppler revealed features consistent with a severe stenosis (circumscribed velocity increase; mean of 116 and peaking at 144 cm/sec) of the right P2 segment of the posterior cerebral artery.

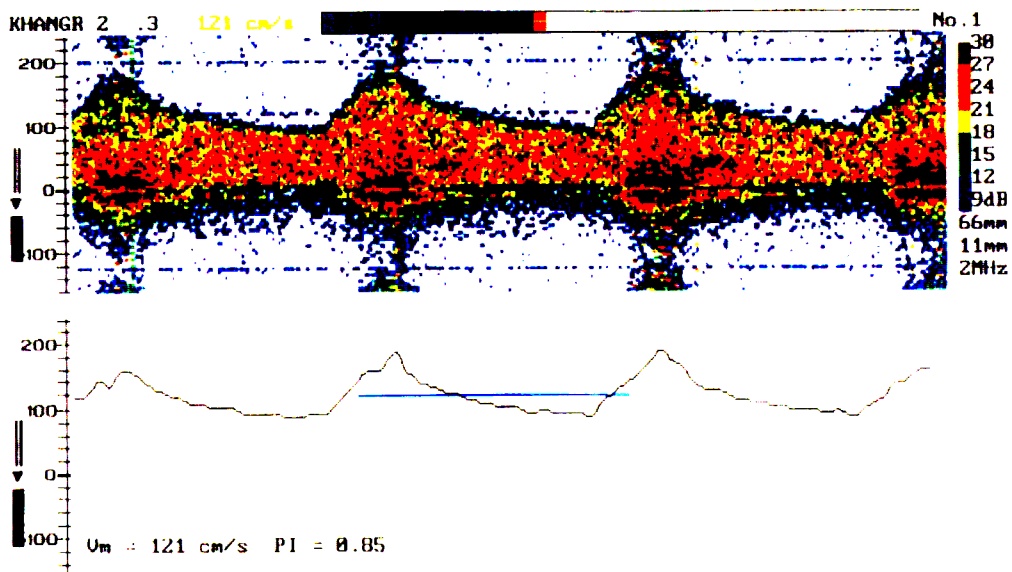
Angiography: The right posterior cerebral artery stenosis was confirmed by noninvasive MR angiography.

Cardiological tests: Normal

Comment: These findings demonstrated the value of transcranial Doppler in detecting intracranial stenoses that are responsible for the symptoms. He required a carotid endarterectomy and anti coagulation for the intracranial stenosis.

Figure 12 a. above. Magnetic resonance angiogram showing a right posterior cerebral artery stenosis (arrow).

Figure 12 b. below. Accompanying high velocity (mean 200 cm/sec) transcranial Doppler signal with features of turbulence.



8. Multimodality magnetic resonance imaging in the rapid aetiological diagnosis of stroke subtype. A patient in whom hyperacute administration of intravenous tissue plasminogen activator was indicated.

Clinical: A 61 year old white man presented with sudden onset right hemiparesis with speech impairment within 90 minutes of onset. His NIH stroke scale score was 10.

Anatomical brain scanning: MRI brain scan was normal.

Diffusion MRI: This revealed a clear hyperintensity of the left parietal region.

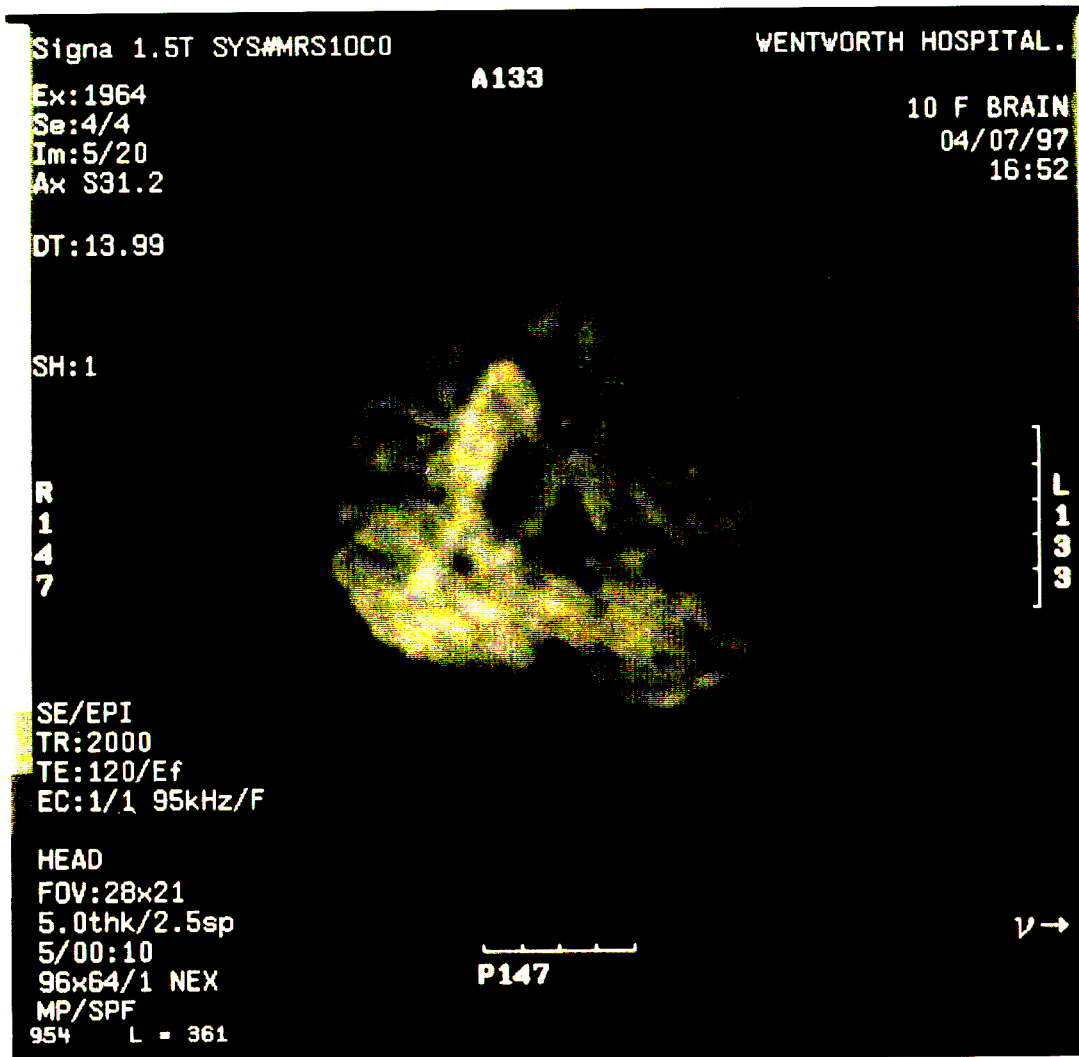
Cardiological tests. Normal

Doppler sonography: Normal

Management: Intravenous tissue plasminogen activator was administered.

Comment: Multimodality magnetic resonance imaging allows rapid work up of the brain parenchyma, large and small intracranial vasculature, cervicocephalic vessels. This assists in rapidly making an aetiological stroke diagnosis and guiding the administration of urgent therapy.

Figure 13. Magnetic resonance diffusion scan. The subcortical hyperintense signal indicates ischaemia or infarction in the acute phase (done 4 hours post ictus). The MRI scan was normal at this time and subsequently revealed a hyperintense T2 signal in the same area - indicative of an infarct.



9. The complementary role of transcranial Doppler and magnetic resonance angiography in non invasively establishing stroke mechanism. A case of bilateral intracranial vertebral artery stenoses.

Clinical: A 61year old diabetic, hypertensive, white man developed sudden onset vertigo, nausea, diplopia and imbalance. These recurred on a daily basis and incapacitating episodes had occurred for several months.

Anatomical brain scan: The MRI brain scan revealed an occipital lobe infarct, multiple cerebellar infarcts and a right thalamic infarct. The basilar artery was dolichoectatic.

Doppler Sonography: The carotid duplex Doppler was normal. The transcranial Doppler study of the posterior circulation showed marked turbulence in the basilar artery at about 85-90 cm depth with mean velocities of 145 cm/sec.

Cardiological tests: electrocardiography and echocardiography normal.

Angiography: MR angiography confirmed the stenoses but this was seen to involve the terminal V4 vertebrals on both sides.

Management: Warfarinization but not antiaggregant therapy completely abolished the episodes.

Comment: The combination of transcranial Doppler sonography and magnetic resonance angiography proved to be excellent complementary methods in detecting an unusual cause of posterior circulation stroke - bilateral vertebral artery stenoses. This allowed specific effective therapy with Warfarin to be given with conviction and with excellent results.

Figure 14. Magnetic resonance angiography. Bilateral terminal intracranial (V4) vertebral artery stenoses (arrows).



10. Intracranial collateralisation in a patient with Takayasu's arteritis.

Clinical: A 14 y black female reported intermittent dizzy spells and seizural episodes for 6 months. Neurologically she was normal.

Anatomical brain scan: The MRI brain scan revealed a small left parieto occipital infarct.

Duplex Doppler: Small calibre left common carotid artery (CCA) with no flow seen in the left internal carotid (ICA) artery. The right CCA and ICA and vertebrals were normal. Transcranial Doppler sonography revealed bilaterally increased velocities in the anterior and posterior circulations.

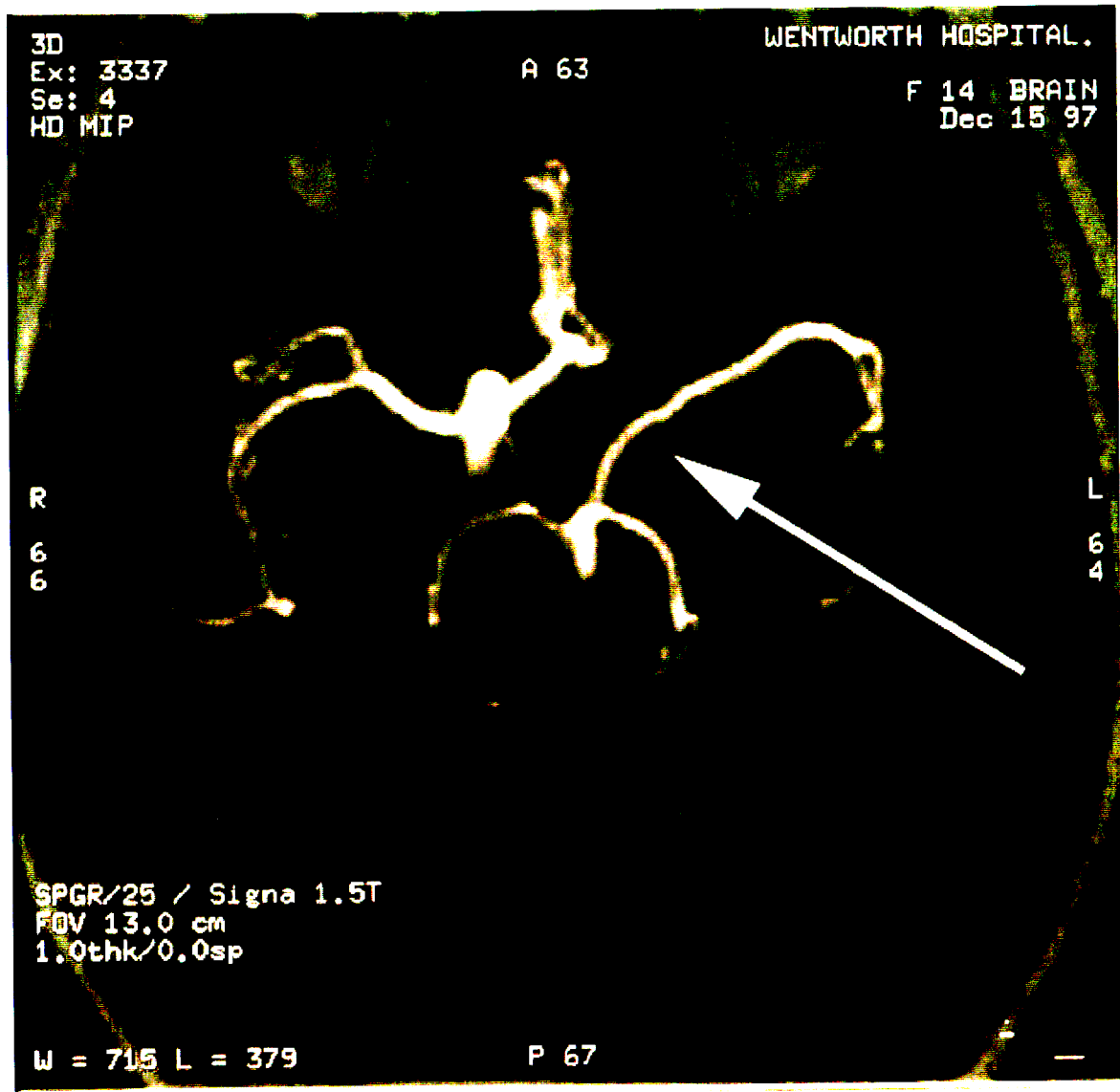
Angiography: Catheter arch angiography and magnetic resonance angiography: Absent left internal carotid artery and Willisian collateralisation from the basilar artery through the left posterior communicating artery to the anterior circle of Willis.

Cardiological tests: Normal

Management: Revascularization for Takayasu's arteritis.

Comment: Good demonstration of pathophysiology - Willisian collaterals noted on transcranial Doppler and magnetic resonance angiography

Figure 15. Magnetic resonance angiogram revealing the posterior to anterior circulation collateralisation from the basilar artery, through the left posterior communicating artery to the left middle cerebral artery (arrow). This patient had an occlusion of the left internal carotid artery due to Takayasu's arteritis.



11. Stroke mechanism. Carotid redundancy - kinks, coils and loops.

Clinical: A 77 year old hypertensive white woman presented with amaurosis fugax.

Anatomical brain scan: The CT brain scan showed a left subcortical corona radiata infarct.

Doppler sonography: 60-80% left carotid stenosis.

Cardiological tests: Normal

Angiography: The spiral CT of the carotids revealed a left ICA kink with the angle close to 70 degrees. At the bulb there was about 50% stenosis with a large irregular plaque that was calcified just proximal to the bifurcation. The plaque extended to involve the bulb.

Management. Revascularization and carotid endarterectomy.

Comment: Carotid kinks have been associated with ischaemia and infarction without concomitant atheroma and are regarded as a stroke mechanism [3].

Figure 16. Spiral computed tomography angiogram. An approximately 70% kink in the internal carotid artery (arrow).



12. Cerebral vasculitis diagnosed by magnetic resonance angiography

Clinical. A 35 year old Indian woman presented with a mild frontal lobe syndrome and paraparesis. The erythrocyte sedimentation rate was 72, haemoglobin 8.2, antinuclear factor positive and haematuria present.

Anatomical brain scan: The MRI brain scan revealed multiple small subcortical infarcts

Cardiological tests: Normal

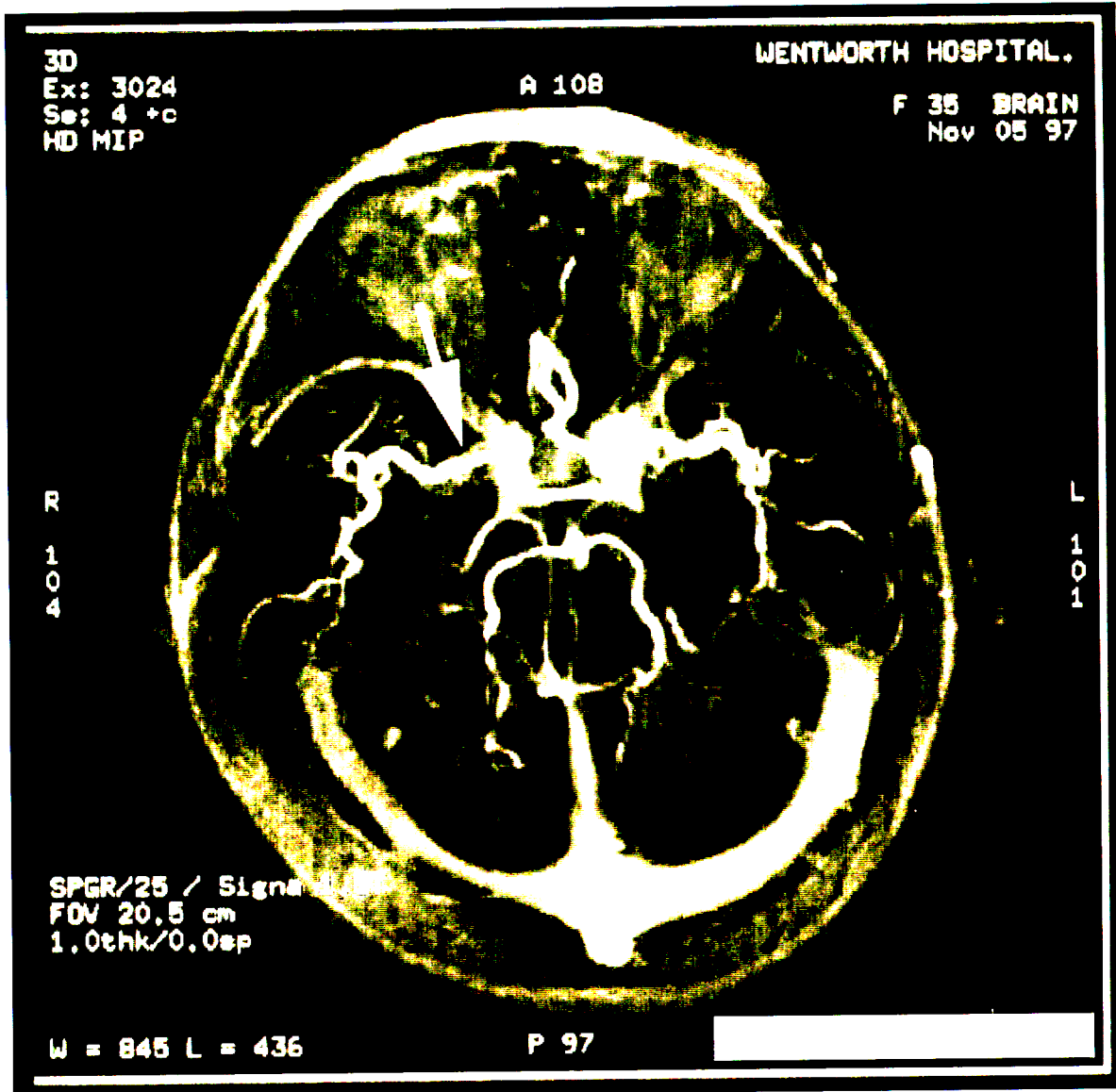
Doppler sonography: Cervical vessels normal.

Angiography: Medium sized vessel irregularity suggestive of vasculitis

Management: Steroids

Comment: A high quality magnetic resonance angiography may suffice to diagnosis medium vessel cerebral angiitis and obviate the need for invasive catheter angiography.

Figure 17. Magnetic resonance angiography. Irregularity of both proximal middle cerebral arteries consistent with angiitis (arrow).



13. Diffusion weighted imaging in assisting differentiation of ischaemia and infarction in eclampsia.

Clinical: An 18 year old black woman presented with eclampsia and simultanagnosia.

Anatomical imaging: The MRI brain scan revealed hyperintense lesions posteriorly in both parieto occipital regions. These persisted on the T2 images at follow up one week later.

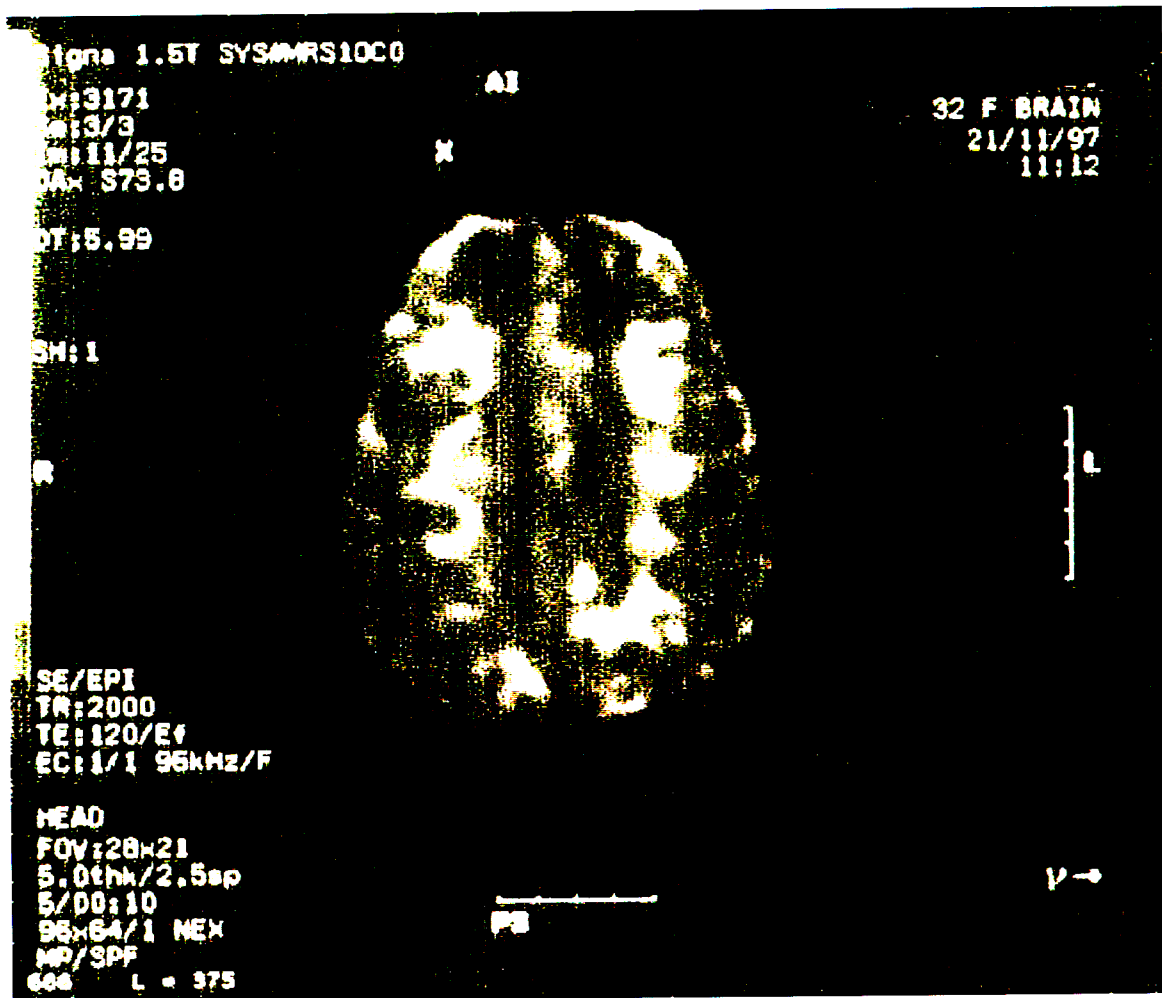
Diffusion weighted MR imaging: This revealed extensive anterior and posterior watershed ischaemia/infarction. These resolved one week later.

Cardiological tests: Normal

Management: Magnesium sulphate. Caesarean section.

Comment: Diffusion weighted imaging allows a better pathophysiological appreciation of the extensive watershed type distribution of lesions in eclampsia and assists in differentiating ischaemia from infarction.

Figure 18. Magnetic resonance diffusion weighted scan in a patient with eclampsia. Note the widespread hyperintense signals in both anterior and posterior watershed territories.



Cognitive dysfunction

14. Frontal lobe syndrome due to isolated left thalamic infarct.

A 48 year old hypertensive white woman awoke with right sided numbness and found to have a frontal lobe syndrome on neuropsychological testing.

Anatomical brain scan: The MRI brain scan revealed a left paramedian thalamic infarct.

Functional brain scanning: The SPECT showed bifrontal hypoperfusion, left more than right as well as left thalamic hypoperfusion.

Doppler sonography: Normal.

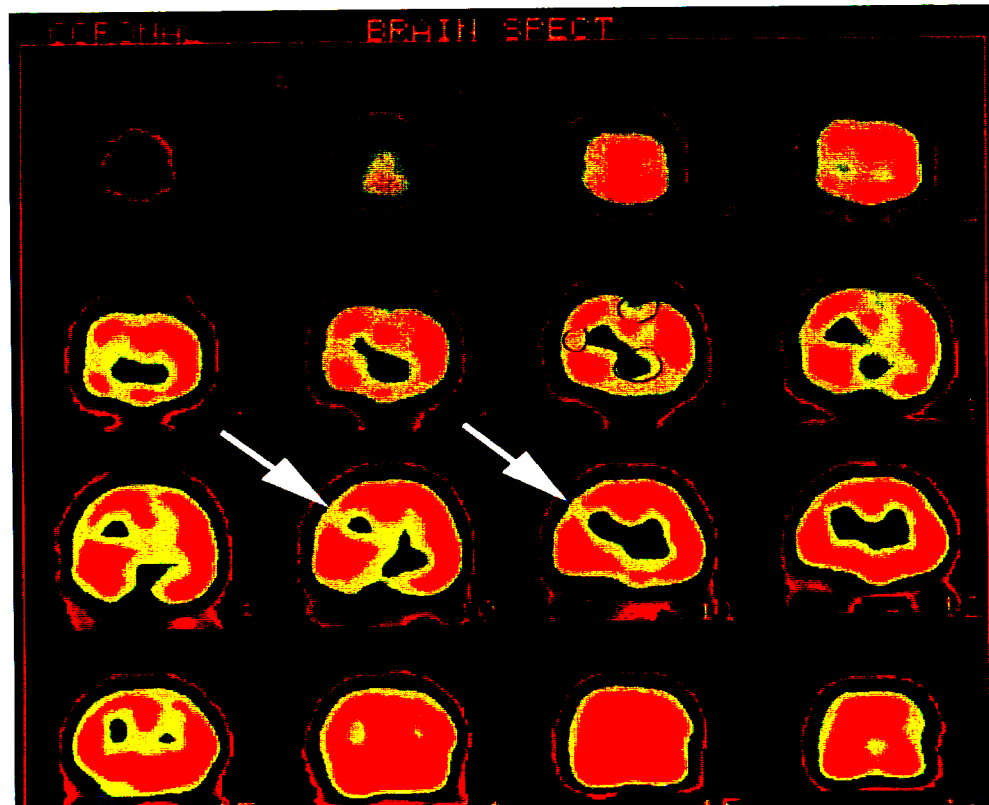
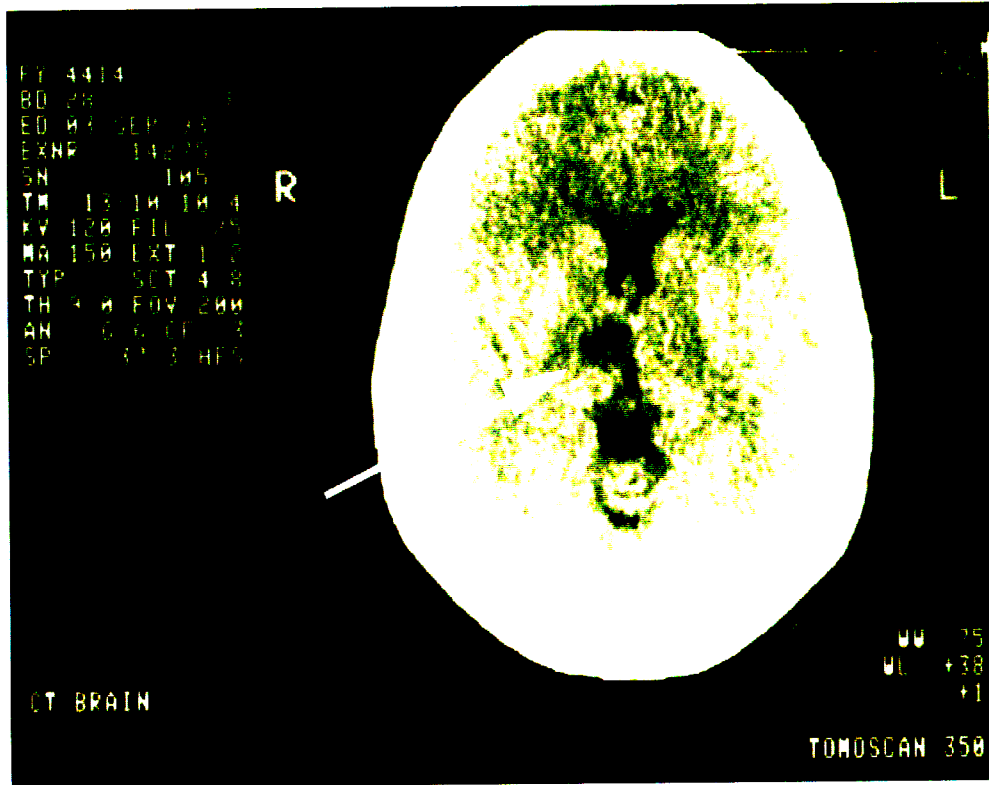
Cardiac evaluation and echocardiography: Normal.

Neuropsychological testing: Frontal lobe syndrome.

Comment: In this relatively young woman the sudden onset of a frontal systems syndrome was correlated with SPECT brain scanning demonstration of frontal hypoperfusion - hypometabolism due to diaschisis?

Figure 19 a. Computerised tomography scan of a paramedian thalamic infarct (arrow) with accompanying SPECT scan revealing bifrontal asymmetric hyperperfusion.

Figure 19 b. SPECT scan. Right thalamic and frontal hypoperfusion



15. Frontal systems syndrome due to caudate nucleus infarction and frontal hypoperfusion on SPECT brain scan.

Clinical: A 39 year old hypertensive white man awoke with headache and abnormal behaviour with apathy and abulia noted on clinical testing.

Doppler sonography: The duplex and transcranial Doppler studies were normal.

Anatomical brain scanning: The MRI scan revealed signals consistent with left caudate nucleus infarction.

Functional brain scanning: The SPECT brain scan revealed extensive left frontal hypoperfusion.

Cardiological evaluation: Normal

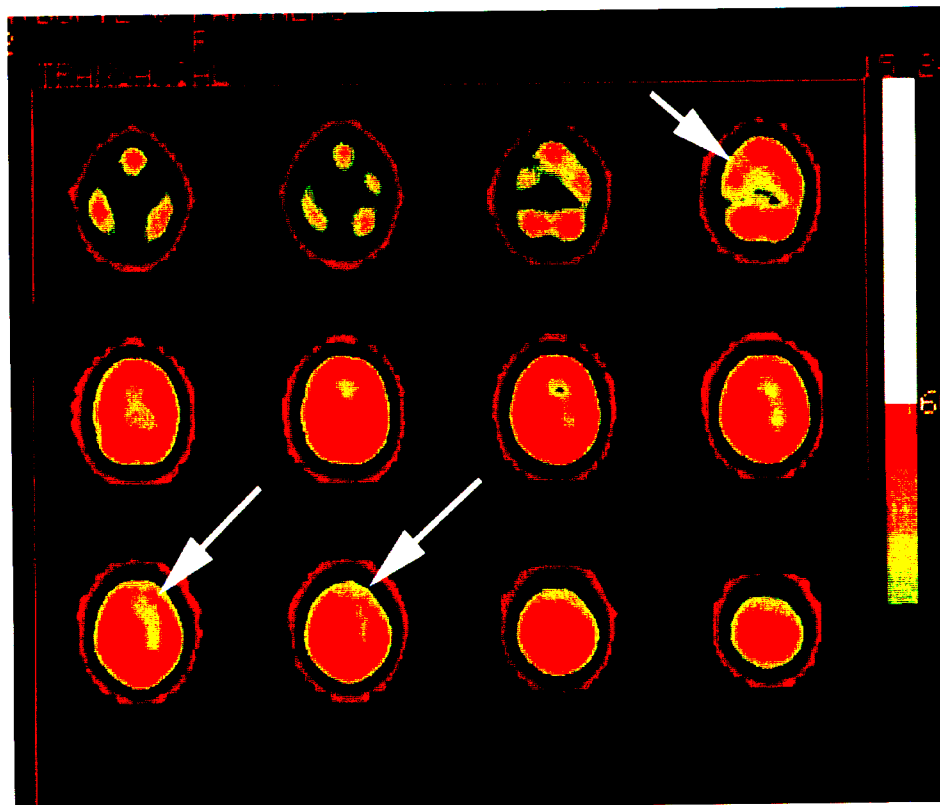
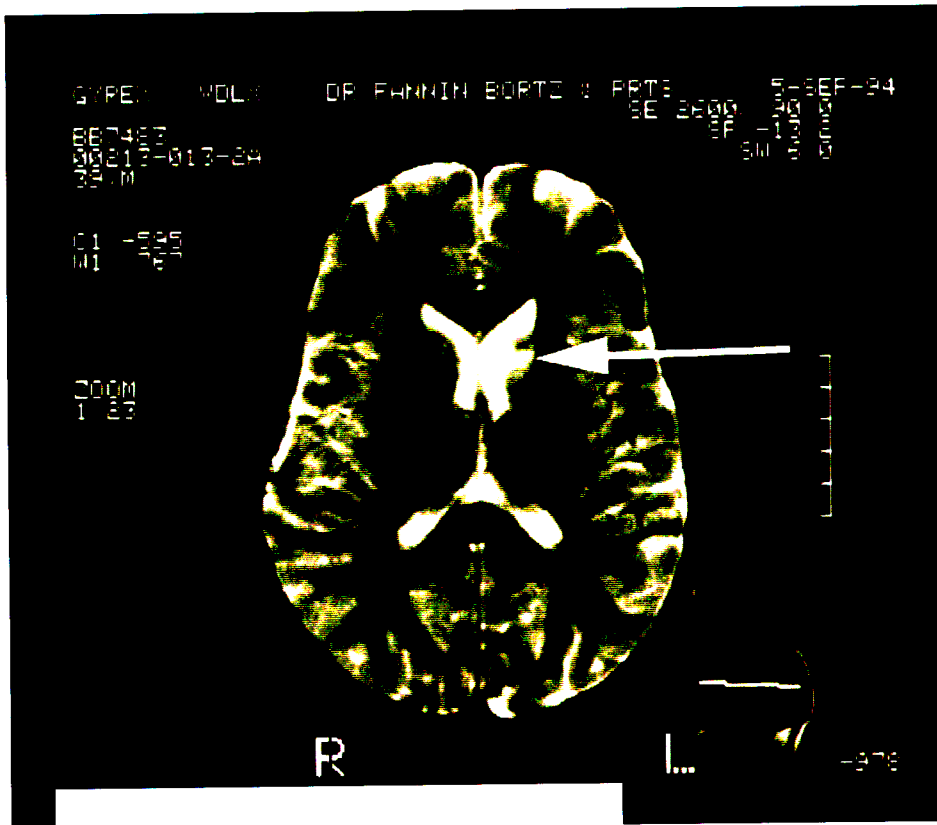
Angiography: Catheter angiography was normal.

Neuropsychological testing: Marked left frontal lobe neuropsychological deficits.

Comment: The frontal systems syndrome due to the caudate nucleus infarction was best correlated with the SPECT functional scan.

Figure 20 a. MRI brain scan of a caudate nucleus infarct (arrow). Clinically a frontal lobe syndrome was evident.

Figure 20 b. SPECT scan showed frontal hypoperfusion (arrows).



16. Frontal lobe syndrome due to isolated pontine infarction and SPECT brain scan correlation.

Clinical: A 77 year old white woman with mild hypertension and hyperlipidaemia developed sudden dizziness, imbalance, mild right sided long tract signs, ataxia and behavioural abnormality in that she felt and was observed to be “odd”. She had previously been healthy in all respects and had not suffered from neurodegenerative disease or depression. Her behavioural changes had occurred suddenly.

Doppler sonography: Minimal atherosclerotic disease in the cervical and intracranial vessels.

Anatomical brain scan: The MRI scan showed a left pontine infarct without other cerebral lesions. The basilar artery appeared dolichoectatic.

Functional brain scan: The SPECT showed bifrontal hypoperfusion.

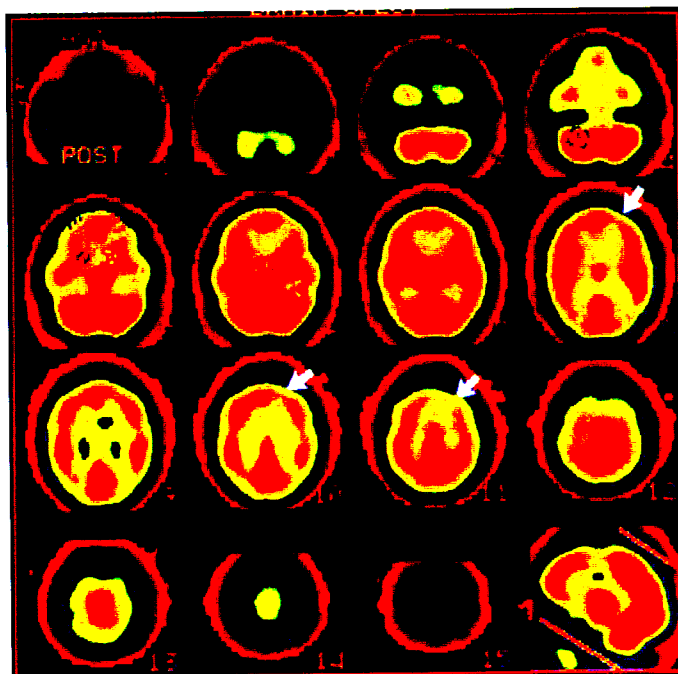
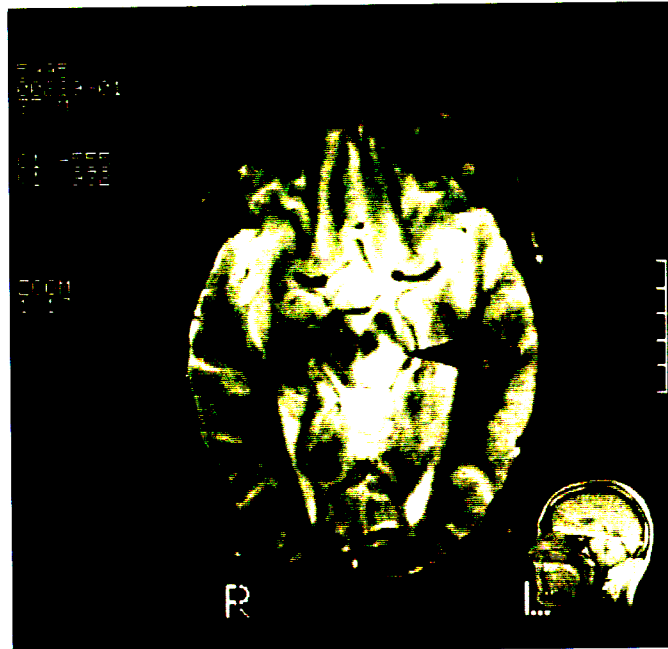
Cardiological evaluation: Normal.

Neuropsychological testing: Frontal lobe syndrome.

Comment: The isolated pontine infarct, probably caused by the dolichoectatic basilar artery was associated with a frontal system syndrome correlated with the SPECT hypoperfusion.

Figure 21a. Isolated pontine infarct presenting with a frontal system syndrome.

21 b. Functional imaging (SPECT) brain scan showing frontal hypoperfusion (arrows).



Diagnostic pitfalls

17. Hyperintense T2 signal on MRI brain scanning - pyramidal tract degeneration

Clinical. A 40 year old black woman presented with right sided hemiparesis and expressive dysphasia.

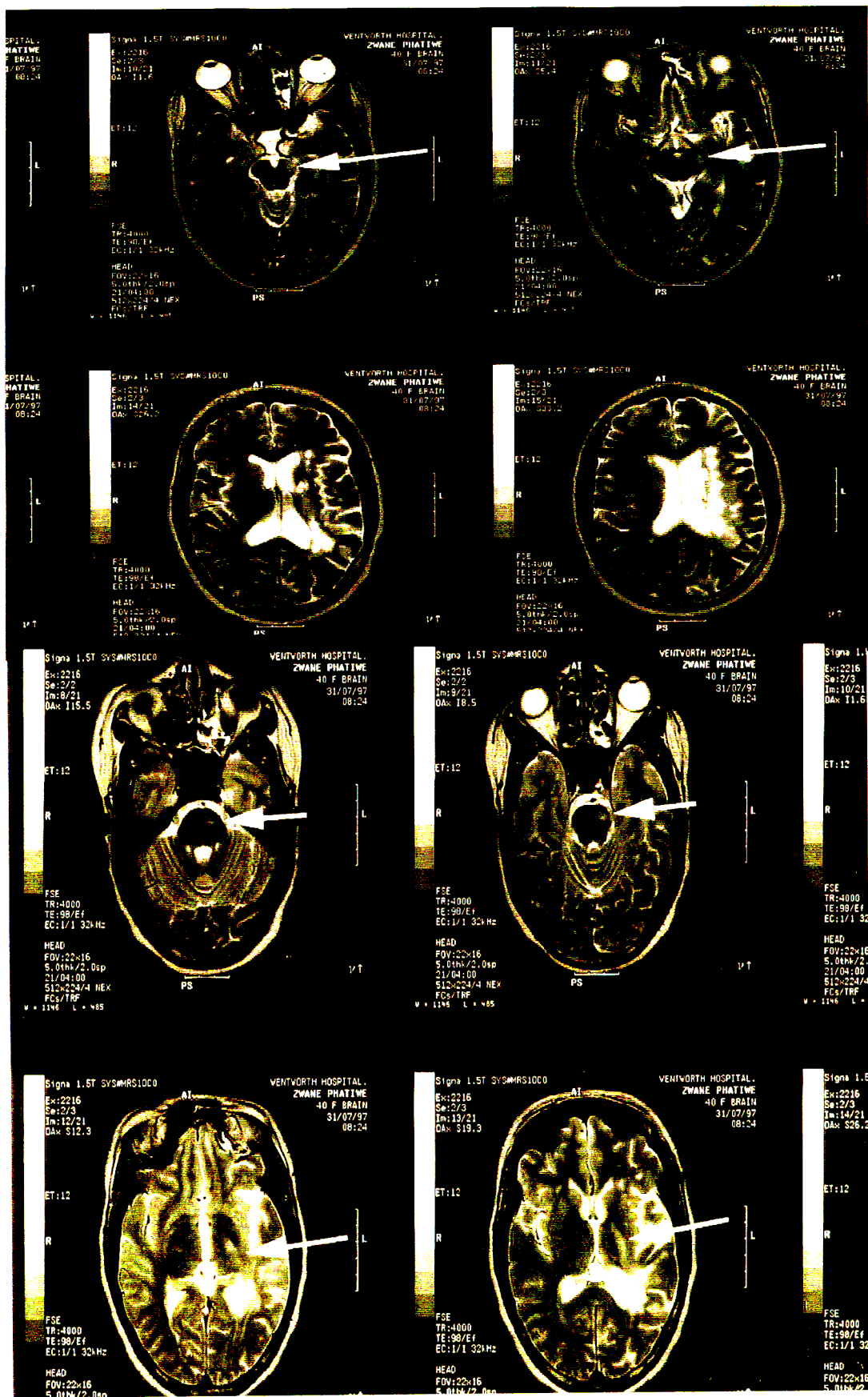
Doppler sonography: Duplex Doppler of the carotid and vertebral arteries was normal.

Anatomical brain scan: The MRI brain scan showed a marked hyperintensity of the deep left middle cerebral artery territory consistent with a large deep MCA infarct and occlusion of the left middle cerebral artery stem. In addition there were hyperintense signals in the left internal capsule, cerebral peduncle, pons and medulla.

Cardiological evaluation: Normal.

Comment: The hyperintense signals in the internal capsule, cerebral peduncle and brainstem were consistent with Wallerian degeneration of the pyramidal tract and not multiple infarcts [4,5]

Figure 22. Left middle cerebral artery infarct and associated hyperintense signal in the brainstem, cerebral peduncle and subcortical area - pyramidal tract degeneration.



18. The value of MR spectroscopy in differentiating stroke from tumour in a patient with coexistence of stroke and brain tumour

Clinical: A 59 year old white man reported poor short term memory, intermittent visual hallucinations, loss of taste and smell and episodes of blank stares interpreted as partial seizures.

Doppler sonography: The duplex and transcranial Doppler studies were normal. Testing revealed dysmnnesia, dyscalculia, dysnomia and quadrantanopia.

Anatomical brain scanning: The MRI and CT showed a right medial occipital infarct and a left parieto temporal lesion.

Functional brain scanning: Magnetic resonance spectroscopy confirmed a right occipital lobe infarct but a high choline and lactate peak and low NAA indicative of a tumour [6] in the left parieto temporal lobe.

Cardiological evaluation: Normal

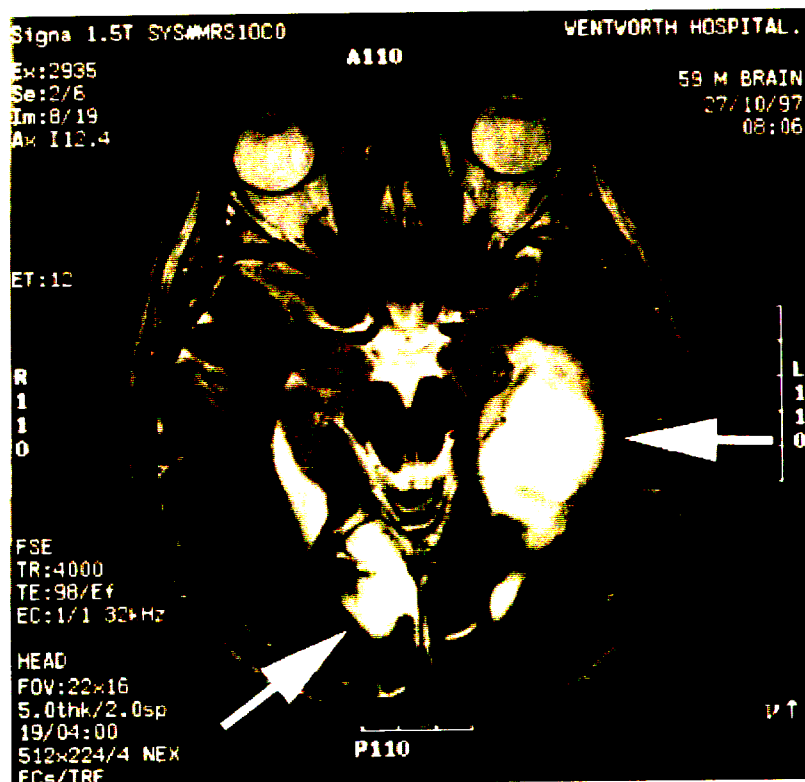
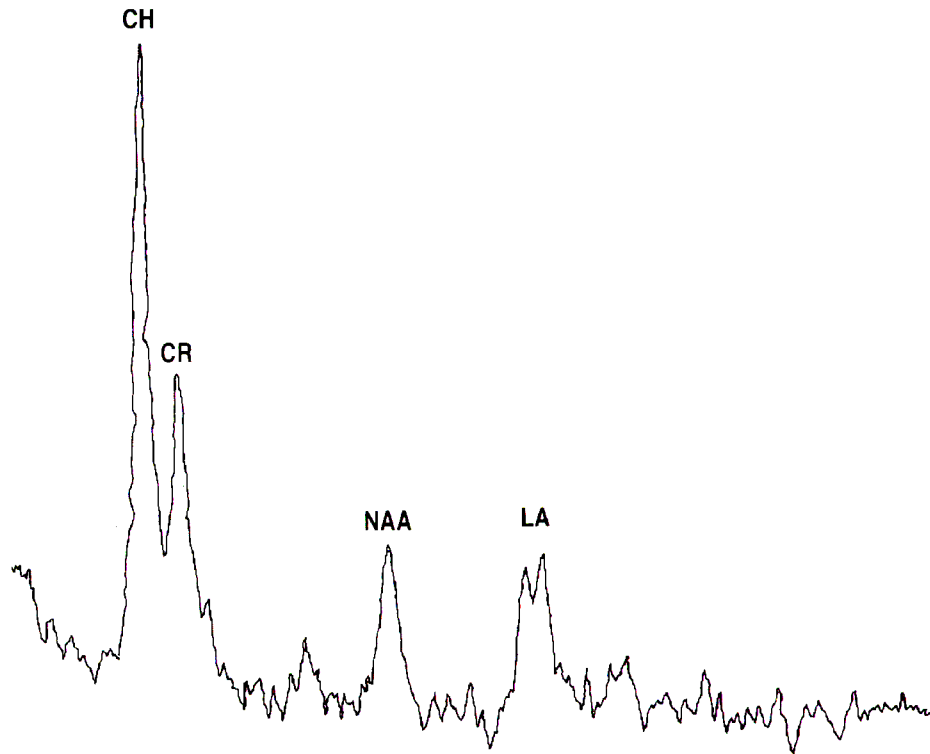
Angiography: MR angiogram was normal.

Brain Biopsy: Grade 2 astrocytoma of the left parietotemporal region.

Comment: The MRS was decisive in resolving the difficulty in differentiating the left parietotemporo occipital lesion clinically and radiologically from a haematoma, infective lesion, inflammatory lesion, tumour or infarct.

Figure 23 a. Magnetic resonance spectroscopy. Typical brain tumour signal of relatively high Choline, high Lactate and low NAA.

Figure 23 b. MRI scan of right occipital infarct and left temporal lesion.



5.2 Cognitive testing results

5.2.1 Descriptive Statistics

1. Overview

One or more HCFD were present in 607 (60.7%) of the patients with 746 instances of higher cortical functions deficits. Patients who were not alert were excluded. This included drowsy patients (n=25), patients in light coma (n=6), patients in deep coma (n=12) and patients that were hyperalert or delirious (n=2).

2. HCFD frequencies

Aphasias	252
Apraxias	145
Amnesias	116
Frontal systems	92
Neglect syndromes	35
Anosognosias	21
Aprosodias	18
Visuospatial	18
Alexias	13
Agnosias	11
Miscellaneous	25

3. HCFD subgroup frequencies

Aphasias

Anomic	103
Broca's	90
Global	43
Subcortical	7
Transcortical Motor	6
Wernicke's	2
Conduction	1
Transcortical Sensory	0
Transcortical Mixed	0

Apraxias

Limb kinetic	67
Ideomotor	62
Orofacial	19
Dressing	4
Sympathetic	3
Ideational	2

Miscellaneous

Achromatopsias	10
Simultanagnosias	9
Prosopagnosias	4
Visual illusions, hallucinations and palinopsias	4
Balint's syndrome	3
Gerstmann's syndrome	2
Angular Gyrus syndrome	1
Anton's syndrome	1
Astereopsis	1
Cortical blindness	1

Cognitive impairment in absence of elementary neurological deficits such as weakness, sensory disturbance or visual impairment.

HCFD abnormal without weakness	193
HCFD abnormal without sensation disturbance	279
HCFD abnormal without visual field defects	566
HCFD abnormal without any of the above	137/608 (22.5%)

5.2.2 Computational Statistics - cognitive issues

5.2.2.1 Higher cortical function screening test sensitivity and specificity (compared to the gold standard - neuropsychological testing)

Table 9. Neuropsychological testing was performed in 76 patients all with abnormal results.

	Neuropsychological Testing		
	<u>Abnormal</u>	<u>Normal</u>	
HCFD Testing			
<u>Abnormal</u>	61	0	61
<u>Normal</u>	15	0	15
	76	0	

Sensitivity: $61/76 = 80.2\%$ (95% CI: 72-88%)

Specificity

Evaluated in 20 normal individuals of whom all had normal HCFD results

Specificity: $20/20 = 100\%$

5.2.2.2 Table 10. Risk factors for higher cortical function deficits: univariate and multivariate associations.

Risk factor	n	% abn. of HCFD	p value	OR (95% CI)
<u>Sex</u>				
male	553	62.21		
female	434	60.37	0.556	1.08(0.83;1.39)
<u>Age *</u>				
0-14	4	50.0		
15-49	241	58.09		
50-59	190	65.79		
60-69	262	58.02		
70-79	203	59.61		
80-89	55	83.64		
90-100	2	100.0	0.002	
<u>Race *</u>				
Black	100	71.13		
Indian	103	51.00		
Mixed	13	53.85		
White	784	61.68	0.052	

Medical conditionsHypertension

yes	414	59.42		
no	574	62.89	0.269	0.86(0.67;1.12)

Cardiac *

yes	175	66.86		
no	813	60.27	0.104	1.33(0.94;1.88)

Diabetes

yes	102	58.82		
no	886	61.74	0.567	0.88(0.58;1.34)

TIA

yes	53	62.26		
no	935	61.39	0.899	1.03(0.59;1.84)

Previous stroke *

yes	62	72.58		
no	926	60.69	0.063	1.71(0.97;3.04)

Hyperlipidaemia

yes	47	55.32		
no	941	61.74	0.377	0.76(0.43;1.38)

Drug abuse

yes	3	66.67		
no	985	61.42	0.85	1.25(0.11;13.9)

Hypercoagulable

yes	10	50.00		
no	978	61.55	0.455	0.62(0.18;2.17)

Migraine

yes	40	52.50		
no	948	61.81	0.236	0.68(0.36;1.29)

Overweight *

yes	32	81.25		
no	956	60.77	0.019	2.79(1.14;6.86)

<u>PVD</u>				
yes	19	63.16		
no	969	61.40	0.876	1.07(0.42;2.76)
<u>Alcohol</u>				
yes	80	66.25		
no	908	61.01	0.356	1.25(0.77;2.03)
<u>Smoking</u>				
yes	263	59.70		
no	725	62.07	0.498	0.90(0.68;1.21)
<u>Oral contraceptive *</u>				
yes	16	43.75		
no	972	61.73	0.143	0.48(0.18;1.31)
<u>Gout *</u>				
yes	33	48.48		
no	955	61.88	0.120	0.58(0.29;1.16)
<u>Sleep apnoea</u>				
yes	4	75.0		
no	984	61.38	0.577	1.89(0.19;18.2)
<u>COAD</u>				
yes	27	66.67		
no	961	61.29	0.571	1.26(0.56;2.84)
<u>Cervical manip.**</u>				
yes	4	0		
no	984	61.69	0.022	0.07(0.004;1.28)
<u>Neck trauma **</u>				
yes	12	91.67		
no	976	61.07	0.035	7.01(1.20;40.9)
<u>Infection (<1m) *</u>				
yes	43	90.70		
no	945	60.11	0.001	6.47(2.29;18.26)

<u>Cancer</u>				
yes	17	52.94		
no	971	61.26	0.468	0.70(0.27;1.84)
<u>Vasculitis</u>				
yes	7	85.71		
no	979	61.26	0.260	3.79(0.46;31.6)
<u>Autoimmune</u>				
yes	9	77.78		
no	979	61.29	0.495	2.21(0.45;10.7)
<u>Collagen Vasc.Dis.</u>				
yes	1	100.0		
no	987	61.40	0.428	1.89(0.08;46.4)
<u>Neurocysticercosis</u>				
yes	2	50.0		
no	986	61.46	0.739	0.63(0.04;10.06)
<u>Tuberculosis</u>				
yes	8	75.0		
no	980	61.3	0.429	1.89(0.38;9.42)
<u>HIV *</u>				
positive	13	92.31		
negative	975	61.03	0.021	7.66(1.35;43.4)
<u>DVT *</u>				
yes	11	81.82		
no	977	61.21	0.163	2.85(0.61;13.27)

Note:

1. The approximated LOGIT approach has been used to estimate the 95% confidence intervals for the Odds Ratio.
2. * Denotes the parameters entered into the multivariate analysis
3. ** Denotes parameters with significant p values but numbers too small for multivariate analysis.

Multivariate analysis

Risk factors with a p value smaller than 0.2 on univariate analysis were entered into the multivariate model. Multivariate Logistic Regression was used to determine which of the risk factors contributed independently to an abnormal HCFD. A backward elimination technique was applied and variables with a p value of <0.05 remained in the model.

5.2.2.3 Table 11. Results of Multivariate Logistic Regression.

Risk factor	Parameter estimate (β)	p-value	OR (95% C.I)
Intercept	6.529	0.0001	
Age	0.126	0.0138	1.134 (1.026;1.254)
Race	-0.339	0.0138	0.713 (0.544;0.933)
Overweight	1.214	0.0147	3.367 (1.271;8.928)
Infection (recent)	1.747	0.001	5.747 (2.02;16.39)

Hence:

$$\underline{\text{Log}(p/1-p)=6.529+0.126 \text{ age} -0.339 \text{ race}+1.214 \text{ overweight}+1.747 \text{ infection}}$$

Age: 1=0-49; 2=50-59; 3=60-60; 4=70-70; 5=>80

Race: 1= black; 2 = white; 3 = Indian; 4 = mixed race

Overweight: 1 = yes; 2 = no

Infection: 1 = yes; 2 = no

Examples of the above equation:

A black man aged 62 years who is overweight and has had a recent infection.

$$p = \frac{\exp(6.529 + 0.126(3) - 0.339(1) + 1.214(1) + 1.747(1))}{1 + \exp(6.529 + 0.126(3) - 0.339(1) + 1.214(1) + 1.747(1))}$$

$$= \frac{\exp(9.529)}{1 + \exp(9.529)}$$

$$= \underline{0.99}$$

A person with the above factors therefore has a high probability of having a cognitive impairment at time of stroke.

5.2.2.4 Table 12. Overall incidence of HCFD in younger (<49y) and older (>49y) patients with stroke

Age	Abnormal	Normal	Total
<49	142	103	245
>49	446	266	712
Total	588	369	957

p-value 0.194 (not significant)

5.2.2.5 Table 13. Incidence of HCFD subgroups in younger (<49 y) and older (>49y) patients with stroke

HCFD subtype	p-value
Aphasia	0.798
Amnesias	0.039*
Apraxias	0.356
Frontal lobe	0.001*
Neglect syndromes	0.817
Anosognosias	0.644
Alexias	0.169
Aprosodias	0.712
Agnosias	0.573
Miscellaneous	0.396

Note: * denotes significance level of <0.05

5.2.2.6 Table 14. Frontal lobe syndromes - cerebral lesion site as determined by functional brain scanning.

Supratentorial

cortical lesions (n=23;25% ; 95 % CI: 16.2;33.8%)

subcortical lesions (n=32;35% ; 95% CI: 27.1;46.9%)

Multiple lesions (n=21;23% ; 95% CI: 14.4;31.6%)

Lesions unclassifiable (n=4;4%)

Of note were subtentorial lesions in the brainstem and cerebellum included under subcortical lesions

Isolated subtentorial

brainstem (n=10;11%)

cerebellum (n=2;2%)

The frequency for the cortical and subcortical groups was significantly different (Binomial Test).

5.2.2.7 Table 15. Frontal lobe syndromes in young and old patients

Young	(15-49 years)	41/246 (16.7%)
Old	(50-100 years)	51/754 (6.7%)
Chi square p value		<0.0001

6.0 DISCUSSION

6.1 Stroke Data Bank Issues

6.2 Cognitive Issues

6.1 Stroke Data Bank Issues

6.1.1 Symptoms

Both the complexity of the brain as well as the heterogeneous causes of stroke intuitively suggest an array of presentations of stroke syndromes. The publicity campaign by the National Stroke Association lists six major symptoms of stroke [1];

sudden onset of;

weakness

numbness

vision impairment

speech impairment

imbalance

headache

Although these accounted for the majority of presentations in the DSDB (n=1388 symptoms, total symptoms 1963; 70.7%;), a much larger number of prospectively defined and evaluated symptom categories (n=23) within the DSDB still did not account for all presentations. In 150 (15%) patients a further undefined symptom was present and in 15 (10% or 0.15% overall). In these patients the “undefined” symptom was the sole manifestation of stroke. Without resorting to an unwieldy and impractical list of stroke presentations, it behoves us to remember that the presentation of stroke may be unusual. As acute stroke treatment is already a reality, with time windows measured in hours, an imprecise diagnosis may result in critical time delays and failure of

effective therapy. A likely explanation for these 'other' symptoms is stroke presenting with a frontal lobe type presentation that defies simple description. This hypothesis is supported by the frequency of frontal systems syndrome within the data bank of 92 patients (9.2%) as will be seen under discussion of cognitive impairment.

6.1.2 Risk factors

Risk factors in stroke may be divided into modifiable and unmodifiable ones. The latter include age, race, sex and hereditary factors and will not be discussed further. The modifiable risk factors include those considered definite by the literature and those that are probable but awaiting confirmation. Since the original design of the DSDB protocol in 1992 several of the latter factors such as; recent infection [2-7], sleep apnoea [8-18], homocystinaemia [16-19] and lipoprotein (a) [20-24] have achieved independent risk factor status. The contribution of the DSDB in the risk factor analysis is two fold. In confirming the importance of recent infection in stroke in a population in whom Tuberculosis, HIV, Neurocysticercosis and Bilharzia are endemic. Secondly the analysis of recent significant and personal stress revealed that this was an important factor in this population.

6.1.3 Signs

Elementary neurological signs that are traditionally and classically associated with stroke are one sided weakness, numbness and vision impairment singly or in various combinations. When present these immediately suggest a cerebrovascular accident and obviate further diagnostic difficulty. Overall, 574 (57.4%) patients had some form of weakness, 484 (48.4%) had some form of sensory impairment and 80 (8.%) a visual deficit. No more than half the time can one rely on elementary neurological deficits to assist diagnostically. Similar findings were reported in the NINCDS Stroke Data Bank Study [25].

6.1.4 The importance of determining stroke mechanism

One of the most important functions of stroke data banks is to determine aetiopathogenesis as this determines treatment. Earlier studies relied heavily on risk factors and clinical syndromes to determine stroke subtypes. With the widespread use of computerised tomography scanning in the 1970's and 1980's the differentiation of haemorrhagic stroke and bland infarction became accurate in vivo [26-31]. Current neurodiagnostics allow a more precise diagnosis of stroke subtype and in many instances a mechanism is deduced. The study by Sacco et al [32], using a more rigorous diagnostic scheme in the NINDS Stroke Data Bank study, revealed a relatively high frequency of cases falling into the diagnostic category of Infarct of Unknown Cause (IUC), with a relatively lesser number falling into the traditional subtypes.

In addition to ascertainment of degree of neurological deficit of which cognitive impairment is a part, it is of vital importance to determine stroke mechanism. With the current popularity and emphasis on clinical trials for secondary prevention of stroke, the more precisely a mechanism of stroke can be determined, the more likely an accurate outcome of the drug study. The index patients described in the results section attest to this.

A plausible explanation for the many successful animal as opposed to human drug and treatment failures in stroke thus far, have suffered from one or both of these aspects. These are either imprecise neurological deficit appraisal or lumping widely differing stroke mechanisms.

A further dimension that deserves mention is the degree of likelihood of the determined mechanism. A hierarchical system was used in the DSDB whereby diagnostic causes such as cardioembolic, vasculitis or prothrombotic states were graded into high risk or low risk causes or definite, probable and possible causes. Such a system as well as carefully itemising those patients in

whom comorbidity is present (eg atrial fibrillation and significant carotid stenosis) allows for more precise and in some retrospective reclassification.

6.1.5 Subtypes of ischaemic stroke. Clinical (OCSP) versus aetiological classification (TOAST)

The OCSP scale allows a rapid bedside identification of stroke subtypes - hence its appeal. As can be seen from Table 6 there was a significant difference in the overall distribution between the clinically determined type of stroke and the stroke type after investigations. No study at the time of writing has reported this save for an abstract [33]. As an example, lacunar syndromes are traditionally correlated with small vessel cerebrovascular disease. The conclusions of these authors were similar to the DSDB in that they showed only half of their clinically diagnosed lacunar syndromes had small vessel disease. The DSDB results showed that only 28% of patients diagnosed as lacunar syndrome had small vessel disease with a large proportion (50%) being due to large vessel disease for example.

These results suggest that a complete diagnostic work up is indicated in all patients with ischaemic stroke no matter the clinical presentation.

6.1.6 Black stroke issues

Given the above considerations and reservations, the causes of stroke in black people in Southern Africa deserves comment. HIV associated vasculopathy emerged as the most common cause of stroke in blacks after unknown causes and small vessel disease. HIV associated vasculopathy was a more common cause of stroke than cardioembolism and large vessel disease. There is to date a paucity of research into causes of black strokes in Southern Africa. In comparison to other stroke studies of black people in Southern Africa [34-37], the causes differed in several respects. Firstly, the fact that the DSDB took place during an HIV epidemic which is still increasing, is a likely explanation

for the high rate of HIV associated strokes. Secondly the high incidence of cerebral haemorrhage (25 -32%) reported in the 3 [34-36] other studies in black South Africans was not seen in the DSDB (11%) bearing in mind that all studies were hospital based referrals and not truly population based. All studies had a similar break down of aetiological entities to the TOAST classification. The largest group comprised of “other” (39%) causes most notably vasculitides, prothrombotic states, infection and numerous less frequent entities in the miscellaneous group. The improved neurodiagnostics that were employed in the DSDB allowed more precise identification of stroke mechanism and the shift from one category to another.

As stroke is currently the second highest cause of death due to chronic diseases of lifestyle in South Africa [38], outstripped only by coronary artery disease, intervention at primary, secondary and tertiary levels are urgent.

6.1.7 Vasculitis

Human Immunodeficiency Virus (HIV) and Takayasu’s arteritis were the two most common entities. The diagnosis was made as per definition; angiographic or biopsy evidence with positive serology and the absence of other possible competing causes of stroke. The diagnosis was presumptive if no angiogram was performed or the angiogram was normal and no other possible explanation of the stroke.

Earlier pathologic studies of infarction in HIV positive patients were ascribed to marantic endocarditis, disseminated intravascular coagulation or hypoxia [1]. More recently it has been appreciated that the causes of infarction in these patients are protean and may be due to other infections (cytomegalo virus, varicella zoster virus, tuberculosis, cryptococcosis, syphilis and toxoplasmosis). Other possible causes include those of associated drug abuse (often cocaine but depending on the population) which may be associated with infective endocarditis, vasoconstriction, platelet aggregations, emboli of

foreign material [2,3]. Even more recently there have been reports alluding to the likelihood of a primary HIV vasculitis [4,5]. Autopsy reports cited the frequency of stroke in AIDS patients at a relatively high 19-34% [6,7] and clinical frequency reports vary from 0.5 to 7% [8,9]. The emergence of a HIV associated vasculopathy or vasculitis is therefore a likely entity.

The endemic proportions of HIV positivity in the black population is reflected in this study by a 13% prevalence rate. No HIV patient in this series abused any drugs but concomitant seropositivity with Toxoplasmosis (2) and syphilis (2), Cryptococcus (1) and Tuberculosis (1) was documented. In view of the ethical aspects of performing brain biopsies in HIV positive patients and the competing causes of a vasculitis in half of the HIV patients in the DSDB the diagnosis must remain generic ie HIV associated vasculopathy/vasculitis as true causality cannot be ascertained.

6.1.8 Dissection

In other stroke data banks this has been purported to be the most common cause of stroke in the young. In the Lausanne Stroke Data Bank dissection of the cerviccephalic vessels and mitral valve prolapse together accounted for 51% of causes in the young stroke patients (≤ 30 years) [1]. A wide variation exists, with the study by Carolei et al [2] of 333 patients with cerebral ischaemia only quoting one patient with dissection as the mooted cause of stroke. A more recent hospital based study by Adams et al quoted a figure of 16.8% in 119 young stroke patients [3]. In a unique study of young stroke patients, all of whom had catheter angiography, dissection accounted for 10% of the causes of stroke [4]. Indeed, it was a relatively common cause of stroke in the young in the DSDB, accounting for 5.3% (n=13 of 245) in the young stroke population and 2% (n=20 of 1000) of all strokes. The literature on arterial dissection typically cites numerous causes [5-17] with about 15% being due to fibromuscular dysplasia and spontaneous in approximately 10% [18-25]. In the DSDB both common and uncommon causes were identified.

Spontaneous dissection in the carotid (n=7) and vertebral arteries (n=4), blunt neck trauma (n=5) and fibromuscular dysplasia (n=2) accounted for the more common causes with one due to chiropractic manipulation and one presenting with a subarachnoid bleed secondary to intracranial dissection of the basilar artery. These figures are similar to those reported in the literature which consists only of case series. Reliable noninvasive detection and monitoring of dissection is well reported in the literature [26-33]. In the DSDB, reliable detection was possible with duplex Doppler and/or magnetic resonance angiography in all patients, with catheter angiography being required in 12.

6.1.9 Prothrombotic states

The causal association of venous and arterial stroke with abnormalities of the coagulation cascade, fibrinolysis and their various control mechanisms is well described [1-7]. Stroke in itself may cause changes in the acute and subacute phase so that measurement during this period is not necessarily indicative of an association [8]. The disorders that are most important include;

Protein C deficiency - congenital and acquired

Protein S deficiency - congenital and acquired

Antithrombin III deficiency - congenital and acquired

Plasminogen deficiency - congenital

Lupus anticoagulant

Anticardiolipin antibody

All of these were identified within the DSDB with 27/58 (47%) patients having a measurable defect. These were mostly due to anticardiolipin antibodies (10/27; 37%). The remaining 31 patients had a described association with a prothrombotic medical condition such as malignancy, ulcerative colitis, polycythaemia, pregnancy, oral contraceptives, connective tissue disease and hepatic failure. Recent work has demonstrated that all these so called prothrombotic states may produce an acquired deficiency of

protein S, protein C and antithrombin III [9]. Anaemia with a raised ESR, identified as the likely mechanism in 9 patients has been described as a probable cause of stroke with the exact mechanism uncertain [10-12]. In at least half the cases a definite explanation of the cause of stroke was possible and in the other half only a possible, but likely, causative association could be proposed. In 13/58 (22%) of the prothrombotic cases there was comorbidity with competing causes such as atrial fibrillation, patent foramen ovale, hypertension, smoking and diabetes.

6.1.10 Young stroke population results

Overview of previous studies of the young stroke population and reasons for the methodology.

The main areas of focus were aetiology, racial differences, stroke severity and prognostication as these are most pertinent in the young population, in this multiethnic young stroke population.

The young stroke patient poses a particularly important diagnostic challenge in view of the varied documented aetiopathogenesis and likelihood of recurrent events. Notwithstanding the clinical urgency of the problem, the available data are discordant with respect to aetiology, therapeutic, rehabilitative and prognostic considerations. There is considerable heterogeneity in the multitude of causes as reported by different investigators as well as variation between races, regions and countries [1-23]. Differing diagnostic protocols, diagnostic armamentarium and variability in the criteria for the probable causes of stroke applied by different investigators make the data currently available non uniform. The predominance of retrospective series and paucity of prospective studies [1,3, 24-26] with the unavoidable fact that information has been collected, often, over a decade or more, with inherent nonuniform testing is a further problem associated with most studies reported at the time of writing. Few studies have employed clinimetric and pathogenetic scales to

allow uniformity of clinical reporting. Many studies included in their series cerebral ischaemia or transient ischaemic events [3,12,16,17,19,21,27,26,29] with (other than those employing SPECT or PET acutely) no hard copy neuroimaging signature of stroke. This is problematic in view of the number of conditions that may masquerade as stroke or ischaemia in young people (tumour, epilepsy, migraine, infective and inflammatory cerebral lesions).

Many studies have concentrated on determining incidence in a specific population such as that in Florence Italy with a 9.0 per 100 000 for males and 8.7 per 100 000 for females [30]. This may be compared with the study from Saudi Arabia where over a 10 year period 25% of all strokes occurred in the age group 15-45 with an approximately equal frequency of cerebral infarction and intracranial haemorrhage in this population [31]. Such studies are important as different parts of the world have markedly different incidences of young strokes, subtypes and different causes. Several studies from the United States such as one from San Francisco where the most common cause of stroke in people under the age of 35 was drug abuse, have highlighted the importance of drug abuse as a cause of young stroke [32]. A Finnish study reported alcohol intoxication as the cause of stroke in 40% [33], a study from the Oxford community reported a traumatic aetiology in 22% [34], a Parisian study considered the oral contraceptive pill causative in 43% [35] of strokes in young women and an Indian study found meningovascular syphilis to be the cause in 15% and cerebral venous thrombosis to be the cause in 20% of their young strokes [36,37].

Finally, a disturbing approximate one third of strokes remained unexplained in the series published to date [4,6,7,8,13,16].

To help address some of these issues, the findings of the Durban Stroke Data Bank (DSDB) is presented as one of the largest prospectively defined young stroke population, with first ever stroke, all proven by neuroimaging using contemporary diagnostic methods available in large centres in the years 1992-

1997. In view of the short time frame of recruitment, a high rate of modern neuroinvestigative modalities was a possibility.

Finally young stroke series reported to date have been largely retrospective, included cerebral ischaemia (transient ischaemic attacks) and have lacked clinical standardisation made possible by clinimetric scales. The present study adds to the experience noted by others that causes of stroke in the young are many. However, being the first young stroke study to be reported out of South Africa, obvious differences are apparent.

A major difference was noted in the frequency of the aetiopathogenetic groups. Four (large vessel, small vessel, other and unknown) of the 5 different aetiological categories differed significantly when compared to the older stroke population. Only cardiogenic causes showed no significant difference between the younger and older stroke patients. Small and large vessel disease reflect atherosclerotic disease in its various forms and were more common in the older patients as might be expected. The 'other' group was the largest group within the young stroke population and more young patients than older ones had strokes of unknown causes.

The TOAST 'other' group which accounted for about half of all the aetiologies emphasises the varied causes and consequently necessitated a comprehensive work up. Overall, the presence of prothrombotic factors, vasculitides of infective origin and dissection were the most common definite or presumed causes in young patients. Non atherosclerotic vasculopathies accounted for 76/245 (31%) of definite and probable causes in the young stroke population. This underscores the importance of angiography, whether catheter, spiral CT or MR angiography with the noninvasive methods often sufficing.

Patent foramen ovale accounted for 7/29 (24%) of the young potential cardiac causes stressing the importance of testing for this condition in young stroke

patients. All represent treatable or potentially treatable entities or avoidable by public health education with obvious personal health and socioeconomic benefits.

Ethnic differences are important to note for many reasons, probably the most notable being the added insight into pathophysiology. Black - white differences are different to ones noted in North American studies [38,39] of stroke in general and even other Southern African studies done more than 10 years previously [40-42]. No doubt investigative advances and the increasing burden of infective causes such as HIV, TB and Syphilis all of which are on the increase are part of the explanation. As the database is ongoing, with increasing numbers of black patients entering the study a clearer picture may emerge. Sociopolitical constraints were the reasons for the relatively low number of black patients enrolled early within a tertiary care facility and having as part of their stroke investigation a brain scan. This is despite the fact that black people account for over 80% of the South African population.

The majority of stroke patients had favourable CNS, Barthel and Rankin scores. Yet a large proportion (54%) had cognitive impairment. Interpretations may be that the majority of patients with stroke, depending on the population sampled and selection bias may have a relatively mild stroke with good recovery and opportunity for effective secondary prevention provided a correct aetiological diagnosis is made. Also the fact that more than half the patients have a neurocognitive deficit implies that this is an important manifestation of neurological deficit that deserves better quantification than current scales allow. This has obvious importance for measuring treatment responses to new drugs and interventions.

The cerebral perfusion index (CPI) proposed by Alexandrov et al [43] appears to be a reliable and valid test for prognosticating in the acute phase of stroke as demonstrated in this relatively small sample of 32 young patients. Alexandrov correlated the CPI with the Canadian Neurological Scale. In the

DSDB it was correlated with the Rankin scale which may be more accurate in terms of overall physical and social disability (handicap).

The young stroke cohort analysis expands the database of stroke in young people in that causes display inter and intraregional variation, may often be relatively mild but with cognitive deficits, the true clinical importance and extent of which remains uncertain. Intensive investigation influences the mode of therapy.

6.1.11 Cardioembolic stroke

The finding of a potential cardiac source of embolism is insufficient grounds for implicating the heart for certain. Rather, stratification into high (cardiac thrombus, valvular vegetations, prosthetic heart valve), medium (atrial fibrillation, cardiomyopathy, aortic or mitral valve stenosis, left ventricular aneurysm) and low (mitral valve prolapse, mitral annulus calcification, septal aneurysm, patent foramen ovale) risk sources is required and the documentation of the presence or absence of concomitant stroke risk factors is necessary. In the DSDB, cardioembolism was diagnosed if a high or medium risk cardiac source was present and no other possible stroke cause was concurrently present. This included the presence of large or small vessel disease diagnosed by sonographic, angiographic or brain scan imaging modalities. Despite the identification of newer cardioembolic risk entities such as patent foramen ovale, atrial septal aneurysms, mitral valve strands and atrial smoke, the true frequency of cardioembolic stroke remains unknown. Stroke registries have reported an incidence of 15-20% [1]. Three prospective stroke registries; the Giessen, Klosterneuburg and Berlin studies, looked specifically at cardioembolism and revealed that most patients can be identified by history, clinical examination, conventional ECG and appropriate use of echocardiography. These studies differed greatly in the use of echocardiography and transoesophageal echocardiography (TEE). Whereas only 24% of the 1048 patients in the Klosterneuberg stroke data bank had an

echocardiography, over 90% of the 516 patients in the Berlin (n=266) and Giessen (n=250) registries performed echocardiography which were mainly TEE. [2]. A potential cardiac source was found in 62% of Giessen SDB, but with stratification of cardiac sources of stroke into high risk (8.4%), medium risk (23.3%) and low risk (30.4%) a more realistic picture emerges. In addition, 71.4% of patients with high risk source and 82.8% of patients with a medium risk source already had some evidence of a cardiac disorder by medical history, clinical examination or routine electrocardiography and 57.9% of all low risk sources were first identified by echocardiography. About 25-30 % of patients in stroke registries may have competing causes of stroke making it difficult to assign a definite cause [3]. In the Giessen SDB 62% of patients had a detectable cardiac source of embolism and only 25.9% of the Klosterneuburg SDB patients were ascribed a final diagnosis of cardioembolism. However when applying the criteria outlined the final diagnosis of cardioembolism was remarkably similar ie 16.8% in the Giessen SDB and 16.2% in the Klosterneuburg SDB [1].

In summary, the application of routine echocardiography, both TTE and TEE identifies an increasing number of minor cardioembolic risk entities and the likelihood of not identifying significant cardioembolic risk factors is low if echocardiography is performed appropriately according to a tailor made protocol.

6.1.12 Patent foramen ovale (PFO)

The presence of a right to left shunt in the setting of a prothrombotic state may account for a number of stroke patients where no cause is found despite extensive diagnostic work up. Studies performed to date consistently report a higher prevalence of PFO in young stroke patients and stroke of unknown origin [1-3]. PFO also occurs in 10-30% of normal controls [1,2,4-7]. Both transcranial Doppler with agitated saline injected in the antecubital vein and transoesophageal echocardiography are approximately equally accurate in the

detection of PFO [8,9]. However TCD with bubble contrast may be more accurate in the detection of small PFO's and in the detection of pulmonary arteriovenous shunts [9]. According to the definition proposed by Meister et al for paradoxical embolism to be causative a venous thrombosis needs to coexist at the time of stroke [10]. It has been established that a deep venous thrombosis is rarely found in patients with stroke ascribed to a patent foramen ovale [7]. Because the clinical significance of PFO in stroke causation remains to be demonstrated, a search for other significant associated factors such as PFO size, atrial septal aneurysm or more proximal venous thrombosis may answer some of these questions [9].

In the DSDB two groups of stroke patients were systematically tested for the presence of a right to left shunt. Young patients who presented with a stroke of unknown cause or patients where the deficit occurred during a valsalva manoeuvre were specifically investigated with transcranial bubble contrast to determine the presence of a right to left shunt. Seven patients were identified, all of them young and all with some other potential risk factor for developing stroke in the setting of a patent foramen ovale (atrial septal aneurysm, congenital heart disease, valsalva manoeuvre, anticardiolipin antibody, recent infection). Clearly some other factor needs to be present in addition to the PFO to explain some strokes. Formation of clot within an atrial septal aneurysm, valsalva manoeuvres and prothrombotic states are some possibilities. The illustrative patient with PFO from the DSDB who suffered a stroke during a bout of severe nausea and vomiting implies that for PFO to cause stroke requires an interplay of factors. The diagnosis and type of PFO [11,12] is important in helping to understand the pathophysiology and in guiding treatment which may consist of antiaggregant treatment in some, or more usually anti coagulation. More recently transcatheter closure has become an option [12].

6.1.13 Dolichoectasia

Elongation and tortuosity (dolichoectasia) of the basal intracranial vessels is

known to cause cerebral ischaemia and infarction, compressive cranial neuropathies, hydrocephalus and a variety of brainstem symptoms [1,2]. Megadolichoectatic basilar artery syndromes have been the most extensively studied by autopsy, angiography, CT and MRI. No distinct clinical syndrome is recognised, probably leading to under diagnosis [1]. The reported incidence is 0.06 - 5.8% but varying criteria have been applied [3,4]. The radiological dolichoectasia criteria used were; ectasia >4.5 mm diameter and the basilar artery lying lateral to the margin of the clivus in the cerebellopontine angle or above the level of the suprasellar cistern [5,6]. Newer imaging procedures can facilitate non invasive diagnosis. The entity has not been subject to prospective analysis [1]. The prospective Durban Stroke Data Bank specifically included this as a predefined entity and the results to date are presented.

This study represents one of the largest series and one of few prospectively evaluated consecutive case series within a large data bank series of dolichoectasia of the cerebral arteries. This has allowed delineation of the frequencies of different stroke syndromes associated with this disorder as well as follow up ie posterior circulation stroke and or isolated symptoms such as facial paresis (“Bell’s palsy”), facial neuralgia and hemifacial spasm. The diagnosis can easily be made in most cases within the first tier (CT brain or MRI brain scanning) of the investigative protocol without resorting to invasive studies. This is an important clinical point as the majority of these patients present with posterior circulation ischaemia or stroke, a syndrome in which invasive angiography is associated with a significant morbidity and mortality.

In this series all patients were identified by CT or MRI brain scanning. MRA was done in 6, catheter angiography in 3 and spiral CT in 1. Angiography in these 10 patients was used to better delineate the ectatic arteries and confirm the diagnosis, the latter often necessitated by the presence of comorbidity. Transcranial Doppler sonography has a specific wave form associated with this syndrome and in agreement with Rautenberg et al [1], in this study it was found to be a useful adjunctive test in cases where there may be some doubt as

to the presence of dolichoectasia.

In agreement with the other larger series on this topic, the three main modes of clinical presentation were ischaemia, cranial nerve compression and mass effect. The most common presentation was ischaemic (85%). In the ischaemic group the vast majority presented with posterior circulation strokes (63%). Patients with posterior circulation ischaemia or infarction should be evaluated for the presence of dolichoectasia, as this can be done noninvasively and secondary preventative treatment is an option with Class III evidence of benefit from Warfarin or Aspirin (see appendix). As most patients in this series were relatively mildly disabled (CNS mean score of 10.7), the opportunity to avoid further strokes by identification of the correct stroke mechanism becomes all the more important. This does not detract from the rare possibility of dissection of the basilar with poor outcome as was seen in one patient.

With respect to the postulated biological mechanism as proposed by Hegedues, Sahlbeck et al and Schwartz et al [1,7,8], the increase in vessel diameter results in reduced blood flow velocity and there may be a plug of inversion or even zero flow near the vessel wall (transcranial Doppler evidence) [1]. Ring shaped layering of thrombus formation occurs with a small patent lumen. Thrombus may occlude the origin of small penetrating vessels of 200-800 micrometers in diameter and give rise to thrombotic occlusion and lacunar infarction in the setting of large vessel (dolichoectatic) rather than small vessel disease. Embolism to more distal vascular territories is also thought to occur from the layered thrombus in the dilated arteries. Both represent different causes of cerebral infarction due to large artery disease mostly in the context of long standing hypertension, which is more typically associated with small vessel disease.

In conclusion, dolichoectasia as a stroke mechanism can be diagnosed noninvasively with established brain parenchymal scanning and with greater

accuracy with newer imaging modalities such as MRA and TCD. It should be suspected in patients presenting with posterior circulation ischaemia or stroke syndrome, particularly if hypertensive and associated with one or more of the symptoms listed. The diagnosis is important as it usually necessitates additional specific therapy such as anti coagulation with Warfarin and in some antiaggregant therapy with Aspirin, Dipyridamole, Ticlopidine or Clopidogrel.

6.1.14 Infection related stroke

The temporal association of infection with stroke has recently been found to be an independent risk factor when occurring within the preceding month [1]. This is particularly so for bacterial infections. Both chronic infections (Chlamydia pneumonia, Helicobacter pylori, Cytomegalo virus, chronic bronchitic patients) and acute infections have been shown to be a risk factor. Mechanisms whereby infection may cause stroke include [2-6];

- dehydration and hyperviscosity
- leucocyte and platelet aggregation
- cytokines and TNF alpha
- coagulation factors such as fibrinogen, protein S and C [7,8].

Black patients for example, who had a stroke of unknown cause and had recent infection - also showed large artery occlusions. This supports the theory that haemostatic and inflammatory pathways mutually interact with each other. The scope of the DSDB did not encompass the measurement of acute phase reactants and cytokines. The frequency of infection as a presumptive cause of stroke in the DSDB merits further research especially as it pertains to black patients in whom TB and HIV are endemic in Southern Africa.

6.1.15 Impairment, disability and handicap and their measurements.

Notwithstanding the popularity of the Barthel Index, experience with the Barthel Index in the DSDB was disappointing as cultural factors detracted from its applicability. The Barthel Index was not a good scale for measurement in the majority of black patients. Because of poor socioeconomic disposition, items such as stairs, wheelchair skills, combing hair and bathing were not as relevant in other populations. As a result it could only be reported as normal and abnormal and a score was inappropriate. To the contrary, the Rankin Scale was found very user friendly and easy to administer to all population groups. Its relative simplicity and application by non medical personnel are major advantages. The large number of near normal, for example scoring 1 (n=443 or 44.3%) which means symptoms but no signs, argue for a more accurate measurement however. The Frenchay Activities Index is the best tool to assess return to “normal living” - the only scale that does this. This was not used in the DSDB but should be a consideration for future data banks.

As can be seen from Table 8, there was moderate agreement (Kappa = 0.543) between the three categories of the CNS scale measuring neurological deficit and the Rankin scale which measures disability and handicap. This issue has not been addressed in large stroke data banks. The Kappa value gives support to the reliability and validity of these two relatively simple stroke measures.

6.1.16 Complications after stroke

The risks for patients with stroke fall into two major complication categories.

1. Those related to the direct consequences of the brain damage and which occur within the first few days
2. Those occurring over the following weeks are due to potentially

preventable problems such as infection, venous thromboembolism and cardiac disease.

Because of this it has been suggested that the effectiveness of acute stroke units in reducing morbidity and mortality may be due to improvements in the prevention, identification and treatment of secondary complications. The present study is prospective whereas the largest study to date on multiple post stroke complications by Davenport [1] was retrospective. There were only five other studies addressing this issue [2-6].

The complications and their definitions as described by Davenport are:

1. Falls - any documented fall regardless of cause
2. Pressure sores - skin break or necrosis from prolonged inactivity
3. Urinary tract infection - Clinical and laboratory confirmation
4. Chest infection - clinical and radiographic characteristics
5. Depression - by direct questioning or volunteered and deemed significant enough to require therapy
6. Confusion - altered cognition lasting more than 48 hours, no easily recognised higher function disorder and interfering with nursing care and the rehabilitative process.
7. Painful shoulder - sufficiently severe to require medication
8. Seizures - Focal or generalised seizures occurring after the onset of stroke
9. Pyrexial illness - temperature >37.5 for more than 48 hours without other identifiable cause
10. DVT - clinical diagnosis or positive imaging
11. Pulmonary embolism - clinical or positive imaging
12. Miscellaneous - any medical or surgical complication attributable to the stroke eg GIT haemorrhage, musculoskeletal pain, cardiac complications etc

In the DSDB the following complications were prospectively sought and defined within the protocol: behavioural abnormalities, seizures, depression,

recurrent stroke, pneumonia, progressing stroke, post carotid endarterectomy stroke, brachialgia and death from any cause. In addition patients were specifically questioned and if appropriate tested for symptoms of sleep apnoea.

In the DSDB falls and urinary tract infections were not recorded as complications as their reliable detection was considered problematical. Pyrexia was not recorded as a complication in view of the wide variety of possible causes other than stroke related infection. Cardiac abnormalities also were not recorded as routine ECG monitoring was not performed. Pressure sores, DVT's and pulmonary embolism were not encountered. The reliability of these statistics may be questioned as such complications may present to other medical specialities.

The frequency of seizures (DSDB 5.3%, Davenport et al 4%) depression (DSDB 4.4%, Davenport et al 5%) were similar. Areas in which the DSDB complication list differed to Davenport's study included the incidence of pneumonia and brachialgia. An item not documented by any other multiple post stroke complication study was sleep apnoea syndrome in association with stroke. Four patients were identified in the DSDB with clinical and polysomnographic verification. In two patients this antedated the stroke and in two appeared to occur only after the stroke. The study by Dyken et al [7] suggested an increased incidence of obstructive sleep apnoea in stroke patients and the work by Palomake et al and Mohensin et al [8-10] supports snoring and sleep apnoea as an independent risk factor for sleep related brain infarction. Proposed potential mechanisms include cardiac dysrhythmias, haemodynamic disturbances, increased levels of catecholamines, disturbances of cerebral blood flow and episodes of hypoxaemia [11]. Few studies have used polysomnography to look at the association between obstructive sleep apnoea and stroke [10,12-14]. The small numbers identified within the DSDB do not allow any conclusions to be drawn other than that the association may exist and that modern portable polysomnographic devices (eg SLEEPIT) facilitate its measurement.

6.2 Discussion: Cognitive Issues. Contributions of the DSDB to cognitive neurology

6.2.1. General - high frequency of cognitive dysfunction during early evaluation and wide spectrum of deficits

6.2.2. Subcortical and subtentorial stroke and cognitive impairment - frontal system syndrome impairment.

6.2.1. General - early evaluation and wide spectrum of deficits

As recently as 1990, in an editorial in the Journal "Stroke", Finlayson remarked that a review of the recent stroke rehabilitation literature would lead one to think that stroke was a disorder of the tongue, arm and leg. A strong warning was sounded regarding the relative neglect of cognitive factors in the management and rehabilitation of stroke patients [1]. A literature review of the previous studies on cognition and stroke revealed that all have one or more of the following shortcomings;

1. The period of evaluation was typically months to years after the stroke
2. Only a limited or selected range cognitive deficits were measured
3. Only quantitative measurements were used and not complemented by qualitative assessment
4. Numbers were generally small [2-15].

These studies were limited in that they focussed on areas such as language, memory, orientation, attention and visuospatial abnormalities, cognitive domains that are relatively easily tested and for which quantitative normative data are available. The wider spectrum of cognitive impairment and specific stroke syndromes were ignored. The frequency of the cognitive impairment in these studies ranged from 21% to 56% [2-15]. The study most comparable to the DSDB was that of Wade et al [12] which had a similar number of patients (n=976), used predominantly bedside mental tests and evaluated 535 patients during the first week. This was also the only population based study. Although only selected cognitive aspects were tested (non verbal reasoning, copying, level of consciousness, orientation with the Hodkinson Mental Scale), interestingly the frequency of cognitive impairment (56%) was similar to the 61% determined in the DSDB. The NINCDS stroke data bank provided pre defined higher functions but specific bedside testing was not given [16]. In addition the DSDB makes provision for the evaluation of a more comprehensive list of cognitive disturbances. Finally, the DSDB has

undertaken a comparison of the higher cognitive function screening tests used in the DSDB in the most mildly affected patients with standard neuropsychological testing, currently the gold standard.

Analysis of the subgroups as a function of age (younger versus older stroke patients) revealed that overall there was no significant difference in the frequency of HCFD. However younger patients had significantly higher frequency of frontal systems syndromes and amnesias. No information was found in the literature on these cognitive aspects in the young stroke population.

Calculations with univariate and multivariate regression analyses concluded that 6 of the prospectively defined risk factors were predictive of developing a HCFD in the stroke setting; age, male gender, black race, overweight, recent infection, cervical manipulation and cervical trauma. The latter two were not considered for the model because of small numbers. This is novel information for the local population and assists with identifying high risk subgroups who would benefit from diagnostic and therapeutic intervention.

6.2.2. Subcortical and subtentorial stroke and cognitive impairment - frontal system syndrome impairment. Current state of knowledge and brief overview

The prefrontal granular cortex enlarges dramatically in phylogenetic evolution [1]. It has no obvious role in sensory and motor function and has rather been implicated in complex mental processes such as;

- judgement
- insight
- foresight
- curiosity
- abstraction
- creativity

Executive function is the usual term applied by investigators to this conundrum of human qualities but the neural basis remains enigmatic. In other parts of the brain, it has been demonstrated that metabolic activity is task dependent. In the frontal lobes one may see activation without regard to the nature of the task [2]. Preferential prefrontal increased metabolic activity is however seen with performance of attentional tasks and reasoning tests but not during their subsequent execution [3-5].

Prefrontal granular cortex has extensive cortico-cortical connections to sensory and paralimbic association cortex. These connections enable it to monitor information flow at all levels of processing and may account for the task independent pattern of metabolic activation [6,7]

As succinctly described by Mesulam, in this manner the frontal lobes are in a position to activate a given network, inhibit another, influence network combinations and perhaps allow internal readouts in a way that disengages the information processing from the response stage. The highest level of internal representation (of networks rather than of sensory data or motor programs) would provide an arena for the various networks to play out different scenarios, the most successful of which would dominate the landscape of neural activity [2].

The computational basis of the executive function would then be twofold

- a high density of connections with other networks
- a relative isolation from direct participation in elementary perception and movement.

Even sizable prefrontal lesions could thus cause little disruption of routine behaviour except under circumstances that place a premium on disengaging customary stimulus response linkages and on executing complex internetwork coordinations.

The major neural connections for the head of the caudate nucleus and the dorsomedial thalamic nucleus come from the prefrontal granular cortex. In accordance with the network theory the frontal lobe syndrome can be seen in patients with lesions not only of in the frontal cortex but also in the caudate nucleus and in the dorsomedial nucleus [6,7]. The Frontal lobe syndrome is also seen in disease processes affecting the brain more diffusely such as multifocal white matter disease and metabolic encephalopathies. The emergence of the frontal lobe syndrome is hardly surprising in view of the physiological role of the frontal lobe in integrating networks for combined action. Multifocal partial lesions - none individually severe enough to disrupt specific cognitive domains (language, memory) collectively undermine the internetwork coordination. Clinical experience suggests that subcortical lesions and toxic metabolic encephalopathies are more frequently encountered causes of the frontal lobe syndrome than lesions which involve the prefrontal cortex directly [2].

The frontal lobes in disease states. The frontal subcortical circuits

These are one of the principal cerebral organisational networks and pivotal to brain behaviour relationship. Frontal subcortical circuits are regarded as effector mechanisms allowing an organism to act in response to environmental challenges. Five frontal subcortical circuits are identified;

1. Motor circuit from the supplementary motor cortex - motor function
2. Oculomotor circuit from the frontal eye fields - eye movement
3. Dorsolateral prefrontal - executive cognitive functions
4. Lateral orbital - aspects of personality
5. Anterior cingulate - motivation

Common to all is the following circuitry:

Frontal cortex - striatum - globus pallidus - substantia nigra - thalamus - frontal cortex [8].

The dorsolateral prefrontal subcortical circuit allows the organisation of information to facilitate a response. The anterior cingulate subcortical system is required for motivated behaviour and the orbitofrontal circuits allows the integration of limbic and emotional information into behavioural responses.

Impaired executive functions, apathy and impulsivity are hallmarks of frontal subcortical circuit dysfunction. Obsessive compulsive disorders occur when the orbitofrontal subcortical structures are affected. The circuits are composed of neurotransmitter systems, receptors subtypes and second messengers. Such systems lend themselves to pharmacological manipulation. As the chemoarchitecture of the circuits becomes known, so will opportunities to construct “a pharmacoanatomy that will guide circuit specific intervention” [8].

6.2.3 DSDB contributions to frontal systems syndromes

Three contributions were noteworthy;

1. Frontal lobe syndromes are frequent in subcortical stroke and not significantly different in frequency from cortical frontal stroke.
2. Isolated brain stem stroke and cognitive impairment (mainly frontal) with corroborating data from neuropsychological testing and SPECT brain scanning.
3. Isolated cerebellar stroke and cognitive findings (mainly frontal) with corroborating data from neuropsychological testing and SPECT brain scanning.

6.2.4 Frontal lobe syndromes in stroke - relation to lesion site.

Detection of frontal lobe damage is notoriously difficult especially if only standard neurological examination is used including cursory higher function evaluation. Standardised, quantifiable schedules were all developed to assess dementia in elderly subjects. Such tests are particularly insensitive to circumscribed cognitive disorders that occur with stroke. Frontal lobe syndrome patients are commonly scored as normal by these tests. They may escape detection even with the use of standardised and validated behavioural psychometric evaluation such as the Wechsler Adult Intelligence Scale. Changes may often only be discerned with reference to the person's previous behaviour, personality and social interaction.

As Mesulam had proposed; "multifocal partial lesions - none individually severe enough to disrupt specific cognitive domains (language, memory) collectively undermine the internetwork coordination. Clinical experience suggests that subcortical lesions and toxic metabolic encephalopathies are more frequently encountered causes of the frontal lobe syndrome than lesions which involve the prefrontal cortex directly" [2].

This finding was confirmed by the DSDB and in addition identified frontal system syndromes from lesions other than subcortical and cortical. These included infratentorial lesions in the brainstem and cerebellum in whom no other identifiable cause was found for the frontal system syndrome.

Ninety two patients with frontal lobe syndromes as delineated by a HCFD screening test were present in the DSDB, of which 36(40%) had formal neuropsychological testing confirmatory for frontal lobe syndromes in all patients. Nineteen patients had SPECT scans or which 17(89%) were abnormal. Frontal hypoperfusion was seen in all 17 (100%) of the SPECT scans and frontal lobe lesions were seen on anatomical imaging (CT or MRI) in only 44 (48%). The degree of agreement for frontal lesion detection

between anatomical and functional imaging was poor.

The present study cannot be regarded as a true reflection of the frequency of frontal lobe syndromes in stroke because of limited assessment time by the screening battery, non routine neuropsychological testing in stroke patients and our current oversimplified appreciation of these diverse disorders. However the proportion of 9.2% detected by the screening test suggests that these syndromes comprise an important neurological/neuropsychological deficit. This is important for cerebrovascular neurologists with the advent of new treatments. Popular stroke scales currently used to assess treatment outcome do not provide for measurement of these important syndromes. Although difficult to evaluate and quantify, they often remain as stroke sequelae and as the most significant cause of impairment and handicap.

SPECT scanning may be the most appropriate paraclinical investigation to help verify and monitor such deficits. Just as the standard neurological examination needs to be complemented by neuropsychological testing (bedside or psychometric), anatomical imaging (CT and MRI) and functional (SPECT) complement each other. The latter is especially relevant in the stroke setting where a strategic subcortical infarct may manifest as a frontal lobe syndrome through remote deactivation and consequently hypoperfusion and hypofunction - presumably by a diaschisis phenomenon. This was first shown by Tatemichi et al leading to the concept of strategic infarct (vascular) dementia [9].

The DSDB experience with frontal systems syndrome has allowed the following deductions;

1. Subcortical strokes are the most common cause of frontal systems syndromes
2. Subtentorial strokes, either isolated brainstem or cerebellar may cause a

frontal system syndrome

3. SPECT scanning was more sensitive to frontal lobe dysfunction detected neuropsychologically than anatomical scanning.

The DSDB findings pertaining to frontal lobe syndromes support the network theory of brain functioning [2]. The DSDB findings also support Mesulam's premise that the most common causes of frontal lobe syndromes are multifocal and subcortical processes [10].

7.0 CONCLUSIONS

Novel findings have emerged from the Durban Stroke Data Bank. These may be summarised as:

1. Cognitive disturbance is present in the majority of all types of stroke. This necessitates a reliable appraisal of this form of neurological deficit in all stroke patients in order to measure the true extent of deficit and monitor treatment and rehabilitation. This has important consequences for acute treatment trials that depend on changes in quantifiable deficit.
2. At times cognitive disturbance may be the sole presentation of stroke, unaccompanied by long tract signs. Therefore inadequate HCFD assessment may miss the deficit altogether.
3. Subcortical stroke is commonly associated with cognitive impairment - usually of a frontal system impairment. Such deficits are best correlated with functional brain scanning and not anatomical brain scanning. This is consistent with the network theory of brain functioning.
4. Risk factors for developing cognitive impairment in the indigenous stroke population included increasing age, black race, overweight body habitus and recent infection. This is an important message for the local population as the latter two are amenable to preventative measures.
5. In the young stroke population, although causes of stroke were numerous, prothrombotic states, infection associated strokes and dissection were the most numerous. All are amenable to primary preventative measures and treatable in the acute phase of stroke.
6. The Durban Stroke Data Bank showed that at least two dozen symptoms in stroke are important. In some instances, the diagnosis of stroke may be missed

altogether if a wide array of symptoms are not entertained on presentation.

7. There were important black white differences in stroke with black people being younger and an increasing rate of HIV associated stroke being documented.

8. Clinical and aetiological post investigative classification is useful in the management of stroke patients with significant differences found in all subgroups. This guides early, emergent stroke investigations and management.

8.0 CONCLUDING REMARKS

The DSDB was an ambitious project to record a comprehensive list of known cognitive disorders in the acute and subacute stroke period, although it may be argued that during this period, cognitive disorders are most likely to change and alter. Cognitive disorders are also inherently difficult to measure and no other study has attempted to measure both a wide range cognitive disorders in the acute and subacute setting. Stroke is now classified as a medical emergency, carrying with it a window of treatment opportunity with acute treatment options available in selected patients (intravenous Tissue Plasminogen Activator) - the precise extent of deficit matters. The emphasis was on bedside clinical tests which are the only ones appropriate in the acute and emergency setting. Although quantitative tests too are important and desirable, they do not cover the wide range of known cognitive disturbances and therefore may miss a neurological (neuropsychological) deficit. No ideal gold standard exists for comparing cognitive deficit measurement scales as these too may detect abnormalities in otherwise 'normal' people.

In the words of Orrin Devinsky “ Behavioural (or cognitive) neurology has recently emerged as an important discipline for studying how the brain subserves cognition, emotion and consciousness. Behavioural neurology straddles the boundaries of numerous more established disciplines - extending from the most fundamental explorations of molecular biology to the broadest questions of philosophy. Yet our knowledge is still remarkably limited. We test what we have tests for, focus on those behaviours we have some knowledge of and ignore those deficits we have not been taught to recognise. Some of the most critical behavioural problems that accompany stroke and dementia - personality change, irritability, loss of will power, impulsiveness - remain poorly defined, their therapy ignored” [1].

Every scientific work endeavours to push the frontiers of knowledge a little further. This thesis has attempted to better the understanding of the range and

import of cognitive impairment as it pertains to stroke. It is my hope that the DSDB with its specific emphasis on cognitive disorders will catalyse more research into these pinnacle aspects of humanity.

9.0 THE FUTURE

What of the future of stroke data banks? In the author's opinion so called Second Generation Expert (or Intelligent) Systems hold great promise for the facilitation of digitisation of data and streamlining decision making in specific disease states such as stroke. These systems are in the embryonic stage of development elsewhere [2,3] and work is in progress in their incorporation into the DSDB II. Such systems involve the patient to a greater degree in the management of his condition. These systems utilise the information technology now available by electronic means and open the way for telemedicine and tediagnosics and management. The relatively low cost input in terms of computer hardware, software, Internet access and E mail facilities yield tremendous savings in doctors consultations, time and money. A recently launched database design available on the Internet called *Powermed* (<http://www.powermed.com>) has some of these features. It is Filemaker Pro based and available to anyone.

10.0 Appendices

Appendix 1. Definitions.

Stroke - definition

“A rapidly developing focal or global loss of cerebral function with symptoms leading to death or lasting >24 hours with no apparent cause other than vascular”. For this study brain imaging with CT, MRI or SPECT scanning had to reveal changes consistent with a stroke. In addition the concept of cerebral infarct with transient symptoms (CITS) was included but only with appropriate imaging definition by CT, MRI or SPECT scanning.

Demographic factors

Race grouped as black (negroid), white (of europoid extraction), Asian Indian, mixed race and other.

Handedness

Handedness - defined as the person’s reported hand preference for writing, using domestic implements, such as a telephone, key, knife and toothbrush. If required corroborating evidence is gleaned from the spouse or family members.

Risk Factors

1. Arterial hypertension

Arterial blood pressure in a rested person free of stimulant agents of ≥ 160 systolic and ≥ 95 diastolic at least twice before stroke or antihypertensive treatment prior to stroke.

2. Diabetes Mellitus

Fasting blood sugar level above 6.0 mmol/L, random above 8.0 mmol/L or positive glucose tolerance test (GTT).

3. Hyperlipidaemia

A cholesterol value of more than 6.5 mmol/L fasting or 8.0 mmol/L random blood cholesterol. The normal triglyceride range was 0.28-1.69 mmol/L.

4. Lipoprotein (a)

In excess of 350 IU/L

5. Smoking

Daily cigarette smoking of 5 or more cigarettes per day over the last month or longer. If not daily then more than 20 cigarettes per week.

6. Alcohol excess

Daily or near daily alcohol intake of 4 or more units of alcohol per day over the last month or longer. One unit was considered to be one standard 340 ml can of beer, one glass of wine or one tot of spirits.

7. Migraine

History of migraine with or without aura according to the International Headache Classification Committee. In brief the definition for migraine with aura; one or more fully reversible aura symptoms indicating focal cerebral cortical or brainstem dysfunction, lasting less than 60 minutes with headache following within 60 minutes with clinical and investigative findings ruling out organic disease. For migraine without aura; at least 5 attacks of a headache lasting 4-72 hours associated with possible features of nausea, vomiting, photophonophobia, unilateral pulsating quality of moderate to severe intensity with clinicoinvestigative findings ruling out organic disease aura. IHS criteria were also used for ophthalmoplegic migraine, retinal migraine, childhood periodic syndromes, complications of migraine and atypical migraine [1].

8. Gout

Attacks diagnosed by medical doctor with a laboratory diagnosed elevation of uric acid level (>0.48 mmol/L) or on maintenance antigout medication.

9. Cardiac disease

Ischaemic heart disease, dysrhythmias, impulse conduction disorders, valvulopathies, mitral valve prolapse, infective endocarditis, hypertensive heart disease. Required the diagnosis to be made by a medical doctor with the minimum investigations including electrocardiograph and chest radiograph. Cardiac disease was further categorized into medium and high risk causes usually with the help of a cardiologist and echocardiography.

High risk cardiac source

Mechanical prosthetic valve, mitral stenosis with atrial fibrillation, atrial fibrillation other than lone atrial fibrillation, left atrial appendage with thrombus, sick sinus syndrome, recent myocardial infarction (<4 weeks), left ventricular thrombus, dilated cardiomyopathy, akinetic left ventricular segment, atrial myxoma, infective endocarditis.

Medium risk cardiac source

Mitral valve prolapse, mitral annulus calcification, mitral stenosis without atrial fibrillation, left atrial turbulence (smoke), atrial septal aneurysm, patent foramen ovale, atrial flutter, lone atrial fibrillation, bioprosthetic cardiac valve, nonbacterial thrombotic endocarditis, congestive cardiac failure, hypokinetic left ventricular segment, myocardial infarction (>4 weeks, <6 months)

10. Transient ischaemic attack

A focal neurological defect of sudden onset occurring in a cerebrovascular territory distribution and recovering without sequelae in less than 24 hours. Specific attention was paid to exclude mass lesions, partial seizures, migrainous events, hyperventilation, drug effects and labyrinthine disturbance.

11. Intermittant claudication

Calf pain on walking with documented vascular disease by a vascular surgeon or physician and/or substantiated by supporting Doppler evidence.

12. Family history of stroke or previous stroke

A history of stroke as diagnosed by a medical doctor with supportive cerebral neuroimaging.

13. Overweight

More than 20 percent over the ideal weight for age and height. May be a personal history or a clinical estimate.

14. Hypercoagulable state

Laboratory evidence of a prothrombotic disorder such as antithrombin III, protein S, protein C, anticardiolipin antibody or plasmin system defect. A probable diagnosis was made if a well defined predisposing cause was present such as pregnancy, dehydration, infection without other causes for stroke found after investigation.

15. Drug or substance abuse

Habitual use of known, illicit, habit forming drugs such as Cocaine, Amphetamines, Lysergic acid and Marijuana.

16. Oral contraceptive use

Use of oral contraceptives during the last month or more.

17. Sleep apnoea/significant snoring

Sleep apnoea as diagnosed by abnormal apnoea index by polysomnography. Snoring occurring nightly or often.

18. Chronic obstructive airways disease

Diagnosed by a pulmonologist or physician with supporting clinical and

radiographic evidence

19. Cervical trauma or neck manipulation

Any blunt or incision trauma or neck manipulation resulting in neck pain in the last month.

20. Recent Infection

Clinical symptoms or signs with laboratory or radiographic evidence of infection such as urinary, chest, upper respiratory or gastrointestinal within the last month.

21. Chronic Infection (HIV, Lues, Tuberculosis, Neurocysticercosis, Schistosomiasis)

Clinical symptoms and signs with documented laboratory or radiographic evidence.

22. Chronic systemic disease (collagen vascular, autoimmune, vasculitides)

Clinical symptoms and signs with documented laboratory or radiographic evidence.

23. Cancer

Clinical symptoms and signs with documented laboratory or radiographic evidence.

24. Personal emotion/stress

Subjective appraisal of a severe emotional or stressful situation within the last month - such as loss of spouse or significant family member, diagnosed life threatening illness, loss of employment or personal assault.

Neurological scales

All Patients

- | | |
|---|--|
| 1. Neurological deficit scale | Canadian Neurological Scale |
| 2. Clinical stroke scale | Oxfordshire Community Stroke Project Scale |
| 3. Aetiopathogenetic | Trial of Org 10172 in Acute Stroke Treatment scale (TOAST) |
| 4. Disability Scale | Barthel |
| 5. Handicap scale | Rankin |
| 6. ICD-9 Neurology | |
| 7. Harvard Cooperative Stroke Registry (items for haemorrhagic stroke only) | |

Patients selected for interventional trials

8. NIH - used for trial purposes only
9. Scandinavian Stroke Scale - used for trial purposes only
10. Unified Neurological Scale - used for trial purposes only.

Neuroimaging

Computerised tomography diagnosis of stroke: hypodensity corresponding to clinical manifestations or when the CT is normal in the setting of a clinically definite stroke. Magnetic resonance imaging diagnosis of stroke: hypointensity on T1 or hyperintensity on T2 weighted imaging in a recognised arterial brain territory.

Stenosis on angiogram

Lumen diameter reduced by at least 50% preferably on two dimensional imaging

Duplex Doppler definitions

Stenoses were graded into categories according to peak velocity ratios reported as percentage stenosis of the distal common and proximal internal

carotid artery of <40, 40-60, 60-80, 80-99 and occlusion. Plaque appearance was graded into echodense, echolucent, complex and calcified

Criteria for the Classification of Carotid Stenosis by Means of Pulsed Wave Doppler Sonography with 4 - 5 MHz probe (Modified from Zwiebel et al) [2]

Diameter Stenosis (%)	<u>Peak Systolic</u>		<u>End Diastolic</u>		Systolic Ratio (ICA/CCA)
	Frequency (kHz)	Velocity (cm/s)	Frequency (kHz)	Velocity (cm/s)	
40-60	>4.0	>120	<1.3	<40	<1.8
61-80	>4.0	>120	>1.3	>40	>1.8
80-90	>8.0	>240	>3.3	>100	>3.7

TCD definitions

Significant TCD abnormality was defined as:

- i) evidence of ipsilateral carotid HITS
- ii) middle cerebral artery stenosis
- iii) carotid siphon stenosis
- iv) other large basal cerebral vessel stenosis (posterior cerebral, basilar)
- v) occlusion of a basal cerebral vessel
- vi) markedly reduced ipsilateral middle cerebral artery velocity (side to side difference greater than 50%) and abnormal pulsatility downstream to the carotid stenosis. TCD sonography included monitoring for high intensity transient signals (HITS) or emboli from either carotid artery or more proximal source such as the heart or aorta. "Bubble TCD" incorporating injection of 10 ml of agitated, aerated saline for diagnosis of PFO was done where clinically indicated.

TCD evidence for collateralization

Collateralization through the anterior part of the circle of Willis if ACA flow ipsilateral to the carotid occlusion was reversed. This usually occurred in conjunction with the acceleration through the contralateral ACA. Through the external carotid artery if the ophthalmic artery flow was reversed and through the basilar artery if the ratio of the ipsilateral to contralateral velocity in the PCA exceeded 50%. [3]

Ultrasound criteria for microembolus detection

1. Characteristic harmonic sound
2. Unidirectional signals within the advancing velocity spectrum, visible on the screen
3. Short duration <0.15 seconds for systolic signals and <0.3 seconds for diastolic signals
4. Random occurrence within the cardiac cycle
5. Intensity > 3dB or more above the background doppler blood velocity spectrum.[4]

SPECT brain scanning

Interpreted by cartographic analysis and counts compared with cerebellum. Divided into normal, high counts, low counts, mixed and absent.

Cerebral perfusion index (CPI). Derived from TCD and SPECT analysis in the acute phase of stroke [5].

TCD

Normal	4
Collateral	3
Stenosis	2
Occlusive	1

SPECT

Normal	5
High	4
Mixed	3
Low	2
Absent	1

CPI

Good	15-20
Medium	6-12
Poor	1-5

Higher cortical function deficits**Aphasias**

As tested by ascertaining spontaneous speech, comprehension, naming, repetition, reading and writing using selected items from the Boston Aphasia Diagnostic Examination. Eight subcategories were defined namely; Broca's, Wernicke's, global, conduction, anomic, transcortical motor, transcortical sensory and semantic aphasia.

Neglect syndromes

Disregard in a field of vision, without total loss of vision in a field as tested by presentation of double simultaneous stimuli for visual neglect, unilateral extinction of bilateral simultaneous auditory stimuli for auditory neglect and consistent inability to perceive one of two simultaneous tactile stimuli for tactile neglect. Three categories were defined; visual, auditory and tactile neglect.

Apraxias

Impaired execution of previously learned movements not explainable by weakness, neuropathy, dystonia or other movement disorders. In constructional cases, inability to copy drawings or block designs. Failure to

accurately carry out previously learned skilled motor acts in response to examiner's command (usually applies to limb commands e.g. throw a ball, stir a cup of tea, show me how you brush your teeth).

Anosognosia

Failure on confrontation inquiry to acknowledge obvious disease of the nervous system.

Agnosias

Inability to recognise objects or pictures of objects presented visually despite preserved vision (can trace or copy or master objects) and normal object naming by other modalities.

Alexias

Acquired inability to read with preserved writing and no significant aphasia or acquired inability to read and write despite normal use of and comprehension of spoken language.

Aprosodias

Poor comprehension of affective components of speech as expressed by prosody or inability to inject affect in speech by altering the prosody of speech.

Frontal lobe syndromes

Relatively sudden onset of disinhibition, apathy or abulia with respect to pre-stroke behaviour. Poor abstraction as evidenced by impaired proverb interpretation. This usually requires collateral sourcing from family and friends.

Miscellaneous Syndromes

Gerstmann Syndrome

Isolated , finger agnosia, dysgraphia, dyscalculia and right/left disorientation

Angular Gyrus syndrome

Anomia, alexia, agraphia, R/L disorientation, finger agnosia, constructional apraxia, occasionally mild fluent aphasia and right visual field defects

Visual hallucinations

These are subjective experiences - elicited direct questioning. such as simple (photopsias, phosphenes, scintillations), complex (such as aware of unreal people, objects or scenes around you)

Visual Illusions

Illusions may be restricted to areas with partial visual loss or affect the entire visual field. The image may be altered in size (micropsia or macropsia), shape (dysmorphopsia or metamorphopsia), position (teleopsia), number (polyopia), colour or movement.

Palinopsia

The persistence or recurrence of visual images after the excitatory stimulus has been removed.

Prosopagnosia

A visual agnosia hallmarked by an inability to recognize previously known human faces (the retrograde effect) and the inability to learn new ones (the anterograde effect).

Simultanagnosia

Tested with the Cookie Theft Picture. The inability to perceive the visual field as a whole also called piecemeal vision. However able to describe minute details that require normal visual acuity. Unable to see more than one or two objects at one time.

Balint's Syndrome

The triad of Simultanagnosia (piecemeal vision), visual ataxia (deficit of visual reaching) and optic ataxia (deficit of visual scanning). Simultanagnosia is the central feature.

Achromatopsia

An acquired disorder of loss of colour perception in part or all of the visual field. The colour loss may vary in degree - shades of grey and black, washed out or bleached. Often accompanied by alexia and quadrantanopia.

Cortical blindness

Distinguished from other forms of blindness in that the pupillary light reflex is present. Such patients are usually unaware of their blindness - Anton's syndrome. These patients act as if their vision intact - walk into walls and bump into furniture and do not take precautions that ocular blind people take.

Complications

Behavioural abnormality.

Significant (interfering with social, work or family interaction) change in character, apathy, inability to cope with work or home circumstances as reported by family members or neuropsychological impairment as diagnosed by a neuropsychologist

Depression

As per DSM III criteria for depression [6]

Seizures

Appropriate history by medical, paramedical or family witnesses of tonic or clonic activity with or without alteration in consciousness within the first month after stroke

Recurrent stroke

A second neurological deficit that clinically and with brain scan supporting evidence supported a stroke within the first month of the initial stroke.

Pneumonia

Clinical, palpatory or auscultatory signs of chest infection with supporting chest radiographic findings within the first month of the stroke.

Pulmonary embolus

Clinical, palpatory or auscultatory signs of chest infection with supporting chest radiographic and radio isotope findings and within the first month of the stroke.

Brachialgia

Ipsilateral shoulder pain and restricted movement with signs of mild, moderate or severe reflex sympathetic dystrophy.

Deep venous thrombosis.

Calf pain and tenderness with a positive Homan's sign within the first month of stroke.

Miscellaneous itemsVolume of infarction

Formula:

$$\text{Volume} = (A \times MF)(B \times MF) \times SN \times ST / 2$$

A - Tranverse diameter

B - Longitudinal diameter

MF - magnification factor

SN - number of slices

ST - slice thickness

ICH volume measurement

Formula for an ellipsoid = $\frac{4}{3} (\text{Pi})(a \times b \times c)$ which can be simplified to $abc/0.52$ or $abc/2$.

Use centimeter scale and round off to nearest half centimeter. The number of 1 cm slices on which the haemorrhage could be seen was recorded and if just visible given 1/2 a point for example. The result is in cm^3 and usual ranges are <30 , 30-60 and >60 cm. [7]

Modified Harvard Cooperative Stroke Registry Definitions of infarct subtype - used for definition of haemorrhagic stroke only

Intracerebral haemorrhage

Gradual onset over minutes to days or sudden onset of focal neurological deficit accompanied by signs of increased intracranial pressure such as vomiting, diminished consciousness and hypertension. Typically no TIA or signs of large vessel disease. The CT and MRI reveal a focal mass of high intensity.

Subarachnoid haemorrhage

Sudden onset of headache usually accompanied by vomiting, syncope with later recovery of consciousness, subhyloid haemorrhages on fundoscopy. The CT reveals changes consistent with blood in the subarachnoid space.

Angiography frequently reveals an aneurysm or arteriovenous malformation in the cerebral arterial system.

Large artery thrombosis

Gradual stepwise or stuttering stroke occurring over less than one week, often with TIA. Evidence of large vessel occlusive disease such as a bruit, angina pectoris or myocardial infarction, peripheral vascular disease. CT/MRI shows

bland infarction, angiography or Doppler reveal evidence of major intracranial (ACA, MCA, PCA, basilar) or cervicocephalic (carotid, vertebral or subclavian) occlusion or stenosis.

Lacunae

Abrupt or gradual onset of deficit compatible with a recognized lacunar syndrome ie pure motor hemiparesis, pure sensory stroke, dysarthria clumsy hand syndrome or crural ataxia. Absence of headache, diminished alertness or vomiting. CT/MRI shows small deep infarct. Angiography and Doppler studies normal.

Embolism

Sudden stepwise or fluctuating onset within 24 hours of a focal neurological deficit usually without TIA's in the same vascular territory. A cardiac source such as atrial fibrillation, myocardial infarction, valvular heart or bacterial endocarditis or systemic embolism, prior stroke or TIA in a different vascular territory. CT reveals low density or hyperintensity on MRI involving arterial territory. May be haemorrhagic infarct [8].

TOAST classification

Large artery atherthrombosis

Cerebral cortical, brainstem or cerebellar impairment with supportive evidence by duplex Doppler or angiography of a stenosis greater than 50% in an extra or intracranial artery. Supporting findings include previous TIA in the same vascular territory, intermittent claudication or diminished peripheral pulses. Cortical, cerebellar or brainstem lesions greater than 1.5 cm in diameter are supportive of potential large artery atherosclerotic origin.

Cardioembolism

Cortical, cerebellar or brainstem lesions greater than 1.5 cm in diameter in a patient with at least one either high or medium risk cardiac source of

embolism. Potential large artery sources of embolism should be eliminated.

Small artery disease (lacunae)

One of the traditional lacunar syndromes in association with a normal brain scan or one revealing a brainstem or subcortical hemisphere lesion with a diameter of less than 1.5 cm. Potential cardiac sources should be absent and large artery stenoses should not be greater than 50% of an ipsilateral artery.

Acute stroke other determined aetiology

Rarer causes of stroke such as nonatherosclerotic vasculopathies, hypercoagulable states, haematologic disorders. The CT or MRI scan shows features of an acute stroke and diagnostic studies such as blood tests, angiography reveal one of these unusual causes of stroke. Cardiac sources of embolism and large artery atherosclerosis should be excluded by other appropriate studies

Stroke undetermined aetiology

In certain cases the cause of stroke cannot be determined with any degree of certainty. Some patients will have no likely aetiology despite an extensive evaluation. In others, no cause can be found but the evaluation was cursory. This category also includes patients with two or more causes of stroke so that the physician is unable to make a final diagnosis eg atrial fibrillation and ipsilateral stenosis of 50%.

Other

Dolichoectasia

Radiological dolichoectasia criteria

Ectasia = >4.5 mm diam

Basilar artery lies lateral to the margin of the clivus in the cerebellopontine angle or above the level of the suprasellar cistern [9,10]

High risk cardiac source

Mechanical prosthetic valve
Mitral stenosis with atrial fibrillation
Atrial fibrillation other than lone atrial fibrillation
Left atrial appendage with thrombus
Sick sinus syndrome
Recent myocardial infarction (<4 weeks)
Left ventricular thrombus
Dilated cardiomyopathy
Akinetic left ventricular segment
Atrial myxoma
Infective endocarditis

Medium risk cardiac source

Mitral valve prolapse
Mitral annulus calcification
Mitral stenosis without atrial fibrillation
Left atrial turbulence (smoke)
Atrial septal aneurysm
Patent foramen ovale
Atrial flutter
Lone atrial fibrillation
Bioprosthetic cardiac valve
Nonbacterial thrombotic endocarditis
Congestive cardiac failure
Hypokinetic left ventricular segment
Myocardial infarction (>4 weeks, < 6months) [11]

Handedness

Inquiry from the patient as to which hand is used for writing, combing hair, picking up a telephone or brushing teeth. If required corroborating evidence is gleaned from the spouse or family members. (This is the method used in the Austin Stroke Data Bank from G. Donnan)

The Oxfordshire Community Stroke Project Study - definitions for subtypes of cerebral infarction.

Total anterior circulation infarcts (TACI)

These were defined as acute stroke with the combination of new higher cerebral dysfunction (for example, dysphasia, dyscalculia, visuospatial disorder); homonymous visual field deficit; and ipsilateral motor and/or sensory deficit of at least two areas of the face, arm, and leg. If the conscious level was impaired and formal testing of higher cerebral function or visual fields was not possible, a deficit was assumed to be present.

Partial anterior circulation infarcts (PACI)

These were defined as only two of the three components of the **TACI**, with higher cerebral dysfunction alone, or with a motor/sensory deficit more restricted than those classified as **LACI** (for example, confined to the limb, or to face and hand, but not to the whole arm).

Lacunar infarcts (LACI)

These were defined as an acute onset of one of the five major recognised lacunar syndromes: pure motor stroke, pure sensory stroke, ataxic hemiparesis, dysarthria-clumsy hand syndrome, or sensory-motor stroke.

Posterior circulation infarcts (POCI)

These were defined as acute onset of focal neurological deficit that included any of the following: ipsilateral cranial nerve palsy with contralateral motor and/or sensory deficit; bilateral motor and/or sensory deficit; disorder of conjugate eye movement; cerebellar dysfunction without ipsilateral long-tract deficit (for example, ataxic hemiparesis); or isolated homonymous visual field deficit.

Appendix 2. Higher cortical function screening test manual.

Bedside screening test
 Scored for every category
 Subtyping of individual categories
 Hierarchical
 Prerequisite: Alert and attentive person

Test Hierarchy

Establish alertness
 Establish attention

1.	Aphasias	1
2.	Amnesias	1
3.	Anosognosias/Neglect syndromes	1
4.	Apraxias	1
5.	Alexias	1
6.	Agnosias	1
7.	Visuospatial	1
8.	Aprosodias	1
9.	Frontal lobe tests	1
10.	Miscellaneous	1

Quantitative score ---

Normative value 0

Level of consciousness

For drowsy, light coma, deep coma and hyperalertness (delirium) give 0 and exclude from HCFD assessment

Alert
 Drowsy
 Light coma
 Deep coma
 Hyperalert (delirium)

Attention

Count to 10
 Days of the week in reverse
 Orientation in time (dd/mm/yy), place and person

1. Aphasia

Definition:

Test Procedure:

1. Conversational (spontaneous) speech. Ask the patient what the major presenting problem is, how it started and associated symptoms. (History of main complaint). Number of words per minute eg Wernicke's up to 200 per minute and Broca's typically 10-12 per minute. Record on Sound edit DSDB.
2. Auditory Comprehension
Close your eyes
Stick out your tongue
3. Naming. Name a pen watch, key, three colours (eg grey, brown, orange)
4. Repetition: 'No ifs, ands or buts'.
5. Reading: The quick brown fox jumped over the lazy dog's tail.
6. Writing: In one sentence explain your occupation. Must make sense and contain a subject and verb.

Characterise aphasias according to table.

Fluency	Comprehension	Repetition	Aphasia
Nonfluent	Intact	Poor	Broca's
		Intact	Transcortical motor
	Poor	Poor	Global
		Intact	Mixed transcortical
Fluent	Intact	Poor	Conduction
		Intact	Anomic
	Poor	Poor	Wernicke's
		Intact	Transcortical sensory

Aphasia present and subtype

2. Amnesias (Explicit)

Definition

Immediate memory (anterograde)

digit span (examiner's 7 digit telephone number forward and back)
three words three shapes test (pen, watch, key and shapes triangle with circle inside, mushroom and Greek cross).

Recent memory (retrograde). Make population/race/individual specific

one important local event in last month
3 items (words) at 5 minutes

Remote memory (retrograde). Make population/race/individual specific

dates of 2 important famous events several years to decades ago (eg school attended, WW1+2)

Transient global

Witnessed sudden onset anterograde and retrograde memory loss with repetitive questioning without other neurological symptoms.

Amnesia present and subtype

3. Anosognosia and neglect syndromes

Anosognosia definition: Denial of disease usually of the left side of the body with varying grades of severity identifiable

Denial of the existence of one side (anosognosia)

Denial of hemiplegia or hemiparesis (anosognosia)

Gross underestimation of the severity of the hemiparesis (anosodiaphoria)

Neglect syndromes

a) Sensory neglect

Presentation of bilateral simultaneous stimuli for visual, auditory and tactile faculties.

b) Visual neglect - bilateral hand movements or two 10 mm red spheres one in each visual field.

c) Auditory neglect- two tuning forks or clicking watches held next to either ear and assess for appreciation of both sounds.

d) Tactile neglect - bilateral simultaneous pin pricks on similar parts of the extremities and assess whether both are appreciated or only one.

e) Motor Neglect tests

1. Bisect this line



4. Apraxia

Use one command only for each category. If uncertain use the others.

a) Ideomotor apraxia

May involve buccofacial, limb or truncal (axial) musculature.

Buccofacial ideomotor apraxia

Blow out a match

Drink with a straw

Stick out your tongue

Cough

Sniff

Puff out your cheeks

Lick your lips

(At the same time look for incomplete, unrelated or opposite motor acts).

Limb apraxia

May involve upper or lower limb and may be unilateral. Test both sides.

Brush teeth

Stir tea

Use a screwdriver, saw, hammer

Wave goodbye

Beckon come here

Truncal apraxia (Whole body)

How does a boxer stand

How does a golfer stand

How does a soldier march

Stand up turn around twice and sit down

Optional: Severity of ideomotor apraxia may be graded:

Mild - failure to perform on verbal commands

Moderate - failure to imitate behaviour

Severe - failure to imitate or perform with an actual object

b) Ideational apraxia

Ideational apraxia is a sequencing disorder in the conceptual organization of complex actions (agnosia of usage). In contrast to ideomotor apraxia, each separate component of a sequence can be successfully performed. Test with the multiple object test:

1. Prepare a letter for mailing - give paper, envelope. Fold the paper in half twice to fit in envelope and seal.

OR

2. Drink a glass of water - jug with cap and a glass is presented.

Look for; clumsiness, omissions, mislocations, misuse and sequence errors

c) Callosal and Sympathetic apraxia

Unable to perform motor acts (as in ideomotor apraxia) in response to commands with their left arm or leg although they execute the commands quite well with right sided limbs.

d) Limb kinetic dyspraxia

Focal clumsiness in performance of fine motor acts - unilateral or confined to one limb only. Test both hands by rapidly touching each finger with the thumb forward and back, once.

e) Dressing Apraxia

Inability to put on a shirt, gown or pyjama top despite normal attention, strength and coordination.

Apraxia present and subtype

5. Alexias

a) Posterior Alexia (Alexia without agraphia)

Acute loss of ability to read despite full retention of ability to write. Use point 5 of aphasia testing. The patient can however recognize words spelled out aloud, written on the palm or words that can be palpated.

b) Central Alexia (Alexia with agraphia)

Inability to recognize words spelled out aloud, written in the palm, or palpable words. In addition inability to write - refer to point 6 of aphasia testing.

c) Anterior Alexia (Third alexia)

Alexia in association with Broca's and transcortical motor aphasia.

Definition of Paralexia (Deep dyslexia)

Substitutions in reading aloud ie synonym substitutions that is called Semantic paralexia. Here aircraft may be read as plane and dog as hound. Paralexia (Deep dyslexia). Adjectives may also be turned into nouns and an inability to read nonsense words.

Use the table to help categorise:

Alexia	Post. Alexia	Central Alexia	A n t e r i o r
Reading	very poor	very poor	partially impaired
Writing	no agraphia	severe agraphia	severe agraphia
Comprehension			
spelled words	good	very poor	some success
Spelling aloud	good	very poor	poor
Verbal output	normal	normal or dysnomia	nonfluent aphasia
Letter naming	variable	severe letter anomia	severe letter anomia
Paralexia	occ. semantic paralexia	semantic paralexia freq.	semantic paralexia rare

Alexia present and subtype

6. Agnosias

Visual agnosia

Test: Name a pen, tie, paper, book, file.

Using only vision only (and not aided by touch or hearing), the person is able to identify and describe the shape, size, contour, edges and position of an object. Agnosic patients can describe the features and shape of an object but fail to recognize it and cannot state what the object is or is used for. Patients with object agnosia are unable to state what it is and what you do with it.

Tactile agnosia

Using only touch only (and not aided by vision or hearing), the person is able to identify and describe the shape, size, contour, edges and position of an object. Agnosic patients can describe the features and shape of an object but fail to recognize it and cannot state what the object is or is used for. Patients with object agnosia are unable to state what it is and what you do with it.

Auditory agnosia

The person is unable to respond to verbal (speech) and nonverbal (environmental) sounds as tested by written requests and answers despite having relatively normal end organ hearing capabilities.

Prosopagnosia

Test: Faces of Mandela, De Klerk and Buthelezi. Ask about recognizing family, friends and relatives by sight. Inability to recognize familiar faces visually but can recognize by auditory and tactile means. A visual agnosia hallmarked by an inability to recognize perviously known human faces (the retrograde effect) and the inability to learn new ones (the anterograde effect).

Simultanagnosia

Testing: Cookie Theft Picture

The inability to perceive the visual field as a whole also called piecemeal vision. Patients appear blind at first glance, unable to detect new stimuli approaching them, bump into walls, don't see cars pass in front of them and make inaccurate movements when reaching for objects. However they are able to describe minute details that require normal visual acuity. Unable to see more than one or two objects at one time.

Agnosia present and subtype

7. Constructional apraxia/Visuospatial

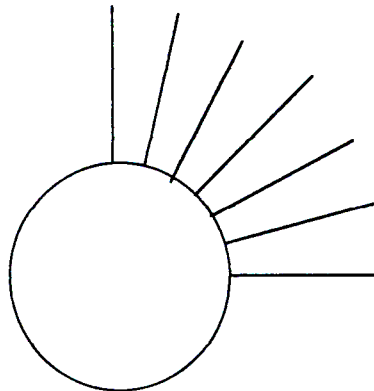
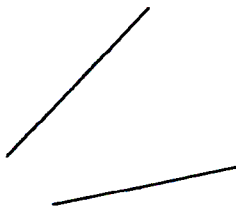
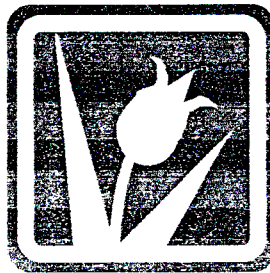
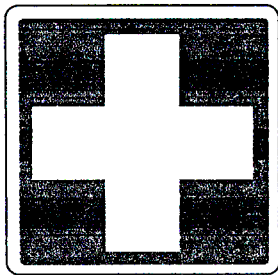
a) Copy two dimensional figures

- daisy
- greek cross

b) Copy 3 dimensional figures

- copy a cube or five pointed star

c) Benton's Line orientation test - modified. Match the two lines in angle.



8. Aprosodias

Infarctions in the right inferior middle cerebral artery are difficult to detect clinically. Although sensorimotor, neglect phenomena and speech deficits may be present they are usually minimal and transient and associated agitational confusional states frequent. Aprosodic speech has been shown to be a specific marker for this relatively "silent" area of the brain [Darby].

Testing

1. Spontaneous affective prosody and gesturing

In the interview, note presence of affective prosody in person's voice, especially when asked emotionally laden questions such as feelings at loss of a loved one or close calls with serious injury or death.

2. Repetition of affective prosody.

A declarative sentence is repeated in a neutral, happy, sad and angry voice.

3. Comprehension of affective prosody

A declarative statement devoid of emotional words is produced by the examiner with different affective tones ie happy, sad and angry. Should stand behind the patient to avoid giving visual clues. Patient is asked to identify what affect was injected into the sentence.

a) Sensory Aprosodia

Excellent affective prosody in speech and active spontaneous gesturing. Auditory comprehension of affective prosody and visual comprehension of emotional gesturing and repetition of affective prosody are severely impaired.

b) Motor or expressive aprosodia

Flat monotone speech with loss of spontaneous gesturing. Repetition of affective prosody is severely compromised with comprehension of affective prosody and visual comprehension of emotional gesturing intact. Impairment of affective expression.

c) Global aprosodia

Flattened affect. Loss of ability to display affect through prosody and gesturing. Comprehension and repetition of affective prosody and visual comprehension of emotional gesturing are severely compromised.

Table Aprosodias

	Motor	Sensory	Global
Spontaneous affective prosody and gesturing	poor	good	poor
Affective prosodic repetition	poor	poor	poor
Affective prosodic comprehension	good	poor	poor

9. Frontal systems syndrome

Tests

a) Motor Programming

Serial hand positions - Luria 3 step test. Fist, edge, palm OR

Go no go. Hands flat on table. Raise one finger for one tap but hold for 2 taps.

b) Set shifting and cognitive flexibility

Alternate sequence test (alternating m-n or triangle and square)

c) Information retrieval

Word list generation (FAS). Use only one letter - other 2 if borderline.
(Normal is ≥ 15 words per letter/min excluding names of people and places)

d) Abstraction

Proverb interpretation. Use any one of the following familiar proverbs

One swallow does not make a summer OR

Too many cook's spoil the broth OR

Make hay while the sun shines.

Categorization

Note any relatively sudden or significant (impacts work or family life) general behaviour and social conduct impairment (not easily testable in the office situation or bed side). This usually requires collateral sourcing from family and friends. Attempt to fit into one of the following frontal lobe symptom clusters:

Disinhibited (orbitofrontal syndrome)

Disinhibited, impulsive behaviour, irresponsible

Profane slovenly, facetious, puerile

Pseudopsychopathic

Inappropriate jocularity

Euphoria

Poor judgement and insight

Apathetic (frontal convexity syndrome)

Apathy (occasional brief angry or aggressive outbursts)

Indifference

Psychomotor retardation

Motor perseveration and impersistence

Stimulus bound behaviour

Poor abstraction and categorization

Akinetic (medial frontal syndrome)

Abulia - paucity of thought, speech and spontaneous motor movement

Lower extremity weakness and loss of sensation

Incontinence

Frontal system syndrome present and category

10. Miscellaneous Syndromes

Angular Gyrus syndrome

Anomia
 Alexia
 Agraphia
 R/L disorientation
 Finger agnosia
 Constructional apraxia
 Occasionally mild fluent aphasia
 Right visual field defects

Gerstmann Syndrome

Isolated
 Finger agnosia
 Dysgraphia
 Dyscalculia
 R/L Disorientation

Other

Cortical sensory loss (loss of 2 point discrimination, agraphesthesia, abaragnosia, astereognosis)
 Stuttering
 Tremor (cortical)
 Limb shaking
 Frontal, parietal, temporal and occipital simple and complex partial seizures
 Episodic altered mental state

Visual hallucinations

These are subjective experiences - elicited direct questioning.

Simple

- i) Photopsias (light flashes)
- ii) phosphenes (blue lights),
- iii) scintillations (zig zags)
- iv) geometric forms, checkerboard patterns
- v) positive scotoma (seen with eyes closed) - halos surrounding a black hole

Complex visual hallucinations

Are you aware of any of the following that others around you do not see

- i) People
- ii) objects
- iii) scenes and landscapes
- iv) animals (zoopsias)
- v) Autoscopia - the hallucination or psychic experience of seeing oneself. This may take the form of a perception of one's own body image projected into external visual space or seeing one's double. The latter form is also called an out of body experience and is the feeling of leaving one's own body and viewing it from a vantage point, usually from above.

Visual Illusions

Illusions may be restricted to areas with partial visual loss or affect the entire visual field.

The image may be altered in

- i) size (micropsia or macropsia)
- ii) shape (dysmorphopsia or metamorphopsia)
- iii) position (telopsia)
- iv) number (polyopia)
- v) colour or movement.
- vi) Upside down vision may occur
- vii) Straight lines appear curved.

Palinopsia

The persistence or recurrence of visual images after the excitatory stimulus has been removed.

Visual dysesthesias

Unpleasant visual sensations precipitated by looking at an object in a defective homonymous and visual hemifield.

Visual Synesthesias

Optic percepts induced by stimuli in other sensory modalities such as auditory or tactile. Patients may see shapes or colours in response to hearing specific sounds.

Visual Allesthesia

Transposition of visual images from one homonymous half field to another. Usually in bilateral cerebral lesions.

Oculomotor apraxia

To verbal command. Look to the right, to the left, up and down. The inability to voluntarily direct gaze toward a specific part of the visual field. Even when telling the patient where to look for an object they are unable to do so as foveal vision cannot be directed properly. Look to the right and left.

Optic ataxia

Touch the examiner's finger held at varying places in front of the patient. The inability to direct movement of an extremity using visual guidance. When using proprioceptive guidance however with the eyes closed, may allow a person to accurately touch a pen in front of them which would elude them when using visual guidance. Finger to nose test.

Balint's Syndrome

The triad of Simultanagnosia (piecemeal vision), visual ataxia (deficit of visual reaching) and optic ataxia (deficit of visual scanning). Simultanagnosia is the central feature.

Achromatopsia

Test: Point to 6 different colours.

An acquired disorder of loss of colour perception in part or all of the visual field. The colour loss may vary in degree - shades of grey and black, washed out or bleached. Often accompanied by alexia and quadrantanopia. May have hemiachromatopsia

Colour anomia

Test: Show me the colour of a banana and the colour of the cloudless sky.

Have normal colour perception and can discriminate hues nonverbally, but cannot name colours or point to a colour when given its name. Almost always associated with alexia and right homonymous hemianopia.

Cortical blindness

Distinguished from other forms of blindness in that the pupillary light reflex is present. Such patients are usually unaware of their blindness - Anton's syndrome (visual anosognosia). These patients act as if their vision intact - walk into walls and bump into furniture and do not take precautions that ocular blind people take. When confronted with this disability they may confabulate about what they are seeing or offer lame excuses such as the lighting is poor

Adapted from references [1-6]

Appendix 3. Digitised score sheet of the DSDB

1. Point and click feature

2. 47 fields each with 2-76 possibilities

3. Digitised - text

- scales

- images (selected patients)

- sound (selected dysphasic patients; HITS)

Report Date	<input type="text"/>	Visits	<input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> 7 <input type="checkbox"/> 8 <input type="checkbox"/> 9 <input type="checkbox"/> 10	Sex	<input type="checkbox"/> M <input type="checkbox"/> F
Last Name	<input type="text"/>	First Name	<input type="text"/>	M Aid	<input type="checkbox"/> Y <input type="checkbox"/> N
Referral	<input type="checkbox"/> Practice <input type="checkbox"/> KEH Med <input type="checkbox"/> Vasc CEA <input type="checkbox"/> KEH Obstetrics		Handedness	<input type="checkbox"/> Right <input type="checkbox"/> Left <input type="checkbox"/> Ambidexterous	
Age	DOB <input type="text"/>	Age Range	<input type="checkbox"/> 0-14 <input type="checkbox"/> 15-49 <input type="checkbox"/> 50-59 <input type="checkbox"/> 60-69 <input type="checkbox"/> 70-79 <input type="checkbox"/> 80-89 <input type="checkbox"/> 90-100		
Race	<input type="checkbox"/> White <input type="checkbox"/> Black <input type="checkbox"/> Indian <input type="checkbox"/> Mixed race <input type="checkbox"/> Other		Address	<input type="text"/>	
Education	<input type="checkbox"/> High school <input type="checkbox"/> Graduate <input type="checkbox"/> Other <input type="checkbox"/> Junior school <input type="checkbox"/> Illiterate		Tel	<input type="text"/>	
Current dx	<input type="text"/>		Comment	<input type="text"/>	
Symptoms	<input type="checkbox"/> Right affected <input type="checkbox"/> Altered sensation <input type="checkbox"/> Dysphagia <input type="checkbox"/> Imbalance <input type="checkbox"/> Vomiting <input type="checkbox"/> Tremor <input type="checkbox"/> Left side affected <input type="checkbox"/> Headache <input type="checkbox"/> Comprehension problem <input type="checkbox"/> Incoordination <input type="checkbox"/> Seizures <input type="checkbox"/> Other <input type="checkbox"/> Weakness <input type="checkbox"/> Speech difficulty <input type="checkbox"/> Confusion <input type="checkbox"/> Invol. movements <input type="checkbox"/> Dizziness <input type="checkbox"/> Numbness <input type="checkbox"/> Memory poor <input type="checkbox"/> Vision impairment <input type="checkbox"/> Gait abn <input type="checkbox"/> LOC				
Risk factors	<input type="checkbox"/> None <input type="checkbox"/> Alcohol excess <input type="checkbox"/> Sleep apnoea/signif snoring <input type="checkbox"/> Collagen vasc disease <input type="checkbox"/> Hypertension <input type="checkbox"/> Int. Claudication <input type="checkbox"/> COAD <input type="checkbox"/> Autoimmune disease <input type="checkbox"/> Cardiac disease (specify) <input type="checkbox"/> Overweight <input type="checkbox"/> Cervical manipulation <input type="checkbox"/> Vasculitis <input type="checkbox"/> Diabetes Mellitus <input type="checkbox"/> Migraine <input type="checkbox"/> Neck trauma <input type="checkbox"/> Cancer <input type="checkbox"/> TIA <input type="checkbox"/> Hypercoagulable state <input type="checkbox"/> Infection in last month <input type="checkbox"/> Personal emotion/stress <input type="checkbox"/> Previous stroke <input type="checkbox"/> Drug/Substance abuse <input type="checkbox"/> HIV positive <input type="checkbox"/> DVT's <input type="checkbox"/> Hyperlipidaemia <input type="checkbox"/> Oral contraceptive <input type="checkbox"/> Tuberculosis <input type="checkbox"/> Other (specify) <input type="checkbox"/> Smoking <input type="checkbox"/> Gout <input type="checkbox"/> Neurocysticercosis				
Exam timing	<input type="checkbox"/> 0-6h <input type="checkbox"/> 7-12h <input type="checkbox"/> 13-24h <input type="checkbox"/> 25-48h <input type="checkbox"/> 3-7d <input type="checkbox"/> 1-4wks <input type="checkbox"/> 1-3mo <input type="checkbox"/> 3-6mo <input type="checkbox"/> 7mo-1y <input type="checkbox"/> >1y specify				
Conscious level	<input type="checkbox"/> Alert CNS 3.0 <input type="checkbox"/> Disorientated and not applic CNS 0.0 <input type="checkbox"/> Receptive deficit CNS 0.0 <input type="checkbox"/> Abulic <input type="checkbox"/> Drowsy CNS 1.5 <input type="checkbox"/> Speech normal CNS 1.0 <input type="checkbox"/> Light coma <input type="checkbox"/> Agitated <input type="checkbox"/> Orientated CNS 1.0 <input type="checkbox"/> Expressive deficit CNS 0.5 <input type="checkbox"/> Deep coma <input type="checkbox"/> Delirious				
Orientation Language	<input type="checkbox"/> Normal <input type="checkbox"/> Left <input type="checkbox"/> Hemiparesis <input type="checkbox"/> Quadriparesis <input type="checkbox"/> Tongue weakness <input type="checkbox"/> Dysarthria <input type="checkbox"/> Other <input type="checkbox"/> Right <input type="checkbox"/> Bilateral <input type="checkbox"/> Monoparesis <input type="checkbox"/> Triparesis <input type="checkbox"/> Dysphagia <input type="checkbox"/> Digital				
Weakness general	<input type="checkbox"/> Face none 0.5 <input type="checkbox"/> Arm prox signif 0.5 <input type="checkbox"/> Arm distal signif 0.5 <input type="checkbox"/> Leg prox signif 0.5 <input type="checkbox"/> Leg distal signif 0.5 <input type="checkbox"/> Face present 0.0 <input type="checkbox"/> Arm prox total 0.0 <input type="checkbox"/> Arm distal total 0.0 <input type="checkbox"/> Leg prox total 0.0 <input type="checkbox"/> Leg distal total 0.0 <input type="checkbox"/> Arm prox none 1.5 <input type="checkbox"/> Arm distal none 1.5 <input type="checkbox"/> Leg prox none 1.5 <input type="checkbox"/> Leg distal none 1.5 <input type="checkbox"/> Arm prox mild 1.0 <input type="checkbox"/> Arm distal mild 1.0 <input type="checkbox"/> Leg prox mild 1.0 <input type="checkbox"/> Leg distal mild 1.0				
CNS weakness grade	<input type="checkbox"/> Face sym0.5 <input type="checkbox"/> Face asym0.0 <input type="checkbox"/> Arms equal1.5 <input type="checkbox"/> Arms uneq0.0 <input type="checkbox"/> Legs equal1.5 <input type="checkbox"/> Legs uneq0.0				
CNS With compreh deficit	<input type="checkbox"/> 0 <input type="checkbox"/> 2 <input type="checkbox"/> -4 <input type="checkbox"/> +4 <input type="checkbox"/> Reflexes <input type="checkbox"/> Normal <input type="checkbox"/> Pathol L <input type="checkbox"/> Hyperreflexia <input type="checkbox"/> Limb hypertonic <input type="checkbox"/> 1 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> Tone <input type="checkbox"/> Asymm <input type="checkbox"/> Pathol R <input type="checkbox"/> Hyporeflexia <input type="checkbox"/> Limb hypotonia				
MRC grade range paresis	<input type="checkbox"/> Normal <input type="checkbox"/> Left <input type="checkbox"/> Face <input type="checkbox"/> Whole arm <input type="checkbox"/> Whole leg <input type="checkbox"/> Digit <input type="checkbox"/> Hyperesthesia <input type="checkbox"/> Right <input type="checkbox"/> Hemi involve <input type="checkbox"/> Distal arm <input type="checkbox"/> Distal leg <input type="checkbox"/> Truncal level <input type="checkbox"/> Hypoesthesia <input type="checkbox"/> Anaesthesia				
Sensation	<input type="checkbox"/> Amaurosis fugax <input type="checkbox"/> Sectoranopia <input type="checkbox"/> Ophthalmoplegia <input type="checkbox"/> Pupil abn. other <input type="checkbox"/> Append incoord <input type="checkbox"/> Other <input type="checkbox"/> Hom Hemianopia <input type="checkbox"/> Gaze palsy <input type="checkbox"/> Int nuclear ophthal <input type="checkbox"/> Horners <input type="checkbox"/> Axial incoord <input type="checkbox"/> Quadrantanopia <input type="checkbox"/> Nystagmus <input type="checkbox"/> Anisocoria <input type="checkbox"/> Cervical bruit <input type="checkbox"/> Ataxia				
Visual Incoord Bstem	<input type="checkbox"/> Normal <input type="checkbox"/> Orofacial <input type="checkbox"/> Expressive <input type="checkbox"/> Balints <input type="checkbox"/> Abnormal <input type="checkbox"/> Dressing <input type="checkbox"/> Receptive <input type="checkbox"/> Akinetopsia <input type="checkbox"/> Neuropsych testing <input type="checkbox"/> Sympathetic <input type="checkbox"/> Alexias <input type="checkbox"/> Achromatopsia <input type="checkbox"/> Aphasias <input type="checkbox"/> Constructional <input type="checkbox"/> Alexia with agraphia <input type="checkbox"/> Pure word deafness <input type="checkbox"/> Brocas <input type="checkbox"/> Agnosias <input type="checkbox"/> Alexia no agraphia <input type="checkbox"/> Allesthesia <input type="checkbox"/> Wernickes <input type="checkbox"/> Tactile <input type="checkbox"/> Hemidyslexia <input type="checkbox"/> Astereopsis <input type="checkbox"/> Aphemia <input type="checkbox"/> Auditory <input type="checkbox"/> Anosognosias <input type="checkbox"/> Autocopy <input type="checkbox"/> Transcort motor <input type="checkbox"/> Visual <input type="checkbox"/> Neglect syndromes <input type="checkbox"/> Palinopsia <input type="checkbox"/> Transcortical sensory <input type="checkbox"/> Colour <input type="checkbox"/> Visual neglect <input type="checkbox"/> Visual illusions <input type="checkbox"/> Conduction <input type="checkbox"/> Object <input type="checkbox"/> Auditory neglect <input type="checkbox"/> Visual hallucin <input type="checkbox"/> Global <input type="checkbox"/> Simultanagnosia <input type="checkbox"/> Tactile neglect <input type="checkbox"/> Cortical blindness <input type="checkbox"/> Anomia <input type="checkbox"/> Prosopagnosia <input type="checkbox"/> Frontal lobe syndromes <input type="checkbox"/> Cortical sensory loss <input type="checkbox"/> Subcortical <input type="checkbox"/> Amnesias <input type="checkbox"/> Orbitofrontal <input type="checkbox"/> Astereognosis <input type="checkbox"/> Semantic <input type="checkbox"/> Anterograde <input type="checkbox"/> Frontal convexity <input type="checkbox"/> Abaragnosis <input type="checkbox"/> Other <input type="checkbox"/> Retrograde <input type="checkbox"/> Medial frontal <input type="checkbox"/> Agraphaesthesia <input type="checkbox"/> Apraxias <input type="checkbox"/> Transient Global <input type="checkbox"/> Miscellaneous <input type="checkbox"/> Defect 2 point discrim <input type="checkbox"/> Limb kinetic <input type="checkbox"/> Short term <input type="checkbox"/> Gerstmanns <input type="checkbox"/> Extinction <input type="checkbox"/> Ideomotor <input type="checkbox"/> Long term <input type="checkbox"/> Angular gyrus <input type="checkbox"/> Dreaming abn <input type="checkbox"/> Ideational <input type="checkbox"/> Aprosodias <input type="checkbox"/> Antons <input type="checkbox"/> Other specify				
HCFD	<input type="checkbox"/> Normal <input type="checkbox"/> Amnesias <input type="checkbox"/> Aprosodias <input type="checkbox"/> Constr dyspraxia <input type="checkbox"/> Speed of info proce <input type="checkbox"/> Abnormal <input type="checkbox"/> Apraxias <input type="checkbox"/> Agrophias <input type="checkbox"/> Right hemisphere dysf <input type="checkbox"/> Other <input type="checkbox"/> Attention/concentration imp. <input type="checkbox"/> Alexias <input type="checkbox"/> Acalculias <input type="checkbox"/> Neglect synd <input type="checkbox"/> Aphasias <input type="checkbox"/> Agnosias <input type="checkbox"/> Visuospatial dysf <input type="checkbox"/> Frontal lobe synd				
Neuropscyh Testing	<input type="checkbox"/> Normal <input type="checkbox"/> FBC abn <input type="checkbox"/> Lipogram <input type="checkbox"/> TFT <input type="checkbox"/> ANF <input type="checkbox"/> Prot S or C <input type="checkbox"/> Brain biopsy <input type="checkbox"/> Abnormal <input type="checkbox"/> Electrol abn <input type="checkbox"/> Lipo a <input type="checkbox"/> LFT <input type="checkbox"/> HIV <input type="checkbox"/> ACA <input type="checkbox"/> Other <input type="checkbox"/> Not significant <input type="checkbox"/> ESR <input type="checkbox"/> Uric acid <input type="checkbox"/> INR <input type="checkbox"/> VDRL/FTA <input type="checkbox"/> AT III <input type="checkbox"/> Hypertension <input type="checkbox"/> Glucose <input type="checkbox"/> Fibrinogen <input type="checkbox"/> PTT <input type="checkbox"/> Blood cultures <input type="checkbox"/> CSF abn				
Laboratory	<input type="checkbox"/> Normal <input type="checkbox"/> MCA territory <input type="checkbox"/> Frontal <input type="checkbox"/> Thalamic <input type="checkbox"/> Int capsule <input type="checkbox"/> Midbrain <input type="checkbox"/> Right hemisphere <input type="checkbox"/> ACA <input type="checkbox"/> Parietal <input type="checkbox"/> Basal nuclei <input type="checkbox"/> Ext capsule <input type="checkbox"/> Wshed <input type="checkbox"/> Left hemisphere <input type="checkbox"/> PCA <input type="checkbox"/> Temporal <input type="checkbox"/> Caudate <input type="checkbox"/> Brainstem <input type="checkbox"/> Other <input type="checkbox"/> Subcortical <input type="checkbox"/> Ant choroidal <input type="checkbox"/> Occipital <input type="checkbox"/> Striatocapsular <input type="checkbox"/> Medulla <input type="checkbox"/> CT <input type="checkbox"/> Multiple strokes <input type="checkbox"/> Cerebellar arteries <input type="checkbox"/> Corona radiata <input type="checkbox"/> Perisylvian/Insula <input type="checkbox"/> Pons <input type="checkbox"/> MRI				
Brain scan	<input type="checkbox"/> 1-10 <input type="checkbox"/> 11-20 <input type="checkbox"/> 21-30 <input type="checkbox"/> 31-40 <input type="checkbox"/> 41-50 <input type="checkbox"/> 51-60 <input type="checkbox"/> 61-70 <input type="checkbox"/> other <input type="checkbox"/> Actual volume <input type="text"/>				
Inf haem vol	<input type="checkbox"/> Done <input type="checkbox"/> Colour Doppler <input type="checkbox"/> Vertebral <input type="checkbox"/> Plaque complex <input type="checkbox"/> sten mod 60-80 <input type="checkbox"/> Other <input type="checkbox"/> Normal <input type="checkbox"/> Carotid unilat <input type="checkbox"/> Other vessel <input type="checkbox"/> Stenosis min <40 <input type="checkbox"/> Sten severe 80-90 <input type="checkbox"/> Abnormal <input type="checkbox"/> Carotid bil <input type="checkbox"/> Plaque smooth <input type="checkbox"/> Sten mild 40-60 <input type="checkbox"/> Occlusion				
Duplex Doppler	<input type="checkbox"/> Done <input type="checkbox"/> Abnormal <input type="checkbox"/> Occlusion <input type="checkbox"/> Low velocity <input type="checkbox"/> PI low <input type="checkbox"/> Tech failure <input type="checkbox"/> Normal <input type="checkbox"/> Stenosis <input type="checkbox"/> Collateral active <input type="checkbox"/> PI high <input type="checkbox"/> Emboli specify <input type="checkbox"/> Other				
TCD	<input type="checkbox"/> Done <input type="checkbox"/> Abnormal <input type="checkbox"/> Spiral CT <input type="checkbox"/> Stenosis <input type="checkbox"/> Vessel irreg <input type="checkbox"/> Aneurysm <input type="checkbox"/> Normal <input type="checkbox"/> MRA <input type="checkbox"/> Not significant <input type="checkbox"/> Occlusion <input type="checkbox"/> Anomaly <input type="checkbox"/> Other				
Angiogram					

SPECT Done Abnormal Hyperfusion Mixed Normal Hypoperfusion Absent perfusion

Cerebral Perfusion Index Done Medium 12-6 Good 20-15 Poor 5-1

Cardiac Invest Normal ECG ischaem CMO PFO TTE Aortic arch dis Spont echo contrast Abnormal Myo infarct Cardiac failure ASA TEE Dyskinetic segment Holter Arrhythmia Valve disease Prolapse CXR Cong Intracavity clot Other

Clinical and Aetopath Dx

<input type="checkbox"/> TAC-OCSP	<input type="checkbox"/> Stroke ill defined (436)	<input type="checkbox"/> Large vessel dis	<input type="checkbox"/> Unknow
<input type="checkbox"/> PAC-OCSP	<input type="checkbox"/> Stroke other Cerebral Athero (437.0)	<input type="checkbox"/> Aortic arch plaque	
<input type="checkbox"/> LAC-OCSP	<input type="checkbox"/> Cerebral venous thrombosis (437.6)	<input type="checkbox"/> Comorbidity	
<input type="checkbox"/> POC-OCSP	<input type="checkbox"/> Vasculitis (437.4)	<input type="checkbox"/> Dissection	
<input type="checkbox"/> SAH (430)	<input type="checkbox"/> Binswanger's (437.1)	<input type="checkbox"/> Prothrombotic state	
<input type="checkbox"/> ICH (431)	<input type="checkbox"/> Moya Moya (437.5)	<input type="checkbox"/> Septic embolism	
<input type="checkbox"/> Haem other eg SDH (432)	<input type="checkbox"/> TGA (437.7)	<input type="checkbox"/> Dolichoectasia	
<input type="checkbox"/> Occ/stenosis of precerebral arteries (433)	<input type="checkbox"/> Amaurosis Fugax (362.34)	<input type="checkbox"/> Metabolic stroke	
<input type="checkbox"/> Occ/stenosis of cerebral arteries (434)	<input type="checkbox"/> Cardioembolism	<input type="checkbox"/> Drug induced stroke	
<input type="checkbox"/> Embolism of cerebral arteries (434.1)	<input type="checkbox"/> Paradoxical embolism	<input type="checkbox"/> Migraine stroke	
<input type="checkbox"/> TIA (435)	<input type="checkbox"/> Lacunar (small vessel disease)	<input type="checkbox"/> Other	

M. Rankin Scale on admission

0. No symptoms at all 6. Died

1. No signif disability despite symptoms. Able to carry out all usual duties, activities

2. Moderate disability. Requires some help. Able to walk without assistance

3. Moderately severe disability. Requiring some help but able to walk without assist.

4. Moderately severe disability. Unable to walk without assistance. Req assist. for bodily needs

5. Severe disability. Bedridden, incontinent and requiring constant nursing care and attention

Barthel Index on admission

<input type="checkbox"/> Normal 20	<input type="checkbox"/> occ accid-b1	<input type="checkbox"/> independ-g1	<input type="checkbox"/> independ-f2	<input type="checkbox"/> wheelchair1	<input type="checkbox"/> unable-s0
<input type="checkbox"/> Abnormal	<input type="checkbox"/> cont-b2	<input type="checkbox"/> toilet	<input type="checkbox"/> transfer bed chair	<input type="checkbox"/> walk aid2	<input type="checkbox"/> help-s1
<input type="checkbox"/> 0-5	<input type="checkbox"/> bladder	<input type="checkbox"/> depend-t0	<input type="checkbox"/> unable-t0	<input type="checkbox"/> independ3	<input type="checkbox"/> independ-s2
<input type="checkbox"/> 6-10	<input type="checkbox"/> incont0	<input type="checkbox"/> help-t1	<input type="checkbox"/> maj help-t1	<input type="checkbox"/> dressing	<input type="checkbox"/> bathing
<input type="checkbox"/> 11-15	<input type="checkbox"/> occ accid1	<input type="checkbox"/> independ-t2	<input type="checkbox"/> min help-t2	<input type="checkbox"/> depend-d0	<input type="checkbox"/> depend-b0
<input type="checkbox"/> 16-19	<input type="checkbox"/> cont2	<input type="checkbox"/> feeding	<input type="checkbox"/> independ-t3	<input type="checkbox"/> help-d1	<input type="checkbox"/> independ-b1
<input type="checkbox"/> Bowels	<input type="checkbox"/> grooming	<input type="checkbox"/> unable-f0	<input type="checkbox"/> mobility	<input type="checkbox"/> independ-d2	
<input type="checkbox"/> incont-b0	<input type="checkbox"/> help-q0	<input type="checkbox"/> help-f1	<input type="checkbox"/> immobile0	<input type="checkbox"/> stairs	

CNS scores admission Rx

Aspirin Antihypertensive Anticonvulsant Speech therapy Other

Dipyridamole Antiarrhythmic Hypoglycaemic/insulin Botox

Warfarin Beta blockers Antidepressant Piracetam

Nimodipine Ca++ chan blocker Antiparkinson TPA

Heparin Lipid lowering agent CEA Nimodipine

Number and intervals of follow up visits

Follow up yes 1 week 1 mo 4 mo 1 y >2y specify Rankin worse

Follow up no 2 week 2 mo 6 mo 1-2y specify Rankin better Rankin same

Rankin 1w Rankin 3w Rankin 2m Rankin 6m Rankin 1 to 2y

Rankin 2w Rankin 4w Rankin 4m Rankin 1y Barthel 2 to 6 months

Other

<input type="checkbox"/> None	<input type="checkbox"/> Pneumonia	<input type="checkbox"/> Depression	<input type="checkbox"/> UTI	<input type="checkbox"/> Falls
<input type="checkbox"/> Yes	<input type="checkbox"/> Cardiac	<input type="checkbox"/> Seizures	<input type="checkbox"/> Pyrexia	<input type="checkbox"/> Died
<input type="checkbox"/> Recurrent stroke	<input type="checkbox"/> Post CEA stroke	<input type="checkbox"/> DVT	<input type="checkbox"/> Brachialgia	<input type="checkbox"/> Other
<input type="checkbox"/> Progressing stroke	<input type="checkbox"/> Behaviour abn	<input type="checkbox"/> Pulmonary embolism	<input type="checkbox"/> Decubitus	

Sound

Images

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Appendix 4

Peer reviewed articles published to date

1. Stroke in the young. Stroke in the Young. The Multiethnic, Prospective Durban Stroke Data Bank Results.

Hoffmann M.

Journal of Stroke and Cerebrovascular Diseases 1998;7:1-11

2. Cognitive Dysfunction in Isolated Brainstem Stroke. A Neuropsychological and SPECT study.

Hoffmann M, Watts A.

Journal of Stroke and Cerebrovascular Diseases 1998;7:24-31

3. Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism. The Durban Cerebrovascular Data Bank (DCDB) experience.

Hoffmann M.

South African Journal of Radiology 1997;2:4-8

4. Carotid endarterectomy after recent stroke. How soon? An interim analysis.

Hoffmann M, Robbs JV, Abdool Carrim ATO. The Durban Cerebrovascular Group.

South African Journal of Surgery 1998;36:63-67

5. Transient Global Amnesia - Acute SPECT Functional Imaging and Neuropsychological Deficits.

Hoffmann M, Watts Runge A.

South African Journal of Radiology 1996;3:30-36

6. Posterior circulation positional transient ischaemic attacks due to persistent primitive hypoglossal artery with redundancy.

Hoffmann M, Corr P.

South African Journal of Radiology 1996;2: 20-23

7. Cerebrovascular neuroimaging: which tests and when?

Hoffmann M.

South African Journal of Radiology 1996;2:6-15

8. An obscure cause of stroke - basilar artery fenestration.

Hoffmann M.

South African Journal of Radiology 1998;4:22-23

Stroke in the Young: The Multiethnic Prospective Durban Stroke Data Bank Results

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Aim: To determine the clinical syndromes, etiopathogenesis, and prognostic factors in a prospectively evaluated multiethnic young stroke population. *Methods:* Only first-ever patients with a World Health Organization definition of stroke and anatomic brain imaging were included. A hierarchy of investigative modalities divided into three tiers was applied and a range of standardized scales scored in each patient. This allowed quantification of clinical deficit, etiopathogenesis, disability, and handicap. Standardized stroke scales included the Canadian Neurological Scale (CNS), the Oxfordshire Community Stroke Project (OCSP) clinical stroke scale, and TOAST (Trial of Org 10172 in Acute Stroke Study) etiological classification. Disability was measured with the Barthel Index and handicap with the Rankin Scale; cognitive impairment was separately evaluated according to predefined criteria. A prognostication measure was made in some patients with the Cerebral Perfusion Index (CPI). *Results:* A total of 236 patients was evaluated of whom 64 were excluded because of no lesion consistent with stroke on brain scanning, leaving 172 for analysis. There were 87 women, 85 men, with a mean age of 43.8 years (range, 15 to 49 years). Despite many different predefined symptoms, 38 patients (22%) could not be classified. Hypertension (31%) and smoking (19%) were the most commonly encountered risk factors, with more recently determined risk factors such as infection (6%) and emotional stress (5%) relatively frequent. With respect to etiology, the TOAST category "other" was the most numerous group, numbering 93 of 172 (55%) with prothrombotic states in 25 (15%), vasculitis in 21 (12%), and dissection in 12 (7%) being the most frequent causes. Proportions of the remaining categories were small vessel disease (16%), cardioembolism (13%), large vessel disease (10%), and unknown (6%). χ -square analysis for an association between the clinical OCSP and TOAST classifications was not significant. Severity of stroke was generally mild as judged by the CNS and Rankin scales. A high proportion of patients had cognitive impairment (54%). A cerebral perfusion index was possible in 31 patients, most of whom had a medium prognosis. *Conclusion:* In this hospital-based consecutive series, most young stroke patients in our region were grouped into nonatherogenic (mostly prothrombotic states, infection associated and dissection) and noncardiac causes with a definite or probable cause found in 94%. The wide variety of stroke symptoms recorded in this study underscores the heterogeneity of stroke presentation and caution in the emergent evaluation of patients. Cognitive impairment in the majority of stroke patients in the acute and subacute stroke period has important implications for degree of clinical deficit especially as it applies to stroke scales and treatment trials. **Key Words:** Author provide.

The young stroke patient poses a particularly impor-

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ant diagnostic challenge in view of the varied documented etiopathogeneses and likelihood of recurrent events. Notwithstanding the clinical challenge of the problem, the available data are discordant with respect to etiology, therapeutic, rehabilitative, and prognostic considerations. There is considerable heterogeneity in the multitude of causes as reported by different investigators as well as variation between races, regions, and countries.¹⁻²³ Differing diagnostic protocols, diagnostic armamentaria, and variability in the criteria for the probable causes of stroke applied by different investigators make the data currently available nonuniform. The predominance of retrospective series and paucity of prospective studies^{1,3,24-26} with the unavoidable fact that information has been collected, often, over a decade or more, with inherent nonuniform testing is a further problem associated with most studies reported at the time of writing. Few studies have used clinical and pathogenetic scales to allow uniformity of clinical reporting. Many studies included in their series cerebral ischemia or transient ischemic events^{3,12,16,17,19,21,26-29} with no confirmation by neuroimaging, other than those employing single-photon emission computed tomography (SPECT) or positron-emission tomography (PET) acutely. This is problematic in view of the number of conditions that may masquerade as stroke or ischemia in young people. Finally, between 10% and 40% of strokes remained unexplained in the series published to date.^{4,6,7,8,13,16}

To help address some of these issues, the findings of the Durban Stroke Data Bank (DSDB) are presented as one of the largest prospectively defined young stroke population with first-ever stroke, all proven by neuroimaging using contemporary diagnostic methods available in large centers in the years 1992 to 1996. In view of the recency of the recruitment period, a high rate of modern neuroinvestigative modalities was a possibility. A wide range of both proven stroke risk factors and other putative risk factors were included, in addition to an expanded pathophysiological classification so as to avoid lumping disparate entities and missing an important association. It is a personal series, devoid of interobserver variability (but not of intraobserver variability) utilizing a hierarchy of five commonly used stroke scales with management and follow-up all done by the same investigator in over 90% of cases. In 10%, management and follow-up remained the primary responsibility of the referring physicians.

Methods

Recruitment

Patients ranged in age from 15 to 49 years and had first-ever stroke between October 1992 and October 1996.

They were admitted to a Durban metropolitan acute stroke unit serving patients with medical insurance and a medical ward in a general hospital catering to indigent patients without medical insurance. Patients did not always require hospitalization, some having their workup on an outpatient basis. The World Health Organisation (WHO) definition of stroke was the criterion used³⁰ but, in addition, all patients had an anatomic brain scan (CT or magnetic resonance imaging [MRI]) showing appropriate changes consistent with stroke.

Stroke Data Bank

Patients were derived from the DSDB, a prospective stroke registry. The "nested" patient cohort were separately and prospectively evaluated according to a set protocol. The DSDB included digital storage of clinical progress and follow-up data, radiographic data, and where appropriate acoustic storage (e.g., aphasia progress). This greatly facilitated accurate storage of data and ease of retrievability. The computer package used was Filemaker Pro 3.0 (Mfr, City, State/Country), a relational database with integrated image, acoustic, and video storage facilities.

Investigations

A three-tier investigative protocol was used, incorporating a basic minimum workup (performed in all patients), tests often used (by clinical need), and tests seldom used. The latter two tiers were used as appropriate, tailored to each individual patient's conundrum of clinical details. The minimum workup included basic stroke-relevant blood tests (complete blood count, platelets, serum electrolytes, urea, creatinine, lipogram, lipoprotein (a), erythrocyte sedimentation rate (ESR), serum glucose, International Normalised Ratio (INR), partial thromboplastin time (PTT), CT or MRI brain scan, chest radiograph, and electrocardiogram (ECG). Additional workup when appropriate (the 2nd tier) included transcranial Doppler (TCD) and duplex Doppler (DD) sonography, MR angiography, SPECT scanning, formal neuropsychological assessment, prothrombotic tests, cerebral angiography, cerebrospinal fluid analysis (CSF), Holter monitoring and transthoracic (TTE) or transoesophageal (TEE) cardiac echocardiography. A category of seldom required tests (the third tier) included examination for rare inherited disorders (including homocysteinaemia, sickle cell disease, hemoglobinopathies, mitochondrial cytopathies, and other genetic and metabolic causes of stroke) and brain biopsy as indicated. Diagnoses were broadly divided into probable (laboratory evidence and absence of competing cause of stroke) and definite (conclusive laboratory or radiographic evidence).

Neurological Scales and Classifications

To facilitate accurate comparison within the registry with other data banks and stroke trials, several standardized scales have been incorporated into the registry protocol. These included the Canadian Neurological Scale (CNS) a neurological deficit scale,³¹ a clinical stroke scale; the Oxfordshire Community Stroke Project Score (OCSP)³² divided into total anterior circulation (TAC), partial anterior circulation (PAC), lacunar (LAC), and posterior circulation (POC), a disability scale; the Barthel Index (BI),³³ a handicap scale; the Rankin Disability Scale (R),³⁴ and an expanded etiopathogenetic classification, Trial of Org 10172 in Acute Stroke Study (TOAST)³⁵ with categories for large vessel disease, small vessel disease, cardiogenic, other, and undetermined. In the other category were included probable or presumed causes of stroke after the investigative protocol failed to determine any cause of stroke. The other category included strokes in association with or directly as a cause of vasculitides, cervicocephalic dissection, aortic arch atheroma, metabolic strokes, drug-induced strokes, prothrombotic states, migraine, Moya Moya syndrome, cerebral venous thrombosis, and dolichoectasia. All patients were assessed clinically and a final diagnosis made with all available investigative data by the same cerebrovascular neurologist. Comorbidity was also documented. For a diagnosis to be made within the frame work of the extended TOAST classification, the diagnosis needed to be one of exclusion in which all clinically indicated tests according to the hierarchical protocol were negative save for the factor in question. It is acknowledged that some would be definite diagnoses, some probable, and some possible by this method.

Cognitive Testing

Cognitive testing was deemed to be important so as not to miss the true extent of neurological deficit, as this is not reflected adequately in the current neurological scales. A higher cortical function deficit (HCFD) screening examination was applied to all alert patients in the DSDB on admission. Formal neuropsychological testing was performed in those alert patients with subtle or very mild deficits on bedside testing or where the screening examination suggested but did not decisively delineate a syndrome. The tests comprising the battery included clinical interviews, Trail Making Test, Symbol Digit Modalities Test, South African Wechsler Adult Intelligence Screen (Digit Span, Block Designs, Object Assembly, Rey Complex Figure Test, Wechsler Memory Scale, Rey Auditory Verbal Learning Test [RAVLT], Verbal Fluency Tests [FAS, Category Naming], Wisconsin Card Sorting Test [WCST], Luria's neuropsychological investigation [South African adaptation] including preliminary conversation, motor functions [optic, spatial organisation], writing [letter], reading [text], and arithmetic skills.³⁶⁻⁴⁴ The neuropsy-

chological assessment procedure incorporated both a qualitative and quantitative data analysis, the latter according to the norms published by Lezak.³⁶ Qualitative analysis proceeded according to a process of hypothetico deduction (a process of systematic hypothesis testing) and was based on the principle of syndrome analysis and double dissociation (checking validity of the findings) as per Luria.⁴⁴

SPECT Brain Scanning

SPECT was performed in patients in whom a discrepancy of clinical signs and anatomic brain scan was present despite appropriate timing of CT or MRI brain scanning. A combination of the TCD results and SPECT results can be computed into the cerebral perfusion index—a recently described, useful prognostic test.⁴⁵ In brief, TCD findings of occlusion, stenosis, collateralisation and normal were given scores of 1, 2, 3, 4, respectively. SPECT brain scanning signal findings of absent, low, mixed, high, or normal were given scores of 1, 2, 3, 4, 5, respectively. The multiplication of these values determines a cerebral perfusion index that may be good (15 to 20), medium (6 to 12), or poor (1 to 5).

Statistical Analysis

The significance of associations between variables was assessed using χ -square test for categorical data or analysis of variance (ANOVA) for numerical data.

Results

Inclusion and Exclusions

Young people meeting the clinical definition of first ever stroke included 236. Of these, 64 were excluded because of no identifiable lesion consistent with stroke seen on either CT or MRI, leaving 172 for further analysis.

Demographics

There were 85 men and 87 women with a racial-group breakdown that included 124 whites, 29 blacks, 15 Indians, 3 of mixed race, and 1 woman of Burmese origin. The mean age was 43.8 years. There were 3 left handed (1.7%) and 3 ambidextrous people (1.7%). Most had medical insurance of some kind (152, 88.4%) with 20 having none (21.6%).

Timing of the Initial Examination and Initiation of Investigations

This was performed within 48 hours in 76 (44.1%) patients of whom 19 (11%) were seen within 6 hours or less, 27 (15.7%) under 12 hours, and 52 (30.2%) under 24 hours. Patients seen within the first-week, day 3 to day 7,

numbered 33 (19.1%), and weeks 1 to 4 numbered 50. Thirteen patients (7.6%) were evaluated later than 1 month mainly due to late presentation of their first stroke. Overall, 63% of patients were evaluated within the first week of their stroke and 92% were evaluated within the first month of their stroke.

Symptoms

The most common symptoms in descending order were unilateral weakness (85%), speech difficulty (51%), unilateral numbness (48%), headache (42%), dizziness (31%), vision impairment (30%), imbalance (12%), and confusion (12%). Although 18 different symptoms were prospectively sought at the time of stroke presentation, 38 patients' symptoms did not fit into one of the categories. Within the category named other, examples of these nonclassifiable symptoms of relatively sudden onset included subdued behaviour, lack of emotion, impaired insight into condition, impaired bladder control (micturating in the bedroom), slowed-up in work environment (for example, unable to manage well-known software programs), slowness of thinking and talking in general, sensation of a thick and swollen tongue, and hearing strange sounds.

Risk Factors

Risk factors were divided into independent and as yet unproven risk factors (Table 1). Smoking was the most commonly encountered one in 53 of 172 (31%), with hypertension the second most common in 32 (19%). Of the so-called atherogenic risk factors (hypertension, smoking, diabetes mellitus, hyperlipidaemia, gout), 7 of 9 were in the top 10 most frequently encountered risk factors. Both infection (established) and recent personal emotional stress (not established) appeared relatively frequently, but in this study were not compared with a control group. Yet others, such as sleep apnea/snoring (established) were not often encountered (6% and 5%, respectively).

Anatomic Brain Scans

Either a CT (105, 61%) or MRI (103, 60%) brain scan or both (37, 22%) were performed in all patients. The distribution of lesions consistent with strokes were 66 in the right hemisphere, 77 in the left hemisphere, and 49 subcortical. The arterial distribution frequencies included 47 in the middle cerebral artery cortical territory, 16 in the brainstem arteries, 7 in the cerebellar cortices, 5 in the anterior cerebral cortical artery territory, and 3 in the posterior cerebral cortical territory. Other identifiable distributions included 18 corona radiata, 8 internal capsule, 7 thalamus, 6 basal nuclei, 4 caudate nucleus, 3 perisylvian/insula, 2 anterior choroidal, 1 watershed, and 0 striatocapsular infarcts. At time of first presentation and

Table 1. Risk factors divided into independent and possible associated with the cause of stroke

	n	%
Independent risk factors		
Smoking	53	31
Hypertension	32	19
Cardiac	17	10
Oral contraceptive use	17	10
Migraine	16	9
Alcohol excess	15	9
Infection	11	6
Diabetes mellitus	10	6
TIA	10	6
Hyperlipidaemia	9	5
Gout	4	2
Previous stroke	2	1
Intermittant claudication	1	1
Sleep apnea or significant snoring	1	1
Possible risk factors and associated significant illness/predisposing conditions		
Recent emotion or personal stress	8	5
Neck trauma	6	3
Hypercoagulable state	5	3
Vasculitis or autoimmune disease	5	3
Deep venous thrombosis	4	2
HIV positivity	3	2
Tuberculosis	2	1
Chronic obstructive airways disease	2	1
Drug/substance abuse	1	1
Neurocysticercosis	1	1
Cervical manipulation	1	1
Cancer	1	1
Other	19	11

first-ever stroke, 20 patients (12%) had more than one lesion consistent with stroke show on the brain scan.

Functional Brain Scanning and Cerebral Perfusion Indices

SPECT scanning was performed as per protocol in 36 patients, and 31 (86%) of these studies were abnormal. These were also used to calculate the cerebral perfusion index (CPI) together with TCD values in acute stroke patients. The CPI was good in 3, medium in 26, and poor in 2. The Rankin scale mean value of these patients showed a significant difference (ANOVA) between the poor and medium, poor and good, but not between good and medium categories.

Sonographic, Laboratory, and Cardiac Investigations

All patients had first tier investigations, hence the number of abnormalities are a fraction of 172. For the second and third tier investigations, the number is listed as a fraction of the total number of investigations done within the category. TCD and DD were performed in 109

Table 2. Cardiac abnormalities

High-risk cardiac source	
Ischemic heart disease and akinetic left ventricular segment	2
Atrial fibrillation	2
Atrial fibrillation with dilated left atrium	1
Mechanical prosthetic valve and atrial fibrillation	1
Rheumatic mitral stenosis, atrial fibrillation, dilated left atrium	1
Left ventricular thrombus	1
Dilated cardiomyopathy with left ventricular clot	1
Atrial myxoma	1
Infective endocarditis	1
Congenital heart disease—Eisenmenger's complex, infective endocarditis	1
Congenital heart disease—Ebsteins anomaly	1
Congenital heart disease—Atrial septal defect-periop- erative repair stroke	1
Medium-risk cardiac source	
Patent foramen ovale	6
Atrial septal aneurysm and patent foramen ovale	1
Mitral valve prolapse	1
Hypertensive heart disease and hypokinetic left ven- tricular segment	1

(63%) and 103 (60%), respectively, according to clinical indication. Testing for patent foramen ovale was carried out in 16 patients, 7 of whom were positive. In 2 patients, high-intensity transient signals (HTS) were detected over a middle/anterior cerebral artery bifurcation in the setting of prosthetic heart valve and atrial fibrillation in 1 patient, and preocclusive stenosis due to fibromuscular dysplasia in 1 patient.

Laboratory findings were notable for the high rate of complete blood count abnormality and relatively few abnormalities for INR, PTT, and ESR. Lipogram abnormalities and glucose elevations correlated with that reported by patients under risk factors. Prothrombotic tests were often positive, numbering 24 of 30 (80%) when tested for under the protocol guidelines or 24 of 172 (14%) overall. In the third tier tests all CSF analyses were abnormal mostly done for suspected neurological infections such as syphilis, human immunodeficiency virus (HIV) infection, tuberculosis, and neurocysticercosis. In 2 patients with clinical and angiographically demonstrated vasculitis, there was a clinical indication for brain biopsy both of which were negative.

Cardiac abnormalities accounted for a relatively smaller number (13%) in comparison with other young stroke data banks.¹⁻²³ High-risk and medium-risk causes as listed in Table 2 were all diagnosed with the help of echocardiography (30 transthoracic and 12 transesophageal). Patent foramen ovale as the most likely factor associated with stroke occurred in almost one third of the cardiac causes (Table 2).

Table 3. Etiopathogenetic breakdown—TOAST classification

	All (%)	White	Black	P value
Other	92 (55)	66	20	
Small vessel disease	28 (16)	20	2	
Cardioembolic	23 (13)	20	3	
Large vessel disease	17 (10)	9	1	
Unknown	12 (6)	9	3	
Total	172 (100)	124	28	0.411 (NS)

Etiologies: TOAST Categories and 'Other' Subgroups

Within the extended TOAST classification, the most numerous group was 'other' (55%) followed by the small vessel disease (16%), cardioembolism (13%), large vessel disease (10%) and those of 'unknown' cause (6%) being the smallest (Table 3).

In the subcategories of the 'other' group (Table 4), frequencies of abnormalities included prothrombotic group (n = 25) with laboratory-determined abnormalities including anticardiolipin antibody elevation (7), protein S deficiency (4), protein C deficiency (2), antithrombin III deficiency (2), elevated fibrinogen (1), and plasmin system defect (1). Conditions predisposing to hypercoagulability included ulcerative colitis (1), pregnancy (1), alcoholic binge (3), recent initiation of oral contraception (4), and polycythaemia (2). Four patients had 2 prothrombotic causes. Using a classification of possible, probable and definite, cases due to prothrombotic states would fall into the category of probable. Probable was determined by a positive laboratory result in the absence of a competing other cause of stroke.

The next most frequent group were the vasculitides (n = 21) with subtypes including HIV associated (positive HIV blood test, MR angiographic appearance consistent with vasculitis, and lack of another cause of stroke) (5), Takayasu's (5), tuberculosis-related vasculitis (3), neurocysticercosis-associated vasculitis (3), neuroleues (2), isolated angiitis of the central nervous system (1), Kawasaki disease-related vasculitis (1), and of presumed viral origin (1). The diagnosis of vasculitis was definite if biopsy proven, which did not apply to any patients with two negative biopsy results. In the rest, the strength of the diagnosis was considered probable in that there was a positive laboratory test in association with typical angiographic features of vasculitis and the absence of a competing other cause of stroke.

Dissection (n = 12) was the third most numerous with the subtypes including spontaneous carotid dissection (4), blunt cervical trauma (4), spontaneous vertebral dissection (2), fibromuscular dysplasia related dissection (1), and temporally related to chiropractic manipulation (1).

Migraine was the most likely cause in 5 patients according to the criteria noted in the appendix, metabolic

Table 4. TOAST group (other) breakdown (including hemorrhagic stroke)

	n	%
Prothrombotic state	25	27
Prothrombotic state (laboratory based)	17	
Prothrombotic, secondary to hypercoagulable state	8	
Vasculitis	21	23
HIV	5	
Takayasu's	5	
TB related	3	
Neurocysticercosis related	3	
Neurolyues related	2	
Isolated angiitis	1	
Kawasaki disease	1	
Uncertain cause (viral?)	1	
Hemorrhage	15	16
Intracerebral	12	
Subarachnoid	3	
Dissection	12	13
Spontaneous carotid dissection	4	
Blunt cervical trauma	4	
Spontaneous vertebral dissection	2	
Fibromuscular dysplasia related dissection	1	
Temporally related to chiropractic manipulation	1	
Migraine	5	5
Metabolic stroke	2	2
Drug/substance abuse	1	1
Moya Moya syndrome	1	1
Miscellaneous	11	12
Cerebral aneurysm with distal territorial embolism	3	
Cerebral venous thrombosis	2	
Dolichoectasia	1	
Arterial redundancy of a persistent hypoglossal artery	1	
Gunshot to neck with carotid artery thrombosis	1	
Brainstem AVM and hemorrhagic infarct/polycystic kidneys	1	
Postcervical spondylotic surgery	1	
Total	92	100

stroke in 2 (hyperhomocysteinaemia), Moya Moya syndrome (1), and due to substance abuse (cocaine) in one. Hemorrhagic stroke accounted for 15 cases, 12 intracerebral hemorrhages and 3 subarachnoid hemorrhages.

In the miscellaneous category, the following most likely causes were identified after a diagnosis of exclusion. Cerebral aneurysm with distal territorial embolism (3), dolichoectasia with artery-to-artery embolism or thrombosis (1), cerebral venous thrombosis (2), arterial redundancy of a persistent hypoglossal artery (1), gunshot to the neck with carotid artery with thrombosis (1), brainstem arteriovenous malformation and hemorrhagic infarct associated with polycystic kidneys (1), and postoperative stroke during cervical spondylotic surgery (1).

Table 5. Severity of stroke on admission

Canadian Neurological Scale		Rankin Scale	
Points	n (%)	Points	n (%)
11.5	81 (47)	0 + 1	91 (53)
7.5-11.0	69 (40)	2 + 3	59 (34)
≤7.0	22 (13)	4 + 5	22 (13)
Total	172 (100)		172 (100)

NOTE. Kappa value 0.58; moderate degree of agreement between admission Canadian Neurological and Rankin Scale.

Etiologies: Racial Differences

Differences were most obvious within the large 'other' group (Table 3), which included 21 of 29 (72%) blacks and 66 of 124 (53%) whites. The vast majority of strokes in blacks studied in this limited sample were attributable to infection-related vasculitides (HIV, tuberculosis, Takayasu's, syphilis, neurocysticercosis) (n = 12, 57%).

Initial Clinical Diagnosis Versus Final Etiological Diagnosis

The initial clinical diagnosis guiding emergent therapy was made according to the OCSF classification and later compared with the final postinvestigational diagnosis as per TOAST classification. No significant differences were found in the four major clinical subgroups of the OCSF classification compared with the TOAST classification.

Severity of Stroke as Assessed by CNS, Barthel, and Rankin Scales

Assessment for initial neurological deficit (by CNS scale), revealed that 47% were normal and a further 40% had a mean score of 9.4. When the Barthel Index was computed, 4% had a normal Barthel index on admission and a further 65% allotted a score of 16 to 19. Measurement by Rankin score, 87% had a score of 0 to 3 (i.e., ambulant). There was moderate agreement between the CNS and Rankin scales (kappa = 0.58) (Table 5). Note that these figures apply to the first examination, which occurred in 44.1% within the first 48 hours, in 63% within the first week, and in 92% within the first month of their stroke.

Cognitive Testing

Cognitive testing results were abnormal by the neurocognitive screening test in 92 (54%) of the patients with 104 instances of higher cortical functions deficits (HCFD). Aphasia (35), apraxia (29), amnesia (13), and neglect syndromes (9) were the most frequently encountered. Aprosodias, frontal lobe syndromes, and anosognosias were encountered in 5 patients each, and agnosias, alex-

ias, and miscellaneous (visual hallucinations, illusions and palinopsias) occurred in 1 patient each. As per protocol, neuropsychological evaluation was required in 36 patients all of whom were abnormal on neuropsychological testing. In 9 of these 36 patients, the HCFD screening test was normal. If neuropsychological testing is regarded as the gold standard for the assessment of cognitive impairment, then the sensitivity of the HCFD screening test is 0.75 (0.61 to 0.89, 95% confidence intervals). The positive predictive value of the HCFD screening test would be 100%. Specificity for HCFD was considered unimportant and was not calculated.

Prognostication

The cerebral perfusion index (CPI) was measured in 32 patients during the course of the study with a good (CPI, 15 to 20) result in 3 of 32 (9.4%), medium (6 to 12) result in 26 (81.3%), and poor (1 to 5) result in 2 (6.3%). Although sample sizes were small, there was evidence to suggest that patients with a poor CPI (2 of 32, 6.3%) had significantly higher Rankin scores than patients with good or medium CPI (ANOVA $P = .029$).

Complications

Eight specific categories of complications were sought according to predefined criteria. In order of the frequency that they occurred, these included behavioral abnormality in 46, depression in 11, seizures in 11, recurrent stroke in 6, pneumonia in 2, and no instances of pulmonary embolus, brachialgia (shoulder and arm pain related temporally to the stroke), and deep venous thrombosis.

Follow-up

Follow-up between 1 month and 1 year was possible in 106 of 172 (62%) of patients by visitation and if telephone follow-up was included, in 154 (90%). Follow-up was recorded at set periods of 1, 2, 4, 6, and 12 months. For each patient for whom follow-up was possible at the time of reporting, the longest time since stroke onset within the first year was recorded and graded according to the Rankin scale. With maximum follow-up at 1 month, there were 23 patients (mean Rankin score, 1.26; range, 0 to 4), at 2 months 22 patients (mean Rankin score, 1.45; range, 0 to 4), at 4 months 23 patients (mean Rankin score, 1.48; range, 1 to 3), at 6 months 13 patients (mean Rankin score, 1.69; range, 0 to 4), and at 12 months 25 patients (mean Rankin score, 1.2; range, 0 to 3). The overall mean Rankin score was 1.4. During the 4-year period of observation 7 patients died.

Treatment

Conventional treatment included antiaggregant therapy with aspirin in 116, anticoagulation with warfarin in 22, with heparin in 20, carotid endarterectomy in 8, and

randomization to either aspirin, heparin, both, or placebo as per International Stroke Trial in 5 patients. Treatment of underlying precipitating conditions included folate and vitamin B therapy for hyperhomocysteinemia (1), treatment for neurocysticercosis (3), antituberculous therapy (3), neurosyphilis (2), HIV (5), venesection for polycythemia (2), surgical aneurysm clipping (3), surgical arterial reconstruction for Takayasu's arteritis (4), and optimization of migraine management and therapy (5).

Discussion

Young stroke series reported to date have been largely retrospective, included patients with transient ischemic attack or cerebral ischemia, and have lacked clinical standardization made possible by clinimetric scales. The present study adds to the experience noted by others that causes of stroke in the young are many. However, being the first young stroke study to be reported out of South Africa, obvious differences are apparent.

This study delineates four major points with respect to the young stroke patient. Although a wide variety of symptoms ($n = 18$) were prospectively recorded, a surprising 38 of 172 (22%) patients had nonclassifiable symptoms. The majority of these nonclassifiable symptoms were consistent with a sudden-onset frontal system syndrome behavior. The National Stroke Association in the United States has been responsible for extensive public education of symptoms of stroke, listing 6 of the most important ones.⁴⁶ By recording symptoms from younger people, there is less likelihood of other concomitant neurodegenerative disease than an older stroke population. In this study, the CNS, Barthel, and Rankin scores on admission indicated that the majority had relatively mild strokes adding to the probability of reliable symptom reporting. The message from this young stroke data bank is, therefore, that over 18 different symptom complexes are possible. By limiting symptoms to 5 or 6 items, albeit a practical approach, a significant number of symptoms in the acute stroke setting may be missed.

Recognizable independent stroke risk factors are increasing all the time and since the establishment of the data bank, infection, lipoprotein (a), sleep apnea, and hyperhomocysteinemia have been accepted as independent risk factors for stroke. To avoid missing a possible association of risk factor and stroke, 26 different risk factors (Table 1) were collected, some well established, others as yet uncertain. In addition to finding the well known risk factors predominating, infection was the only and probably the most likely cause of stroke in 6% and recent emotion or personal stress the sole factor in 5%. The fact that more instances of sleep apnea were not encountered may well be an investigative logistical problem as not all patients have the test and no further inferences can be drawn from the results at this time.

Although this study is not population-based but a

hospital-based case series, there were differences compared with other hospital-based young stroke studies (Table 4). A major difference was noted in the frequency of the etiopathogenetic groups. The TOAST 'other' group, which accounted for about half of all the etiologies, emphasises the varied causes and the consequent necessity of a comprehensive workup. Overall, the presence of prothrombotic factors, vasculitides of infective origin, and dissection were the most common definite or presumed causes in young patients. All are treatable, potentially treatable, or avoidable through public health education, with obvious personal health and socioeconomic benefits.

Ethnic differences are important to determine for many reasons, probably the most notable being the added insight into pathophysiology. Black/white differences noted are different from those noted in North American studies^{47,48} of stroke in general and even other Southern African studies done more than 10 years previously.⁴⁹⁻⁵² No doubt investigative advances and the increasing burden of infective causes such as HIV, tuberculosis, and syphilis, all of which are on the increase, are part of the explanation. As the database is ongoing, with increasing numbers of black patients entered into the study, a clearer picture may emerge, especially as the database will incorporate a regional hospital that will be population based with respect to blacks. Sociopolitical constraints were the reasons for the relatively low number of black patients enrolled early within a tertiary care facility and having as part of their stroke investigation a brain scan. This is despite accounting for over 80% of the South African population.

Regardless of the initial clinical categorization according to the OCSF classification, this had little bearing on etiology as presented within the TOAST categories. This excludes the 15 patients who had intracerebral or subarachnoid hemorrhage. Therefore, a comprehensive workup as to cause is warranted, no matter the clinical presentation. As an obvious example, a clinically diagnosed lacunar syndrome according to the OCSF was only classified as a small artery disease after appropriate investigations in 6 of 17 (35%) patients. Although clinical classification was found to be helpful in guiding the initial sequence and nature of investigations (e.g., CT for clinical cerebral hemorrhage and MRI for posterior circulation strokes), ultimate diagnosis by TOAST classification showed no significant association with the clinical OCSF classification.

The majority of stroke patients had favorable CNS, Barthel, and Rankin scores (Table 5), yet a large proportion (54%) had cognitive impairment. Interpretations may be that the majority of patients with stroke, depending on the population sampled and selection biased may have a relatively mild stroke with the advent of good recovery and opportunity for effective secondary prevention, provided a correct etiological diagnosis is made. Also, the fact

that more than half of patients have a neurocognitive deficit implies that this is an important manifestation of neurological deficit that deserves better quantification than current scales allow. This has obvious importance for measuring treatment responses to new drugs and interventions.

The data bank also enabled the testing of early prognostication with newer modalities such as the cerebral perfusion index.⁴⁵ During the time of data collection, 31 patients had a transcranial Doppler study and SPECT brain scan within the subacute stroke period. The correlation with the mean Rankin score at 48 hours showed no significant differences for the medium and good outcome prognostication indices, but showed significantly adverse outcome for the poor index group.

Potential criticisms of the current study would include selection bias of the population studied, not administering second tier investigations to all patients, and reliance on bedside clinical testing of cognitive disturbance only without formal neuropsychological investigations in all patients. Solutions to the first would include local patient and medical personnel cerebrovascular education and gradual rectification of past, racially influenced tertiary care availability. Because patients often have several risk factors and more than one possible cause of stroke (e.g., atrial fibrillation and carotid artery stenosis), ending the workup at the first positive test may not be the optimal approach. As a complete battery of extensive investigations in every stroke patient is neither ethically acceptable nor clinically necessarily of advantage, a tailored and hierarchical protocol was designed. This could also be viewed as being a cost-effective method of investigation for such a complex problem. As pointed out by Adams,⁵³ until various algorithms are compared, stroke diagnostic plans must be individualized with a recommended minimum workup in all patients and additional work up in selected patients. The algorithm of the current study is similar to ones used in other studies in that it is a tailored protocol with the investigations guided by the clinical presentation. It differs from all the studies referenced¹⁻²⁹ in that a greater number of standardized scales, symptoms, risk factors, and cognitive disturbance were collated. In mitigation of the three-tier investigative protocol, the study of Hornig et al.⁵⁴ of cardioembolic stroke from three current stroke data banks, revealed that widespread screening of stroke patients with TEE ($\geq 90\%$) in the registries did not appreciably increase the proportion of patients with a final diagnosis of cardioembolism when compared with a tailored protocol as in the present study. The rationale of having a comprehensive screening test but with in-depth neuropsychological evaluation in selected patients appears to be warranted in view of the impracticality of administering a time-consuming battery of demanding tests to acute and subacute stroke patients. The 25% false-negative rate of HCFD submitted for

further cognitive testing underscores the need to have a hierarchical approach to this problem with a need for both methods.

In conclusion, this study expands the database of stroke in young people in that causes display inter-regional and intraregional variation, and may often be relatively mild but with cognitive deficits, the true clinical importance and extent of which remains uncertain. Intensive investigation influences the mode of therapy.

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Cognitive Dysfunction in Isolated Brainstem Stroke: A Neuropsychological and SPECT Study

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In a prospective series of patients with brainstem stroke ($n = 73$) of the Durban Stroke Data Bank ($n = 752$), five patients with first-ever, isolated brainstem stroke were studied neuropsychologically and with single-photon-emission computed tomographic (SPECT) scanning. Magnetic resonance brain scanning showed four pontine infarcts and one midbrain infarct without accompanying diencephalic or cerebral convexity lesions. Frontal ($n = 5$) and parietal ($n = 5$) hypoperfusion was detected by SPECT scanning and comparison in terms of mean counts made to five age-matched controls with a significant P value of .01 and .02, respectively. Neuropsychological testing showed a frontal system syndrome in all five patients and parietal lobe signs in two. Excellent medical recovery ensued in four of the five patients and a moderately good recovery in one as judged by the Canadian Neurological Scale, Barthel Index, and Rankin Scale. The three relatively young patients in this series were unable to resume their former employment. This was attributed to a significant frontal system syndrome. Brainstem stroke may cause significant cognitive impairment best delineated by formal neuropsychological evaluation, and SPECT scanning may be more sensitive than structural neuroimaging techniques in this setting. **Key Words:** Brainstem stroke—Neuropsychology—SPECT brain scanning.

Patients with isolated brainstem stroke are characterized by combinations of cranial nerve and long tract signs and reticular formation deficits. They are not expected to have higher cortical function deficits (HCFD) such as aphasias, apraxias, agnosias, hemineglect syndromes, amnesias, or frontal lobe syndromes. Visual or auditory peduncular hallucinosis, in itself rare, has been the most frequently described cognitive derangement with such

strokes.¹⁻⁵ A neurobehavioral disturbance in such patients has been inferred in only a few such reports^{6,7} and has not been systematically studied neuropsychologically or with functional imaging techniques such as single-photon-emission computed tomographic (SPECT) and positron-emission computed tomography (PET) scanning.

The concept of strategically placed small deep cortical (lacunar) infarcts, resulting in functional deactivation and a neurobehavioral syndrome such as a frontal lobe syndrome, has been described^{8,9} and recently in association with capsular genu infarction by Tatemichi et al with corroborative neuropsychological and SPECT data.¹⁰ The diaschisis phenomenon, with contralateral hypoperfusion of the cerebellum and hemispheric stroke, may be seen in up to 50% of stroke patients.¹¹⁻¹³ Similarly, contralateral cerebral hemispheric perfusion has been shown to be depressed in patients with unilateral cerebellar vascular lesions.^{14,15} More recently, brainstem stroke with both pontine and medullary lesions has been shown to cause a

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presumed functional deactivation in the cerebellum.¹⁶⁻¹⁹ In their study of brainstem stroke and contralateral cerebellar hypoperfusion as measured by SPECT scanning, Fazekas et al¹⁶ incidentally noted two instances of ipsilateral frontoparietal hypoperfusion in two of six patients with unilateral brainstem (pontine) stroke. No clear association between SPECT perfusion changes and clinical findings could be found in their two patients. Rousseaux et al¹⁷ also documented low regional cerebral blood flow in two patients with medullary infarcts with no cortical lesion on magnetic resonance imaging (MRI) brain scanning. In neither study was concomitant higher-function cortical function impairment noted. The postulated explanation was disruption of the corticopontocerebellar fiber system with the lesion having both anterograde and retrograde effects, which remains unproven. The association of brainstem infarction with ipsilateral cerebral hypoperfusion had not been reported previously.

In the studies to date, concomitant thalamic lesions, neurodegenerative disease, multiple infarcts, white matter hyperintensities, and other subclinical infarction not identified by computed tomography (CT) are potential confounding variables in the few patients studied. The two studies addressing brainstem infarction and cortical hypoperfusion^{16,17} each had patients with other lesions on the MRI scans in addition to the lesion thought to be relevant. The present study addresses all of these potential confounding variables. MRI is used for diagnosis of infarction; only first-time, single, small infarcts or hemorrhages limited to the brainstem were studied and relatively young stroke subjects were used.

Methods

Stroke Data Bank

Patients were derived from the Durban Stroke Data Bank (DSDB), a prospective stroke registry. The minimum work-up includes basic stroke-relevant blood tests, brain scan (CT or MRI), chest radiograph, and electrocardiogram. Additional work-up when appropriate includes transcranial Doppler, duplex Doppler sonography, MR angiography, SPECT scanning, in-depth neuropsychological assessment, prothrombotic tests, cerebral angiography, cerebrospinal fluid analysis, Holter monitoring, and transesophageal cardiac echo. A category of seldom-required tests that includes examination for rare, often-inherited disorders and brain biopsy is also catered to. To enable comparison with other data banks and stroke trials, the Canadian Neurological Scale (CNS), Oxfordshire Community Stroke Project Score (OCSP), Trial of ORG 10172 In Acute Stroke Treatment (TOAST) pathophysiological classification, Rankin Disability Scale (R) and Barthel Index (BI) have been incorporated into the registry.

Cognitive Testing

A HCDF screening examination is applied to all alert patients in the DSDB in the first 2 weeks of presentation. Neuropsychological testing is performed in those alert patients with mild deficits on bedside testing or in whom the screening examination suggests but does not decisively delineate a syndrome. A formal battery of neuropsychological tests was administered to 70 of the 752 patients of the DSDB by these criteria by the same neuropsychologist within 1 month of the stroke onset. The tests comprising the battery included clinical interviews, Trail Making Test,^{20,21} Symbol Digit Modalities Test,^{22,20} South African Wechsler Adult Intelligence Screen (Digit Span, Block Designs, Object Assembly),²³ Rey Complex Figure Test,²⁰ Wechsler Memory Scale,²⁴ Rey Auditory Verbal Learning Test (RAVLT),²⁰ Verbal Fluency Tests (FAS) (adapted from Benton and Hamsher 1976 and cited in Lezak in 1995),²⁰ Category Naming (adapted from Newcombe 1969 and cited in Lezak in 1995),²⁰ Wisconsin Card Sorting Test (WCST),²⁵ and Luria's Neuropsychological Investigation (South African adaptation),^{26,27} which includes preliminary conversation, motor functions (optic-spatial organization), writing (letter), reading (text), and arithmetic skills. The neuropsychological assessment procedure incorporated both a qualitative and a quantitative data analysis, the latter according to the norms indicated above. Qualitative analysis proceeded according to a process of hypothetical deduction and was based on the principle of syndrome analysis and double dissociation per Luria.²⁸

SPECT Scanning

SPECT scanning is performed in patients with discrepancy of clinical signs and anatomical brain scan, and 20 millicuries 99m technetium-HMPAO 99 is administered intravenously. Ceretec with technetium produces a lipophilic complex that crosses the blood-brain barrier and is retained in the brain, allowing assessment of regional cerebral blood flow. Imaging is begun 2 to 3 minutes after the injection of the tracer. The patient is positioned as comfortably as possible with the room slightly darkened and is encouraged to be as relaxed as possible. Scans are obtained for 20 seconds, with regular 6° rotation of the camera head around the patient, completing a 360° rotation with approximately 60 images obtained. This requires cooperation from the patient for a period of about 30 to 40 minutes. A medium- to high-resolution collimator was used on the gamma camera. Reconstruction was performed with positioning of the patient in the orbitomeatal line, in the transverse, coronal, and sagittal planes. Transaxial slices were contiguous, 16 in number, and 3.3 mm thick. Three-dimensional reconstruction was also performed. Images were interpreted on the computer screen comparing right and left regions of interest. This was done both visually in a qualitative manner by a

radiologist blinded to the anatomical scan and semi-quantitatively, the latter adapted from methods by Podreka et al²⁹ and Steinling et al.³⁰ The transaxial slice with the largest perfusion defect was identified and a circular region of interest (ROI) traced over that area. These circular ROIs were also obtained for six areas of the gray matter. These included the cerebellum, thalami, basal nuclei, frontal, parieto-occipital and temporal regions. These areas and their mirror images on the homologous region of the other hemisphere were stored on a template and adjusted for surface area when required for a particular scan. The ROI radioactive counts from homologous regions of both hemispheres were taken to compare side-to-side perfusion differences and expressed as an asymmetry index. An asymmetry index percentage (AI) was calculated according to the formula $A-B/[A + B/2] \times 100$ where A and B represent right and left sides. AI comparison was done with five age-matched controls (on a case-by-case basis) and matched on education but not social class. Follow-up scans were not routinely performed.

Transcranial Doppler

The basal cerebral vessels and all major branches of the circle of Willis were insonated via the temporal and suboccipital windows with the EME-Transcan transcranial Doppler using mounted 2-MHz probes. Flow velocities and pulsatility indices (Gosling) were measured with special attention to the identification of intracranial stenoses and emboli detection (15-minute monitoring).

Inclusion and Exclusion Criteria

Entry criteria included only first-time, isolated single infarcts or discrete hemorrhages in the brainstem. For the study on brainstem stroke and cognitive derangement, patients had to be alert within 1 week, without other disease such as encephalopathy, drug, infective, or metabolic process. Alzheimer's disease, early dementia, and depression were excluded according to DSM-IV criteria.³¹ Patients with additional supratentorial cortical or subcortical (including leukoaraiosis, unidentified bright objects) infarcts or any other lesions were not considered for inclusion in this case series. If CT was the only imaging available, such patients were also excluded because of its poor sensitivity for brainstem stroke. Cognitive assessments performed more than 1 month after the event were not considered for inclusion in this series.

Statistical Analysis

The Wilcoxon Two Sample Test was used to compare the mean counts of the frontal and parietal regions of the patients with the frontal and parietal regions of the control group. A *P* value of $<.05$ was considered significant.

Results

Five patients met the criteria stipulated. The DSDB cascade for infarct topography and exclusion criteria among those with brainstem stroke is detailed in Fig 1. The relevant clinical details including risk factors, neuroimaging findings, and sonographic, neuropsychological, and functional imaging findings are recorded in Table 1. Two patients had four-vessel cerebral angiography, both normal. Four of five patients had cervicocephalic and transcranial Doppler studies, with only patient 5 having a reported possible abnormality, in that asymmetric velocity was detected in the right carotid siphon with a degree of turbulence suggesting a minor degree of stenosis. Four of the five patients had pontine infarcts, and one had a hemorrhagic midbrain infarct. MRI brain scanning excluded the presence of any other infarct, white matter changes, and leukoaraiosis in all five patients. The brainstem lesion and accompanying SPECT scan of patient 1 is shown in Figs 2 and 3, respectively. The absence of large-vessel disease as depicted by normal angiography and sonographic findings in all patients (except possibly patient 5) exonerates any other identifiable lesion causing the cognitive impairment. No history of Alzheimer's dementia was present in any of the patients, all of whom were normal as judged by DSM-IV criteria,²⁴ their spouses, and family. Three of the five patients also fell into the category of the young stroke population, as defined in the DSDB, at 15 to 49 years of age.

All five patients had a frontal system syndrome diagnosis on formal neuropsychological testing (Table 1), and all five patients had corroborating frontal hypoperfusion on SPECT scanning (Table 2). The full battery of neuropsychological tests could not be administered to all five patients because factors such as medical and physical impairment (for instance, right hemiparesis in patient 3, who was right handed) precluded the administration of certain tests. All had executive dysfunction (i.e., disability in planning, initiating, and executing activities and impaired self-monitoring according to the qualitative analysis per Luria²⁸). Executive and frontal system dysfunction was also evident on quantitative analysis. For example, patients 1 and 5 had the lowered and fluctuating learning plateaus on the RALVT associated with executive dysfunction in that because of a failure to organize the material to be learned, repeated presentation did not lead to an increase in the quantity retained (patient 1: 6, 9, 10, 10, 9; normal is > 12 by the fifth trial, and patient 5: 5, 5, 5, 4, 4).²⁰ Patient 1 also had impaired performance on the WCST with a significant number of perseverative errors (52 of 128 trials). This is consistent with frontal lobe dysfunction according to Lezak²⁰ (mean number of perseverative errors made by patients with dorsolateral frontal lesions is 51.5). The same patient also showed impaired performance consistent with frontal system abnormalities on several other quantitative tests. For example, his

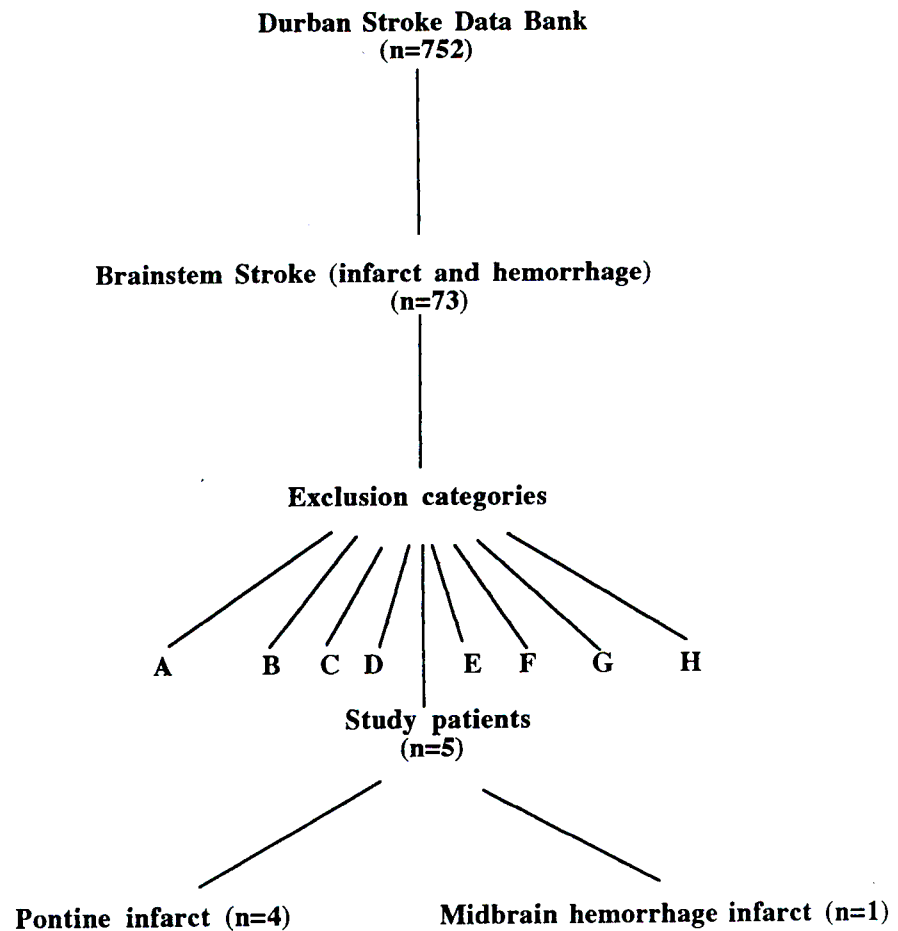


Figure 1. Durban Stroke Data Bank cascade of patients with brainstem strokes, exclusion criteria, and those included (n = 5).

Exclusion categories	n
A - Normal cognitive screening test	36
B - Concomitant other infarct noted; usually part of cerebellum and thalamus	30
C - Unidentified bright objects noted elsewhere on MRI scan	26
D - Infarct confirmed by CT brain scan only. No MRI	11
E - Neuropsychological testing done more than one month after ictus or not done	3
F - Patient not alert. Usually drowsy	1
G - History of other neurodegenerative disease such as Alzheimer's and hydrocephalus	1
H - Clinically depressed according to DSM-IV criteria	1

poorly organized copy of the Rey Complex Figure led to size and relationship errors (scoring on the tenth percentile), as well as a resultant impoverished recall from memory (scoring at the seventh percentile; normal range 25th to 75th percentile). That his poor recall or the complex figure was primarily caused by a lack of organization is borne out by his ability to recall the simpler, visual reproduction designs of the Wechsler Memory Scale (patient's score 12; mean 10.09; standard deviation 3.01). This pointed to "frontal amnesia."³² He also showed decreased verbal fluency on the Category Naming Test, scoring 17 for objects (mean is 30.2) and 13 for animals (mean is 16.9).²⁰ In patient 2, an executive problem was, for instance, noted in that the copy of the Rey Figure was

poorly planned and fragmented, with the result that as with patient 1, his immediate recall was impoverished, also falling at the fifth percentile (normal range is 25 to 75).²⁰ His ability to accurately recall simpler, visual designs on the South African adaptation of Luria's Neuropsychological Investigation for Zulus confirmed that his poor recall of the complex figure was caused by poor organization. Patient 4 showed marked verbal fluency problems on the Category Naming Test, achieving only four objects (mean, 30.2) and nine animals (mean, 16.9).²⁰ The assessment of patient 3 was limited on account of a severe right hemiparesis, and the diagnosis of a frontal system syndrome was made on the basis of predominantly qualitative data. His RALVT scores were, however, impaired (4,

Table 1. *Clinical, investigative, neuropsychological, and SPECT findings*

Patients/age/ race/sex	Clinical	MRI scan	Doppler/angio	Neuropsychology 1	SPECT scan
1. 37-year-old white man	Right hemiparesis, left temporal headache, blurring of vision. Expres- sive dysphasia, familial poly- cystic kidneys, hyperlipidemia	Left mesencephalic midbrain/pontine hemorrhagic infarction	Four-vessel cerebral angiography normal	Frontal lobe syn- drome, particu- larly left frontal lobe syndrome. Parietal lobe signs: visuospatial impairment	Left frontal and pari- etal hypoperfu- sion
2. 48-year-old black man	Left hemiplegia. Diabetic and hypertensive	Extensive right hemipontine infarct	Cervicocephalic duplex Doppler and TCD normal	Frontal lobe syn- drome. Parietal lobe signs: con- structional dys- praxia	Left frontal and pos- terior parietal hypoperfusion
3. 68-year-old white man	Right hemiparesis, oscillopsia, nys- tagmus, bilateral eye abduction weakness. Hyper- tensive	Anterior segment, left pontine infarct. Basilar artery dolichoec- tasia	Duplex Doppler normal. TCD-low basilar velocity, high pulsatility index	Frontal lobe syn- drome	Right frontal and parietal lobe hypoperfusion
4. 49-year-old white man	Vertigo, imbalance, dysarthria, nausea. Hyperten- sive	Midpontine infarct	Cerebral angio, Duplex Doppler and TCD normal	Frontal lobe syn- drome	Left frontal and left parietal hypoper- fusion
5. 70-year-old white woman	Right monoparesis, right hemihypos- thesia, dysnomia. Smoker. Myocar- dial infarct	Bilateral pontine infarcts	Duplex Doppler normal. TCD- right siphon ste- nosis query	Frontal lobe syn- drome	Left parietal and left basal hypoperfu- sion

Abbreviation: TCD, Trancranial Doppler.

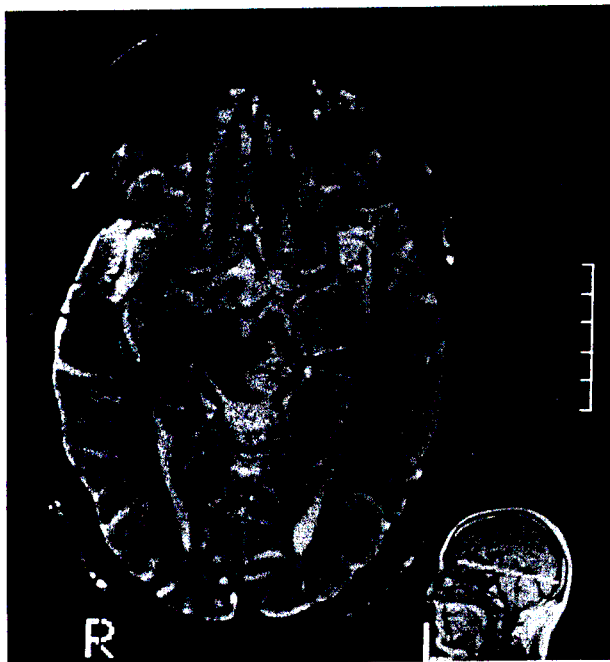


Figure 2. MRI brain scan of patient 1 showing the left midbrain stroke-hemorrhagic infarct (arrow).

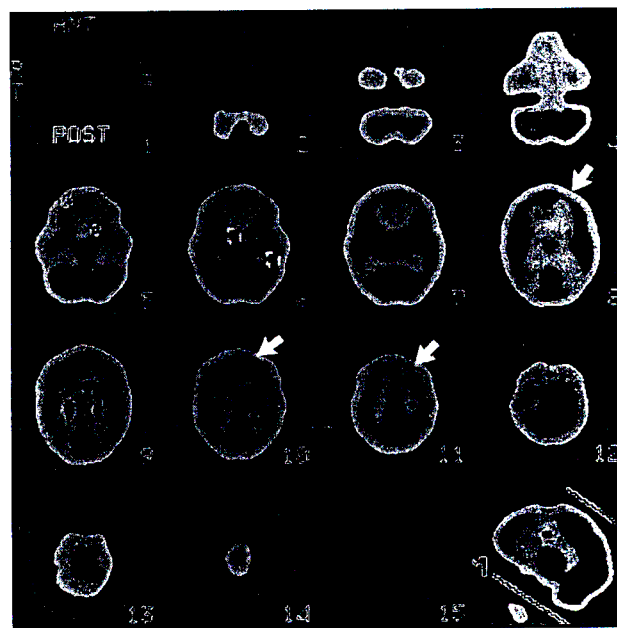


Figure 3. SPECT brain scan of patient 1 showing areas of frontal hypoperfusion (arrows).

Table 2. Asymmetry indices percentage on SPECT scanning in the five patients and five age-matched controls

Patients	Frontal region		<i>P</i> value	Parietal region		<i>P</i> value
	Mean	SD		Mean	SD	
1	12.6			17.1		
2	10			6.6		
3	36.1			8.6		
4	12.3			10.1		
5	8			18		
Mean value	15.8	11.5	.01	12.1	5.2	.02
Controls (mean)	1.9	1.97		4.2	2.7	

7, 7, 7, 9 where, as noted above, normal is 12 or more by trial 5).²⁰ In addition to frontal lobe impairment, patients 1 and 2 also displayed visuospatial problems (Table 1). Patients 1 and 2 had abnormal scores on the Block Design Test of 6.0 and 5.0, respectively (normal is 10.0 ± 2).²⁰ When provided with a plan in the form of a grid placed over the designs so that the constituent blocks were evident, they had greater difficulty than before, because the additional information exacerbated their visuospatial difficulties. This pointed to parietal systems dysfunction.³²

The timing of the SPECT scans was within 3 days poststroke for patients 2, 3, and 5, 4 weeks poststroke for patient 1, and 4 months poststroke for patient 4 (mean, 31.4 days). As an example, the MRI scan and accompanying SPECT scan of patient 1 are shown in Figs 2 and 3, respectively. All five also had some degree of parietal hypoperfusion, with patients 1 and 2 displaying parietal lobe neuropsychological impairment. Cartographic analysis of the SPECT scans guided the ROI counts and the AI calculation. These were compared against five age-matched normal control patients (study patients' mean age was 54.4 years, and controls' was 55.6 years). Analysis by Wilcoxon Two Sample Test comparing the AIs of the frontal regions of the patients with those of the control group was significant at a *P* value of .01. In comparison of the parietal regions, patients compared with the control group had a *P* value of .02. The nonparametric test was used because of the inhomogeneity of the variations of AIs.

Admission and follow up (6 months) grading with CNS score, R, and BI indicated that the patients all had an excellent recovery as determined by a neurological deficit score (CNS, impairment score [BI], and handicap score [R]) (Table 3). However, the residual neuropsychological disability in all proved to be the most significant problem in adapting to their former occupations and social interaction. The poststroke behavioral problem, identified as a frontal system syndrome on formal neuropsychological testing, was of varying degree and caused significant handicap in the neurocognitive sphere in that the three young patients (patients 1, 2, and 4) were unable to continue with their former occupation, whereas two were

medically boarded as a consequence. The current clinical follow-up of patients 1, 2, and 4 at time of reporting was 30, 24, and 20 months (mean, 24.6 months) with negligible long tract signs on examination, but collateral sources reported significant interpersonal and occupation-related problems. Patient 3 died at 9-month follow-up, and patient 5 is retired.

Discussion

Remote deactivation as evidenced by SPECT functional imaging has been well documented in patients with cortical and cerebellar infarction. Infarction in either may be accompanied by hypoperfusion in the contralateral hemisphere.¹¹⁻¹⁵ Brainstem lesions in the pons and mid-brain were subsequently noted to be associated with frontoparietal hypoperfusion by Fazekas et al,¹⁶ and Rousseaux¹⁷ documented medullary infarcts associated with cerebral cortical hypoperfusion. Cerebellar perfusion changes were not assessed in the current study, and radioactivity counts were also not compared with the cerebellar counts in view of these previously documented changes of both ipsilateral and contralateral cerebellar hypoperfusion with pontine infarction.^{18,19} Similar to the two patients of Fazekas et al (the only other study to our knowledge showing cortical hypoperfusion with SPECT scanning) all of our patients had frontoparietal hypoperfusion. Our patients differed from theirs in that all had normal MRI cerebral convexity scans, without the bilateral white matter hyperintensities noted in one of their two cases with neocortical hypoperfusion. This may have reflected more widespread subclinical cerebrovascular disease in their patients, and it is possible that the white matter hyperintensities represented minor ischemia or infarction.

The present study shows that such functional deactivation has a clinical correlate in terms of neuropsychological impairment, and more importantly that this may occur with isolated brainstem stroke. The normal MRI scans devoid of infarction or white matter lesions in any part of the brain other than the brainstem infarct greatly strengthen the case for remote deactivation caused by the

Table 3. Canadian neurological scale, Barthel index, and modified Rankins score on admission and follow-up at 6 months

Patients	Admission values			At 6 months		
	CNS	Barthel	Rankin	CNS	Barthel	Rankin
1	9.5	18	2	10.5	20	1
2	5	6	4	8	15	2
3	6.5	6	4	10.5	20	1
4	11.5	20	1	11.5	20	1
5	8	19	2	11.5	20	1

isolated brainstem lesion under study and not by other concomitant subcortical lesions. The frontal system ($n = 5$) and parietal system ($n = 2$) neuropsychological deficits noted were corroborated by an appropriate hypoperfusion on the functional scan (SPECT). The three patients without clinical or neuropsychological parietal signs but SPECT parietal hypoperfusion may have had subclinical involvement, or the timing of investigations may be an explanation. In agreement with previous studies,³³ the deficits tended to be less severe and more transient than superficial cortical infarcts. They may nevertheless significantly impact the extent of quantifiable neurological deficit, medical management, and both physical and psychological rehabilitation. In terms of functional recovery of such lesions, evidence points to a synaptic reactivation of neurones, and this may be augmented by rehabilitation.³³

The postulated mechanism is a remote effect (diaschisis) of the brainstem lesions on one or more of the five delineated frontal subcortical circuits.³⁴ This may be via one of the open efferent and afferent connections to these circuits. Only patient 1 had a midbrain lesion, the others had pontine lesions. Strictly speaking, only the substantia nigra forms part of the frontal subcortical circuitry.³⁴ Another mechanism of remote effects is via the corticopontocerebellar fibers, which in turn project to the red nucleus and ventrolateral nucleus of the thalamus and to the frontoparietal cortex.³⁵ The corticopontine fibers are derived principally from the frontal and parietal lobe. This postulate presumes an anterograde and retrograde functioning of the corticopontocerebellar fibres. Four of the five patients had frontal and all five had a degree of parietal hypoperfusion as seen on SPECT scanning. This may reflect the functional deactivation or diaschisis process of the pontine (four patients) and midbrain (one patient) lesions on the frontoparietal cortex. Other possible mechanisms could involve brainstem-hemisphere tracts, including those that traverse the pons, such as the reticulothalamic, spinothalamic, or vestibulocortical fasciculi.^{36,37} The cerebellum has been implicated in nonmotor cognitive functioning.³⁸ Interestingly, in the study of Daum et al,³⁸ patients with cerebellar and brainstem, but not those with only cerebellar pathology, showed cognitive impairment predominantly of a frontal lobe nature. These findings lend some support to our own study.

Neuropsychological impairment that correlated with the functional SPECT scanning abnormality was noted in these patients, but its significance in terms of future disability and handicap only became evident at follow-up at 4 to 6 months. The most significant problem in terms of impairment and handicap as measured by the R scale was probably neuropsychological. This was a frontal system syndrome in all five patients. As a result, three of the relatively young patients were unable to continue work despite their otherwise excellent medical outcome at 6 months as assessed by CNS, BI, and R (Table 3). The

discrepancy between the scored items and neuropsychological handicap was most profound in the younger patients, because the two elderly patients (3 and 5) were retired, making this yardstick inappropriate.

Potential criticisms of the article are several. Because it is impractical to administer neuropsychological batteries to every stroke patient in large stroke data bank case series, it is quite possible that some patients had normal cognitive screening test results yet might nevertheless have had impairment on more rigorous neuropsychological testing. Only a cursory depression scale assessment was administered, and it is possible that depression may have played a part in more than the one patient so identified. Attentional impairment as a confounding factor, on the other hand, was unlikely to have been a factor because all patients had digit span scores within normal age-adjusted norms. SPECT scans were not done at the same time in all patients, and this too may have influenced results in the patients under discussion and excluded others. Logistically, neuropsychological testing and SPECT scanning were not performed at the same time, and this also may have influenced results. We regard this as a pilot study generating a hypothesis worthy of testing in a larger sample of patients because the small number of observations may be too small to justify the conclusions based on statistical analyses.

Isolated brainstem stroke may be associated with significant cognitive impairment, which may be the most important impairment, and with subsequent later disability handicap. Neuropsychological testing as an extension of the neurological examination (for recording the true extent of neurological deficit) and functional brain scanning (SPECT) are pivotal modalities required for diagnosis.

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Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

The Durban Cerebrovascular Data Bank (DCDB) experience

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Abstract

Intracranial artery dolichoectasia is recognised as an underdiagnosed yet potentially treatable stroke mechanism. A prospective analysis of patients in the Durban Cerebrovascular Data Bank (n=762) was undertaken over a 4 year period and 32 patients identified as meeting established criteria. No significant difference was found between those patients presenting with stroke as opposed to transient ischaemic attacks. There was a trend to a preponderance in males and most patients had hypertension and presented with posterior circulation ischaemia or

infarction. All patients were identified by first tier investigation with conventional brain scanning (MRI or CT) but contemporary imaging modalities such as MRA and transcranial Doppler sonography aided in the diagnosis. Six patients were treated with anticoagulation after failing antiaggregant therapy with aspirin with no recurrent events over a 15.6 mean month follow up period.

Background

Most drug interventions in acute stroke have been negative.¹⁻³ Those recently published, that are beneficial, have shown a disappointing small benefit ratio⁴⁻⁵ implying subgroups in the stroke population may have a better or worse response. Stroke in itself is considered too generic for a single treatment to be effective and the focus appears to be emerging that we will need to identify mechanisms of stroke to tailor treatment more effectively, clinically and to save cost.

Elongation and tortuosity (dolichoectasia) of the basal intracranial vessels is known to cause cerebral ischaemia and infarction, compressive cranial neuropathies, hydrocephalus and a variety of brainstem symptoms.⁶⁻⁷ Megadolichoectatic basilar artery syndromes have been the most extensively studied by autopsy, angiography, CT and MRI. No distinct clinical syndrome is recognised, probably leading to under-diagnosis.⁶ The reported incidence is 0.06-5.8% but varying criteria have been applied.^{8,9} Newer imaging procedures can facilitate the non-invasive diagnosis. The entity has not been subject to prospective analysis.⁶

Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

from page 4

The prospective Durban Cerebrovascular Data Bank specifically included this as a predefined entity and the results to date are presented.

Methods

Recruitment

All patients with stroke or transient ischaemia between October 1992 and October 1996 admitted to a Durban metropolitan acute stroke unit were recruited for the study. The definition of stroke was that of the WHO definition of stroke¹⁰ but in addition those with appropriate brain scan (CT, MRI or SPECT) changes consistent with stroke were entered into a digitised registry. A transient ischaemic attack (TIA) was defined as a sudden onset neurological deficit, reversible within 24 hours with migraine, seizures, cerebral mass lesions and metabolic causes excluded clinically and by appropriate investigations.

Investigations

A three tier investigative protocol was used, incorporating a basic minimum workup, tests often used and tests seldom used. The latter two tiers were used as appropriate - tailored to each individual patient's conundrum of clinical details. The minimum workup included basic stroke relevant blood tests - complete blood count, platelets, serum electrolytes, urea, creatinine, lipogram, erythrocyte sedimentation rate, serum glucose, International Normalised Ratio (INR), partial thromboplastin time (PTT), brain scan (CT or MRI), chest radiograph and electrocardiogram. Additional workup when appropriate, the second tier, included transcranial Doppler, duplex Doppler sonography, MR

angiography, SPECT scanning, in-depth neuropsychological assessment, prothrombotic tests, cerebral angiography, cerebrospinal fluid analysis, Holter monitoring and trans oesophageal cardiac echo. A category of seldom required tests, the third tier, included examination for rare, often inherited disorders (including homocystinuria, sickle cell disease, haemoglobinopathies, mitochondrial cytopathies, other genetic and metabolic causes of stroke) and brain biopsy to diagnose some of the vasculitides is also catered for.

Neurological scales and classifications

To enable comparison with other data banks and stroke trials, the stroke patients were further categorised into several standardised scales incorporated into the registry protocol. These are a clinical stroke scale; the Oxfordshire Community Stroke Project Score (OCSP) divided into total anterior circulation (TAC), partial anterior circulation (PAC), lacunar (LAC) and posterior circulation (POC), a neurological deficit scale; the Canadian Neurological Scale (CNS), a disability scale; the Barthel Index (BI), a handicap scale; the Rankin Disability Scale (R); and an expanded aetiopathogenetic (TOAST) classification with categories for large vessel disease, small vessel disease, cardiogenic, undetermined and other. In the "other" category were included probable or presumed causes of stroke after the investigative protocol failed to determine another cause of stroke. Comorbidity was also documented. The other category included strokes in association with vasculitides, cervicocephalic dissection, aortic arch atheroma, metabolic

strokes, drug induced strokes, prothrombotic states, migraine, Moya Moya syndrome, cerebral venous thrombosis and dolichoectasia. All patients were assessed clinically and a final diagnosis made with all available investigative data by the same cerebrovascular neurologist.

For a diagnosis to be made within the framework of the extended TOAST classification, the diagnosis needed to be one of exclusion in which all clinically indicated tests, according to the hierarchical protocol, were negative save for the factor in question. It is acknowledged that some would be definite diagnoses, some probable and some possible by this method.

Radiological dolichoectasia criteria

Ectasia=>4.5mm diam

Basilar artery lies lateral to the margin of the clivus in the cerebellopontine angle or above the level of the suprasellar cistern.^{11,12}

Cognitive testing

This was deemed to be important so as not to miss the true extent of neurological deficit as this is not reflected adequately in the current neurological scales. A HCFD screening examination is applied to all alert patients in the DCDB in the first two weeks of presentation. Neuropsychological testing is performed in those alert patients with mild deficits on bedside testing or where the screening examination suggests but does not decisively delineate a syndrome. A formal battery of neuropsychological tests was administered to 70 of the 762 patients of the DCDB by these criteria by the same neuropsychologist within one month of the stroke onset.

to page 6

Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

from page 5

Statistics

For proportions, a univariate analysis was done using Chi-square tests of association. For continuous variables, the t test was used for significance of means, and the non-parametric median test for judging the significance of differences in median values.

Results

The dolichoectasia radiographic diagnoses were sought in stroke (n=762) and TIA patients (n=312) and were not significantly different in terms of frequencies or mean age. Gender differences attained marginal significance (Table I). Hypertension was by far the most common vascular risk factor

were noted (Table III). Anatomical brain scan imaging revealed posterior

Table III: Clinical presentations

I) Syndromes	
Posterior circulation	16
Anterior circulation	1
Partial anterior	1
Isolated symptoms	1
Isolated cerebellar syndrome	1
II) Isolated symptoms and the following	
Facial paralysis	1
Vertigo	1
Facial neuralgia	1
Facial paresthesia	1
Ataxia	1
Diplopia	1
Facial numbness	1
Facial weakness	1
Facial numbness and weakness	1

Table I: Demographics

	Stroke	TIA	P-value
Number	762	312	
Gender (male/female)	306/456	132/180	0.08
Age (range/mean/median)	50-89/68/65	50-89/68/65	

Table II) and the most common syndrome presentation was a posterior circulation presentation (Table III). In addition, however, isolated symptoms such as facial neuralgias, dysesthesias, paresthesias, vertigo, facial paresis (Bell's palsy), ataxia, and diplopia

Table II: Associated medical and neurological conditions in the stroke cohort

Hypertension	234
Hypercholesterolemia	172
Diabetes	112
Myocardial infarction	72
Chronic renal disease	52
Chronic heart disease	42
Stroke	32

circulation infarcts in 69% of the dolichoectasia stroke subgroup with multiple infarcts also seen anteriorly in 31% of the stroke subgroup. Ventricleomegaly was noted in 4 patients

and was thought to be an aetiopathogenetic factor in 3 of the 4 patients who presented with a frontal lobe syndrome.

With respect to the aetiopathogenetic diagnoses according to the TOAST classification, all received the label of "Other" but concomitant pathology was diagnosed in 9 patients. These included 4 cardiac, 2 with significant carotid stenosis, 1 with small subdural haematoma, 1 with facial herpes Zoster, vasculitis and 1 with sleep apnoea syndrome with a respiratory disturbance index of 17 diagnosed by polysomnography.

The radiographic investigations listed in Table IV, reveal that all

patients' dolichoectasia were diagnosed by parenchymal brain imaging. Those that required angiography, both invasive and non-invasive, had these for

Table IV: Radiological investigations

I) Brain parenchymal imaging and angiography (MRA, catheter angiography, spiral CT)	
Arterial territories	n (%)
Basilar artery	32 (100)
Vertebral artery	2 (6)
Anterior circulation - carotid arteries	1 (3)
Anterior circulation - middle cerebral arteries	1 (3)
Aortic arch with Shanny aorta syndrome	1 (3)
II) Brain parenchymal imaging abnormalities in the stroke cohort (CT and MRI)	
Posterior circulation infarcts	27 (100)
Multiple	18/26 (69)
Ventriculomegaly	4/31 (13)
III) Sonography - Transcranial Doppler	
Low velocity and increased pulsatility	18/25 (72%)

reasons of comorbidity and for verification of the diagnosis. TCD revealed a typical low velocity, high pulsatility signal in the majority (72%) of patients in whom this investigation was done.

In the stroke cohort, patients generally presented with minimal deficit as evidenced by the Canadian Neurological Scale mean value of 10.7 (maximum score is 11.5, minimum 0). Table V reveals the preponderance of posterior circulation infarction as defined by the standardised OCSP scale.

Table V: Clinical neurological scale (OCSP)

	n	(%)
POC	19	(70)
PAC	5	(19)
IAC	2	(7)
STAC	4	(14)
Total	27	(100)

to page 7

Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

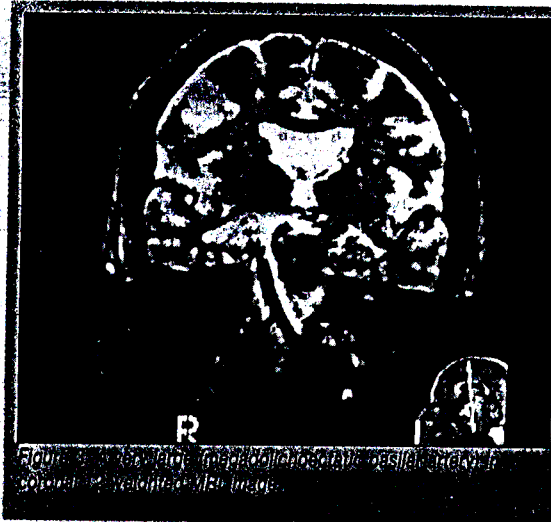
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Treatment

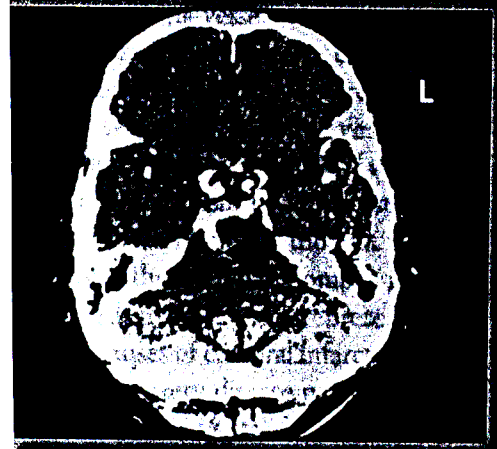
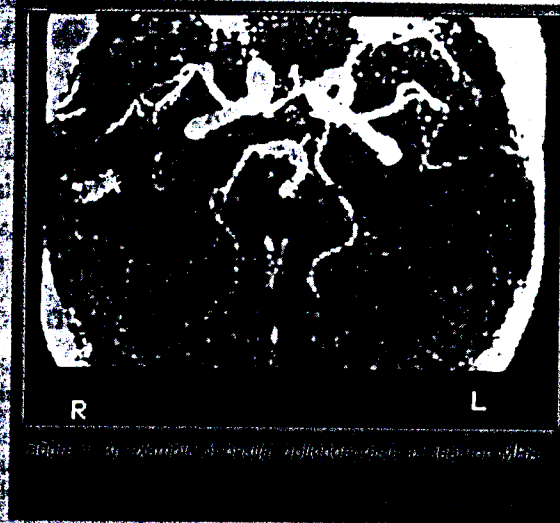
All patients except one (who was thought to have dissection of the basilar artery and possible subarachnoid haemorrhage) received aspirin in the first instance. In 6 patients who had recurrent symptoms while on aspirin (aspirin failures), including recurrent strokes in 4, warfarin was instituted with an INR range of 2.0-3.0. Over a mean period of 15.6 (range 3-36) months no further symptoms were reported in these 6 patients.

The figures represent typical examples of vertebrobasilar dolichoectasia as imaged by contrast enhanced brain CT scanning, MRI brain scanning and MRA. Figures 1 and 2 show two

different appearances of the dilated and laterally displaced basilar artery on contrast enhanced CT scanning. Figure 3 shows a very large



associated with this disorder as well as follow up i.e. posterior circulation stroke and/or isolated symptoms such as facial paresis (Bell's palsy), facial neuralgia and hemifacial spasm. The diagnosis can easily be made in most cases within the first tier (CT brain or MRI brain scanning) of the investigative protocol, negating the necessity of resorting to invasive studies. This is an important clinical point as the majority of these patients present with posterior circulation ischaemia or stroke, a syndrome in which invasive angiography is associated with a significant morbidity and mortality.



(megadolichoectatic basilar artery) in coronal T2 weighted MRI image and Figure 4 an example of basilar dolichoectasia as seen on MRA.

Discussion

This study represents one of the largest series and one of few prospectively evaluated consecutive case series within a large data bank series of dolichoectasia of the cerebral arteries. This has allowed delineation of the frequencies of different stroke syndromes

In this series all patients were identified by CT or MRI brain scanning. MRA was done in 6 patients, catheter angiography in 3 and spiral CT in 1. Angiography in these 10 patients was used to better delineate the ectatic arteries and confirm the diagnosis, the latter often necessitated by the presence of comorbid-

ity. Transcranial Doppler sonography has a specific wave form associated with this syndrome and in agreement with Rautenberg *et al*⁶, in this study it was found to be a useful adjunctive test in cases where there may be some doubt as to the presence of dolichoectasia.

In agreement with the other larger series on this topic¹³⁻¹⁶, the three main modes of clinical presentation - ischaemic, cranial nerve compression and mass effect - were noted, albeit mostly ischaemic (85%). In the ischaemic

to page 8

Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

from page 6

Treatment

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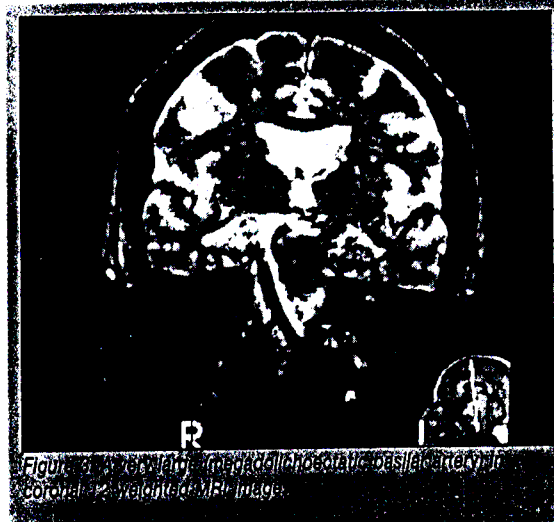


Figure 3: A very large, dilated, and laterally displaced basilar artery in coronal T2 weighted MRI image.



Figure 1

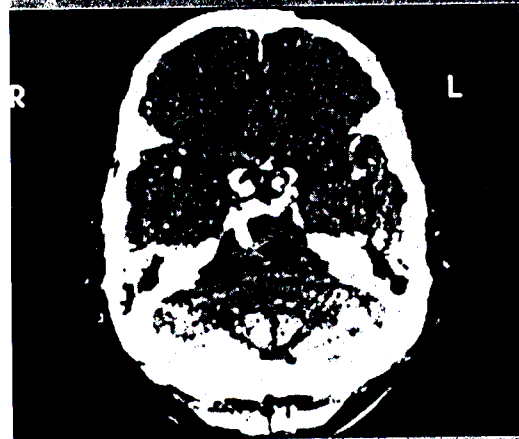
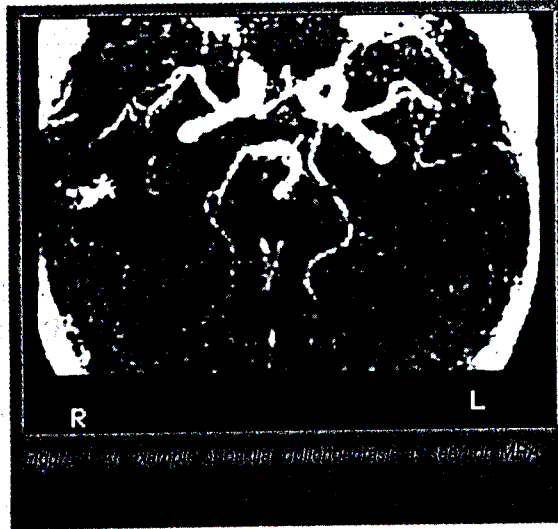


Figure 2

Figures 1 and 2: Two different appearances of the dilated and laterally displaced basilar artery on contrast enhanced CT scanning.



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associated with this disorder as well as follow up i.e. posterior circulation stroke and/or isolated symptoms such as facial paresis (Bell's palsy), facial neuralgia and hemifacial spasm. The diagnosis can easily be made in most cases within the first tier (CT brain or MRI brain scanning) of the investigative protocol, negating the necessity of resorting to invasive studies. This is an important clinical point as the majority of these patients present with posterior circulation ischaemia or stroke, a syndrome in which invasive angiography is associated with a significant morbidity and mortality.

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to page 8

Dolichoectasia - an easily identifiable and potentially treatable stroke mechanism

from page 7

group the vast majority presented with posterior circulation strokes (63%). Patients with posterior circulation ischaemia or infarction should be evaluated for the presence of dolichoectasia, as this can be done non-invasively and secondary preventative treatment is an option with Class III evidence (Appendix) of benefit from warfarin or aspirin. As most patients in this series were relatively minimally disabled (CNS mean score of 10.7), the opportunity to avoid further strokes by identification of the correct stroke mechanism becomes all the more important. This does not detract from the rare possibility of dissection of the basilar artery with poor outcome as was seen in one patient. With respect to the postulated biological mechanism as proposed by Hegedues, Sahlbeck *et al* and Schwartz *et al*^{6,17,18}, the increase in vessel diameter with dilatation, blood flow velocity is reduced and may show a plug of inversion or even zero flow near the vessel wall (transcranial Doppler evidence).⁶ Ring shaped layering of thrombus formation occurs with a smaller patent lumen and the thrombus may enter the origin of small penetrating vessels of 200-800 micrometers and give rise to thrombotic occlusion and lacunar infarction in the setting of large vessel (dolichoectatic) rather than small vessel disease. Embolism to more distal vascular territories is also thought to occur from the layered thrombus in the dilated arteries. Both represent different causes of cerebral infarction due to large artery disease mostly in the context of long standing hypertension which is typically associated with small vessel disease.

In conclusion, dolichoectasia as a stroke mechanism can be diagnosed

non-invasively with established brain parenchymal scanning and with greater accuracy with newer imaging modalities such as MRA and TCD. It should be suspected in patients presenting with posterior circulation ischaemia or stroke syndrome, particularly if hypertensive and associated with one or more of the symptoms in Table III. The diagnosis is important as it usually necessitates additional specific therapy such as anticoagulation with warfarin and, in some, anti-aggregant therapy with aspirin, dipyridamole or ticlopidine.

Acknowledgements

The author is most grateful to his medical colleagues in the Durban region for referral of most of the patients included in this study; to Eleanor Gouws of the Medical Research Institute, Durban Branch, for the statistical calculations and comments; and to Drs Bortz, Lake and partners for permission to publish the brain scan figures.

Appendix

Posterior circulation (one or more of the following)

Dizziness, vertigo, nausea, vomiting, drop attacks, diplopia, tinnitus, bilateral weakness or numbness, hiccoughing, imbalance, ataxia, blurring of vision.

Anterior circulation (one or more of the following)

Unilateral weakness and/or numbness, aphasia, apraxia, anosognosia, aprosodia, neglect syndrome, visuospatial impairment.

Levels of evidence from clinical trials (adapted from the American Academy of Neurology)

Level I. Evidence provided by means of one or more well designed randomized controlled clinical trials. Low false positive (alpha or specificity) and low false negative (beta or sensitivity) errors.

Level II: Evidence provided by one or more well designed observational studies with concurrent controls such as case control and cohort studies. Also data from randomized trials with high false positive (alpha) and a high false negative (beta) errors.

Level III: Evidence provided by expert opinion, case series, case reports and studies with historical controls.

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Carotid endarterectomy after recent stroke — how soon?

An interim analysis

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Summary

Aim. To determine whether timing of carotid endarterectomy (CEA) was significant in terms of morbidity and mortality for significant carotid stenosis in a prospectively evaluated cohort of patients with recent stroke.

Methods. A tailored protocol using contemporary neuro-imaging modalities including transcranial Doppler and non-invasive angiography. Standardised clinical scores, neurological deficit scores, an aetiopathogenic scale and disability stroke scales were used in the two groups. Statistical analysis was done to compare differences in two groups: CEA done less than 6 weeks after stroke (group 1) and CEA done more than 6 weeks after stroke (group 2).

Results. Patients formed part of the Durban Stroke Data Bank ($N = 655$), with 26 patients in group 1 (CEA a mean of 16 days after stroke) and 34 in group 2. There were no statistically significant differences between the two groups with regard to demographic factors, clinical scales, neurological deficit scores and investigative findings. There was 1 post-CEA stroke and 1 death in each group ($P = 0.781$), which was not significantly different.

Conclusion. Timing of CEA after stroke may be unimportant with regard to mortality and morbidity in patients with relatively small stable neurological deficits. Other causative factors, as yet unclear, remain to be identified.

Carotid endarterectomy (CEA) currently has definite indications with improved outcome in a subgroup of patients shown to have tight symptomatic and asymptomatic carotid stenosis.¹⁻⁴ In clinical practice, however, the timing of surgery after stroke, especially in patients with fluctuating neurological status or progressing stroke, remains unsettled. A period of 6 weeks has been the traditional interval advised in patients with recent stroke requiring CEA. However, the limits of this initial 'period of grace' remain undetermined. The reasoning behind the 6-week delay dates back to the 1960s when morbidity and mortality in the range of 50% were recorded in

patients with stroke undergoing early CEA.⁵⁻⁹ This was mainly due to presumed postoperative intracerebral haemorrhage.

Since then major advances in neuro-imaging and functional imaging have helped define subgroups at risk more precisely in some instances. During this waiting period there is a significant risk of further stroke from the untreated stenosis, estimated to be in the region of about 10%.¹⁰ Progressing and stuttering stroke, continuing crescendo transient ischaemic attacks (TIA) or 'unstable cerebral ischaemia' akin to unstable angina in some patients prompted review of this policy by several investigators. Piotrowski *et al.*¹¹ retrospectively studied 129 patients operated on more than and less than 6 weeks after stroke and found no significant difference with respect to morbidity and mortality. However, studies to support both early (before 4 - 6 weeks) and delayed (after 6 weeks) surgery continued to appear.¹²⁻¹⁵

It has been suggested in case report series that certain criteria should be met to lessen the risk of adverse events, including a normal level of consciousness, relatively small cerebral infarction without a mass effect on computed tomography (CT), and meticulous control and monitoring of systemic blood pressure during the peri-operative period.¹³⁻¹⁶ The urge to operate sooner is prompted by the common clinical experience that patients with subtle and mild neurological deficits readily fitting the description of a transient ischaemic attack have a critical stenosis or an ulcerative lesion with fresh thrombus. The likelihood of repeat embolisation before the arbitrary 6-week wait period is up is substantial in these patients.¹¹⁻¹³

We report on our own prospective series in which clinical, neurological and investigative details were documented using standardised scales and the pre-operative investigations were performed using contemporary neuro-imaging facilities.

Methods

Investigations

The 'nested' patient cohort was separately and prospectively evaluated according to a set protocol over a 2-year period and formed part of the Durban Stroke Data Bank (DSDB), itself a prospective stroke registry. The minimum work-up includes basic blood tests relevant to stroke, brain CT or magnetic resonance imaging (MRI), chest radiograph, electrocardiogram, duplex Doppler (DD) sonography and

transcranial Doppler (TCD). Additional work-up where appropriate included arch angiography, MR angiography, spiral CT of the carotid system, single photon emission computed tomography (SPECT) scanning, in-depth neuropsychological assessment, prothrombotic tests, cerebral angiography, cerebrospinal fluid analysis, Holter monitoring and trans-oesophageal cardiac echo. All patients in the present series had DD and TCD sonography studies to help define the cerebral haemodynamics more precisely. TCD sonography included monitoring for high-intensity transient signals (HITS) or emboli from either the carotid artery or a more proximal source such as the heart or aorta. Significant TCD abnormality was defined as: (i) evidence of ipsilateral carotid HITS; (ii) middle cerebral artery stenosis; (iii) carotid siphon stenosis; (iv) other large basal cerebral vessel stenosis (PCA, basilar); (v) occlusion of a basal cerebral vessel; and (vi) markedly reduced ipsilateral middle cerebral artery velocity (side-to-side difference 50%) and abnormal pulsatility downstream to the carotid stenosis.

Neurological scales and classifications

To enable comparison with other data banks and stroke trials, several standardised scales have been incorporated into the registry protocol. These are a clinical stroke scale; the Oxfordshire Community Stroke Project Score (OCSP) divided into total anterior circulation (TAC), partial anterior circulation (PAC), lacunar (LAC) and posterior circulation (POC),¹⁷ a neurological scale; the Canadian Neurological Scale (CNS),¹⁸ a disability scale; the Barthel Index (BI),¹⁹ a handicap scale; the Rankin Disability Scale (RDS),²⁰ an aetiopathogenetic (TOAST) classification with categories for large-vessel, small-vessel, cardiogenic, undetermined and other disease;²¹ and *International Classification of Diseases (ICD-9-CM)* systems.²² All patients were assessed clinically and a final diagnosis was made with all available investigative data by the same cerebrovascular neurologist.

Criteria for early surgery

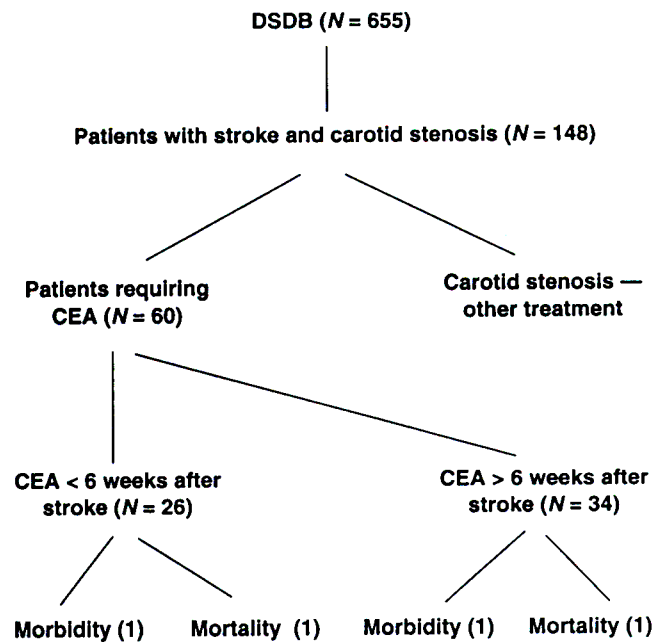
These included a stable, minor neurological deficit (PAC, LAC) with significant ipsilateral carotid stenosis ($\geq 60\%$) or moderate stenosis (40 - 60%) with ulceration, or crescendo TIA resulting in infarction in the presence of significant ipsilateral carotid stenosis. In such cases the investigations were expedited and surgery was arranged for the next available operating list. A postoperative event was considered to have occurred if a stroke or death took place within 1 month of surgery. The late surgery group included those patients in whom surgery was performed in the time frame more than 6 weeks but less than 2 years after the stroke.

Statistical analysis

The two patient groups (CEA < 6 weeks and CEA > 6 weeks) were statistically compared using Student's unpaired *t*-test for continuous data and a χ^2 test for categorical data. Fisher's exact test was applied to 2 x 2 tables where expected cell sizes were smaller than 5.

Results

Of the 655 patients in the Durban Stroke Data Bank, 148 (22.6%; 95% CI 18.7 - 25.1%) were found to have occlusion or stenosis of the precerebral arteries (Fig. 1). CEA was considered appropriate in 60 of these patients with stroke. In 26 patients CEA was done within 6 weeks of the stroke (group 1)



DSDB = Durban Stroke Data Bank.

Fig. 1. Carotid surgery timing cascade.

and in 34 it was done after 6 weeks (group 2). Surgery was performed within the first week in 7 patients, during weeks 1 - 2 in 4, during weeks 2 - 3 in 8, during weeks 3 - 4 in 4, and during weeks 4 - 5 in 3; no patient was operated on during weeks 5 - 6 (mean 16 days, range 3 - 35 days). In group 2 surgery was performed a mean of 22.5 weeks after stroke (range 7 - 104 weeks). Our groups were closely matched in terms of demographic factors (age/sex/race), main risk factors (ischaemic heart disease, diabetes, lipid status, hypertension, smoking), clinical stroke classification (OCSP: TAC, PAC, LAC, POC; $P = 0.686$ NS), degree of deficit as defined by the CNS, RDS before surgery, carotid DD profile, and degree of intracranial upstream abnormality. These demographic, clinical and investigative details are set out in Table I. Within the TOAST pathophysiological classification, comorbidity, i.e. having both a small-vessel or cardio-embolic source and a large-artery cause, applied to 1 person in group 1 and 4 in group 2. The expected significant difference in the RDS between groups 1 and group 2 reflects the fact that patients with a more severe deficit should be allowed to stabilise — beyond 6 weeks after stroke if necessary. In all patients in groups 1 and 2 the diagnosis of stroke was made clinically and confirmed by anatomical brain scanning (CT or MRI). Brain scans included 45 CT scans, 16 MRI scans and 6 SPECT scans. All patients had DD sonography, and 57 of the 60 (95%) had a successful TCD sonographic study with hyperostosis the presumed principal cause of technical failure in the latter investigation. Significant abnormalities were found in 28 patients. Angiography was performed in 27 of the 60 and included conventional angiography in 12 patients, spiral CT angiography in 11 and MR angiography in 4. Surgery was performed a mean of 16 days after the stroke in group 1 (range 3 - 35 days).

There was 1 post-CEA stroke and 1 death in each group (Table II). A brief description of each case follows.

Case 1. The patient presented with right-sided weakness and disorientation without aphasia. A CT scan of the brain revealed a left internal capsule infarct. DD revealed an appropriate significant stenosis of 60 - 80% with ulceration on the

TABLE I. CLINICAL AND INVESTIGATIVE FINDINGS IN THE TWO GROUPS

	CEA < 6 weeks	CEA > 6 weeks	P-value
Demographics			
Males	14	17	NS
Females	12	17	NS
White	23	23	NS
Indian	2	9	NS
Mean age (yrs)	64.1	64.7	NS
Risk factors - Ischaemic heart disease	8	7	NS
Clinical stroke subtype			
TAC	1	4	NS
PAC	15	24	NS
LAC	3	3	NS
POC	6	6	NS
Canadian Neurological Scale (mean)	10.8	10.4	NS (0.67)
TOAST pathophysiological classification			
Large-vessel disease	25	30	NS
Small-vessel disease	0	3	NS
Cardio-embolic	0	1	NS
Other	1	0	NS
Undetermined	0	0	
Rankin disability scale, pre-CEA	1.35	2.06	0.0027
Carotid stenosis degree			
< 40% with ulceration	1	1	NS
40 - 60% with ulceration	1	2	NS
60 - 80%	15	17	NS
80 - 90%	9	14	NS
Total	26	34	NS
Significant TCD abnormality	10	18	NS
HITS	1	1	NS

TABLE II. MORBIDITY AND MORTALITY IN THE TWO GROUPS

	CEA < 6 weeks (N = 26)	CEA > 6 weeks (N = 34)	P-value
Post-CEA stroke	1	1	
Post-CEA mortality	1	1	
Total	2	2	0.781

side and 40 - 60% stenosis on the right. TCD sonography revealed significantly reduced right middle cerebral artery velocities. This could have indicated impaired collateral activity of the circle of Willis. Two days after CEA he developed right hemiparesis and dysphasia. A large left middle cerebral artery territory infarct was noted on the CT scan. Carotid Doppler sonography was normal after surgery, while TCD revealed absent right MCA flow and significantly depressed left MCA flow of approximately 20% of normal. This was probably a result of inadequate Willisian collaterals.

Case 2. The patient presented with intermittent right-sided weakness and mild dysnomia. DD sonography showed bilateral stenosis, 80 - 90% on the left and 40 - 60% on the

right. TCD sonography showed no abnormality. A CT brain scan revealed a right caudate nucleus infarct and bilateral small high-convexity watershed infarcts. After CEA the patient's right-sided weakness worsened from grade +4/5 to 2 - 3/5 with Broca's dysphasia. An appropriately timed (5 days) post-CEA brain scan revealed no new infarcts. The patient had improved to her presurgery state at follow-up 1 month later. Carotid DD sonography revealed patent carotid arteries. No cause for the increased deficit could be determined in this case.

Case 3. The patient presented with a fluctuating dysphasia and right arm weakness with a 80 - 90% relevant left internal carotid stenosis and watershed infarction in the left hemisphere. TCD sonography revealed significantly decreased ipsilateral left middle cerebral artery velocity and pulsatility index and a spiral CT scan of the carotids showed features of a clot and localised dissection. At surgery sub-plaque haemorrhage with a pre-occlusive stenosis was found. The patient's condition deteriorated; he developed seizures and remained obtunded. Carotid DD sonography revealed no abnormality. He died suddenly after a seizure without a CT scan of the brain having been possible. The possible cause of stroke may have been inadequate Willisian collaterals.

Case 4. The patient presented with amaurosis fugax and intermittent left arm weakness with bilateral 80 - 90% internal carotid stenosis on DD sonography. TCD sonography revealed basilar artery stenosis and middle cerebral artery stenosis as well as bilateral carotid siphon stenoses, confirmed on MR angiography. An MRI scan of the brain revealed bilateral watershed infarcts. After a second CEA she became comatose and subsequently died, CT scan of the brain revealing a right parietal infarct and a large brainstem infarct. DD sonography of both carotid arteries revealed normal flow without evidence of a flap or clot. It was postulated that intracranial basilar artery stenosis had caused the post-CEA brainstem infarction.

A fifth patient presented with a posterior circulation disorder with visual illusions. DD sonography showed left-sided internal carotid artery stenosis of 80 - 90% and TCD sonography right posterior cerebral artery (PCA) stenosis confirmed on MR angiography. CT scan of the brain revealed a right occipitoparietal infarct. Symptoms were better correlated with the intracranial (PCA) stenosis than the internal carotid artery stenosis. A left CEA revealed a pre-occlusive lesion with sub-plaque haemorrhage. Transient right-sided hemiparesis and dysphasia lasting 30 minutes occurred during the recovery period without change noted on a CT brain scan. A postoperative DD sonogram of the carotid arteries showed no abnormality. One postulated cause of the patient's symptoms and the neurological findings was intracranial disease-related ischaemia/infarction. Because of the rapid resolution without CT evidence of infarction, he was not regarded as having had a postoperative stroke.

All the patients who experienced post-CEA ischaemia or stroke had small partial anterior stable stroke when they first presented, i.e. all had minor strokes as determined clinically and by brain scans. Patients 3 and 4 had fluctuating neurological or 'unstable' deficits. TCD sonography revealed a significant abnormality in 4 of the 5 patients described (patients 1, 2, 4 and 5). The overall morbidity/mortality for the entire patient cohort was 6.7%. Importantly, 5 of 34 patients (14.7%) in group 2 had a recurrent stroke documented clinically and with neuro-imaging during their wait period.

Discussion

In the present series no significant difference was found between the group who underwent CEA less than 6 weeks after their stroke and that in which it was done after more

than 6 weeks ($P = 0.392$; NS). Previous studies obtaining similar results, i.e. no significant difference in morbidity or mortality, did not define their groups accurately in terms of clinical and investigative parameters and were retrospective.¹¹⁻¹⁶

The causes of post-CEA stroke remain unclear. Hyperperfusion causing cerebral haemorrhage on an impaired autoregulatory basis was thought to be the most common cause. None of the patients in our series suffered hypoperfusion injury or cerebral haemorrhage. A recent large, prospective study on the causes of post-CEA stroke revealed that this was due to thrombotic occlusion in the majority of cases.²³ The rarity of cerebral haemorrhage probably reflects the current practice of meticulous intra- and postoperative blood pressure control. Now that improved blood pressure control to prevent hyperperfusion and cerebral haemorrhage is routine, the causes of post-CEA thrombotic cerebral infarction need to be addressed. The least we can do to minimise the approximately 10% risk of further stroke in the first few weeks after a stroke in a patient with significant carotid stenosis is to operate when the patient's neurological condition has stabilised and adequate pre-operative assessment and investigation has been performed in order to ascertain as precisely as possible whether the standard conditions for CEA exist. If timing is not crucial, are other factors? Recent advances in TCD sonographic detection of emboli suggest that high-intensity transient signals represent an unstable carotid plaque.²⁴ In addition, marked hypoperfusion detected by SPECT scanning is another emerging tool that is particularly useful for identifying patients with critical cortical ischaemia.²⁵ Such functional rather than anatomical scanning may be more appropriate in patients presenting with symptoms related to carotid stenosis.

The current morbidity and mortality of groups 1 and 2 combined is 6.7%. This is in keeping with our previously reported audit of 6%.²⁶ However, a subgroup of patients in this previous series who had a stroke within 1 year preceding their CEA had a much higher morbidity and mortality of 20.2%. Our current series shows a marked improvement in this subgroup. We consider that the most likely reason for the markedly improved outcome of CEA in stroke patients is improved clinical cerebrovascular evaluation and neurodiagnostics, which is the only variable that has changed between the two series.

It has been suggested that CEA after stroke can be done safely if the patient's level of consciousness is normal, CT scanning shows the infarct to be relatively small and without a mass effect, and systemic blood pressure is precisely controlled and monitored during the peri-operative period.¹⁶ Meticulous attention was paid to all these factors in the 5 patients with morbidity and mortality in our series. Our findings suggest that other more significant factors might be involved in adverse outcome, such as presence of intracranial disease, inadequate Willisian collaterals (watershed infarction on brain scanning and typical TCD findings), and degree of ischaemic heart disease. These can all be ascertained pre-operatively and a more accurate risk/benefit profile can be included in the decision making. Despite our series being among the largest addressing this problem, the small numbers preclude firm deductions despite appropriate statistical tests for the group sizes. In addition, our study protocol did not allow for randomisation and therefore represents a case series.

Our findings support some of the situations in which Rutherford and Patt¹³ have previously recommended early surgery, i.e.: (i) acute stroke patients with a high-grade stenosis and a mild and stable neurological deficit; (ii) patients with crescendo TIAs or stroke in evolution which is not steadily or rapidly worsening, in whom Doppler or angiographic investigation confirms a high-grade lesion; and (iii) patients in whom progression to total occlusion can be documented to have occurred within 24 - 48 hours and has resulted in sparse

neurological deficit or negative CT.

The most comprehensive contemporary guidelines for CEA were issued by the American Heart Association in June 1994.²⁷ The issue of timing of surgery after recent stroke was not addressed. Rather than focus on temporally based strategies, it may well be more appropriate to focus on tissue-based abnormalities, i.e. ischaemic signatures of ischaemic tissue histopathology. This information can be obtained with magnetic resonance diffusion weighted imaging and already has relevance in acute stroke thrombolytic therapy.²⁸ With this technique it is possible to delineate subgroups of patients who have compromised but salvageable tissue that is nevertheless destined for large necrosis and is associated with increased risk of intracerebral haemorrhage, and it appears to hold promise for the future.

Now that accurate cerebrovascular investigation can be done non-invasively in the majority of patients destined for CEA with lessening of the risk of arch and cerebral angiography (80% in our series), attention can be given to other peri-operative factors causing stroke. Our series indicates that timing of surgery may not be an important factor in stable, acute stroke patients with an appropriate high-grade lesion.

We wish to record our grateful thanks to Mrs Eleanor Gouws (Department of Biostatistics, Medical Research Council of South Africa) for assistance with the statistical analysis.

Summary

Doel. Om te bepaal of tydsberekening van karotis-endarterektomie (KEA) beduidend was m.b.t. morbiditeit en mortaliteit vir aansienlike karotis-stenose in 'n prospektiewelik geëvalueerde kohort pasiënte met onlangse beroerte.

Metodes. 'n Toegespitste protokol wat gebruik maak van aktuele neurobeeldende modaliteite insluitend transkraniale Doppler en nie-indringende angiografie. Gestandaardiseerde kliniese tellings, bepaling van neurologiese tekort, 'n etiopatogeniese skaal en gestremdheid beroerte skale is in die twee groepe gebruik. Statistiese ontleding is gedoen om verskille in die twee groepe te vergelyk: KEA wat minder as 6 weke na beroerte gedoen is (groep 1) en KEA meer as 6 weke na beroerte (groep 2).

Resultate. Pasiënte was deel van die Durban Beroerte Databank ($N = 655$), met 26 pasiënte in groep 1 ('n KEA gemiddelde van 16 dae na beroerte) en 34 in groep 2. Daar was geen statisties beduidende verskille tussen die twee groepe wat betref demografiese faktore, kliniese skale, neurologiese tekort en ondersoekbevindings nie. Daar was 1 post-KEA beroerte en 1 sterfte in elke groep ($P = 0.781$), wat nie beduidend verskillend was nie.

Gevolgtrekking. Tydsberekening van die KEA na beroerte mag onbelangrik wees wat betref mortaliteit en morbiditeit in pasiënte met relatief klein stabiele neurologiese tekorte. Ander kousatiewe faktore, tot nog toe onduidelik, moet nog geïdentifiseer word.

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Invited comment by Martin Veller, Vascular Surgery Unit, Department of Surgery, University of the Witwatersrand, Johannesburg

It is now well established, on the basis of two large randomised multiple-centre collaborative trials, that CEA in patients presenting with a history of a minor ischaemic stroke or transient ischaemic attack and with severe (70 - 99%) ipsilateral internal carotid artery stenosis significantly reduces the risk of stroke when compared with best medical treatment.^{1,2} Both of these trials have demonstrated that most of the stroke-free survival benefit for patients undergoing carotid surgery is accrued during the early phase of follow-up (NASCET approximately first 20 months, ECST first 12 months) and that the rate of ipsilateral strokes developing after this period is roughly similar to that in the medically treated control group. These findings have demanded a critical re-evaluation of the conventionally accepted interval of 6 weeks between neurological event and CEA, based on non-randomised reports from the 1960s suggesting that there is a high incidence of stroke (up to 50%), due to intracerebral haemorrhage, in patients who have early surgery.

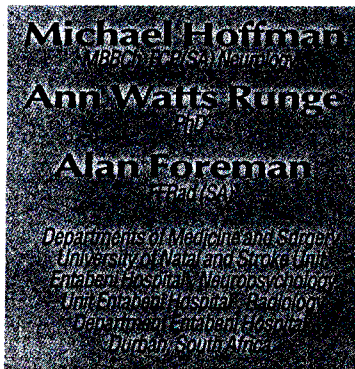
Theoretically, the rationale for early CEA in patients with acute cerebral infarction is: (i) by improving cerebral blood flow, neuronal death due to ischaemia may be limited; and (ii) early stroke recurrence or progression due to further emboli from the diseased carotid artery may be prevented.

On the other hand, the hazards of early surgery include the risk of neuronal damage developing due to an ischaemia-reperfusion injury, and the risk of cerebral haemorrhage due to poor or absent cerebrovascular autoregulation. To date this conundrum has not been answered by randomised studies. In a review of this topic (using a Medline search; all retrospective studies), Mead *et al.*³ collected data from more than 2 000 patients in whom operative mortality ranged from 0% to 100%. Very few conclusions could be drawn from these heterogeneous data, and the role of early carotid surgery remains uncertain.

Our present practice in Johannesburg is similar to that of Hoffmann *et al.* In carefully selected patients with suitable carotid artery lesions, we wait until the symptoms and signs have stabilised and, once this has occurred, perform CEA as soon as possible. This policy is not evidence-based, and we will modify our approach when data from adequate randomised studies, which are currently being considered,³ are available. As the rate of suitable endpoints in such studies is low, and a large number of patients need to be recruited and followed up in order to produce meaningful results, the answers will not be available for some time.

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Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits



The importance of transcranial Doppler ultrasound and HMPAO SPECT in functional imaging of the brain is emphasised.

Abstract

Five patients with transient global amnesia (TGA) were seen clinically and studied neuropsychologically and with SPECT scanning within 24 hours in four and one within 48 hours of the attack. The memory deficits were characteristic of TGA and the magnetic resonance brain scans were normal in all patients. The SPECT scans showed hypoperfusion in the frontal and thalamic regions in all patients. In addition biparietal hypoperfusion was seen in one, parieto occipital in two and unilateral temporal in two patients. Transcranial Doppler studies were performed in three of the five patients and revealed abnormalities of possible relevance in one. Two of the SPECT studies had normalised when repeated at approximately 2 months post ictus. These five patients represent relatively "pure" forms of TGA as they

all had normal MRI scans which excluded other disease processes such as subclinical or silent strokes. The frontal hypoperfusion in all five patients is of interest given the role of the frontal lobes in memory processing.

Transient global amnesia (TGA) remains a clinical diagnosis of unknown pathophysiology with no corroborative laboratory or radiological test. Despite over one thousand case reports in the literature,¹⁻⁹ neuropsychological assessment at time of or immediately after the ictus is limited to less than a dozen cases.^{1,3-5} Strict definition as recommended by the Oxford criteria was not used in the majority of studies.¹ Several functional scanning studies, mainly single photon emission computed tomography (SPECT) reports and one positron emission computed tomography (PET) study, report of thalamic and/or neocortical hypoperfusion with hippocampal, temporal, frontotemporal, thalamus, hemicortical and mesial temporal sites of decreased cerebral blood flow.^{3,10-19} Functional imaging with SPECT and PET may be useful in elucidating the cause for the most popular proposed mechanisms which include cerebral ischaemia, seizures and migraine. To date 10 such studies have been published describing 13 patients. In these studies, magnetic resonance imaging (MRI) scans were not reported on, or not performed in six studies and were abnormal in a further two. In the remaining two studies MRI scans were performed 10 days and three

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 30

months post ictus.^{3,10-19} This report describes five patients in the acute phase, all with normal MRI scans. To our knowledge, this study represents the largest case series of TGA patients with normal MRI scans but abnormal SPECT scans.

Methods

The five patients were derived from the Durban Stroke Data Bank (DSDB), (n=600) with presumed stroke as the admitting diagnosis. They were evaluated according to the tailored protocol of the DSDB which incorporates a prospective, contemporary stroke investigative evaluation including duplex and transcranial Doppler, MRI or computerised tomography (CT) brain scanning, prothrombotic screens cardiac evaluation including transoesophageal echo, angiography and SPECT scanning where appropriate. Special attention is given to the assessment of higher cortical function deficits (HCFD) with a screening examination. In brief, this encompasses eight major groups of HCFD (aphasias, amnesias, apraxias, agnosias, alexias, neglect syndromes, frontal lobe syndromes and miscellaneous group) with subcategories, all predefined. Focussed neuropsychological testing is performed in those patients with HCFD abnormality.

Clinical

The Oxford definition of TGA was used to define the clinical syndrome (Table I).

Neuropsychological examination was performed by a neuropsychologist in four patients and by the first author in patient 2. In all patients, the focus of the assessment was on memory functioning.

SPECT scanning

Twenty Millicuries 99m Technetium - HMPAO 99 is administered intravenously. Ceretec with Technetium produces a lipophilic complex which crosses the blood brain barrier and is retained in the brain,

Table I: The Oxford TGA study diagnostic criteria for Transient Global Amnesia¹

allowing assessment of regional cerebral blood flow. Imaging commenced 2-3 minutes after the injection of the tracer. The patient is positioned as comfortably as possible with the room slightly darkened and is encouraged to be as relaxed as possible. Scans are obtained for 20 seconds, with regular 6 degree rotation of the camera head around the patient, completing a 360 degree rotation with approximately 60 images obtained. This required cooperation from the patient for a period of about 30-40 minutes. A medium to high resolution collimator was used on the gamma camera. Reconstruction was performed with positioning of the patient in the orbitomeatal line, in the transverse, coronal and saggital planes. Three dimensional reconstruction was also performed. Images were interpreted on the computer screen comparing right and left regions of interest. This was done both visually and semi quantitatively. The transaxial slice with the largest perfusion defect was identified and a circular region of interest traced over that area. These circular regions of interest (ROI) were also obtained for six

areas of the grey matter. These included the cerebellum, thalami, basal nuclei, frontal, parieto occipital and temporal regions. These areas and their mirror images on the homologous region of the other hemisphere were stored on a template and adjusted when required for a particular scan. The ROI radioactive counts were compared to the mean count of the two cerebellar hemispheres and expressed as a percentage of the mean cerebellar count according to the formula (1 - ROI/mean cerebellar count).

Transcranial Doppler

The basal cerebral vessels and all major branches of the circle of Willis were insonated via the temporal and sub occipital windows with the EME-Transcranial Doppler using mounted 2 MHz probes. Flow velocities and pulsatility indices (Gosling) were measured with special attention to the identification of intracranial stenoses and emboli detection (15 minutes monitoring).

Case reports

Patient 1

An alert, attentive 57 year old woman brought to hospital by her husband with complaints of not remembering and repeating herself since 11h00 one morning. A sudden onset of occipital pain was reported by her husband which the patient no longer remembered. During the initial clinical encounter it became apparent that her memory was defective until the prior evening. Stroke risk factors included significant smoking and previous mild hyperlipidaemia. The medical history was otherwise unremarkable. Clinical neurological examination with specific attention to aphasias, apraxias, agnosias, neglect syndromes, alexias and frontal lobe function was normal. Defective short term memory as tested by digit span and 5 minute recall was noted. The Boston Naming Test score

to page 32

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 31

was 50/60. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

A neuropsychological assessment was performed within 5 hours of the attack.

The tests administered included the Wechsler Memory Scale, Rey's Auditory Verbal Learning Test, Rey's Complex Figure Test, South African Wechsler Adult Intelligence Scale, Trail Making Test and Symbol Digit Modalities Test. Abnormalities detected by these tests are noted in Table II.

Neuroradiological investigations

T1 and T2 weighted MRI brain scanning was performed 12 hours after the onset and was normal. Transcranial Doppler sonography revealed abnormally low basilar artery velocity of 10-18 cms/sec. SPECT brain scanning approximately 10 hours after presentation,

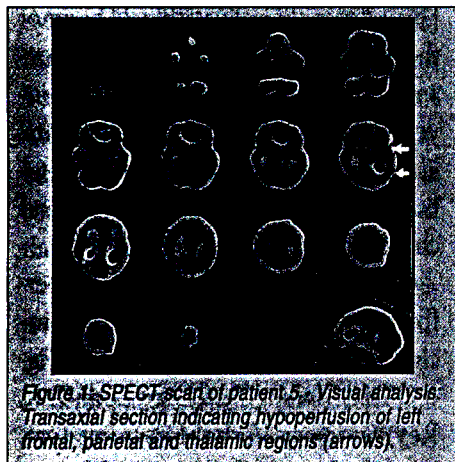
Table II: Neuropsychological and SPECT findings

Patient	Oriented	Immediate memory	Verbal memory	Nonverbal memory	Intelligence	Language skills	SPECT scan	ROI (cerebro-cortical) % Difference: R	ROI (cerebro-cortical) % Difference: L
Patient 1	Oriented	Intact	Verbal memory: severely impaired (Wechsler Memory Scale)	Nonverbal memory: severely impaired (Rey's Complex Figure Test)	Intact	Intact	Bilateral: Frontal, Parietal and Occipital hypoperfusion	38	33
Patient 2	Normal	Intact	Verbal memory: severely impaired (Wechsler Memory Scale)	Nonverbal memory: severely impaired (Rey's Complex Figure Test)	Intact	Intact	Bilateral: Frontal, Parietal and Occipital hypoperfusion	44	49
Patient 3	Disoriented to time and place	Intact	Verbal memory: severely impaired (Wechsler Memory Scale)	Nonverbal memory: severely impaired (Rey's Complex Figure Test)	Intact	Intact	Bilateral: Frontal, Parietal and Occipital hypoperfusion	45	46
Patient 4	Disoriented to time	Intact	Verbal memory: severely impaired (Wechsler Memory Scale)	Nonverbal memory: severely impaired (Rey's Complex Figure Test)	Intact	Intact	Bilateral: Frontal, Parietal and Occipital hypoperfusion	44	36
Patient 5	Oriented to time and place	Intact	Verbal memory: severely impaired (Wechsler Memory Scale)	Nonverbal memory: severely impaired (Rey's Complex Figure Test)	Intact	Intact	Bilateral: Frontal, Parietal and Occipital hypoperfusion	41	38

Abbreviations: ROI - region of interest; R - right; L - left

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 32



revealed visually appreciated perfusion defects in the left frontal, superior right parietal and left parietal regions (Figure 1). The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II. Follow up 2 months post ictus revealed normal neurological and focussed neuropsychological testing, normal transcranial Doppler insonation of the basilar artery and the SPECT brain scan showed normal perfusion bilaterally.

Patient 2

A financial advisor aged 53 years awoke normally one Sunday morning, read the newspapers with his wife, had sexual intercourse and immediately thereafter kept repeating himself and could not remember details of the preceding day. Some events over the preceding week were also defective according to his wife. Within three and a half hours he had recovered back to normal as judged by himself and his wife. Stroke risk factors were not present apart from personal stress and an occasional moderate alcohol intake. His past medical history was unremarkable. He was seen within 3 hours of the attack. The neurological examination was normal and neuropsychological examination performed. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

The screening neuropsychological assessment comprised a clinical memory evaluation and the Boston Naming Test. The assessment findings are detailed in Table II. Formal testing for aphasias, apraxias, agnosias, neglect syndromes, alexias and frontal lobe function were normal. The tests administered included orientation - normal for date, time, place, person, the Rey Osterreith Complex Figure Test, Modified Famous Faces Test (last 6 US Presidents), Digit span at 5 minutes, Three Words/Three Shapes Test, confrontation naming (Boston Naming Test) and FAS Test. The abnormalities detected are summarised in Table II.

Neuroradiological investigations

The T1 and T2 weighted MRI brain scan performed approximately 24 hours after the event was normal. Transcranial Doppler 4 hours after the onset showed was notable for non insonation of the right posterior cerebral artery. The left posterior cerebral artery was easily insonated and the basilar artery flow normal. SPECT scanning was performed within 12 hours and revealed a visually appreciated left parieto-occipital perfusion defect. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II. Follow up 2 months post ictus revealed a persistent animal specific naming defect but this had improved. The transcranial Doppler and SPECT brain scan were repeated at this time and were both normal.

Patient 3

A 54 year old woman awoke one morning unable to remember either the month or year or why she was at the place they were on holiday. She could recite accurately her home address and personal names. Repetitive questioning as to what she and her husband were doing at the holiday venue followed for the next few hours. No stroke risk factors were present and her relevant past medical history was otherwise unremarkable.

Examination, both systemic and neurological was normal. Bedside autobiographical review made it clear that her memory defect stretched back several weeks prior to the ictus. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal. She normalised clinically over a 12 hour period.

Neuropsychological evaluation was performed within 6 hours. The neuropsychological tests administered were the Wechsler Memory Scale, Rey's Auditory Verbal Learning Test, Luria's Neuropsychological Investigation expanded by the second author to include autobiographical and general semantic memory and a Famous Faces Test. Overall she presented preservation of immediate memory, anterograde amnesia for both verbal and nonverbal material and retrograde amnesia characterised by a difficulty in recalling autobiographical episodes. Her orientation and immediate memory was normal as tested by the Digit Span Task. Anterograde deficits for verbal memory was severely impaired and displayed a typical lowered and fluctuating plateau associated with frontal lobe impairment. Recognition memory was poor and recall of information during assessment was intermixed with word repetitions. Recall of material presented in context was severely impaired. Visual memory was mildly impaired. The neuropsychological assessment findings are noted in Table II.

Neuroradiological investigations

CT and MRI (T1 and T2) brain scans and duplex and transcranial sonography were all normal. SPECT scanning done within 12 hours of the ictus revealed visually appreciated hypoperfusion defects in the left frontal and parietal regions. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

to page 34

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 33

Patient 4

A 62 year old overweight retired accountant was free diving in the surf zone for crayfish with his son one day. When he surfaced he was behaving strangely in that he was unable to recall recent events and was concerned about not having their crayfish licence that they had recently acquired. His son had noticed that he had spent an abnormally long time in a pool amongst rocks that does not normally have crayfish. He tied a handkerchief around his head and seemed to have a headache. Thereafter he kept rambling about the past and repeating himself. On arriving home, he stood looking bemused at items that he himself had packed on a car trailer the day before and asked family members what these were doing there. Current items on his workbench that he was busy with the day before also puzzled him. He was taken to the doctor still in his gear used for diving which he did not wish to change out of first. This was most unlike him as he was normally fastidious about his appearance. He had also become very docile and agreed to everything which was also unusual for him. Repetitive questioning was ongoing. His only relevant past history and stroke risk factors were hypertension on treatment with Captopril and Aspirin and attacks of gout in the past. General and neurological examination was normal apart from a blood pressure initially of 220/115 subsequently reduced to 175/100. He normalised with respect to the above deficits within approximately 6 hours. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

A clinical bedside neuropsychological assessment with a focus on memory evaluation was performed within 5 hours of the episode. Tests administered included the Rey Osterreith Complex Figure Test,

Modified Famous Faces Test (last 6 US Presidents), Digit span at 5 minutes, Three Words/Three Shapes Test, confrontation naming (Boston Naming Test) and FASTest. The abnormalities detected are summarised in Table II.

Neuroradiological investigations

The MRI brain scan and duplex Doppler sonography of his cervicocephalic vessels were normal. The SPECT scan performed 24 hours after presentation revealed to visual inspection a marked right hemisphere hypoperfusion including the right frontal lobe and the right thalamic region. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

Patient 5

A 48 year old man suddenly questioned the type of shirt he was wearing while sitting on the edge of his bed one morning soon after waking. The details were derived from his wife as he did not recollect anything about the event. He kept asking where he was, did not know that he had bought a new car 2 weeks previously. He asked about the shirt he was wearing at least 4 times and kept blinking his eyes, asked about the day of the week, where he was, asked questions about the rugby magazines next to his bed that he had just been reading. His wife recalled him touching his forehead and saying he had a "funny headache". The repetitive questioning lasted for about 20 minutes but for the rest of the day he seemed to be "floating and not with it" and he felt "fuzzy". He was in a very stressful situation at the time, setting up his own business venture which was not going according to plan. Two weeks prior to the event he was away for the weekend with his wife and recalled details accurately according to his wife. His past history was unremarkable with no previous illness or surgery and no cerebrovascular risk factors.

He was seen clinically within 24 hours of the attack and general and neurological examination was normal. Routine stroke investigations including blood counts, lipogram, glucose, erythrocyte sedimentation rate, electrolytes electrocardiogram and chest radiograph were normal.

Neuropsychological testing was performed within 48 hours and tests included the Rey Osterreith Complex Figure, Trail Making Test, Digit Span Test, Rey Auditory Verbal Learning Test, Wechsler Memory Scale, Logical Memory Task, FAS Test, Famous Faces Task, Category Naming Test, Autobiographical Incidents Schedule and selected tasks from Luria's Neuropsychological Investigation.

Neuroradiological investigations

The MRI brain scan and duplex Doppler sonography of his cervicocephalic vessels were normal. The SPECT scan performed 48 hours after presentation revealed marked visually appreciated left hemisphere hypoperfusion, including the left frontal lobe and hypoperfusion of both thalamic regions. The percentage decrease of ROI greater than 15% with respect to the mean cerebellar count is noted in Table II.

Discussion

The five patients described are unique in that they presented with classical features of TGA as required by the Oxford TGA study diagnostic criteria, had normal MRI scans and abnormal SPECT scans in the acute stage. The SPECT scans and neuropsychological testing were performed within 24 hours of onset of the first symptoms in 4 patients and within 48 hours in one. Neuropsychological assessment was consistent with TGA in which the pervasiveness of anterograde and retrograde amnesic dysfunction is rapid in onset and in striking contrast to the preservation of immediate memory and the relative sparing of other higher mental functions. The

to page 35

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 34

dysexecutive findings in patients 1, 3 and 5, mildly impaired verbal fluency in patient 5 and behavioural abnormalities in patient 4 are consistent with a mild frontal disturbance. The SPECT scans of these 5 patients revealed frontal hypoperfusion as part of the SPECT abnormalities.

MRI brain scanning is the most sensitive anatomical scan to exclude small infarcts and might be regarded as a prerequisite to exclude small or previously clinically silent infarcts in such patients. TGA remains a clinical diagnosis and one of the requirements is the absence of other neurological deficits. MRI scanning is an accurate method to exclude subclinical deficits in this setting. If sensitive paraclinical and radiological testing is also normal, as in these five cases, a purer form of TGA presentation may be studied.

Table III: Sites of hypoperfusion in the acute stage of TGA as noted by functional scanning (SPECT and PET) in studies to date^{3,10-19}

Region	Side
Hippocampal	Bilateral
Temporal or frontotemporal	Right and left
Temporal and frontal	Bilateral
temporal	Left
Parietas	Right and left
Thalamus and midline	Bilateral
Medial temporal	Bilateral
Hippocampal and amygdala area	Left
Medial temporal and thalamus	Left

The studies performed to date using PET^{10,18} or SPECT^{3,11-17} and 133Xenon¹⁹, have indicated a variety of sites with perfusion defects, both bilateral and unilateral, in the acute stage of TGA - Table III. The patients under discussion, with perfusion deficits noted both frontal and thalamic regions in all patients, the parieto occipital regions in 2 and unilateral temporal regions in 2, is to our knowledge, the largest case series of

functional scanning in acute TGA together with normal MRI brain scans. Although a variety of lesions, including cerebral infarcts and haemorrhages have been reported in the temporal lobes and more commonly the thalami on CT brain scans²⁰⁻²² of TGA patients, it may be argued that such cases no longer represent pure forms of TGA. In these cases, a transient neurological deficit may have been present very briefly at the onset of ictus with brain scan paraclinical evidence of a vascular lesion akin to the events described as CITS (cerebral infarcts with transient symptoms).

The perfusion deficit might reflect a diaschisis effect of primarily thalamic dysfunction or neocortical in origin. In the study of Ott *et al* of unilateral amnesic stroke²³, a particular vulnerability for TGA was postulated with dysfunction in the left amygdalohippocampus or diencephalon. Whatever the mechanism, a primary diencephalic insult seems plausible based on clinical and functional scanning data. All five of our cases showed relative thalamic hypoperfusion. With regard to the aetiology of TGA, the normal MRI scans performed within 24 hours of onset argue against a cerebral infarct and subclinical brain damage. A recently proposed hypothesis posits that cerebral hypoperfusion may be secondary to a neuronal hypometabolism itself initiated by excitotoxic neurotransmitter release temporarily impairing memory function.¹ The finding of the SPECT hypoperfusion in neocortical regions is consistent with such an hypothesis, the normal MRI scans marshalling evidence against cerebral ischaemia as the primary mechanism. A recent positron emission computed tomography study in acute TGA demonstrated matched flow metabolism depression more consistent with neuronal dysfunction such as due to a seizure or migraine spreading depression mechanism.¹⁰

Certain neuropsychological findings are worthy of further comment. The dysexecutive findings in patients 1, 3 and 5 and probably also patient 4, are consistent with a disruption in the organisation and control of the learning, retention and retrieval process highlighted by Baron *et al*.¹⁰ The confrontation naming difficulty in patient 2 has also been noted by Kritchevsky *et al*.²⁴ The SPECT scan revealed a left parietal perfusion deficit which may be the basis of this problem. In patients 3 and 5 visual memory was not as severely affected as verbal memory. A similar finding has been made by Walsh²⁵ in some of his cases. Patient 5 was assessed 48 hours post TGA onset and in this case the discrepancy may reflect the earlier recovery of non verbal memory described by Okado *et al*.²⁶ in their two cases. The neuropsychological assessment findings would seem to support this in that although the main features of TGA were the same in all five patients, there were individual differences in the severity and nature in which the symptoms manifested in each case. Constraints on neuropsychological assessment include the rapid onset and brevity of attack. Distress and frequently marked repetitive questioning frequently preclude a lengthy wide ranging neuropsychological assessment.

Our study reports on individuals free of cerebrovascular disease with minor risk factors, no previous illness of note, neocortical hypoperfusion with no evidence for a stroke mechanism on MRI scanning. Recent studies with relatively large numbers of TGA patients argued strongly against a thromboembolic aetiology of TGA.²⁷ The transcranial Doppler (TCD) of low velocity in the basilar artery in case 1 may have reflected a cerebral hypometabolism. In case 2, the finding of an absent signal from the left posterior cerebral artery and low basilar artery velocity with subsequent normalisation are

to page 36

Transient global amnesia - acute SPECT functional imaging and neuropsychological deficits

from page 35

consistent with posterior circulation embolic mechanism residua. The TCD findings, though interesting do not permit conclusions, as the findings are nonspecific.

SPECT scanning does not permit pathophysiological conclusions as a distinction between flow reduction caused by cerebrovascular disease or flow reduction due to neuronal dysfunction cannot be made. Cortical flow reduction secondary to thalamic diaschisis itself due to a posterior circulation ischaemia is a possible explanation. The 5 patients represent relatively pure TGA cases both clinically and on investigation with varying cortical hypoperfusion on SPECT scanning which normalised at one month follow up in 2.

TGA may be a core syndrome with several sites of dysfunction within the neuronal network subserving memory possible.¹⁰ In addition, support for a neuronal dysfunction rather than vascular mechanism, possibly thalamic based with secondary and transient cortical hypoperfusion seems most plausible in the cases described. This was first suggested by Trillet in 1987 using Xenon inhalation in TGA.¹⁹ The case series described, gives support to such an hypothesis because of the normal MRI scans in all five patients with its proven sensitivity for detecting cerebral infarction. The transient relatively mild frontal lobe disturbance noted in 4 of the 5 patients hints at a secondary disturbance such as that seen with diaschisis. Recent neuropsychological, PET and functional MRI data²⁸⁻³¹ provide strong support for the prefrontal cortex in human working memory. Activation of this area has been noted in cognitive tasks that are thought to be involved in declarative episodic or working memory.²⁸ The frontal hypoperfusion in our 5 patients is consistent with such findings and also supports the theory of Baron *et al*¹⁰ of a prefrontal metabolic depression, itself secondary due to thalamic dysfunction.

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Addendum:

Posterior circulation positional transient ischaemic attacks due to persistent hypoglossal artery redundancy (SAJR Vol 1 No 2 May 1996)

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Posterior Circulation Positional Transient Ischaemic Attacks due to Persistent Primitive Hypoglossal Artery with Redundancy

Introduction

Four different primitive arteries connect future anterior and posterior circulations in the embryonic state.¹ The trigeminal, otic, hypoglossal or proatlantal arteries normally regress and are replaced by the posterior communicating arteries but may persist in adult life. These four arteries may persist with differing frequencies and varying complications such as cerebral aneurysms,² cranial nerve palsies³ and as a route of anterior to posterior circulation embolism.⁴ Brain ischaemia and infarction have recently been described with such primitive anastomoses without any other cause of embolism or in association with carotid stenosis at the presumed donor emboligenic site.⁵⁻⁷ Hypoglossal arteries are said to be present in 0.05% of cerebral angiograms and have been reported to be associated with aneurysms,^{8,9} arteriovenous malformations,¹⁰⁻¹² moyamoya disease¹³ and Arnold Chiari malformation.¹⁴ Cerebral ischaemia has been described in one case.¹⁵ The mere presence of the congenital anomaly alone is insufficient to imply causation. A relatively young patient, free of cerebrovascular risk factors is presented with a hypoglossal artery with the additional abnormality of extensive coiling (redundancy) of the vessel in the neck.

Case report

A 48 year old right handed, white woman reported a sudden onset of bilateral visual impairment lasting several minutes, followed by intermittent shaking on both sides of her body lasting about 2 hours. Episodes of the body becoming "spastic" every 4-5 minutes were observed by her husband, lasting about 5 minutes at a time. He described the attacks as the arms and legs extending, and her lifting off the bed. The neck would become very stiff and she would arch her spine consistent with opisthotonic posturing. She was totally

Abstract

A persistent primitive hypoglossal artery was the sole identifiable stroke risk factor for a patient presenting with positional, posterior circulation ischaemic episodes. Diagnosis was made by magnetic resonance arteriography and verified by conventional angiography. Tortuosity and coiling of the hypoglossal artery was also present. Dynamic transcranial Doppler sonography was normal and SPECT brain scanning revealed an area of posterior hemisphere hypoperfusion. Redundancy of the primitive hypoglossal artery is the postulated mechanism of cerebral ischaemia.



Posterior Circulation Positional Transient Ischaemic Attacks

conscious during these episodes. Pins and needles were perceived on both sides but more on the right. Numbness of the tongue, partial deafness of the right ear and dizzy spells were other frequent intermittent symptoms. A second similar attack occurred one week later. Of note is that turning her head to the left for more than 1-2 minutes invariably provoked dizziness. Looking down, such as when going down stairs and turning her head to either side would provoke dizziness. Tinnitus was invariable. No headache, weakness, diplopia or imbalance was associated. Her past history was notable in that she was diagnosed to have had a right sided "Bell's palsy" (of sudden onset) on the 20 July 1995 which lasted about 2 weeks. She had no cerebrovascular risk factors. General and neurological examination was normal save for mild dysmnnesia and visuospatial impairment, the latter tested with the Rey Complex Figure Test. The clinical assessment at time of first visit included a differential of posterior circulation ischaemia, partial seizures or cardiac dysrhythmias.

The basic cerebrovascular relevant blood screen, chest radiograph, electrocardiogram, electroencephalogram, computerised tomography brain scan and cardiac investigations including cardiac echogram were normal. The magnetic resonance imaging (MRI) brain scan showed a very small hyperintense focus in the left frontal region of dubious significance. An abnormal signal void due to a carotid basilar anastomosis was detected (Figure 1). This anastomosis was confirmed on time of flight magnetic resonance (MR) angiography as a very dilated tortuous hypoglossal artery with an aplastic right vertebral and hypoplastic left vertebral artery (Figure 2). Selective angiography confirmed the MR angiogram findings (Figure 3). The single photon computed tomography (SPECT) brain scan showed



Figure 1. Axial MRI scan demonstrates hyperintense focus in the frontal region (arrow) and signal void in the posterior region (arrowhead).



Figure 2. MR angiogram demonstrates a very dilated tortuous hypoglossal artery (arrow) with an aplastic right vertebral and hypoplastic left vertebral artery (arrowheads).



Figure 3. Selective left vertebral angiogram confirms the tortuous left hypoglossal arterial anastomosis (arrow).



Figure 4. SPECT scan showing significant left parieto-occipital hypoperfusion (arrowheads).

with Aspirin 150 mg daily and presently remains well at 2 months follow up.

Discussion

A series of case reports has implicated primitive caroticovertebral arteries in stroke and cerebral ischaemia. There is also a known stroke risk associated with cervicocephalic redundancy, with various mechanisms such as thrombosis and embolism postulated and dissection significantly associated.¹⁶ The most likely mechanism of ischaemia in our patient is a transient hypoperfusion or thromboembolism from the redundant coils of the primitive

hypoglossal artery which was the main posterior circulatory supply vessel in this patient. When these primitive arteries persist, aplasia or hypoplasia of the vertebrobasilar system is usual as in the patient under discussion. Positional ischaemia in anatomically normal vessels and atherostenosis with neck turning is well described by Sturzenegger *et al.*¹⁷ In our patient, head turning to either side but more to the left as well as flexion provoked dizziness. Both embolic and haemodynamic mechanisms could be pathomechanisms with the normal dynamic transcranial Doppler study marshalling evidence against the latter. This could be a mechanism of ischaemia especially as the abnormal hypoglossal artery served as the sole posterior circulation supply without the benefit of the normally dual vertebral arterial supply. Although no posterior circulation infarct was imaged with the aid of an MRI brain scan, functional imaging with SPECT scanning revealed left posterior hemisphere hypoperfusion, a finding that would correlate well with the symptomatology. The reported Bell's palsy was more likely to have been a minor pontine infarct as the clinical presentation was compatible with brain stem ischaemia. Although surgical reconstruction of carotid redundancy has been reported to abolish symptoms of cerebrovascular insufficiency, such treatment would theoretically be contraindicated in our patient in view of the anatomically abnormal posterior circulation.

This case demonstrates the utility of MR angiography in the detection of uncommon vascular abnormalities in patients with unexplained transient ischaemic attacks. The hypoglossal artery when present is usually the only functional artery to the brain stem and cerebellum and is associated with aplasia or hypoplasia of the vertebral arteries as demonstrated in our patient.¹⁸

To our knowledge, this is the first

reported instance of a primitive, persistent hypoglossal artery associated with redundancy without other identifiable cause of positional cerebral ischaemia/infarction. The causal relationship of these dual stroke risk factors seems certain. The need to exclude such vasculopathy in patients presenting with posterior circulation insufficiency is emphasised as the mechanism is amenable to treatment. Diagnosis by non-invasive magnetic resonance angiography should suffice.

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Cerebrovascular neuroimaging: which tests and when?



Cerebrovascular neuroimaging requires careful clinical and radiological correlation for interpretation. With a profusion of tests available, what is the best investigation and when?

Determination of brain pathology and pathophysiology was for a long time largely deductive with no objective evidence. Early neurologists had to wait for autopsy information for a definitive diagnosis. Both the impervious, intact skull and the dearth of clinically useful brain treatment strategies contributed to the "dark ages of the brain". The situation today is vastly different in that we are overwhelmed with an ever increasing array of new investigative tools. These include colour duplex Doppler flow imaging (CDFI), transcranial Doppler (TCD), magnetic resonance imaging (MRI), magnetic resonance angiographic imaging (MRA), single photon emission computed tomographic imaging (SPECT), spiral computerised tomography (helical or spiral CT) and positron emission tomography (PET). Coincident with such a wide choice of brain imaging methods, are the imminent acute stroke therapies (antithrombotics, thrombolytics, neuroprotective and gene based therapies) that are anticipated within the next few months to years. Despite the complexity of the brain, outward manifestations of impairment remain limited to long tract signs, visual deficits and cognitive deficits, underscoring the need for paraclinical evidence of malfunction.

Colour duplex flow imaging (CDFI) has become a routine test for extra cranial arterial assessment with excellent sensitivity and specificity as compared to angiography.¹ Plaque characteristics are most accurately

assessed with CDFI and area stenosis as measured by Doppler as opposed to diameter stenosis as measured by angiography is a more accurate correlate of the true anatomical degree of stenosis.² A recent and at present still clinical investigation extension of CDFI is power Doppler imaging (PDI). This new modality generates intravascular colour signals from the amplitude of the echo signal, which in turn depends on the intensity of the sampled red blood cells. It overcomes the two major limitations of CDFI which are the assessment of high grade stenosis and the intrastenotic diameter and area reduction in heavily calcified plaques, which are commonly encountered. In addition the method is angle independent and free from aliasing artifacts which is a limitation of CDFI. The PDI contrasts the lumen with colour similar to angiography. In this respect it essentially bridges the gap between angiography and CDFI whose major limitations were inability to image the outer vessel boundary and residual vessel lumen.^{3,4}

Transcranial Doppler (TCD) has established applications for the reliable diagnosis of intracranial vessel stenosis, vasospasm, Willisian collateralisation and arteriovenous malformations. In addition, it is useful for the detection of vasomotor testing and monitoring and brain death.⁵ A more recent and highly clinically relevant application is in the detection of intracranial emboli, whether of cardiac, large artery or exogenous source. The diagnosis of patent foramen ovale, an important predisposing factor in a significant proportion of young stroke patients of "undetermined aetiology", is most easily and cheaply done by contrast ("bubble") TCD.⁶ The differentiation of symptomatic from asymptomatic carotid stenoses can also be facilitated by determining the degree of artery to artery embolisation by TCD by performing HITS (high intensity transient signals) counts.⁷ Both duplex and power TCD

to page 7

from page 6

are currently in the clinical investigational stage with promise for considerable widening of their applications.

Magnetic resonance imaging has afforded the excellent anatomical detail of the brain especially in areas which do not show up well on computerised tomographic (CT) scanning such as the brainstem, cerebellum and spinal cord. Routine MR imaging by spin echo sequences, the best known being T1, T2 and proton density weighted images. T1 images enable high tissue to tissue differentiation (anatomy), T2 images are most useful for intratissue characteristics (pathology) and proton density weighted images aid differentiation of focal tissue changes adjacent to free fluid such as the subarachnoid space and ventricles. This has resulted in unheralded accuracy of diagnoses of posterior circulation infarction especially of the brainstem, cerebellum and diencephalon. Thrombolysis with tissue plasminogen activator is now indicated for a subset of acute stroke patients.⁸ The accurate, early detection of this treatable subgroup of patients is dependent on the appropriate investigative technique. As a consequence, the requirement for ultra early detection of infarctive and haemorrhagic components is of vital importance. Two new investigative techniques, MR diffusion (MRD) and MR perfusion (MRP) allow tissue changes of cytotoxic oedema to be seen within 1 hour of onset.⁹ Ultrafast echoplanar imaging may reduce this to about 30 minutes and allows imaging of ischaemic tissue that has been experimentally reversed in the animal model by drugs such as NMDA antagonists.^{10,11} Although not routine in clinical practice, these methods hold promise. MR angiography (MRA) has already reached routine clinical practice with the two principle techniques; namely, time of flight (TOF) and phase contrast (PC) each having their particular attributes.¹² Most usefully combined with transcranial Doppler and duplex

Doppler to grade stenoses, a two and three dimensional cerebrovascular tree can be imaged entirely noninvasively. MRA adds only about 10 minutes to the conventional MRI scan of the brain and it is easy to see that this may rapidly become a routine part of cerebrovascular imaging. Finally, magnetic resonance spectroscopy (MRS) although not yet in clinical use, may detect the earliest possible changes of ischaemia at cellular level by measuring increases of lactate and a fall in high energy phosphates.¹³

Computerised tomographic brain scanning has improved with respect to definition and speed of examination with each new generation of scanners. Because of its inherent drawbacks it is relegated to the task of characterisation of sudden brain syndromes into either mass lesions or stroke, and in the case of stroke, to differentiate haemorrhage from bland infarction. However due to its popularity and relatively lower cost it will probably retain its position as the most widely used brain scanning method. The novel application of helical CT scanning of blood vessels has become so useful clinically that even dissection of carotid arteries, until recently the domain of conventional angiography, can be reliably diagnosed by this method.¹⁴

SPECT has been shown to be a sensitive indicator of cerebral perfusion and the most sensitive brain scan for the demonstration of ischaemia and infarction in the acute phase. Three different tracers are available for clinical use; HMPAO, Iodine 123 and Tc ethyl cysteinate dimer. The radionuclide is injected intravenously and accumulates in different areas of the brain proportionate to the rate of delivery of nutrients/blood flow to that volume of brain tissue. Technology has allowed the combination of gamma cameras and computerised tomography to create three dimensional construction of images. The major advantage of SPECT is its functional imaging capacity which complements the

standard anatomical imaging using magnetic resonance and the older computerised tomography scans. SPECT is also affordable and considerably cheaper than positron emission tomography (PET). The latter is globally limited by cost and the necessity for proximity to radionuclide processing (a cyclotron). In fact, the cost of SPECT is similar to the conventional CT scan without contrast. The major advantage of PET over SPECT is improved resolution and its capability for the measurement of regional cerebral metabolism. Biochemical information from receptor activity measurement such as muscarinic, benzodiazepine, serotonergic and dopaminergic receptor systems are possible but are not in routine clinical use and remain experimental at the time of writing.¹⁵

The quest for pathophysiological subtyping in acute stroke has never been more urgent. The long list of animal-effective, human-failure stroke drugs has been blamed squarely on the unrealistically long time window of 24 - 48 hours or more for patient recruitment. Now that we appreciate that "time is brain" and strive for sub 6 hour recruitment period for acute stroke intervention, this may nevertheless be unnecessarily rigid and exclude potentially salvageable patients with slightly longer time frames.¹⁶ Such subtyping can only be done with the strategic choice of a combination of functional and structural neuroimaging. By means of TCD and MRA the site of arterial occlusion can be defined in order to determine the desirability of thrombolytic therapy and to exclude patients with distal arterial or branch occlusion or those without occlusion. Tissue viability can be determined to some degree by early SPECT, diffusion weighted MRI and extent of hypoperfusion can be deduced by CT. The exact choice, timing and interpretation of these modalities remains within the domain of the art and science of medicine.

to page 8

from page 7

All the tests have the capability of measuring either anatomical or functional derangement of the brain or indeed both and many have the added capability of depicting pathophysiological events in three axes (x, y and z axes) and four (time) dimensional domains. In combination with the specialities of cardiovascular medicine and vascular surgery it can readily be appreciated that the heart and the entire cerebrovascular tree can be evaluated noninvasively. This constitutes not only the heart, but also the aortic arch and its major branches, the cervicocephalic vessels (vertebral arteries V1-V3, common, external and internal carotid), the intracranial carotid (siphon region and V4 vertebral sections) and the circle of Willis and its major branches. Conventional angiography today seems destined largely for the exclusion of infrequent vasculitic disorders and clarification of discrete anatomical features of aneurysms and arteriovenous malformations.

The current approach to cerebrovascular diagnostics demands an immediate appraisal of the stroke mechanisms as all early and secondary preventative treatment is entirely dependent on determination of the pathophysiology. In the acute stroke situation, the initial three questions the clinician has to answer before initiating treatment are - is it a stroke (and not a neoplasm, seizure or migraine), if it is a stroke, is it bland infarction or haemorrhage; and if bland infarction what subtype (because these have different treatments). Broad categories include 1) small vessel atherosclerotic disease (lacunar), 2) large vessel atherosclerotic disease (carotid, vertebral or intracranial stenoses), 3) cardioembolism (disrhythmias, valvular, dyskinetic segments, paradoxical embolism), 4) other (dissection, prothrombotic, vasculitic) and 5) undetermined groups. Briefly, treatment options include: antiaggregant therapy and risk factor control for small vessel disease, carotid

endarterectomy and at times aortic branch vessel bypass for large vessel disease. Most cardiac diseases are eminently treatable: antithrombotics for dissection, anticoagulants for many prothrombotic disorders and immunosuppressive agents for many of the vasculitides constitute effective albeit not always curative treatment today.

Using combinations of the neurodiagnostic armamentarium to advantage is the key to accurate diagnosis and hence cost efficacy. The latter is particularly relevant given current (and very likely future) financial restraints and managed health care. In the clinical context it may be readily appreciated how MRA may clearly depict a stenosis in a large brain supplying vessel which may be graded by transcranial Doppler. Likewise, spiral CT may complement duplex Doppler of a brain supplying cervicocephalic vessel. In both instances invasive intra-arterial angiography is obviated. Transcranial Doppler and duplex Doppler not only rapidly and cost effectively diagnose large artery disease but may also diagnose high intensity transient signals (HITS), diagnostic of emboli in most instances and whether the embologenic site is cardiac, major vessel (carotid bifurcation) or intracranial stenosis. SPECT and TCD have been usefully combined for prognostication and stroke subtype classification, to guide therapy and to deduce a cerebral perfusion index.¹⁷ Both TCD and SPECT may be used to estimate cerebrovascular reserve using CO₂, Acetazolamide or paper bag rebreathing as vasodilatory agents.¹ Such subtyping of cerebral ischaemic symptomatology allows refinement of treatment options such as earlier and more appropriate carotid endarterectomy (CEA). SPECT is currently the best early stroke imaging test and provides objective evidence for diaschisis type neurological deficits, seen with a variety of stroke patients both cortical and subcortical.¹⁵

As one of many possible illustrative examples, it is easy enough to appreciate that a clinical diagnosis of posterior circulation ischaemia or minor infarction (so called vertebrobasilar insufficiency) is rarely made with confidence. Such patients are notoriously difficult to diagnose and usually have had numerous speciality consultations and a long list of costly nondiagnostic investigations, mainly because they present with a plethora of symptoms that may fluctuate with time. Even isolated tinnitus and vertigo may be presenting features and masquerade as otologic problems, but more commonly a nondescript "wooziness" is reported, much to the despair of the clinician. With a clinical suspicion though, in the absence of other disease, MRA of the vertebral and basilar arteries, usefully combined with transcranial Doppler might detect the responsible vertebral artery origin disease or basilar stenosis. Antiaggregant treatment may be then prescribed with conviction or changed to Ticlopidine or Warfarin as required. Both doctor and patient will benefit from more precise diagnosis of the neurological symptomatology.

Biotechnology has rewarded us with remarkably clear pictures of the brain structure and function that impact on management. The most challenging issue facing the clinician and radiologist today is the knowledge of discriminatory use of these modalities. Clearly, no exact step by step flow diagram for stroke investigation can be presented as every stroke patient is different. Investigation must be tailored and individualised. Stroke should be recognised as a multidisciplinary syndrome and so too is the investigation. The way forward seems certain to be a close multidisciplinary liaison for each individual patient. The effective, orderly use of tests can save time, speed up diagnosis and save the patient from undergoing unnecessary, expensive and at times potentially harmful tests. Despite the ever increasing fractionation of medical sub

to page 15

Endovascular occlusion of intracranial aneurysms with electrically detachable platinum coils

from page 14

No aneurysm perforation or rebleed was reported in any of these patients.

Conclusion

With the advent of Guglielmi detachable coils a new chapter in the treatment of certain cerebral aneurysms has been introduced.

Development in this direction over the next years may well prove to be of major importance.

The costs involved can be a problem especially with the present exchange rate of the Rand to the US Dollar.

The small and medium aneurysms with narrow necks seem to be the easiest to treat by this method while coil compaction appears to be present in the majority of giant aneurysms.

A team effort is absolutely necessary where the neurosurgeons, neuro-interventional radiologists, neurologists and anaesthetists work closely together as a team.

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REVIEW

from page 8

Cerebrovascular neuroimaging: which tests and when?

Specialities, a more cohesive interaction between the relevant specialities is becoming a prerequisite for optimum patient evaluation. Never before has clinical acumen been more important in guiding the optimum use and non-use of the wide array of neurodiagnostic tools.

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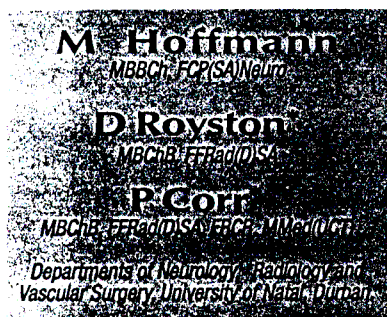
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An obscure cause of stroke - basilar artery fenestration



Introduction

Cerebral artery fenestrations or intravascular bridges represent developmental anomalies, that may be incidental findings but sometimes of clinical significance.¹ These embryological abnormalities may also take the form of duplication of an artery. For the basilar artery, the incidence has been cited as 5.3% for the general population,² the most frequently involved intracerebral arterial system being the vertebrobasilar system.^{3,4} The most important consequence is the tendency to develop arterial aneurysms at the site of fenestrations with a 3% incidence in a retrospective analysis of 5 190 angiograms.⁴ Current pathophysiological data has shown that medial defects of the arterial walls predispose to aneurysm formation. Fenestrations have been described in the basilar, vertebral, middle cerebral, anterior cerebral, aortic arch and posterior cerebral

arteries.^{1,4} In addition to a propensity to form aneurysms, a number of other neurological presentations have been described in association with fenestrations including cerebral ischaemia,^{5,6,7} trigeminal neuralgia,⁸ cervical myelopathy⁹ and symptomatic arteriovenous malformations.¹⁰

Case report

A 71 year-old white man suffered progressively more debilitating attacks of dizziness, diplopia, imbalance and inco-ordination over a seven year period with several daily attacks occurring at time of presentation.

History

He first reported intermittent diplopia eight years prior to presentation, lasting about 90 minutes. A second attack occurred nine months later. He was seen by his general practitioner and ophthalmologist at the time with no abnormality noted. One year later the attacks increased in frequency to one every few months culminating in a much more severe attack with dizziness lasting two hours but without abnormality seen on a MRI scan. During the next four years the diplopia increased dramatically varying from under one minute up to 30 minutes and could occur up to seven times per day.

An episode occurred subsequently with dysphasia, imbalance and dizziness lasting about 30 minutes but with complete return to normality. A second MRI brain scan done at the time was normal. He was given various diagnoses such as transient ischaemic attacks and migraine by different neurologists. An even more disabling attack occurred six years after his first symptoms wherefrom he awoke with speech impairment, inability to walk, loss of co-ordination and difficulty in handling objects. This time a stroke was diagnosed and he improved again only to have a marked exacerbation of his symptoms one month later with intermittent attacks of a similar nature occurring 2-3 times per day lasting about between 30-60 minutes. He was quite disabled by these and described the left sided image (referring to his diplopia) as "coming and going all the time". The most recent presentation was associated with almost continuous diplopia and dizziness. He was otherwise in good health and had no cerebrovascular or cardiovascular risk factors, no deleterious habits and no general or neurological illness.

Examination

Examination revealed a rational man of normal body habitus with a BP of 145/90 and a pulse of 68 per minute regular. The cardiac, chest and abdominal examinations were normal and no stigmata of generalized disease were noted. No cervical or supraclavicular bruits were heard. Neurologically higher functions and cranial nerves were normal. Motor testing was normal save for bilateral upper limb relative hyperreflexia, left more than right. Sensation and limb co-ordination were normal and gait markedly ataxic with tandem gait impossible.

An obscure cause of stroke - basilar artery fenestration

from page 22

Clinical assessment

The clinical assessment included a differential of posterior circulation ischaemia and/or infarction due to vertebrobasilar vascular abnormality.

Investigations

Routine blood tests, prothrombotic screen, chest radiograph and electrocardiogram were normal. Doppler sonography of the cervicocephalic and intracranial vessels was normal. Echocardiography and coronary angiography were normal. The third MRI brain scan was also normal.

Cerebral MR angiography proved diagnostic in that a proximal basilar artery fenestration was seen. This was first suspected due to the presence of a dilated mid basilar section with intravascular hypointense signal (Figure 1).

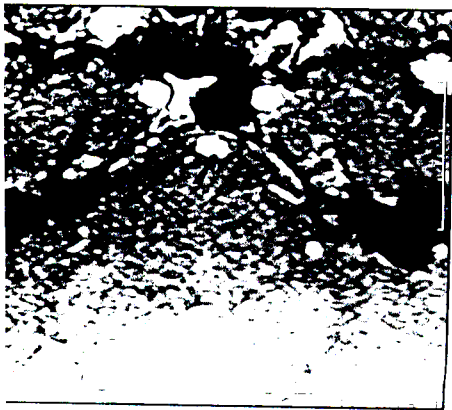


Figure 1: Magnetic resonance angiogram of the vertebrobasilar system. A dilatation of the mid basilar artery with an intravascular hypointense signal (arrow).

Transaxial magnetic resonance angiogram revealed a biconcave appearance of the basilar artery typical of a fenestration (Figure 2). Functional brain scanning with SPECT brain, revealed occipito-parietal hypoperfusion.

Management

He was initially treated with Warfarin without relief of symptoms. Subsequent treatment with Aspirin

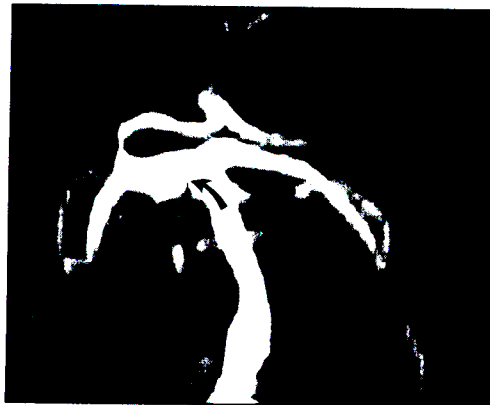


Figure 2: Transaxial magnetic resonance angiogram revealing the biconcave appearance of the basilar artery typical of a fenestration (arrow).

alleviated some of the symptoms which further decreased with the addition of Persantin.

Discussion

Recognition of cerebral artery fenestrations in the context of cerebral ischaemia or stroke is important for at least three reasons:

1. It may represent the mechanism for the ischaemia or stroke.
2. Various treatment options are available which include medical, interventional radiological (Guglielmi coils)¹¹ and surgical options such as aneurysm clipping. The realisation that aneurysms may be part of this developmental abnormality should demand a comprehensive appraisal of the cerebral circulation by angiography.
3. A precise diagnosis as early as possible will also save unnecessary costly investigations (in this patient three MRI scans) and guide appropriate therapy.

In the case under discussion, presumably turbulent blood flow at the site of the fenestration lead to *in situ* thrombosis with distal embolisation and/or intermittent haemodynamic disturbances. This scenario is especially likely in that all other causes of posterior circulation ischaemia were

excluded by a comprehensive stroke work up. In this patient Warfarin failed to alleviate symptoms whereas antiaggregant therapy led to a marked improvement. With the advent of newer antiplatelet agents such as Ticlopidine, Clopidogrel and combination formulae such as Asasantin, such high flow white thrombus type lesions are amenable to mechanism specific treatment.

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