STRESS RESPONSES IN ACUTE ISCHAEMIC STROKE: PREDICTIVE VALUE OF SERUM CORTISOL IN RELATION TO SEVERITY AND OUTCOME.

BY

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BEING A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA IN PART FULFILMENT FOR THE AWARD OF FELLOWSHIP OF THE FACULTY OF INTERNAL MEDICINE (SUBSPECIALTY OF NEUROLOGY).

MAY, 2006
DECLARATION

I hereby declare that this work is original in its entirety. It has not been presented to any journal, nor submitted to any other fellowship body as dissertation.

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CERTIFICATION

We certify that this work was carried out by Dr B.C. Ajuonuma of the Department of Medicine, Nnamdi Azikiwe University Teaching Hospital Nnewi, under our supervision

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Sign  ....................................................

Date  ....................................................
DEDICATION

This work is dedicated to my lovely family: my dear wife Dr (Mrs.) Juliet, and my children: Chinwe, Uchenna, Tochukwu, Chiamaka and Chukwuemeka.
ACKNOWLEDGEMENT

I remain grateful to the Almighty God for his abundant grace.

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Ethical Committee Approval
Re: The relation of Stress Response to outcome of Acute Ischaemic Stroke, Predictive Value of Serum Cortisol measurement

I write to inform you that after due consideration of your proposal/revised proposal, approval is hereby conveyed for you to commence the study.

Dr. P.T. Eke
Chairman, Ethical Committee

Mrs. J. U. Igueokwu
See Ethical Committee
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SUMMARY

Background

Acute cerebral injury is typified in acute stroke. Stroke is a major stressful event to the sufferers, physically emotionally and economically, the impact of which tends to endure beyond the acute phase of the event. The cerebral and systemic pathophysiological events triggered off as a result of acute stroke include ionic shifts, haemodynamic changes, endocrine and metabolic alterations as well as inflammatory responses. Some of these events, both local and systemic, may be adaptive, but recent evidence suggests that some of them may be damaging, and may potentiate the ischaemic damage to neurones. These effects could induce secondary brain damage in acute stroke.

This study set out to find the extent of acute stress response following stroke, measured by single cortisol estimate in the acute phase of the illness. It also sought to find out the benefits or otherwise of such responses in terms of stroke severity and outcome.

Method

A prospective study was carried out among patients with acute ischaemic stroke as shown by the Siriraj criteria at the Nnamdi Azikiwe University Teaching Hospital Nnewi. A total of fifty (50) patients, 22 males (44%) and 28 females (56%) who met the diagnostic criteria were studied. Another group of fifty subjects matched for age and sex to the patients, were included in the study as controls, and made up of two subgroups of 25 each comprising 11 males
(44%) and 14 females (56%). One subgroup C1 was made up of individuals who had hypertension and/or diabetes mellitus, while the other subgroup C2 was made up of healthy individuals. The age range of the study populations was 30-90 years. The mean ages of the males in the patient group, controls groups 1 and 2 were 59.30 ± 13.40 years, 59.00 ± 13.70 years and 58.10 ± 12.60 years respectively. The mean ages of the females were 66.60 ± 12.60 years, 66.60 ± 14.20 years and 65.90 ± 13.5 years respectively for the patients and the control groups 1 and 2. The patients and the controls were clinically assessed, and their morning serum cortisol, and random blood sugar estimations were done. The National Institutes of Health Stroke Score (NIHSS) (severity score) on admission, as well as their functional outcome at 30 and 90 days after stroke, using the modified Rankin scale (mRs) were determined. The mortality at 7, 30 and 90 days after stroke were also estimated.

Results

The results showed that serum cortisol levels were significantly higher in stroke patients when compared with controls (280.60 ± 101.30 ng/ml for the patients, 182.70 ± 39.20 ng/ml and 146.80 ± 21.20 ng/ml for C1 and C2 respectively), F = 32.7 p<0.001. Male patients had higher cortisol levels than male controls:- 326.7 ± 93.9 ng/ml for the patients, 191.2 ± 20.4 ng/ml and 147.4 ± 26.2 ng/ml for control groups 1 and 2 respectively (f = 9.5, p< 0.025). Female patients also had higher cortisol level than controls:- 244.3 ± 93.1 ng/ml for the
patients 176.1 ± 48.5 ng/ml and 146.4 ± 17.4 ng/ml for the controls 1 and 2 respectively. (F=10.1, p<0.025)

Random blood sugar was significantly elevated among the patients 7.40 ± 4.86 mmol/l, when compared with the controls 5.22 ± 2.03 mmol/l for C1 and 4.40 ± 0.47 mmol/l for C2, F = 4.92 p< 0.01.

Serum cortisol correlated with random blood sugar in the patient group (p<0.01, coefficient of correlation 0.90).

All patients had moderately severe stroke (NIHSS 5-20) on presentation. The mean admission cortisol levels showed no relationship with stroke severity at presentation: correlation coefficient r = 0, p>0.999 for mild stroke (NIHSS 1-4): r = 0.19 n=50, p>0.1 for moderate stroke (NIHSS 5-20): and r = 0 p>0.999 for the severe stroke.

Admission serum cortisol in the patients did not relate to functional outcome at 7, 30 and 90 days after the stroke event. Viz at 7th day: good outcome (mRs 0-2): – n = 0, r = p>0.999; moderate outcome (mRs 3-4): n= 41, mean cortisol 261.51 ± 124.1ng/ml, r = -0.36 p < 0.05; poor outcome (mRs 5-6): –n=9, mean cortisol 378.0 ± 182.0, r = 0.48, p > 0.01. For the 30th day good outcome: –n=9, cortisol 235.4 ± 79.7, r = 0, p>0.999; moderate outcome: –n=21, cortisol 248.34 ± 87.10, r=-0.18, p>0.1; poor outcome: –n=12, cortisol 391.0± 58.9, r=0 p> 0.9999. For 90th day, good outcome: –n=36, cortisol 244.28 ± 82.3ng/ml, r = -0.009, p>0.8; moderate outcome: n = 0; r=0, p>0.9999; poor outcome: n=14.cortisol 388.29 ± 31.1 ng/ml r = 0 p> 0.999.
The difference in the mean cortisol levels of the fatalities within 7 days of 417±117ng/ml n=2 compared with those of the survivors 275 ± 97.6 n=48 did not reach significance; (z = 1.69 p>0.05.). Though the mean admission serum cortisol level was not found predictive of 7th day mortality after stroke. It however related significantly to the 30th and 90th day case fatalities. The admission cortisol level for those that died between 7 and 30 days, n=10, was 387.7 ± 50.6 ng/ml compared with that of the living within the period: 253.9 ± 92.6 ng/ml n=38, (z=6.17, p<0.001.)

At the end of the study ie 90 days, 28% fatality was recorded with mean cortisol level of 388.4 ± 53.1 ng/ml, compared to the survivors 72% with mean cortisol level of 238.6 ± 82.2 ng/ml. The finding showed predictability of admission cortisol to 90th day fatality (z=7.59, p < 0.01).

**Conclusion**

Single admission serum cortisol levels in the acute phase of ishaemic stroke did not relate to stroke severity at presentation, neither did it predict functional outcome at 7, 30, 90 days but could predict mortality at 30 and 90 days after the event.

Serum cortisol did not correlate to the 7th day mortality among patients (p > 0.05), but was found to be a predictor of death at 30 and 90 days after stroke.

**CHAPTER ONE**

**INTRODUCTION**
Stroke ranks first in frequency and importance among all the neurological diseases of adult life, constituting over 50% of neurological disorders seen in the general setting.\(^1\)

It is the third most common cause of death, after heart disease and cancer in the United States of America and many industrialized countries.\(^2\) Estimates by the World Health Organization (WHO) in 1999, indicated that cerebrovascular disease was the second leading cause of death world-wide.\(^3\)

Stroke remains the leading cause of disability in adults. About 30% of stroke survivors require assistance with activities of daily living (A.D.L.), 20% require assistance with ambulation while close to 20% require institutional care.\(^2\)

Present evidence indicates decline in the incidence and mortality of stroke in industrialized nations. The different patterns of risk factors among others may explain the differences observed in stroke incidence in different parts of the world.\(^1,2\)

The human and financial costs of stroke are enormous. The annual economic impact on our society both directly in health care, and indirectly in lost income further highlights the significance of stroke.\(^2\) Immediate family members, relations and dependants of stroke survivors are often saddled with the task of providing for the physical, emotional and health needs of these patients, even in countries where some form of social services are available.

Stroke is a major stressful event to the sufferers, physically, emotionally and economically. Although stroke varies in severity, the impact of these stress
upheavals tends to endure through out the acute periods, and even the subsequent rehabilitation\textsuperscript{4}.

The pathological process in stroke goes beyond the gross aspects of embolism, thrombosis, dissection and rupture of the vessel.\textsuperscript{5} The parenchymal changes in the brain include ischaemia with or without infarction, and haemorrhage. A cascade of secondary events triggered include such mechanisms as ionic alterations, haemodynamic/haemorrheological changes, enzyme activations, endocrine/metabolic, and inflammatory responses. Most of the events though originating at the local and cellular levels, have been found to evoke systemic events as well. These have been viewed as protective, homeostatic and reparative. However recent evidences suggests that some of them may have negative impacts on the pathological process or recovery.\textsuperscript{5}

Systemic blood pressure elevations observed in the first few days following stroke, have often been attributed to Cushing’s reflex, stress response and rises in catecholamine levels. Studies indicate worse outcome in patients with high reactive and sustained hypertension.\textsuperscript{6}

In a similar manner, hyperglycaemia observed in the acute phase in stroke patients, without prior history of diabetes mellitus has been linked to a major stress response. Studies have indicated its negative impact on stroke severity and outcome.\textsuperscript{7}

The endocrine/metabolic responses following stroke have been known to include rises in serum cortisol, catecholamines, glucagon, adrenocorticotrophic hormones among others.\textsuperscript{6}
Statement of the problem

Endocrine and metabolic responses occur in acute phase of stroke. Several studies elsewhere have documented these responses. Their nature is not exactly known. Whereas some relate it to stroke severity, others think otherwise, and consider it epiphenomenal.

The hypothesis in this study therefore is that elevated cortisol levels following an acute stroke event has a negative impact on stroke severity and outcome.

Relevance of study

Single estimation of cortisol as a factor in evaluating stroke severity and outcome may contribute to stroke care, and subsequent associated measures to stem the stressors may alter the outcome of stroke.

CHAPTER TWO

LITERATURE REVIEW ON STROKE

Stroke – Definition and Overview

Stroke is a clinical syndrome of rapidly progressive symptoms and signs of focal or global neurological deficit lasting more than 24 hours, or leading to death, of which there is no apparent cause other than of vascular origin.
Stroke therefore excludes transient ischaemic attacks (TIA), epidural and subdural haemorrhage/haematoma or deficits from brain tumours. A TIA is a temporal focal “non marching” neurological deficit of sudden onset related to the brain, retina or cochlear, and lasting less than 1 hr., without any objective evidence of infarction in the affected region\(^2\). Stroke includes reversible ischaemic neurological deficits (RIND) in which neurological deficits last longer than 24 hours but less than 3 weeks. Stroke is broadly classified as ischaemic or haemorrhagic. African series show that cerebral infarction is the commonest type and accounts for up to 60% of cases, while intra-cerebral and subarachnoid haemorrhages account for 20% and 10% respectively. This an agreement with findings in western countries\(^9,10,11\)

**Epidemiology**

Stroke is responsible for over 5 million deaths each year making cerebro-vascular disease the second leading cause of death world wide\(^1, 2\). Every year at least 15 million people suffer non-fatal stroke, and about one third of them are disabled as a consequence\(^2\). Among survivors of stroke, or of transient ischaemic attack (TIA) the risk of repeat stroke is very high, about one in six suffer another stroke episode within five years\(^12\).

Stroke causes huge economic, social and psychological stress on the patient, the family and the society. Health care delivery systems are maximally stretched. Rehabilitation schemes hardly cope with the increasing number of cases. The quality of life (QOL) of stroke survivors is greatly affected
irrespective of the severity: Physical handicaps e.g. self care, activity of daily living, speech problems, loss of hand function, and cognitive impairments e.g. communication, memory, vision, emotion, thought and personality; all lead to various degrees of dependent life. Psychological well-being is impaired and depression among survivors is common. The overall health-related quality of life score depends on some factors bordering on social support available, social class of patient, functional status, age and co-morbidity among others. The American Heart Association with a record of ≥ 85,000 new cases of stroke in the USA annually, had estimated in the year 1999, the economic burden (direct and indirect costs) of stroke to be 5.1 billion US dollars, just as in the United Kingdom which records ≥ 25,000 new cases annually, 5% of the health budget annually is devoted to stroke care. The estimated annual economic impact has been on the increase with the American estimate escalating to approximately 41 billion U.S. dollars in 2003.

Stroke data from case series, case-control studies, and large population cohort studies, show that the incidence rates for all strokes and stroke-types vary widely between and within populations. In Western Europe and United States of America (USA) incidence rates approach 200 per 100,000 population per year which constitute about 50% of neurological consultations. These figures are comparable to those found in Japan and South Asia, but lower than figures for China and South America which are 1½ – 3 times higher. Even in the USA, stroke rates were up to 3 times higher in the so called stroke-belt,
with similarly higher rates observed for African- and Hispanic-Americans. Hospital population studies in Africa show figures that closely resemble that for the Asian population. Stroke accounts for 0.9 – 4% of admissions and 0.5 – 45% of neurological admissions. Osuntokun et al found a community prevalence of 58 – 400/100000; a crude annual mortality rate of about 700/100000 per year, and an age-specific mortality in the elderly of about 100/100000 per year. The stroke incidence in Ibadan Nigeria of 26/100000 is less than that reported for Western Countries (50 – 400/100000).

**Risk factors**

The risk factors for stroke can broadly be classified into (a) non-modifiable and (b) modifiable

**Non modifiable risk factors**

(i) **Age**: Advanced age is the most powerful risk factor for both first and recurrent stroke. The incidence of stroke doubles each decade after the age of 55 years. Age may be considered as a marker for the duration of some risk factors acquired at a younger age (e.g. smoking) while some other risk factors (e.g. hypertension and diabetes mellitus) tend to become more evident with advancing age. Among Africans the peak age of incidence has been found to be 1 – 2 decades earlier than that in the western population, where it is reported that more than half of the cases occur in people older than 70 years.
(ii) **Gender**: Men are known to develop stroke at higher rates than women, particularly in the pre-menopausal age range. This immunity seems to be less important post menopause when available reports show leveling up of both rates\(^\text{20}\).

(iii) **Race**: The rate of cerebral infarction is higher in blacks than in whites and the Hispanics. The higher prevalence of hypertension, diabetes and atherosclerotic occlusive disease in blacks may partly explain the difference\(^\text{20,21}\).

(iv) **Genetics**: The concordance rate for stroke is higher among monozygotic twins than among dizygotic twins. A parental history of stroke is associated with a higher likelihood of stroke in their offspring, and a family history of stroke in any first-degree relative is also associated with increased stroke risk. Overall, there is an estimated 40\% likelihood of a parent or sibling of a stroke patient having had a stroke\(^\text{22,23}\). Single gene mutations have been associated with stroke-like disorders such as found in Mitochondrial Myopathy, Encephalopathy, Lactic Acidosis and Stroke (MELAS)\(^\text{24}\) and Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leucoencephalopathy (CADASIL),\(^\text{25}\) as well as in individuals with the homozygous (DD) genotype of the angiotensin converting enzyme gene\(^\text{26}\).

There are also other inherited conditions associated with increased disposition to stroke e.g. Ehlers-Danlos syndrome (type iv), Marfan’s syndrome, familial atrial myxoma, idiopathic cardiomyopathies, and inherited haematological conditions like protein C and S deficiencies. Cerebral ischaemia is known to
occur in approximately 15% of patients with the homozygous (Hb SS) sickle-cell gene.$^{27}$

**(b) Modifiable risk factors**

(i) **Hypertension:** Arterial hypertension defined as systolic blood pressure (SBP) greater than 140mmHg or diastolic blood pressure (DBP) greater than 90mmHg is the most dominant and modifiable risk factor for stroke,$^{11,28}$ conferring a three to four-fold higher rates of stroke regardless of age and sex. The stroke producing potential is as much for increasing systolic hypertension as for elevated pulse pressure and elevated diastolic blood pressure. Blood pressure treatment resulting in a reduction of SBP of 10 – 12 mmHg and DBP reduction of 5 – 6 mmHg was associated with a 38% reduction in stroke incidence in one series.$^{29}$ The Systolic Hypertension in the Elderly Study Programme (SHEP) showed a 36% reduction in nonfatal and fatal strokes over a 5-year period in persons aged 60 years and above when isolated systolic hypertension was treated.$^{29}$ The Framingham Heart Study$^{30}$ examined the effect of high normal blood pressure (130-139/89 mmHg) on cardiovascular end points, including stroke, in those aged 65 years and above, and found crude event rates in this blood pressure range to be 19.5 for women and 28.1 for men, with an adjusted hazard ratios of 2.5 and 1.6 for women and men respectively. It was inconclusive on benefits of treatment or otherwise.

The PROGRESS Trial$^{31}$ evaluated the effect of Perindopril (angiotensin converting enzyme) and indapamide (a diuretic) on the risk of stroke in patients with histories of stroke or TIA in the prior 5 years, and found that
regardless of blood pressure at entry, patients clearly benefited from treatment. In the presence of other risk factors, hypertension further increases stroke risk. 

(ii) **Diabetes mellitus:** Diabetes mellitus increases the risk for ischaemic stroke two to four-fold compared with the risk in people without diabetes. The excess stroke risk is known to be independent of age or blood pressure status. Diabetes associated with arterial hypertension adds significantly to stroke risk with a more than four-fold increase in the relative risk of cardiovascular event among patients with both conditions than among those without them. Macrovascular disease is the leading cause of mortality among patients with diabetes, while it is reported that diabetics with autonomic neuropathy and retinopathy appear to be the group at particularly high risk for ischaemic stroke. In addition diabetes mellitus increases morbidity and mortality after stroke.

(iii) **Dyslipidaemia:** High levels of total cholesterol, and low density lipoprotein (LDL)–cholesterol, show positive correlation with increasing atherosclerosis. Studies have shown a positive relationship between serum cholesterol levels and deaths resulting from non-haemorrhage stroke. The Heart Protection Study did a randomized study of 20536 individuals between 40 – 80 years of age with a nonfasting total cholesterol of at least 135 mg/dl, and a history of coronary heart disease, stroke, TIA; carotid endarterectomy, peripheral vascular disease, diabetes, or treated hypertension, using simvastatin (lipid lowering agent) 40mg daily and placebo. Over a 5 year period, deaths were reported significantly less frequent in the simvastatin
treated group, as well as coronary death and nonfatal myocardial infarction. There was also 25% reduction in the rate of first stroke with a 30% reduction in ischaemic stroke, but no difference in haemorrhagic stroke rate. Fatal disabling and less severe strokes were all reduced with also significant reduction in TIA risk. The overall risk of major vascular events was reduced by 24% and the benefits of simvastatin were evident irrespective of baseline cholesterol levels, extent of LDL-cholesterol lowering, age, sex, smoking hypertension treatment, and the use of aspirin, beta-blockers, and angiotensin converting enzyme inhibitors. This result suggested that statins (e.g. simvastatin) may decrease stroke risk by other effects termed “non-lipid” effects which may involve regulation of vascular tone, plaque stabilization, and antioxidant activity. Also the Scandinavian Simvastatin Survival Study (4S) 35 investigated the benefit of cholesterol lowering using simvastatin in persons with coronary heart disease and hypercholesterolaemia and found significant relative reduction in the total mortality rate, major coronary events and number of cardiac revascularization procedures, as well as in fatal and nonfatal strokes and TIA.

(iv) **Atrial fibrillation**: Atrial fibrillation is an independent risk factor for strokes 36. Chronic non-valvular atrial fibrillation (NVAF) is associated with approximately five to six-fold risks for stroke, and a mortality of about twice that of age and sex matched without atrial fibrillation. The prevalence increases with advancing age:- about 0.5% of patients aged 50- 59 years, 8.8% for those aged 70 – 89 years. Prior stroke, or TIA, and age more than 75 years
increases the risk of embolism in patients with NVAF. The presence of left atrial thrombus, mitral stenosis, and/or concomitant risk factors e.g. hypertension or cardiac failure, further increases the risk. Randomized studies have shown that the use of warfarin to achieve an international normalized ratio (INR) of 2-3 drastically reduces the relative risk of first or recurrent stroke by 68% in patients with atrial fibrillation: in the European Atrial Fibrillation Trial (EAFT) study 37. The stroke risk is relatively low in those with “lone” atrial fibrillation.

(v) Smoking: Cigarette smoking especially on the long term, is a major and preventable risk factor for coronary heart disease, stroke, and peripheral vascular disease. It is an independent risk factor for ischaemic stroke in men and women of all ages, with two to three times greater increase in risk than in non smokers 38. Smoking enhances atherogenesis, reduces capacity of oxygen delivery, induces cardiac arrhythmias and arterial spasm.

(vi) Alcohol abuse: There is a reported J-shaped relationship between alcohol consumption and ischaemic stroke 14. Light to moderate use (up to two drinks per day spread evenly throughout the week) confers protection against ischaemic stroke, while heavy drinking and binging is associated with increased risk of total stroke (ischaemic and haemorrhagic).

(vii) Obesity and physical inactivity: A body mass index (BMI) of 30 and above and particularly truncal or abdominal obesity carries an increased risk for cardiovascular disease in men and women of all ages, as well as a relative risk of between 1.75 and 2.37 for ischaemic stroke. 2 There is evidence that
physical activity can reduce stroke risk. The Nurses Health Study (NHS) demonstrated with multivariate analyses, an inverse relationship between increasing exercise and ischaemic stroke \(^{39}\).

(viii) **Extracranial and intracranial large artery stenosis:** Atherosclerotic narrowing of extracranial and intracranial large arteries (carotids particularly internal carotid) whether symptomatic or asymptomatic is an important and treatable risk factor for large vessel stroke. The risk factors for internal carotid artery (ICA) stenosis are similar to those for coronary artery disease (e.g. hypertension, smoking, hyperlipidaemia), which are largely modifiable. More so non-invasive facilities for vascular assessment for diagnosis, and surgical treatment options are being increasingly recognized. Positron emission tomography (PET) studies demonstrate “misery perfusion” of the brain with decreased blood flow and increased oxygen extraction despite largely being asymptomatic because of collateral circulation from the contralateral side. Such compromised areas of the brain are at increased risk for future ischaemic events.

The North American Symptomatic Surgical Endarterectomy Trial (NASCET) \(^{40}\) and the European Carotid Surgery Trial (ECST) \(^{41}\) demonstrated that patients who had carotid endarterectomy (CEA) had a 65% relative risk reduction, and a 17% absolute risk reduction in ipsilateral stroke or death compared with best medical treatment. Though asymptomatic, carotid disease has been found to carry a greater risk of vascular death from coronary artery diseases than from stroke, recent follow up studies have found also that it carries an estimated
annual risk for stroke of 1.5% at 1 year and 7.5% at 5 years. A stenosis of less than 75% carries a stroke risk of 1.3% annually, while stenosis of greater than 75% increase the risk of combined TIA and stroke to 10.5%, though plague structure may be another critical factor. It has also been reported by the asymptomatic carotid atherosclerosis study that plague removal in such asymptomatic patients (with ≥60% stenosis) reduced the stroke rate from 11% to 5%.

(ix) **Previous TIA or stroke:**

Patients who suffered TIA’s are at approximately three-fold greater risk than normal controls for stroke or death from vascular causes. Reported series indicate that about 15%-25% of those experiencing stroke have TIA before their stroke, with those who suffered hemispheric TIA at more risk than those who had retinal TIA. It is reported that one third of TIA leads to ischaemic stroke in the range of 20% in the first month and 50% within the first year. First stroke also carries substantial risk for recurrent stroke, just as it is reported that recurrent stroke has poorer prognosis especially if contralateral to the first event.

(x) **Hyperhomocysteinamia:**

High homocysteine levels can result from mutation of either cystathione-b-synthetase or methylenetetrahydrofolate reductase enzymes, but more importantly from dietary deficiency of vitamin B12 or folic acid. Hyperhomocysteinaemia reportedly carries an over all odds ratio (OR) for stroke of 2.5 and this relationship becomes more significant with increasing
homocysteine levels. Levels of homocysteine in the highest quartile (greater than 13.8 mmol/L) are reported to have an OR of 8.7 for large-artery disease-associated stroke when compared with that for the lowest quartile level (less than 9.0 mol/L)\textsuperscript{45}.

High homocysteine levels are also encountered in about 10% of patients with venous thrombosis suggesting possible role in oxidative vascular injury, altered endothelial function and thrombogenicity.

(xi) **Hormone replacement therapy, Pregnant state, and Oral Contraceptive Pills:**

The World Health Initiative Study (WHIS)/Heart and Oestrogen-Progestin Replacement Study (HERS) in a study of post-menopausal women treated with oestrogen and progestin for primary prevention of coronary heart disease (CHD) and invasive breast cancer, observed a hazard ratio of 1.41 for stroke\textsuperscript{46}. The absolute excess risk per 10,000 person-years attributable to oestrogen plus progestin were seven-fold for CHD, eight-fold each for stroke, pulmonary embolism, and invasive cancers. The study was however terminated prematurely because risks outweighed benefits. Also in a related aspect of the study, it was reported that use of equine oestrogen (premarin) in a cohort of post-menopausal women with coronary heart disease resulted in no reduction in the incidence of stroke. Stroke is reported to be uncommon in women of child bearing age. However, the risk for thrombosis associated with pregnancy is known to be high in the post-partum period (first 6 weeks after child birth) and is associated with increased frequency of cerebral infarction – which
however is rare during pregnancy \textsuperscript{47}. Oral contraceptive pills have long been associated with stroke risk and the overall risk for ischaemic stroke in users of low dose (oestrogen plus progesterone) pills quoted as 1 – 3 times for cerebral infarction and slightly higher (2-3 times) for cerebral haemorrhage. The World Health Organization (WHO) collaborative study \textsuperscript{48}, found an overall Odds Ratio (OR) for ischaemic stroke of 2.99, among users of oral contraceptives which rose to 7.20 in those who smoked, and 10.70 in those who were hypertensive.

(ii) **Hypercoagulability:**

Haemostatic and haemorrheological factors may be important risk factors for cerebro-vascular disease. Elevated haematocrit, elevated fibrinogen and blood viscosity, excess plasminogen activator inhibitor-I activity, and excess levels of factor VII are reported to increase the risk factor for coronary heart disease. Hypercoagulable states resulting from either primary causes (e.g. factor V-Leiden mutation, prothrombin G 20210 A mutation, protein-C-S and antithrobin III deficiency etc) or secondary causes (Antiphospholipid syndrome, neoplasms, sickle cell disease, nephrotic syndrome, myeloproliferative disorders, etc) are known to confer substantial risk for both arterial and venous thromboembolic cerebral infarction \textsuperscript{49}.

(iii) **Drug Abuse:**

Substance abuse is an important risk factor of consideration in stroke especially in the young \textsuperscript{20, 21, 22}. Use of cocaine and its crack version, is particularly associated with both ischaemic and haemorrhagic stroke. Other
drugs of abuse include the amphetamines, pentazocine – plus pyribenzamine (T’s and blues), phencyclidine, heroin, and glue sniffing. The use of anabolic steroids and recombinant erythropoietin (blood doping) by young athletes, and the use of ephedra (a weight reducing drug) have all been associated with substantial stroke risk. Most of these studies are case reports and observations linking temporal sequence of events leading to stroke. The exact mechanism for stroke in these instances has not been elucidated. Potential mechanisms involved are thought to include vasopasm, arrhythmia induction, and haemorrhheological factors.

(xiv) Snoring and Sleep Apnoea Syndrome:
The relative risk of stroke in snorers or individuals with sleep apnoea syndrome is reported to range between 2.08 to 10.30, even after adjustments for other risk factors. The reports postulated decreased cerebral perfusion/oxygen saturation, increased fibrinogen levels, enhanced platelet aggregation in persons with this syndrome.

(xv) HIV and Stroke:
There are reports of cerebral infarction and other stroke-like events complicating HIV infection. The pathobiology remains unclear but may be related to vasculitis, (HIV associated vasculopathy) due to deposition of immune complexes on the vascular wall, increased frequency of antiphospholipid antibodies, rapid progression of early syphilis to neurosyphilis or complication of the disease process and therapy.

(xvi) Diet, Metabolic Syndrome and Other Risk Factors:
The association between specific dietary factors and stroke risk is not well established but evidence suggest that increased intake of fruits, vegetables whole grain and fish as well as maintenance of adequate intake of vitamins B6, B12 and folic acid may be associated with decreased stroke risk. The metabolic syndrome, (insulin resistance syndrome or syndrome X) with abdominal obesity, hyperinsulinaemia and associated peripheral insulin resistance, is reported to increase stroke risk. This expectedly may be related to other features of this syndrome which in themselves contribute to stroke risk through hypertension, glucose intolerance/hyperglycaemia, dyslipidaemia, increased plasminogen activator inhibitor –I activity, vascular endothelial dysfunction, and vascular inflammation. Other less definable risk factors include presence of anticardiolipin antibodies, elevated fibrinogen and C-related protein, seropositivity for Chlamydia pneumoniae, presence of periodontal disease and chronic Helicobacter pylori and Cytomegalovirus infections.

**PATHOGENESIS OF STROKE**

Cerebrovascular disease results from one or more of many pathological processes involving the cerebral blood vessels and circulation.

(a) Processes intrinsic to the vessel e.g. atherosclerosis, lipohyalinosis, inflammation, and amyloid deposition, which account for the great majority of thrombotic stroke subtypes.
(b) Processes that originate remotely, eg as a result of dislodgement of embolus from the heart or extracranial circulation, resulting in embolic stroke.

(c) Processes that result in inadequate cerebral blood flow, due to decreased perfusion pressure or increased blood viscosity.

(d) Processes that result in rupture of a vessel in the subarachnoid space or intracerebral tissue causing haemorrhagic strokes.

This has led to the classic but imperfect division of stroke into thrombotic, embolic, and haemorrhagic, which however underscores the fact that multiple factors may be operative in any stroke subtype, as well as not accounting for the strokes of undetermined causes.

Ischaemic strokes mostly result from the first three processes which may cause transient cerebral ischaemia or permanent cerebral infarction. The frequency of the different stroke types has been difficult to ascertain but various data including those from the Harvard stroke series, the Boston City Hospital (BCH) autopsy series, and recently from the National Institute of Neurological Disorders and Stroke (NINCDS) registry agree that the ratio of infarcts to haemorrhages is in the range of 4:1.

**Athero-thrombotic cerebral infarction :- atherosclerosis.**

(i) **The process**

Athero-thrombotic process as a cause of cerebral infarction may involve large, small or the penetrating arteries of the brain. All the coats of the vessel become impregnated with hyaline-lipid material in a process classically described by Fisher as lipohyalinosis. The segments so affected may weaken, lose their
resilience or allow the formation of dissecting aneurysms (Charcot-Bouchard aneurysm). Although atheromatosis is known to have its onset in childhood and adolescence, only in the middle and late years of life is it likely to have clinical consequences\textsuperscript{58}. Atherosclerosis is multifactorial; comorbidities frequently overlap and risk factors are often addictive. Hypertension, and diabetes mellitus are known to aggravate the process. As with coronary and peripheral vascular atherosclerosis, low levels of high-density lipoprotein (HDL)-cholesterol, and high levels of low-density lipoprotein (LDL)-cholesterol, particularly dispose individuals to cerebral atherosclerosis. Added to these well known established risk factors is the possible role of excess homocysteine levels and a speculative role of chronic infection particularly with Chlamydia pneumoniae. The effect of atherosclerosis reflects not only stenosis of vessels but also plague complications: ulceration with artery to artery embolization, or thrombosis in the setting of pre-existing arterial stenosis.

(ii) Sites

There is a tendency for atheromatous plaques to form at the branches and curves of the cerebral arteries:- They are reported to be rarer beyond the first major branchings of the cerebral arteries, and unusual in the cerebellar and ophthalmic arteries. The common carotids and the vertebral arteries at their origins from the aorta are frequently involved as well, but seldom give rise to occlusive cerebral ischaemia probably because of collateral arterial pathways.
Growth and regression

Atheromatous lesions develop and grow silently over 20 or more years and may become symptomatic in the event of superimposed thrombosis. However, the more the severity of atheromatosis, the more the likelihood of thrombotic complications though not in a parallel relationship. Atheromatous lesions may also regress under the influence of diet and certain drugs, but some serial studies indicate that the process is progressive in majority of cases. Degeneration of or haemorrhage into the walls of atherosclerotic vessels due to rupture of the vaso-vasorum may occur causing damage to the endothelium, deposition of fibrin and platelet adhesion, which further compromise the lumen of the distal vessels. These events in the atherosclerotic-thrombotic process probably account for clinical manifestations in the form of prodromal ischaemic attacks, stroke in evolution and completed stroke which may be significant in relation to therapy and prognosis.\(^5^9\).

(iii) Thrombus formation

The process of thrombus formation involves the interplay among three components – the endothelium, circulating platelets and the biochemical events collectively termed the coagulative cascade:- in what Rudolf Virchow (1821-1902) described as a triad. A localized endothelial damage following atherosclerosis initiates thrombus formation from fibrin deposition and platelet aggregation. Prostacyclin production from arachidonic acid causes dilatation in the regional blood vessels as well as being a chemoattractant for platelets. Nitric oxide (derived from relaxing factor in the vessel wall) accumulates and
leads to vasoconstriction. Vasomodulin and protein C which are also secreted by the endothelium and which normally inhibit formation of fibrin from thrombus are reduced in concentration or consumed at the site, the effect of which is induction of clotting. The platelets also discharge their granules under the influence of thromboxane-A2 synthesized in the injured vessel wall. There is in addition release of coagulation proteins, (including thrombin and Willibrand’s factor) and other elements of the coagulative cascade. There is evidence to suggest an enhancing role of homocysteine in the coagulative process. The deficiency of protein C (a vitamin K dependent protease) and its cofactors (protein S and antithrombin III) or resistance to their activated forms, which normally inhibit coagulation, may predispose to in situ thrombus formation within either the arterial or venous system.

Embolic infarction:

Cerebral embolic infarction results from emboli arising from the heart, intraarterial (systemic), or rarely paradoxically from the pulmonary (right-sided) circulation, while some may still be from undetermined sources.

(i) Cardioembolism

Cardioembolism accounts for between 20-57% of all ischaemic strokes if defined by the presence of a cardiac structural abnormality or dysarrythmia, that predisposes to the formation of thrombi within the cardiac chamber. The Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classified sources of cardio-embolic into high or medium risk sources of cerebral embolism. Brain embolism is a known manifestation of heart disease and about 75% of
cardiogenic emboli lodge in the brain. Most cardio embolic infarcts involve the cortex of the cerebral hemispheres and frequently cause isolated branch artery syndromes, though subcortical infarcts occur in up to 20% of cases. Imaging studies tend to suggest that cortical infarcts, especially if in multiple vascular territories, or in the presence of evidence of systemic embolism, are likely to be of cardiac origin\textsuperscript{62}. Atrial fibrillation (AF) is probably the most common substrate for cerebral cardioembolism. AF is also a known independent risk factor for stroke \textsuperscript{20, 22} though an estimate of only 65% of strokes in persons with atrial fibrillation are cardioembolic. In A.F., purposeful atrial pump is lost which promotes blood stasis and thrombus formation in the atrial chambers. The presence of left atrial thrombus, mitral stenosis and other concomitant risk factors including older age, hypertension, diabetes mellitus, cardiac failure, and echocardiographic left ventricular dysfunction adds to the risk. Lone atrial fibrillation as well as paroxysmal atrial fibrillation or flutter also carry substantial risk, though less than that of the chronic variety\textsuperscript{63}.

Acute myocardial infarction (AMI) may result in damaged endocardium, aneurysmal formation, dysrhythmias, and cardiogenic shock (low cardiac output and hypotension) which acting singly or in concert predispose to thrombus formation. An estimation of 2% to 5% of consecutive patients with acute myocardial infarction experience a stroke typically within the two weeks following the cardiac event; the risk being particularly high with anterior infarctions in which mural thrombi have been quoted to be seen
in up to 40% of cases on echocardiography, when compared with 4% in inferior infarctions ⁶⁴.

Congestive cardiac failure (CCF) was found to increase stroke risk by a factor of up to 5 and ranks second to AF in the Framingham study ³⁶. Cardiac failure treatment trials recorded stroke rates in the range of 1.3% to 3.5% per year, a risk that was found unrelated to the degree of heart failure but appeared to increase with diminishing left ventricular ejection fraction ⁶⁵: a dilated left ventricle appearing to have a thrombogenic potential similar to that of large left atrium in AF.

Systemic embolization may be the first presentation of mitral stenosis (M.S.) in 9% - 14% of cases, and between 60 % and 75% of them may have cardioembolic cerebral infarction ⁶⁶ especially in the presence of atrial fibrillation. Aortic valve calcification with or without stenosis has not been found to increase stroke risk, but the picture is different with mitral valve annular calcification ⁶⁶. Mitral valve prolapse (MVP) except when complicated is reported not to be associated with increased stroke frequency. The vegetations of acute and sub-acute infective endocarditis (IE) form sources of cardioembolic cerebral infarction in up to 15%-30% of patients, and embolism may be systemic or pulmonary. This risk is reported to be higher with mitral valve involvement as well as vegetations of more than 10mm in size ⁶⁷. Marantic or nonbacterial thrombotic endocarditis (NBTE) was found to be responsible for up to 30% of an autopsy series of sufferers of endocarditis who had cerebral infarction ⁶⁸.
Intra-cardiac shunts with right to left blood flow enable micro thrombi formed in the peripheral venous system, which ordinarily would be filtered by the pulmonary capillary bed, to enter the systemic circulation and predispose to cerebral embolic infarction. Cerebral infarction from such paradoxical emboli have been reported to be responsible for the increasing incidence of cerebral infarction in children and adolescents with congenital cyanotic heart disease. The risk of cerebral events appear to correlate with the size of the atrial defects.\textsuperscript{69}

Athero-sclerotic disease of the aorta is a potential source of cerebral embolism. Ulcerated plagues may be found in up to 60\% of patients with cryptogenic stroke. The risk of recurrent stroke increases with increasing thickness of the plague, as well as if the plague is complex (protrusion into the lumen) or if it is mobile.\textsuperscript{70}

Cardiac surgery e.g. the coronary artery bypass surgery (CABG) has an incident post-operative neurologic sequelae of approximately 2\%-6\%, most of which is due to cerebral-athero-embolic infarction from the atheromatous aorta. Two-thirds of strokes occur by the second post-operative day and predominantly affect the cerebral hemispheres.\textsuperscript{71} Other cardiac surgical manipulations may carry some risk for cerebral thrombo embolism.

(ii) Non cardiogenic embolic cerebral infarction

Emboli of non-cardiac origin that may cause cerebral infarction may arise from sites of arterial dissection or fibro muscular dysplasia (FMD) of the carotid and vertebral arteries. Other sources include thrombus formed in the
pulmonary veins and pelvic/lower extremity venous thrombi. Fat and Air embolism may result from bone trauma and surgery, from acquisition of venous access, and catheterization, as well as from cerebral angiography.

(iii) **Undetermined sources** – The point of origin of embolism to the brain may be unidentified in up to 30% of cases of presumed embolic infarction in autopsy series.

**Non atherosclerotic vasculopathies**

Vessel diseases not involving atherosclerosis may be responsible for minority of ischaemic strokes. These include arterial dissection, traumatic cerebrovascular disease, radiation vasculopathy, moya-moya disease, fibromuscular dysplasia, cerebral vasculitides and migraine. These uncommon conditions may represent up to 5% of all strokes and seem relatively common in children and young adults.

(i) Arterial dissection occurs when there is a tear in the vessel wall (intima), resulting in tracking of blood into the vessel wall forming an intramural haematoma which may remain limited to the media or extend into the subadventitia. The consequences include vessel stenosis/occlusion, aneurysmal dilatation or mass effect. It affects the aorta and the extra cranial segments of the internal carotid artery and the vertebral arteries with less involvement of the basilar arteries. The aetiology of arterial dissection in most patients remain unknown but many are spontaneous, while others may be related to trauma including trivial ones, blunt and penetrating neck trauma, vigorous chiropractic manipulations of the neck and sporting activities. Some occur in connection
with certain connective tissue disorders like Marfan’s syndrome, and Ehlers-Danlos syndrome. The most common sites for internal carotid and vertebral artery dissections are at the base of the skull opposite cervical segments C₁ and C₂ vertebrae where they are fixed, and where they have the greatest susceptibility to stretch following neck movements. The peak age incidence for most cervico-cephalic arterial dissections is 40-45 years but they can occur in children and older adults. The recurrence rate is generally thought to be less that 10% and seems to be lower with dissections after the age of 45 years.

(ii) Fibromuscular dysplasia (FMD)

This is a segmental non-inflammatory dysplastic non-atheromatous arterial disease of unknown aetiology affecting predominantly young and middle aged women. It is uncommon, and affects less than 1% of the population, and whites more than blacks. The most common site is the cervical part of the carotid arteries in the region of the first and second cervical spine segments, often bilaterally. The intracranial parts of the vessels are less affected. The renal and iliac arteries are often involved. Some familial cases have been reported and there is reported association with $\alpha_1$-antitrypsin deficiency. The consequences of the medial layer dysplasia of the arterial walls include “tubular” narrowing giving them the sequential beading appearance often with saccular aneurysmal dilatation. These may lead to arterial dissection, with predisposition to thrombus formation and even subarachnoid bleed.
(iii) Moya-Moya disease

This is a chronic progressive non-atheromatous non-inflammatory non-amyloid occlusive intracranial arteriopathy of unknown aetiology, initially described in Japan, but has long been found in other communities. Pathologically it is characterized by fibro-cellular thickening of the intima and smooth muscle proliferation with increased accumulation of elastin, in the arterial walls. The media layers of such vessels are also thin and tortuous with multi-layered internal elastic lamina. There is an extensive net work of small perforating and anastomotic vessels around and distal to the circle of Willis, often in conjunction with segmental stenoses and occlusion of the terminal parts of both internal carotid arteries-(the so called ”extensive basal cerebral rete mirabile”) Thrombotic microaneurysms are frequently seen at the circle of Willis. This pathological scenery is depicted in the characteristic “haze” or “cloud or puff of smoke” seen in cerebral angiography in patients with this condition. This disease entity has a bimodal age distribution but affect mainly infants, children and adolescent; more than half of the patients are below 10yrs of age, and less that 4% are adult beyond 40yrs of age. Opinions seem divided as to whether this represents a congenital vascular malformation in the form of persistent embryonal arterial network or a rich collateral vascularization secondary to stenosis or occlusion of the internal carotid artery early in life. There are reported associations between moya-moya disease and Down’s syndrome, and certain major histocompatibility leucocyte antigen (HLA) subtypes which may favour the hereditary hypothesis 75.
(iv) Binswanger’s Disease

This is a term given to widespread degeneration of cerebral white matter presumed to be of vascular causation and often observed in the context of hypertension, atherosclerotic narrowing of small arteries of the brain and multiple strokes. Histologically, there is rarefaction of the white matter with demyelination and astrocyctosis, which was termed subcortical arteriosclerotic encephalopathy (SAE). The age of onset is between 55 and 75 years and both sexes are affected equally. Small deep cerebral infarcts are frequently noted and the clinical presentations vary including acute stroke syndrome or TIAs, which sometimes are in combination with dementing illness, seizures, parkinsonism, pseudobulbar signs, frontal lobe syndrome and pyramidal tract signs.

(v) CADASIL.

A familial subcortical infarction called cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is often regarded as an inherited variety of Binswanger’s disease. However it is often not seen in context of hypertension and is linked to several European families. It is due to a mutation in chromosome 19. The defective gene is the notch-3 gene, in the same locus as the gene for familial hemiplegic migraine, which encodes for a large transmembrane receptor. The age of onset may be before 30 years of age or after 60 years reflecting the reports that the gene penetrance may not be complete until after 60 years of age. The pathological hallmarks of CADASIL include, periodic-acid-schiff (PAS)-positive, congo-
red-negative, granular arteriopathy affecting penetrating and leptomeningeal arteries in which there is granular deposition of electron dense, osmiophilic material in the media of capillaries and arterioles.

(vi) Vasculitides

Vasculitis of the central nervous system may be pathogenetic to cerebral infarctions. They may be primary (primary angitis of the central nervous system PACNS) which requires histological analysis for diagnosis, and which has non-specific clinical presentation, or secondary which are consequent on a systemic disorder. Inflammatory vasculitides can be a result of many infections and multisystemic non-infectious inflammatory conditions. These may affect any size of vessel including the pre-capillary arterioles and the post-capillary venules. They may result in ischaemic and haemorrhagic strokes especially in the young. Examples include: meningo-vascular syphilis, tuberculous endarteritis, acute purulent bacterial meningitis, acquired immunodeficiency syndrome(AIDS), and other infective agents like varicella-zoster virus, coxsackie-9 virus, hepatitis-C virus, mycoplasma pneumoniae, Borrelia burgdorferi, and cysticercosis. Cerebral vasculitis is a possible mechanism for cerebral ischaemia seen in illicit drug use. A variety of multisystem vasculitides are known to be complicated by cerebral infarction. These include systemic lupus erythematosus (SLE), Takayasu's arteritis, and giant cell/temporal arteritis.
(d) Hypercoagulable states: Prothrombotic states.

Alterations in haemostasis are shown to be associated with increased risk for ischaemic stroke and may account for a considerable percentage of cryptogenic strokes, which make up to 1% of all strokes and between 2% to 7% of ischaemic strokes in the young. Hypercoagulable states may be primary or secondary. The primary category involves cases with specific and inherited abnormalities of haemostasis, most of which are due to deficiencies of proteins of the coagulation cascade, or the fibrinolytic system. They seem to be more associated with venous thrombotic events. The secondary category includes cases in which no specific or inherited abnormality is found but thrombotic events are secondary to other multifactorial defects. It is conceivable that prothrombotic states are as prevalent in older individuals as in younger ones, but the presence of vascular risk factors and atherosclerosis in the former clouds their relative contribution to thrombosis.

(i) Primary states Primary disorders include deficiencies of proteins C, S, and antithrombin-III, (AT-III), activated protein C (APC)-resistance, and the dysfibrinogenaemias, all of which lead to inherited thrombophilia. These primary disorders are mostly inherited in autosomal dominant fashion, but may also be acquired in association with certain disease conditions like, disseminated intra-vascular coagulation (DIC), and adult respiratory distress syndrome (ARDS). Resistance to activated protein-C is due to a single point mutation in the factor-V-Leiden gene. This and another mutation in the prothrombin G 20020A gene are both associated with increased frequency of
cerebral thrombosis, even though the Physicians Health Study (PHS) found no association between these two conditions and ischaemic stroke.\(^{80}\)

(ii) **Secondary states**: The antiphosphohpid antibody syndrome (APAS) may have ischaemic stroke as its initial manifestation. The syndrome is characterized by the classic triad of thrombosis (arterial or venous), recurrent abortions and thrombocytopenia.\(^{81}\) Though primary cases where no underlying disease exists occur, most cases are secondary to an autoimmune disease (usually SLE). About 10% of patients suffering from SLE test positive for the antiphospholipid antibodies. In this syndrome many autoantibodies are produced by the underlying disorder but two are currently of diagnostic and clinical significance: The most familiar antiphospholipid antibodies include the anti-cardiolipin antibodies tested by the venereal disease research laboratory (VDRL) test which targets cardiolipin found predominantly in mitochondrial membranes. The lupus anticoagulant (LA) is also mediated by antiphospholipid antibodies and is demonstrated when a prolonged partial thromboplastin time (PTT) does not correct with the addition of a normal plasma. Antiphospholipid antibodies can also occur in other disease states eg. human immunodeficiency virus (HIV) infection, bacterial endocarditis, and even in normal individuals, thus, making the presence of anticardiolipin antibody or lupus anticoagulant nonspecific for diagnosis of antiphospholipid antibody syndrome (APAS)\(^ {81}\)

Neoplasms and systemic cancer have been known to be associated with higher risk of both arterial and venous thromboses. Classically cancer is associated with recurrent migratory venous thrombophlebitis (Trousseau’s
syndrome) and DVT, the incidence of which depends on the type of cancer; gastrointestinal cancers being notoriously associated with hypercoagulable states.\textsuperscript{82}

Renal diseases like nephrotic syndrome and renal failure are often associated with systemic thrombosis. This may be related to urinary loss of anti-thrombin-111, elevated levels of coagulation factors, low protein C and S levels, and platelet hyperactivity in such patients.\textsuperscript{83}

Haematological disorders like polycythaemia (primary or secondary) and plasma cell disorders (multiple myeloma and Waldenstrom’s macroglobulinaemia) increase the risk of cerebral ischaemia by virtue of increased blood cells and proteins in circulation, as well as alterations in the regulatory control of haemeostasis. Haematocrit levels of more than 60% appear to carry increased risk for cerebral infarction through rheological complications.\textsuperscript{84}

Sickle cell disease (HbSS) is associated with abnormal erythrocyte adhesion, and rouleaux formation, platelet activation, abnormal endothelial function, and vascular intimal hyperplasia, which are aggravated by hypoxia. These all together lead to rheological abnormalities and tendency for ischaemic arterial thrombotic effects.\textsuperscript{56}

Some pharmacological agents are known to increase tendency for venous and arterial thrombosis. Platinum-based chemotherapy, the use of oral contraceptives and anabolic steroids, and hormone replacement therapy are notable examples.
CEREBRAL AND SYSTEMIC PATHOPHYSIOLOGICAL RESPONSE TO STROKE

A. Brain microcirculation and physiology.

The morphological structure of intracranial arteries is similar to those in other vascular bed, except for the absence of external elastic lamina. The brain microcirculation comprises the smallest component of the vascular system – the arterioles, capillaries, and venules, and is responsible for delivering blood to its target by regulating blood flow and distributing oxygen and glucose to the brain while removing by products of metabolism.

To maintain normal structure and function, the brain requires:

i. Average blood flow of 55ml/100g/minute (75ml/100g/min for the gray and 30ml/100g/min for white matter)

ii. Energy substrate delivery of glucose 5mg/100g/minute which gets depleted within 2 minute of cut-off supply.

iii. Oxygen need of 3.5ml/100/min.

iv. Cerebral perfusion pressure of 70 – 100mmHg maintained by physiological auto regulatory mechanism i.e. difference between mean arterial pressure (MAP) and intracranial pressure (ICP).

Electrical activity considerably slows down below blood supply level of 25ml/100g/min, and ceases (isoelectric EEG) at levels below 15ml/100g/min. i.e. functional threshold; while at levels below 10ml/100g/min neuronal death ensues i.e. morphological threshold.
B. Cerebral Response

i. Cellular injury – Ischaemic cascade

A cascade of complex biochemical/metabolic events termed the ischaemic cascade occurs seconds to minute following cerebral ischaemia, which results from reduced or total disruption of blood supply to the microcirculation. The initial cellular/metabolic response to ischaemia is largely mediated by a massive release of the excitatory neurotransmitter glutamate, triggered by sodium ion entry into the depolarizing ischaemic neurones, and astrocytes. The high concentration of extracellular glutamate activates the receptors (N-methyl D-aspartate (NDMA), & - amino-3 hydroxy-5 – methyl isoxazole – 4 – propionic acid (AMPA) and the metabotropic/kainite) on the membranes of adjacent cells causing further depolarization with resultant excessive influx of sodium and calcium ions. These ionic shifts lead in turn to increased intracellular water, neuronal swelling, membrane disruption and eventual death; an effect that is maximal at the central ischaemic core. Thus arterial occlusion results in a central area of irreversibly damaged cells – the infarct core (umbra) surrounded by an area of tissue where some residual perfusion persists because of collateral vessel architecture and local perfusion pressure – the penumbra. The activation of the metabotropic receptors also causes increase in intracellular inositol – triphosphate and diacylglycerol. The enormous rise in intracellular calcium ions amplifies the process by inducing a positive feedback loop through activation of the sodium – calcium membrane.
transporters, opening of voltage-gated calcium channels and release of calcium from the endoplasmic reticulum.

Zinc ions present in the synaptic vesicles of excitatory nerves are released extracellularly during neuronal depolarization, and gain entry into neurones by way of the activated voltage-gated calcium channels, sodium transport exchangers and the NMDA and AMPA receptors channels, and may contribute to cellular necrosis or apoptosis, via zinc neurotoxicity.86

One of the effects of increased intra cellular calcium is the activation of intra cellular phospholipase – A (PLA – 2) which increases production of arachidonic acid and platelet aggregating factor (PAF). These cause local vaso- constriction and platelet aggregation. These agents along with the interleukins and leukotrienes mediate the chemotaxis of inflammatory cells into the ischaemic area and cause the disruption of the blood brain barrier (BBB) thus inducing cerebral oedema.87 There is also the activation of many enzymatic processes which produce free radicals under ischaemic conditions. One of such is protein kinase C. which cause membrane receptor and ion-channel dysfunction potentiating further glutamate release.88. The other involves nitric oxide synthesis through activation of nitric oxide synthetase (N0S), whose activity is usually regulated by very small changes in intracellular calcium concentration. This enzyme exists in three different isoforms each with differing roles in response to ischaemia.89 : the neuronal – NOS (n – NOS), the endothelial – NOS (e – NOS) and the inducible – NOS (i– NOS). The neuronal and the endothelial forms are present within neurones and
perivascular tissue, and the vascular endothelium respectively, and are active under physiological conditions. The inducible – NOS is only expressed within astrocytes, microglia, and inflammatory cells following ischaemia. The cerebral nitric oxide concentration is elevated within 5 min of ischaemia as a result of increased n – NOS and e – NOS activities, as well as the increased expression of i – NOS, to a level few hundred fold, which overrides it’s clearance rate by the metalloproteins. Early nitric oxide synthesis by e – NOS is neuroprotective going by animal models, as it causes local vasodilatation, but this benefit in human seems to be outweighed by enormous release of nitric oxide, which at such high levels have been found to be damaging to many essential cellular processes including mitochondrial respiration. Also animal models have demonstrated reduction in infarct size by selective i – NOS inhibition 24 hours after stroke. Microglial cells in the penumbra proliferate and demonstrate up-regulated i – NOS activity in addition to producing proteases and a wide range of cytokines particularly, interleukin – 1B, - 6 and – 8 and tissue necrosis factor – α, which stimulate neutrophils to migrate into the ischaemic tissue 90. The influx of inflammatory cells causes further release of damaging cytokines, and increases cellular damage within the penumbra.

Alterations in gene transcription occur in response to ischemia and result in changes in protein metabolism. Caspases (a family of proteases that mediate apoptosis) are activated in the ischaemic penumbra and influence DNA repair
enzymes, structural proteins and cell-cycle regulatory proteins, as well as activity of the Bcl-2 family of anti-apoptotic and proto-apoptotic genes. Caspase-1 activity is known to enhance production of interleukin –1 which is pro-inflammatory ⁹¹. The effect of local inflammation following ischaemic insult (mediated by these cytokines and leucocytes trafficking) is also reported to be most pronounced following reperfusion.

**ii. Microcirculatory and rheological changes.**

Reduction in perfusion pressure results in a compensatory vasodilatation in the areas at risk, as a result there are localized areas of relative hypo-perfusion and hyper-perfusion within the ischaemic penumbra ⁹². This auto regulatory vasodilatation termed stage–1 haemodynamic failure initially tends to preserve normal cerebral blood flow, but with decreasing blood flow, the so called stage – 2 haemodynamic failure sets in, which is characterized by increased oxygen extraction from the available blood supply in an attempt to maintain functional oxygen metabolism. These compensatory mechanisms fail as perfusion further declines. The vasodilatation observed in some areas of the penumbra is thought to be due to increased potassium ion concentration, adenosine, prostacyclin, and locally elevated carbondioxide, while the areas of hypo perfusion may be as a result of vasoconstriction mediated by thromboxane-A₂, and platelet aggregation factor. Rheological factors such as heamoconcentration, sludging of red blood cells, increased blood viscosity, and leucocyte and platelet plugging in the blood vessels all act to impair
further the microcirculation. These factors further prevent the penumbra from recovering.

C. (i) **Systemic responses.**

**Endocrine response:** The cerebral responses to ischaemia are local in their nature and extent, but their induction stimulates the activation of systemic physiological systems. Some of the systemic responses are probably mediated by increased activity of the hypothalamic–pituitary–adrenal axis (HPA–axis) and the adrenal medulla. Blood levels of adrenocorticotrophic hormone (ACTH), cortisol, the catecholamines and glucagon are raised in acute stroke patients. ACTH and cortisol concentrations are known to be markedly elevated within 4 hours of stroke in humans; the degree of ACTH release reportedly being proportional to the size of the infarct. Though the level of ACTH falls back to normal levels after about 8 hours, cortisol levels appear to be persistently elevated for at least 7 days in most patients. The renin–aldosterone–angiotensin system also appears to be activated as well, measured by increased plasma renal activity, which is reported to occur at a later time than the rise in catecholamine levels.

Hyperglycaemia is seen to be present in up to 50% of acute stroke admissions, and is thought to be as a result of the hormonal responses.

(ii) **Cardiovascular response:**

Systemic and diastolic blood pressures are known to be elevated within 20 minutes of acute stroke in up to 75% of patients. Cardiac output is also
raised in acute stroke patients when compared with controls. Patients with lacunar strokes and primary intracerebral haemorrhage appear to show the greatest degree in initial blood pressure elevation. Blood pressures tend to fall spontaneously over the following hours or days after acute stroke although up to 30\% of the patients may remain hypertensive at 1 week. Some studies have also shown that there is blood pressure variability following stroke, particularly in patients with primary intracerebral haemorrhage. It is likely that endocrine responses particularly increased catecholamine release are the major effectors of blood pressure and other cardiovascular changes after acute stroke.

(iii) Other responses: Changes in bone and calcium metabolism have been reported in patients from 7-14 days after stroke event, and are thought to be as a result of immobility and dietary changes rather than a direct metabolic consequence of stroke. Demineralization in paralyzed limbs tends to correlate with the time from onset and has been demonstrated within 3 months. Most patients undergoing rehabilitation after stroke have significant vitamin – D deficiency probably due to a combination of inadequate dietary intake and reduced sunlight exposure.

CLINICAL DIAGNOSIS AND EVALUATION OF STROKE

(i) CLINICAL DIAGNOSIS

Clinical features: The clinical features of stroke depend on the type, the blood vessel, (or vascular territory involved), and the site in the brain. Ischaemic stroke is considered in any individual presenting with an acute-onset-
neurologic deficit (focal or global) or altered level of consciousness. Common symptoms and signs of acute stroke include abrupt onset of motor weakness (hemiparesis or hemiplegia, monoparesis or monoplegia, quadriparesis or quadriplegia); speech and language difficulties (aphasia, dysphonia, deafness); visual defects, monocular or binocular (complete or partial loss, visual field deficits, diplopia); movement disorders (ataxia, vertigo, nystagmus); sensory defects (sensory loss, abnormal perception and sensations); visual perception abnormalities (loss of ability to recognize objects, pictures, graphic signs); swallowing difficulties (dysphagia); loss or decrease in level of consciousness; and sudden onset severe headaches, vomiting, neck stiffness, and seizures.

These symptoms may occur alone or in combination. In relation to the blood vessel involved and the anatomical sites affected, the symptoms and signs may relate to the carotid artery or the anterior circulation territory (middle cerebral artery, anterior cerebral artery and anterior choroidal artery) or the vertebrobasilar and the posterior cerebral artery territory (the posterior circulation).

Some other features may reflect affection and involvement of the deep penetrating branches of the vessels giving rise to the lacunar stroke syndromes.

No historical feature distinguishes ischaemic from haemorrhagic stroke, although nausea, vomiting and change in level of consciousness are more common in a haemorrhagic stroke.
Establishing and focusing on medical history, identification of risk factors, time of onset of symptoms, relationship of onset to activity, as well as the temporal profile or evolution of the symptoms are relevant to stroke-typing and possible initiation of thrombolytic therapy.

(ii) **Clinical Diagnosis:** The clinical diagnosis of ischaemic stroke is made using the World Health Organization (WHO) (appendix iv) or the Siriraj stroke scores (SSS)/criteria (appendix v). The clinical accuracy of distinction of stroke from non-stroke has a sensitivity of up to 95% with specificity of between 66% - 97%, while the frequency of misdiagnosis of clinical stroke ranges from 1.0% to 34.6%. A clinico-pathological study in Nigeria before the advent computerized tomography scan reported a misdiagnosis of stroke in 8.6% of 152 patients. The accuracy of stroke diagnosis however drops significantly when stroke subtypes have to be distinguished with sensitivity of 68% and specificity of 67%. In a Nigerian study Siriraj stroke score (SSS) had a sensitivity of 50% for cerebral haemorrhage and 58% for cerebral infarction, specificity of 62.5 % for haemorrhage and 55% for infarction with an overall accuracy of 54.2%. The WHO criteria has sensitivity of 73% for haemorrhagic stroke and 69% for infarction, with an overall accuracy of 71%.

**Diagnostic imaging:**

Diagnostic imaging studies of the brain in stroke serves to confirm the diagnosis of stroke, distinguish ischaemic from haemorrhagic subtypes, as well as identifying important characteristics of the infarct (eg size,
vascular distribution and multiplicity) and may provide clues to the aetiology of stroke.

**Computerized Tomography (C-T) Scan:**

Brain CT scan is the modality most frequently used. The attenuation abilities of the various tissues in the brain (bone, brain parenchyma, air, fluid/blood) as conventional x-rays pass through them is made use of, making it possible to distinguish their computerized density-related images. CT is confirmatory in cases of bleeds/collections of more than 0.5mm diameter within minutes of onset. CT findings are frequently normal during the first hour after ischemic stroke, but subtle changes can be seen in some patients as early as a few hours after stroke onset. Some of these early signs of infarction include – blurring of the internal capsule, loss of the insular ribbon, loss of differentiation between cortical gray and subjacent white matter, swelling of the cortical gyri, sulcal effacement, and probably the increased attenuation in the middle cerebral artery (hyper dense MCA sign). CT scan was found to be positive in only 54% of cases of cerebral infarction by the 2nd day, and its accuracy approaches 100% in cerebral hemorrhage and 90% in cerebral infarction by the 4th day. Negative C.T scan can occur in stroke patients who have small capsular or basal ganglia infarctions or reversible ischemic neurological deficit (RIND), and small lacunar infarcts, as well as posterior fossa lesions. (eg cerebellar infarcts because of the poor resolution). Isodense lesions may be seen in stroke patients with severe anemia, which may be regarded as negative CT scan. The accuracy of CT scan in diagnosis of stroke
have been studied variously with differing figures based on various protocols viz. Guy’s hospital study 81%, Stockholm study 69% and Nigerian study 57%\textsuperscript{104}. The availability and cost of this desirable non-invasive imaging technique in stroke, hinders its wide applicability in the developing world.

**Magnetic Resonance imaging (MRI)**

When tissues (with different water and thus hydrogen ion content) are subjected to a powerful magnetic field, and brief pulses of radio-frequency waves applied, the hydrogen ion (protons) undergo alignments and relaxations which involve absorption and then emission of radiofrequency energy. The emitted energy gives rise to magnetic signals which passing through electro-magnetic receivers and scanners, are used to construct tissue images. Different tissues have different proton relaxation rates, thus yield different signal intensities, and therefore tissue contrast. MRI is essentially a map of hydrogen content of tissues which is also influenced by the physical and chemical environment of hydrogen atoms.\textsuperscript{105} MRI has advantages over CT: It does not use ionizing radiation; it provides better resolution of different tissues. Because of the high degree of contrast between the white and the gray matter, all discrete nuclear structures and lesions inside them can be identified. Deep lesions in the temporal lobe, the posterior fossa, and the cervico-medullary junction are seen much better than with CT, because the images are not marred by bony artefacts from signals arising from adjacent skeletal structures. Demyelinating lesions appear with greater clarity, and infarcts can be seen at an earlier stage than with C.T. Each breakdown products of
haemoglobin (methaemoglobin, haemosiderin and ferritin) can be recognized which enables determination of the age of a haemorrhage as well as its resolution. Lacunar infarcts and small cortical infarcts are also more readily visualized with MRI. Some other MRI – sequences like the T1, T2, FLAIR (fluid attenuated reversion recall), the spin-echo, and the gradient – echo, have found special applications in the better visualization of infarcts and haemorrhages. The MRI has a particular disadvantage because its powerful magnetic field can cause dysfunction and dislocation of ferro-magnetic devices like aneurysm chips, pacemaker, and heart valves, dental and hip prostheses etc. It also requires special housing and cooling system. It is expensive and not readily accessible especially in the developing world.

(iii) Diffusion weighted imaging (DWI) Diffusion weighted MRI:

The derangement in the diffusion of water into and out of tissue following different pathologies is made use of in this imaging technique. (e.g ischaemic tissues which under energy failure and resultant alterations in apparent diffusion coefficient (ADC) of water in the area). DWI can recognize an infarct within 30 minutes after onset of ischaemia when both conventional MRI and CT images are normal. The ADC of an area of infarction undergoes changes over time and these time-dependent phenomenon can be used in distinguishing acute infarct from chronic ischaemic changes.

(iv) Magnetic Resonance Perfusion imaging (MRPI)
Cerebral perfusion can be assessed using MRI after an injection of a bolus of gadolinium-based contrast agent. This is measured by recording time-dependent changes in signals, as well as analyzing images obtained during the first pass of the contrast through the brain. Some patients imaged early have MRPI deficits that are not associated with either DWI or conventional MRI abnormalities, and such areas have been known to typically progress to infarction on later scans.\textsuperscript{107}

(v) Vascular Assessment:

The use of conventional X-ray angiography to assess integrity of extra- and intra-cranial vessels, has largely been replaced by the advent of CT and MRI. Catheter angiography is accepted as a gold standard for the evaluation of neuro-vasculature, because of its superior resolution, but it carries a 1.5\% to 2.0\% risk of morbidity or mortality which led to the development of non-invasive vascular diagnostic techniques like the ultrasound, the magnetic resonance angiography (MRA) and CT-angiography (CTA)\textsuperscript{108}

**Carotid and vertebral duplex ultrasound scanning:** uses the combination of gray-scale images of the vessels with superimposed Doppler interrogation (insonation) to determine flow velocities and to display waveforms. Colour-coded Doppler flow images use super imposed colour to show the direction of flow, while the velocities of flow are encoded in the change in colour, which allows visualization of the regions of highest velocity, as well as obtain Doppler measurements. A retrospective analysis of carotid duplex ultrasonography compared with angiography found a sensitivity and specificity
of about 70%.\textsuperscript{109} These techniques can detect vascular stenosis, dissection, and reversed or collateral flows.

**Pulsed – wave transcranial Doppler (TCD):** is a noninvasive technique used to assess the intracranial vessels.\textsuperscript{110} Vessels are interrogated at various depths and locations via several “windows” into the skull. TCD studies are clinically useful in the detection of intracranial stenosis, assessment of collateral flow patterns in occlusive vascular disease, and the assessment of vasospasm in patients after subarachnoid haemorrhage.

**Magnetic resonance angiography (MRA):** is a non-invasive technique that demonstrates vascular anatomy, and occlusive disease without use of contrast material. It capitalizes on the differential characteristics of blood flowing in an area of interest to create images of the cerebral vessels. However the accuracy of MRA in assessing haemodynamically significant stenosis of intracranial vessels has not been well studied; as it is found to overestimate the degree of stenosis in certain regions of the carotid artery.\textsuperscript{105}

Spiral CT – angiography outlines the anatomy of the vascular lumen in a fashion similar to conventional angiography, and has an accuracy of approximately 90% when correlated with conventional angiography for the detection of internal carotid artery (ICA) stenosis.\textsuperscript{105} It can also be combined with conventional imaging in patients with acute stroke.

**B.i. Other Investigations:** Complete Blood count (CBC) which includes the haematocrit, white blood count (WBC), platelet count, the erythrocyte sedimentation rate (ESR). These serve as baseline investigations, but may
reveal a cause for the stroke (eg polycythaemia, sickle cell disease, thrombocytosis, thrombocytopenia and leukemia) or provide evidence of concurrent infection (anaemia and leucocytosis).

ii. A chemistry panel which includes blood sugar estimation, lipid profile, urea and electrolytic. These also serve as baseline but may reveal a stroke mimic (eg hypoglycaemia or hyponatraemia), reveal risk factors (eg diabetes mellitus, dyslipidaemia, renal diseases).

iii. Coagulation screen – prothrombin time (PT), partial thromboplastin time (PTT). These may reveal a coagulopathy, and are useful when considering use of thrombolytics or anticoagulants.

iv. Toxicology screen may be necessary in selected cases.

v. Electrocardiography: This is necessary since as many as 60% of all cardiogenic emboli are associated with atrial fibrillation or acute myocardial infarction.

vi. Echocardiography: This investigation may be necessary when cardiogenic cause is suspected.

vii. Venereal Disease Research Laboratory (VDRL) test, Human Immunodeficiency Virus (HIV) screening test, and antibody screens may be necessary.

viii. Lumbar Puncture (LP) may be necessary to exclude sub-arachnoid haemorrhage, and meningitis, stroke-typing using the WHO criteria.

ix. Skull X-ray: may be necessary to rule out intracranial masses
Neurologic Evaluation:

The neurologic evaluation after stroke documents all major neurologic deficits at onset, which serve as baseline estimate of the severity of the event, and when done serially gives an insight into the progression of the illness. It may also serve as a basis for some interventional measures in the acute phase, and may have prognostic value. Some of the instruments used in the assessment include:

a. Glasgow coma scale (G.C.S) (appendix vii)
b. National Institute of Health Stroke Scale (NIHSS) (appendix iii)
c. Modified Ran Gin scale (appendix vi) or the Glasgow outcome scale,

PROGNOSIS AND MORTALITY

Case fatality rates average about 35% but could be as low as 14.9% or as high as 77% when due to cerebral haemorrhage.

Predictors of outcome in stroke include:

i. Age: Outcome worsens with advancing age:

ii. Level of consciousness: Conscious state at admission has favourable outcome, and the deeper the level of unconsciousness the worse the outcome.

iii. Stroke Severity: The poorer the stroke score (by NIHSS) the worse the outcome.

iv. Stroke type: haemorrhagic strokes are worse than ischaemic types.

v. Stroke location/site: deep seated or posterior lesions, as well as ventricular extension of cerebral bleed carry higher mortality.
vi. Later progression of neurological signs/deficits due to cerebral complications like cerebral oedema with raised intra-cranial pressure, transtentorial herniation, acute hydrocephalus, haemorrhagic transformation, seizures and depression. It is noteworthy that most of these occur in the acute phase of stroke.

vii. The systemic stress-related predictors which include: Fever, hypoxia, hypertension, hyperglycaemia, cardiac arrhythmias, aspiration, and inappropriate ADH secretion, are all operative in the acute phase, while in the later phases predictors like deep vein thrombosis (DVT), pulmonary embolism, infections, septicaemia, and decubitus ulcers, come to attention.

viii. Second stroke or reoccurrence carries worse prognosis.
CHAPTER THREE

STRESS RESPONSE: MECHANISMS, AND EFFECTS ON ACUTE STROKE SEVERITY AND OUTCOME

A. Stroke Response Mechanisms

The concept of “milieu interior” – the internal environment, was first put forward by the French physiologist Claude Bernard over 150 years ago in describing the principle of dynamic equilibrium: that constancy or steady state in the internal bodily environment is essential for survival; and that changes in the environment must be reacted to, and compensated for as well, for survival. The neurologist Walter Cannon in describing the principle of “Homeostasis” was the first to trace the “fight or flight” response in man and animals to release of powerful neurotransmitters or messengers from the adrenal gland, which were later known to be the catecholamines. Hans Selye a stress scientist expounded Walter’s observation by noting the pituitary gland and its control by the adrenal cortex was part of the body’s stress response system (negative feedback by cortisol on pituitary). The “stress syndrome” was coined to describe all the so-called adaptive responses observed during acute stress, but surprisingly these included enlargement of the adrenal glands, development of gastro-intestinal ulcers, and wasting away of the immune system. This was the first pointer that in the event of sustained stress, these responses though adaptive (healthy and appropriate) could become much like illnesses i.e if the adaptive processes become excessive, they could be damaging to the body systems. Healthy human stress response involves three components:
a. The brain mediates the immediate response: the locus ceruleus, (the central pace-maker sensor), secretes catecholamines, notably nor-epinephrine, and via its many neuronal connections activates the entire sympathetic nervous system (SNS), and the adrenal medulla.

b. The hypothalamus and the pituitary gland initiate the slower maintenance response via activation of the hypothalamic-pituitary-adrenal axis (HPA axis) resulting in increased secretion of cortisol by the adrenal cortex through corticotrophin releasing factor (CRF) from hypothalamus, adrenocorticotropic hormone (ACTH) from the pituitary: in a positive feedback mechanism.

c. Many neuronal circuits are involved in the behavioural response e.g. increased arousal and attention, reduced pain perception and redirection of behavior. It is known that over seventeen hormones are released during acute stress response ¹¹¹

B. Stress and Acute stroke:

The concept of systemic pathophysiological stress response to acute brain injury dates back to over 150 years, when Claude Bernard noticed that an experimentally induced lesion in the 4th ventricle of a rabbit caused a peripheral hyperglycaemia.¹¹¹ A stress response consisting of increased levels of cortisol, catecholamines, glucagon, and other stress hormones in the first week of stroke event has been known since the 1950s’, and there is the HPA – axis dysregulation, and abolition of circadian rhythm, indicated by failure of
dexamethasone suppression of cortisol levels.\textsuperscript{112} The cortisol response has been observed in both infarctive and haemorrhagic strokes\textsuperscript{112}.

C. Stress response and stroke outcome

Stroke management aims at improving outcome; reducing mortality and morbidity., and may be achieved by combating the factors that effect outcome.

Stroke management is contemporarily divided into acute (day 1-7) sub acute (2\textsuperscript{nd} – 4\textsuperscript{th} wk) and maintenance (beyond 4 wk) phases.\textsuperscript{113} Most mortality in stroke is known to occur in the acute phase, and in patients surviving beyond the first week the causes of death may not directly be related to the stroke itself, but rather to one of the secondary complications.\textsuperscript{113} This implies that those influences may be direct consequences of the cerebral and systemic pathophysiological stress responses mounted in the acute phase. It is estimated too that the systemic stress response may play a role in the genesis of the causes of death after the acute phase.

(i) Serum Cortisol: Effects on acute stroke severity and outcome.

High cortisol levels have been related to poor outcome after stroke. Fiebel et al\textsuperscript{114} studied the systemic metabolic response following acute vascular damage in 65 consecutive stroke patients (56 with cerebral infarction and 9 with subarachnoid haemorrhage). Greater mortality and eventual disability were significantly found in patients excreting more than 200 micrograms of urinary norepinephrine and epinephrine daily in their acute illness. These patients also had significantly elevated plasma cortisol levels. They concluded that the measurement of the stress/metabolic response may prove useful in predicting
prognosis after stroke. They also opined that cardiac abnormalities (e.g., arrhythmias) arising probably from the elevated catecholamines may have contributed to the excess mortality in those patients with intense stress response.

Hanne Christensen et al.\(^ {115} \) did a prospective study of 179 acute stroke patients (162 with cerebral infarction and 17 with intracerebral haemorrhage) who were not on steroid therapy; to find the relationship of single serum cortisol level measured on the first 24 hrs of stroke onset, with the neurological deficit (severity) at onset, the progression of the illness and eventual outcome. The study found that serum cortisol was independently related to death within 7 days of stroke onset. The serum cortisol levels correlated with the stroke severity measured by the Scandinavian Stroke Scale (SSS), body temperature, pulse rate, lesional size on CT scan, and blood sugar. The study concluded that acute stroke mortality related to increasing serum cortisol levels. It also showed that serum cortisol level was not however a predictor of death or dependency within three months.

In one study which involved only 12 acute stroke patients Johansson A. et al.\(^ {116} \) studied the relationship between serum cortisol level estimated in the first 48 hours following stroke, and the level of inflammatory response measured by levels of tissue necrosis factor - \( \propto \) (TNF - \( \propto \)) and interleukin – 6 (IL – 6) also within the same time frame. The study found a correlation between the two measurements. This subset of patients were found to have had higher scores in
the neurologic deficit chart (the Scandinavian stroke scale) indicating greater severity.

In another related study of 70 stroke patients in their acute phase of illness, Slowik et al \(^{117}\) demonstrated a positive correlation between serum cortisol levels estimated in the first 72 hours of stroke onset with white blood cell count. The authors opined that increasing steroid levels, and increasing white blood cell count, reflected increased local cerebral and systemic inflammation in these patients, which may also reflect the stroke severity/outcome.

In an attempt to possibly counter the effects of acute neural inflammation in acute stroke (e.g cerebral oedema) which is known to accompany focal expanding cerebral lesions, and which plays a major role in the mortality and morbidity after stroke \(^{118}\), various trial groups had used steroids in the acute illness management, but this has consistently shown to be of no benefit. In a Nigerian study Ogun S.A et al \(^{119}\) studied the effect of short-course high-dose dexamethasone (a steroid with marked anti-inflammatory property) therapy given in the acute phase of stroke, on the morbidity measured by modified neurological deficit scale of Graham, and mortality at days 1,7,14,21,28 and monthly for 6 months. The study found that this regimen did not significantly improve mortality in acute stroke. Indeed patients who received dexamethasone died earlier than those who received placebo, while the mortality rates at one month were 80\% and 85\% in the two groups of patients respectively. These findings contrasted with that of beneficial effects of steroids in brain tumours,
traumatic brain and spinal cord injuries, and bacterial meningitis. If steroid elevation in acute stroke were protective, this study would have shown otherwise. Probably steroid elevations were not anti-inflammatory but damaging. It may also be deduced that this metabolic/stress response was not suppressible by use of dexamethasone supporting the reported H.P.A –axis dysregulation in acute stroke.

(ii) **Hyperglycemia and stroke severity/outcome**: Stress hyperglyceamia (result of endocrine response to acute stroke), and the presence of diabetes mellitus have reportedly been associated with poor stroke outcome. Weir et al\textsuperscript{122} in a prospective study of 645 acute stroke patients, 86% of whom had ischaemic type; who were seen within 72 hours of stroke onset, found that admission hyperglycaemia was associated with higher mortality even after correction for other prognostic variables, and that it predicted a poorer chance of independence. In a retrospective study of 656 acute stroke patients Williams et al\textsuperscript{7} found that hyperglycaemia which was present in 40% of the patients at admission was associated with longer hospital stay. Also that hyperglycaemia independently increased the risk of death at 30 days, and even up to 6 years after stroke, and thus that hyperglycaemia was associated with increased short and long-term mortality. Candelise et al\textsuperscript{123} in a study of the prognostic significance of hyperglycaemia in acute stroke found that in non-diabetic patients with stroke, the admission blood glucose level correlated with the neurologic score, and with the lesion size on brain CT scan. It was concluded that reactive hyperglycaemia due to a major stress response accounted for
worse prognosis in the patients. Parsons et al 124 using magnetic resonance spectroscopy studied the influence of blood glucose level on admission in acute stroke patients, on the final infarct size. The study established that admission hyperglycaemia played an important role in the progression of the at-risk neural tissue (penumbra) to infarction, and the influence was related to the clinical outcome. In a multicentre study which involved 624 patients with acute ischaemic stroke, Bruno et al 125 concluded that higher admission glucose levels in acute stroke patients who had thrombolysis treatment, were associated significantly with lower odds for desirable clinical outcomes and significantly higher odds for symptomatic intra-cerebral haemorrhage regardless of rt-PA (thrombolysis) treatment.

(iii) Catecholamines and hypertension in stroke outcome:

Acute elevations in both systolic and diastolic blood pressures are common after acute stroke, and have been attributed to such factors as Cushing’s reflex, previous hypertension, stress response (increased catecholamines), and autonomic dysfunctions. Van kooten et al 126 in study of 91 acute stroke patients found that 28% of them had increased norepinephrine levels above normal ranges and 70% of them were hypertensive at onset. The study revealed that significantly increased stroke severity and mortality (measured by neurologic score at onset and serially, and the 30-day mortality rate) was recorded among those with increased norepinephrine levels and elevated blood pressures. Fogelholm et al 127 did a study on the prognostic value of first day mean arterial blood pressure in patients with spontaneous supratentorial intra-
cerebral haemorrhage. The study reported that first day elevated blood pressures were significantly associated with the lesional sizes on brain CT scan, as well as with bad prognosis. Yoon-Ho Hong et al.\textsuperscript{128} in a 131-patient study, found strong correlation between severe systolic hypertension and headache, in acute stroke patients on presentation with worse outcome. Norris et al.\textsuperscript{129} in a study of sudden death after stroke related nor-epinephrine levels to electrocardiographic findings. The study demonstrated increase in the occurrence of ventricular and atrial premature beats, and atrial fibrillation following hemispheric as opposed to brain stem stroke, and concluded that it may be due to the significantly increased norepinephrine levels in these patients, which also may explain the increased mortality observed among them.
CHAPTER FOUR

A. AIMS AND OBJECTIVES

General objectives

The general objective of this study is to evaluate the cortisol response in adult Nigerian with acute stroke.

Specific objectives

a. To assess the level and degree of cortisol-response in the acute phase of ischaemic stroke in adult Nigerians.

b. To study correlation of cortisol levels with blood sugar levels in acute phase of stroke.

c. To evaluate the prognostic value of single cortisol measurement in the acute phase, to stroke severity and outcome.
CHAPTER FIVE
MATERIALS AND METHODS

Study Design

A prospective study of stress responses was done in patients with acute ischaemic stroke to evaluate their relationship with stroke severity at presentation. The patients were further followed up to evaluate severity, disability and outcome at days 7, 14, 21, 30 and 90 or death in relation to the initial cortisol/stress response.

Study period

This study lasted between August 2004 and November 2005 (16 months).

Study location

This study was conducted at the Nnamdi Azikiwe University Teaching Hospital Nnewi, Anambra State, Nigeria: - a tertiary health institution, and a referral center for primary and secondary health institutions East and West of the Niger. The town which has a population of over six hundred thousand, is a commercial and industrial area and harbours virtually all ethnic groups in Nigeria as well as immigrants from the West-African sub region and beyond.

Study population

The study involved adult Nigerians above the age of 18 years, and comprised:

A) Patients with acute ischaemic stroke

B) A control group of the same number as the patients, who did not suffer stroke and made up of two sub-groups: i) one half of them matched with the patients for age, sex, and two known dominant stroke risk factors –
hypertension and diabetes mellitus  ii) The other half was matched for only age and sex, and the subjects were adjudged clinically healthy.

**Sample size determination**

The out-patient load and the corresponding stroke (CVA) cases in the hospital for three consecutive years were as follows.

<table>
<thead>
<tr>
<th>Year</th>
<th>OPD</th>
<th>CVA</th>
<th>Per 1000</th>
<th>Per 10,000</th>
<th>Per 1000 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>2001</td>
<td>29731</td>
<td>41</td>
<td>1.38</td>
<td>13.8</td>
<td>138</td>
</tr>
<tr>
<td>2002</td>
<td>35974</td>
<td>42</td>
<td>1.17</td>
<td>11.7</td>
<td>117</td>
</tr>
<tr>
<td>2003</td>
<td>27871</td>
<td>47</td>
<td>1.69</td>
<td>16.9</td>
<td>169</td>
</tr>
</tbody>
</table>

The calculated average hospital prevalence is about 14/10,000 with no distinction to first-ever or repeat strokes.

The sample size N for this hospital based study using the hospital prevalence was calculated using the formula:

\[ N = \frac{Z^2 \times P \times (1-P)}{D^2} \]

\[ N = \text{desired sample size when population is } > 100,000 \]

\[ Z = \text{standard normal deviate corresponding to 95% confidence interval} \]

which is taken as 1.96

\[ P = \text{prevalence i.e. } 0.14 \]

\[ D = \text{desired precision limit, assumed at 10%} \]

Thus \[ N = \frac{(1.96)^2 \times 0.14 \times 0.86}{(0.1)^2} = 47 \]

The sample size was adjusted to 50 (fifty) patients for easy computation.

**Controls**

76
The control group therefore comprised

(a) Twenty-five (25) adults matched for age, sex, hypertension and diabetes, with the patients

(b) Twenty-five (25) healthy adults matched for only age and sex with patients.

**METHODOLOGY**

Adult patients presenting with sudden-onset neurological deficits or altered state of consciousness/coma, who were seen at the Accident/Emergency (A&E) unit or admitted into the ward within the previous twenty-four hours (24 hrs) were reviewed by the researcher. Personal data was obtained to ascertain age, sex, occupation and marital status. A detailed medical history was taken. Information sought included sudden-onset loss or alteration in awareness, seizures/fits falls, headaches, vomiting, limb or body weakness, gait abnormalities, sensory loss, language and speech defects, visual defects, drooling of saliva, deviation of eyes or mouth and swallowing difficulties. Information was also sought for past medical history of hypertension, diabetes mellitus, intermittent claudication, transient visual loss, anginal pains or previous episode of neurological deficits. Social and drug histories were obtained (use of recreational addictive drugs and also oral contraceptives in the case of the females). Relevant family history was obtained. The time of onset, the prevailing activity, at the time of stroke onset, the temporal profile of the complaints/symptoms, as well as details of first-aid medications were obtained.
Detailed physical examination, and complete neurological examination (including assessment of the Glasgow coma score, cranial nerves motor and sensory systems and higher cerebral functions), were done by the researcher. Information obtained were documented in the profoma (appendix ii). These were compared with information documented by the admitting doctor(where different from the researcher), and disparities cross checked by immediate combined re-evaluation. Resuscitation and necessary medications were instituted.

**Clinical diagnosis**
The clinical diagnosis of stroke was made using the Siriraj criteria (appendix v)

**Inclusion criteria:**
The patients who met the following criteria were enlisted for study.

(a) Age 18 years and above

(b) Willingness to be included in the study indicated by giving informed consent by self or close relative (appendix i)

(c) Satisfying Siriraj Criteria for Ischaemic stroke (score < -1). Those in the gray/indeterminate zone (score > -1+1) were required to do brain C.T. (Computed Tomography) scan.

(d) First-ever stroke

(e) Completed stroke

(f) Presentation within first week of event.

**Exclusion criteria:** Those excluded from the study include

(a) Aged below 18 years
(b) Repeat stroke

(c) Satisfying Siriraj criteria for haemorrhagic stroke (score > +1)

(d) Presentation after one week of event

(e) On steroid therapy

(f) Known to have phaeochromocytoma

(g) Moderate-severe dementia

(h) Evidence of malignancy, thyrotoxicosis and renal failure

**Ethical Approval and patients consent**

Approval for this study was obtained from the Ethical and Research Committee of the Nnamdi Azikiwe University Teaching Hospital, before the commencement.

Informed consent were also obtained from all the enrolled patients (Appendix i)

**Clinical Monitoring**

(A) **Baseline**

(i) **Blood Pressure:**

The blood pressure of the patients were measured using the mercury column sphygmomanometer made by Accossions of Germany. The Korotkoff phase V was used for diastolic pressure recording. The standard cuff size (23X12cm bladder size) was used except for the obese (extra sized cuffs used), and the right arm pressure was routinely obtained except where inaccessible or inconvenient. Differences in arm blood pressures were looked out for and noted. Readings were approximated to the nearest 5mmHg. The blood pressures were recorded on admission, six-hourly for the first 24hrs, 12-hourly
for subsequent 48 hrs, and routinely till the rest of hospital stay. The average
daily blood pressures for the first 14 days in admission were computed and
documented in the profoma (appendix ii)

**Temperature:** The body temperatures of the patients were routinely taken
using the standard mercury clinical thermometer (by UNICEF). Axillary
recordings were used. This was done daily unless during febrile periods when
more readings per day became necessary. The average daily readings in
degrees Celsius (°C) were recorded in the profoma (appendix ii)

**Pulse:** Pulse rates per minute were measured using the brachial or radial
arterial pulsation by palpation method, counted through one minute, and
compared with the heart rate. Other peripheral pulses were palpated for
presence as well as synchrony. Arterial wall thickenings were noted. The
average daily pulse rates from admission to the 14th day were documented in
the profoma (appendix ii)

(B) **Severity Indices**

(i) **Glasgow coma scale (G.C.S):** The mental and the neurological status of the
patients was measured by assessing the state of the eye-opening, the best
verbal and the best motor responses to various stimuli, employing the Glasgow
coma scale (appendix vii). In this study, scoring was done on admission and
daily subsequently till the 14th day. This allowed for evaluation of progression,
improvement or deterioration. The scores obtained were documented.

(ii) The National Institute of Health Stroke Scale (NIHSS): The neurological
examination of the patients on admission included assessment of the
patients’ degree of alertness, orientation, as well as the best speech and language ability, the visual fields and gaze status, the integrity of the facial nerve, and the best sensory and motor function, using the NIHSS system. (appendix iii) The scale affords a quick and reliable insight into the functional status and the degree of severity following stroke. It was also used in subsequent monitoring of patients’ condition on days 7, 14, 21, and 30. The maximum score of 42 represents the most devastating of strokes, while the score of 0-4 depicts normal or near-normal function.

(C) The modified Rankin scale (M R S)

The physical abilities, the degree of disability and degree of dependence or need for assistance for the activities of daily living were estimated using the modified Rankin scale (appendix vi). It is a measure of functional recovery or depreciation which invariably reflects functional neuronal state. The M R S scores of the patients on admission were the baseline for comparison with those made on days 7, 30 and 90.

(D) Laboratory Investigations

Venous blood from the patients were collected for investigations which included cortisol estimation, blood sugar, total white blood cell count, absolute eosinophil count and erythrocyte sedimentation rate. Routine urinalyses were also done.

(i) Serum cortisol estimation: Morning (8am – 10am) blood samples were collected. Five millimeters (5 ml) of venous blood obtained using size 21 G needle through the ante-cubital fossa with tourniquette in place, was drawn
into a plain test tube. The sample was allowed to clot, centrifuged and the supernatant (serum) separated into another plain test tube. The sample sera were stored frozen at temperature $-10^\circ$C in a research laboratory freezer till time of determination. They were transported to Immunoassay Laboratories (Nig) Ltd, Lagos Nigeria, in miniaturized deep freezer maintaining the samples at frozen temperatures. The laboratory is licensed for hormone and immune assays by the Federal Ministry of Health, as well as for research purposes. The samples were analyzed in batches of ten. In the laboratory the samples were allowed to thaw. The immuno radio metric assay (I R M A) technique was used. (appendix viii). The test-kits made by M.P.Biomedicals U.S.A. included standards containing predetermined cortisol concentrations of 0, 3, 10, 100 micrograms per milliliters ($\mu$g/ml). There were also Quality control samples containing solutions with known cortisol concentrations in the ranges of low, normal and high values. The kits, standards and the controls were stored at temperatures $2 – 8^\circ$C. Essentially, the solid phase was the test tube which was coated with anti-cortisol antibodies. The analyte was the serum to be assayed which contains cortisol as antigens. The liquid phase was the labeled cortisol (cortisol – $1^{125}$) in solution as labeled antigen. Prior to estimation, the coated test tube, the analyte, the labeled cortisol, the standards and the controls were brought to room temperatures. Twenty-five microliters (25 µl) of each standard, control and test sample of that batch was pipetted into the respective coated tubes. One milliliter (1 ml) of the labeled cortisol (cortisol -$1^{125}$) was
added to each tube. These were incubated for forty-five (45) minutes at 37°C. The contents of each tube was aspirated or decanted. The principle was that the cortisol in the test sample and the labeled cortisol compete for binding sites in the solid phase. The tubes were thereafter counted in a gamma counter calibrated for 1125. (GENESYS AUTOMATED GAMMA COUNTER) The counter was fully automated to perform the calculations and bring out the concentrations of cortisol in the test samples. However, the same results could be estimated by using the formula

\[
\frac{\text{% Bound in sample}}{\text{% Bound in standard}} = \frac{\text{cortisol conc in sample}}{\text{cortisol conc in standard}} \times 100
\]

Also it was possible to directly read off the cortisol concentration in the samples from a plotted graph of percentage bound against cortisol concentrations of all the standards 0 – 100 µg/ml. Additionally, reliability and accuracy of assays were monitored by making sure there are no discrepancies in the stated values in the standard solutions. Also the spectrum of quality control values enabled the procedure to pick values in the low, medium or high ranges. Estimated serum cortisol concentrations of the patients were documented

The manual on the laboratory procedure is attached (appendix viii)

(ii) Blood sugar estimation

The estimation of the patients blood sugar were done at the same time as the cortisol samples were taken. These were done as arterial blood values using the automated One-touch glucometer (Lifescan Co USA). The test strips
came in batches of 25 (twenty-five) strips in dessicated containers. There were also standards of zero and known concentrations for standardization of the instrument before use.

Sterilized and individualized lancets were used to prick patient’s finger pulp after antiseptic swabbing. The ensuing drop of arterial bleed was dotted on the test-strip and read off the automated counter. The principle was that the strip contained glucose oxidase in its test area. This enzyme hydrolyzed the glucose in blood to products which could be quantified by the machine already calibrated for the products. The readings were in mmol/l. The obtained readings were documented. These results were correlated with venous blood samples drawn from such patients, and done routinely in the chemical pathology laboratory as venous blood sugar estimates. In cases with markedly disparate results from same patients, the venous blood glucose determination were repeated.

(iii) Other investigations

Urinalysis and haematocrit were done routinely for all patients in the hospital laboratory. Serum electrolytes, urea, creatinine, blood lipid profile, electrocardiogram, and echocardiogram were requested where necessary.

Neuroimaging: Computed Tomogram scans (C.T. scan) of the brain were requested.

Outcome Index:- the modified Rankin scale (mRs)

A detailed assessment of each patient was done on admission, 7th, 30th and 90th day following stroke. The emphasis were on identifying and
documenting residual symptoms, extent of physical and mental abilities, or disabilities, ability to carry out activities of daily living, ability to walk and degree of ambulation with or without assistance, and the ability to return to usual pre-stroke duties and activities, and the degree of dependence. This was performed employing the modified Rankin scale (appendix vi). Obtained scores were documented. The maximum score of 6 was for the dead while score 0 depicts complete recovery and rehabilitation of physical and mental function.

**CONTROLS**

The investigations carried out on the control subjects included serum cortisol estimation, random blood sugar estimation, and white blood cell count. The same protocols observed for the patients were applied. Their relevant medical characteristics and the results of the investigations were also documented.

**Termination of Research**

All enrolled patients were followed up till 90 days after enlistment, unless abruptly terminated by death.

**DATA ANALYSIS**

Observations from the patients, as well as the results of the laboratory investigations were all recorded in patients case-notes and simultaneously into data proforma. Data analysis was done using Epi info version 6 (2002).
The mean values of the ages of the patients and the control subjects as well as their distribution according to sex were determined. The mean values of serum cortisol and random blood sugar in the patients and control subjects, as well as their distribution according to age and gender were also determined. The severity scores as measured by the NIHSS on admission was analyzed in relation to the admission serum cortisol.

The outcome measured as morbidity or dependency using the modified Rankin scale, and the fatality at 7, 30 and 90 days were analyzed in relation to the admission serum cortisol.

The t-test was applied in comparing the mean values of the ages of the patients and controls according to sex, the mean cortisol levels in the male and female patients, and the mean cortisol levels in the survivors and the dead.

The f-test was applied in comparing the mean values of the age, serum cortisol, and random blood sugar among the study and control groups.

Level of significance was fixed at $p<0.05$.

CHAPTER SIX

RESULTS

A (i) Study Population:

A total of fifty (50) patients who satisfied the clinical diagnosis of acute ischaemic stroke using the Siriraj score ie $\leq -1$ were enrolled in this study.
A total of fifty (50) subjects consisting of two groups of 25 each (groups 1 and 2) were included in the study to serve as controls. The 25 individuals who made up the control group 1 were those who had hypertension and/or diabetes mellitus as risk factors for stroke, while the other 25 individuals were healthy individuals. Each group comprised 11 males and 14 females.

The age ranges for both the study and the control groups were between 38 years and 85 years.

The mean age of the patients was 63.50 ± 13.30 years, while those of the control groups 1 and 2 were 63.30 ± 14.20 years, and 62.50 ± 13.80 years respectively.

There was no significant difference in the age distribution among the study group (patients) and the control groups 1 and 2 (f = 0.05, p > 0.1).

The male to female ratios in the study group and the two control groups (1 and 2) were 11:14 (1:1.3).

The mean age of the males in the study group was 59.3 ± 13.4 years, while those for the control groups 1 and 2 were 59.0 ± 13.7 years and 58.1 ± 13.6 years. There was no significant difference among their age distribution (f = 0.05, p ≥ 0.05).

The mean age for females in the study group (patients) was 66.6 ± 12.6 years, while those for the control groups 1 and 2 were 66.6 ± 14.2 years and
65.9 ± 13.5 years respectively. There was no statistically significant difference in the age distribution as well (f = 0.05, p > 0.05).

(ii) Age incidence of stroke in the study.

The frequencies of stroke was highest in the ages 50 years to 79 years (74% = 22+24+28) with a peak in the 8th decade (28%). 4% of the strokes occurred among those aged 39 years and below, while 10% involved those aged 80 years and above.

(iii) Prevalence of Risk Factors:

28 patients (46%) were hypertensive, 5 patients (10%) were both hypertensive and diabetic. 12 patients (24%) had history of significant alcohol intake and cigarette smoking. 7 patients (14%) had no identifiable risk factor.

(iv) Symptoms and Signs at Presentation

Majority of the patients were conscious and alert on enrolment/admission in the study (n =43, 86%). Four (4) of the patients (8%) were found drowsy on presentation. Six (6) patients (12%) had headaches as part of presenting complaints, six (6) patients also had evidence of atheroma markers (eg thickened peripheral arteries), and four (4) of the patients (8%) were aphasic on presentation. Ten (10) patients (20%) had sensory deficits while only two patients (4%) were febrile on presentation.

B. cortisol distribution/pattern in patients and controls

The mean cortisol levels according to age, in the study group and the control groups 1 and 2 are shown in Table 1.
Table 1: The mean cortisol levels in ng/ml by age in study and control groups

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Study Group</th>
<th>Control Group 1</th>
<th>Control Group 2</th>
<th>F-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-49</td>
<td>8</td>
<td>5</td>
<td>5</td>
<td>5.77</td>
<td>p&lt;0.025</td>
</tr>
<tr>
<td>50-69</td>
<td>23</td>
<td>10</td>
<td>12</td>
<td>17.5</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>
The mean cortisol level in the study group was $280.6 \pm 101.3$ ng/ml and those for the control groups 1 and 2 were $182.70 \pm 39.2$ ng/ml and $146.80 \pm 21.2$ ng/ml respectively. The differences in the pattern of cortisol levels in these three groups were statistically significant ($f=32.7$, $p<0.001$). The difference in mean cortisol level of the subjects when analyzed according to the age groups (under 50, 50-69, and above 70 years) also reached statistical significance.
The mean cortisol levels among the male and female subjects i.e patients, in the study is shown in Table 2 and 3.
Table 2: The mean cortisol levels in ng/ml compared between male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>Study Group</th>
<th>Control Group 1</th>
<th>Control Group 2</th>
<th>F-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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Table 3: The mean cortisol levels in ng/ml compared between male and female subjects

<table>
<thead>
<tr>
<th></th>
<th>No cortisol</th>
<th>No cortisol</th>
<th>No cortisol</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>22 326.7±93.9</td>
<td>11 191.2±20.4</td>
<td>11 147.4±26.2</td>
<td>9.5</td>
<td>p&lt;0.025</td>
</tr>
<tr>
<td>Female</td>
<td>28 244.3±93.1</td>
<td>14 176.1±48.5</td>
<td>14 146.4±17.4</td>
<td>10.1</td>
<td>p&lt;0.025</td>
</tr>
<tr>
<td>Total</td>
<td>50 280.6±101.3</td>
<td>25 182.7±39.2</td>
<td>25 146.8±21.2</td>
<td>32.7</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Group</td>
<td>frequency</td>
<td>Male</td>
<td>Female</td>
<td>z-score</td>
<td>p-value</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------</td>
<td>-------</td>
<td>--------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>Study</td>
<td>12</td>
<td>326.7±93.9</td>
<td>28</td>
<td>244.3±93.1</td>
<td>3.09</td>
</tr>
<tr>
<td>Control 1</td>
<td>11</td>
<td>191.2±20.4</td>
<td>14</td>
<td>176.1±48.5</td>
<td>1.05</td>
</tr>
<tr>
<td>Control 2</td>
<td>11</td>
<td>147.4±26.2</td>
<td>14</td>
<td>146.4±17.4</td>
<td>0.11</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>248±105.6</td>
<td>56</td>
<td>202.8±82.1</td>
<td>2.34</td>
</tr>
</tbody>
</table>

The mean cortisol levels of the male subjects were 326.7±93.9ng/ml for the study group, and 191.2±20.4ng/ml and 147.4±26.2ng/ml for the control groups 1 and 2 respectively. The values for the female subjects were 244.3±93.1ng/ml, 176.1±48.5ng/ml and 146.4±17.4ng/ml respectively for the
study groups and control groups 1 and 2. The observed differences among males in the three groups were statistically significant (f=9.5, p<0.025). The same was observed among the females (f=10.1, p<0.025). There was also a significant difference observed between the male and female subjects (z=3.09, p<0.002). However, the differences observed between males and females in the control groups 1 and 2 were not statistically significant. (control group 1: z=1.05, p>0.05, control group 2: z=0.11, p>0.2)

C. Random blood sugar levels in patients and controls.

The mean random blood sugar levels in the study group and the controls are shown in Table 4.

Table 4: The mean blood sugar levels in mmol/l by age in study and control groups

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Study Group Mean Blood Sugar (mmol/l)</th>
<th>Control Group Mean Blood Sugar (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td></td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Age Group</th>
<th>Study Group</th>
<th>Control Group 1</th>
<th>Control Group 2</th>
<th>F-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Yrs)</td>
<td>No</td>
<td>RBS Mean±SD</td>
<td>No</td>
<td>RBS Mean±SD</td>
<td></td>
</tr>
<tr>
<td>30-49</td>
<td>8</td>
<td>5.34±1.20</td>
<td>5</td>
<td>4.68±0.39</td>
<td>5</td>
</tr>
<tr>
<td>50-69</td>
<td>23</td>
<td>7.07±4.07</td>
<td>10</td>
<td>5.54±3.10</td>
<td>12</td>
</tr>
<tr>
<td>&gt;70</td>
<td>19</td>
<td>7.42±2.95</td>
<td>10</td>
<td>5.19±0.63</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>50</td>
<td>7.04±4.86</td>
<td>25</td>
<td>5.22±2.03</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
The mean random blood sugar level for the study group was 7.04 ± 4.86 mmol/l, while those of the control groups 1 and 2 were 5.22 ± 2.03 mmol/l and 4.40 ± 0.47 mmol/l respectively. There was significant difference in the blood sugar level distribution among these groups of subjects. (f = 4.92, p<0.01). This is also depicted in figure 2.
Fig 2: Chart of mean RBS levels in the subject groups
D. Cortisol and random blood sugar

The correlation between the measured mean serum cortisol levels and the mean random blood sugar (RBS) for patients and controls is shown in table 8.
Table 5: Correlation of blood sugar levels (mmol/l) with cortisol serum levels (ng/ml) in the subjects

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Study group</th>
<th>Control group 1</th>
<th>Control group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean serum cortisol ± SD</td>
<td>280.6±101.3</td>
<td>182.7±39.2</td>
<td>146.8±21.2</td>
</tr>
<tr>
<td>Mean blood sugar ± SD</td>
<td>7.04±4.86</td>
<td>5.22±2.03</td>
<td>4.4±0.47</td>
</tr>
<tr>
<td>Correlation coefficient (r)</td>
<td>0.90</td>
<td>0.70</td>
<td>0.001</td>
</tr>
<tr>
<td>$r^2$</td>
<td>0.80</td>
<td>0.49</td>
<td>0.0000001</td>
</tr>
<tr>
<td>t-test</td>
<td>14.2</td>
<td>4.9</td>
<td>0.001</td>
</tr>
<tr>
<td>P&lt;value</td>
<td>P&lt;0.001</td>
<td>P&lt;0.01</td>
<td>P&gt;0.9999</td>
</tr>
</tbody>
</table>
There was a strong positive correlation between the measured mean cortisol level in patients of 280.6 ± 101.3 ng/ml, and the mean random blood sugar in this group i.e. 7.04 ±4.86 mmol/l.(correlation coefficient r = 0.90). This observation was also statistically significant (p<0.001).

A similar but less strong correlation existed between the mean cortisol levels (182.7 ± 39.2 ng/ml) and the mean random blood sugar level (5.22 ± 2.03 mmol/l) among individuals in control group 1 (r = 0.70), and this was also statistically significant.(p<0.01).

However among individuals in control group 2, the observed weak positive correlation between the mean cortisol level (146.8 ± 21.2 ng/ml) and the mean RBSs value was not statistically significant (r = 0.001, p>0.9999).

E. cortisol and stroke severity.

Table six (6) shows : Relationship between serum cortisol measurement and Stroke Severity at presentation.
Table 6: Relationship between serum cortisol measurement and Stroke Severity at presentation.

<table>
<thead>
<tr>
<th>Severity (NIHSS Score)</th>
<th>frequency</th>
<th>mean cortisol +SD</th>
<th>Correlation coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild (1-4)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>&gt;0.9999</td>
</tr>
<tr>
<td>Moderate (5-20)</td>
<td>50</td>
<td>280 ±101.3ng/ml</td>
<td>0.19</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>Severe (&gt;20)</td>
<td>0</td>
<td>-</td>
<td>0</td>
<td>&gt;0.9999</td>
</tr>
</tbody>
</table>

Note: linear regression equation
\[ y = 8.9 + 0.05x \]

\( y \) = severity score (NIHSS) \hspace{1cm} \( x \) = cortisol level

Mild Stroke = NIHSS 1-4

Moderate = 5-20

Severe = >20
All the patients enrolled in this study had moderately severe stroke (NIHSS 5-20) at presentation. There was a positive correlation between the single serum cortisol measured in the acute phase and the stroke severity on enrolment. However the relationship was statistically insignificant p>0.1

(f) Cortisol and outcome.

Acute stroke outcome was measured in terms of morbidity (disability) or case-fatality (death)

(i) Morbidity: The functional outcome after stroke was measured using the modified Rankin scale (mRs) score system (appendix), done on 7th, the 30th and 90th days after stroke. The outcome scores for the patients on 7th, 30th and 90th days after stroke are shown in table 7.

Table 7: Relationship of cortisol level with outcome. (mRs) scores
among study group  

### Outcome: Morbidity (mRs score)

<table>
<thead>
<tr>
<th>Dur.</th>
<th>freq.</th>
<th>Cort. ng/ml</th>
<th>correlation</th>
<th>p value</th>
<th>freq.</th>
<th>Cort. ng/ml</th>
<th>correlation</th>
<th>p value</th>
<th>freq.</th>
<th>Cort. ng/ml</th>
<th>correlation</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>Cort. ng/ml</td>
<td>Cort. ng/ml</td>
<td></td>
<td></td>
<td>Cort. ng/ml</td>
<td>correlation</td>
<td>p value</td>
<td></td>
<td>Cort. ng/ml</td>
<td>correlation</td>
<td>p value</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>41</td>
<td>261.51±124.1</td>
<td>-0.36</td>
<td>&lt;0.05</td>
<td>9</td>
<td>378.0±182.9</td>
<td>0.48</td>
<td>&gt;0.1</td>
</tr>
<tr>
<td>30</td>
<td>9</td>
<td>235.4±79.7</td>
<td>-</td>
<td>&gt;0.999</td>
<td>29</td>
<td>248.34±87.10</td>
<td>-0.18</td>
<td>&gt;0.1</td>
<td>12</td>
<td>391.0±58.9</td>
<td>0</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>&gt;0.999</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>36</td>
<td>244.28±82.3</td>
<td>-0.009</td>
<td>&gt;0.8</td>
<td>0</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>14</td>
<td>388.29±81.1</td>
<td>0</td>
<td>&gt;0.999</td>
</tr>
</tbody>
</table>

**Good (mRs score 0-2)  moderate (mRs score 3-4)  poor (mRs score 5-6)**

**NOTE: regression equation.**

7th day; \( y = 4.04+0.002x \)

30th day; \( y = 0.07 + 0.013x \)

90th day; \( y = 1.11 + 0.003x \)

\( y = \text{outcome (mRs score)} \times \text{cortisol level} \)
At 7 days, none of the patients had good functional outcome. There was a negative but significant correlation between the mean admission cortisol levels and dependence score among those with moderate outcome. Among those with poor outcome, a positive but insignificant correlation was found between their mean admission cortisol level and their degree of disability. At 30 days, there were no relationship between admission cortisol and disability scores in those with good and poor outcomes, while the negative correlation found among those with moderate disability was statistically insignificant. The 90th day analysis of the admission serum cortisol and outcome scores similarly showed no positive correlation.

(ii) Cortisol and case-fatality

The 90 day case fatality rate in the study was 28% as shown in table 8
Table 8: Mean admission serum cortisol levels compared between the survivors and the dead in the study group

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Study group survivors</th>
<th>Study group dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency (%)</td>
<td>36 (72%)</td>
<td>14 (28%)</td>
</tr>
<tr>
<td>Mean serum cortisol ± SD</td>
<td>238.6 ± 82.2</td>
<td>388.4 ± 53.1</td>
</tr>
<tr>
<td>z-score</td>
<td>7.59</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>P&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
The mean first day single cortisol estimate for the survivors was 338.6 ± 82.2 ng/ml, while that for the fatalities was 338.4 ± 53.1 ng/ml. This observed difference between these two groups was statistically significant (p< 0.01).

Table 9 shows Cortisol levels in ng/ml among the dead and living at the various days of assessment.
Table 9: Cortisol levels in ng/ml among the dead and living at the various days of assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>Frequency</th>
<th>Mean ± SD</th>
<th>Frequency</th>
<th>Mean ± SD</th>
<th>Frequency</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>2</td>
<td>417 ± 117</td>
<td>10</td>
<td>387.7 ± 50.6</td>
<td>2</td>
<td>363.5 ± 17.7</td>
</tr>
<tr>
<td>Alive</td>
<td>48</td>
<td>275 ± 97.6</td>
<td>38</td>
<td>253.9 ± 92.6</td>
<td>36</td>
<td>277.2 ± 101.7</td>
</tr>
<tr>
<td>z-score</td>
<td>1.69</td>
<td></td>
<td>6.17</td>
<td></td>
<td>4.47</td>
<td></td>
</tr>
<tr>
<td>p. value</td>
<td>p&gt;0.05</td>
<td></td>
<td>p&lt;0.001</td>
<td></td>
<td>p&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>
The mean serum cortisol for cases who died within 7 days was $417 \pm 117$ ng/ml compared to that of the survivors $275 \pm 97.6$. The observed difference was not statistically significant ($p>0.05$).

The mean admission cortisol of those that died between the 7th and 30th days after stroke ($n=10$, cortisol $387.7 \pm 50.6$) compared with that of the survivors showed a statistically significant difference ($z=6.17$, $p<0.001$). Between the 30th and 90th days, two case fatalities were recorded, and their mean admission cortisol level when compared with the survivors within the period attained statistical significance.
CHAPTER SEVEN

DISCUSSION

Stress response factors and their roles in the pathophysiology of acute stroke have variously been studied, but there are few studies on the prognostic value of such influences on the severity and outcome. Studies on the degree of cortisol response as a marker of acute stroke severity, progression, and outcome are quite few, and no such study has been done in Nigeria.

a. Patients characteristics age distribution, risk factors and clinical presentation.

The age range of the patients in this study was between 38 years and 85 years with a mean age of 63.5 ± 13.3 years. Previous studies in Nigeria on stroke reported mean ages of 60 ± 4.3 years and 56 ± 13.6 years 131. However the studies did not involve only clinically judged ischaemic stroke sub-types.

The peak age of occurrence in the study was in the 8th decade of life. 84% of the event involved those aged 50 year and above, while 16% occurred in ages below 50 years. The great majority of the patients were between 50 and 79 years of age. This finding agreed with that in earlier reported studies which demonstrated exponential rise in stroke incidence with advancing age, and in which cerebral infarction was also found to be highest in the 8th decade, and in which the peak age among Africans was found to be 1-2 decades younger than that found in the western populations 16,18. Several studies have earlier found stroke among Africans to be more in the young. Some of such series
found majority of stroke in the under 60yrs of age\textsuperscript{130, 131, 132, 133}, with about one-third of strokes occurred in those under 45years one series\textsuperscript{18}. Osuntokun et al\textsuperscript{16} in a community stroke survey showed that the age related incidence from cerebrovascular accident in Nigerian-Africans was not different from that in the Caucasians. These varying reports can be explained by the fact that none studied any stroke sub-type exclusively. Moreover, the age related incidences of all strokes and stroke sub-type are known to vary widely between and even within populations.

The male to female ratio in this study was 1.0:1.3: Similar ratio in the range of 1.0:1.10 were found in some earlier reports\textsuperscript{14,16}. This study found a female preponderance in those aged above 50 years (26 Vs 16), and the 3 patients aged 80 years and above were women. One earlier report did find higher incidence of stroke among Nigerian housewives, however with a conclusion that the stroke data did not reflect the real stroke incidence in the studied community\textsuperscript{14}. The finding of this study did not agree with widely reported male preponderance of stroke, both in the Nigerian African and in the western world\textsuperscript{18,20}. Recent study by Danesi et al found a male to female ratio of 2:1 in Lagos Nigeria. There are also reports that beyond the age of 85 years in the industrialized world, more females suffer stroke\textsuperscript{14}. The observed differences may be center dependent. However 1983 census figures showed that more women lived beyond 80 years of age.

Hypertension remained the most common risk factor for stroke in this study. 46% of the patients were hypertensive. This observation agrees with
those in many earlier studies. More than 60% of the patients studied who were aged 50 and below were hypertensive. 10% of the patient population in this study were diabetic, a percentage that was higher than that reported in studies done earlier in Ibadan and Ethiopia\textsuperscript{131, 132, 133}. In our patients population, none of them below the age of 50 was diabetic. This was similar to the findings of Nwosu et al\textsuperscript{18}. Ninety-six percent of the patient population was conscious at presentation, just as headaches was not found to be a major presenting complaint.

\textit{b. Cortisol distribution}

The cortisol levels were significantly higher among the study group than the controls. This was in agreement with other studies on stress response in acute stroke patients\textsuperscript{112,114, 115}. This study found an equally significant rise in cortisol levels among those who were hypertensive and or diabetic. This may be suggestive that the presence of one or both conditions act as stressors. Though illnesses may have stressful effects on sufferers, there has been no study to quantify the degree of stress in terms of cortisol levels, or other quantitative measurements.

Males had significantly higher serum cortisol levels than the females among the studied subjects. There was significant difference in the levels of cortisol among male patients and males in controls 1 and 2. This observation was also true when the females were similarly compared. There were also differences observed between male patients and their female counterparts. This observed male-female difference was statistically significant between the patients but
not in either of the control populations. Males may thus be assumed to have more intense stress response than females in acute stressful events/ situations (stroke inclusive) which may not be true in normal health. Available reports have indicated no sex differences in the normal cortisol levels in health, rather the time of the assay in the day (morning or evening,) which reflects the physiological circadian rhythm is what is important.\textsuperscript{134}

c. Blood sugar values

The random blood sugar (RBS) was significantly higher among the patients in this study. The prevalence of admission hyperglycemia among acute stroke patients had been studied extensively in many earlier studies, and hyperglycaemia had been known to have adverse effect on stroke outcome\textsuperscript{122,123, 124}. The finding in this study was in line with those of these studies.

d. Correlation between cortisol and blood sugar

Cortisol correlated with random blood sugar in the studied subjects, the correlation being strongest among the patient population. Similar finding have been reported in earlier studies, which had found cortisol levels to relate to body temperature and blood sugar, the two basic para-clinical measures that have been found related to stroke severity \textsuperscript{114, 115, 116, 117}. The relationship between hypertension and development of diabetes mellitus, and vice versa, are current areas of interest that are yet to be established. The observation of the highest correlation among stroke patients might suggest that the hyperglycaemia observed in these patients may have been stress-related.
e. **Cortisol and stroke severity at presentation**

In this study, serum cortisol levels did not correlate to stroke severity at presentation. This finding was however at variance with an earlier reported study in which admission cortisol reflected acute stroke severity expressed as neurological deficit, infarct volume on brain CT and right insular cortex involvement, as well as to inflammatory response expressed as concentrations of interleukins –1 and –6 \(^{115, 117, 118}\).

f. **Cortisol in relation to functional outcome and dependence**

This study found no positive correlation between admission serum cortisol levels in patients to their functional outcome measured as modified Rankin scale scores at 7\(^{th}\), 30\(^{th}\) and 90\(^{th}\) day after the stroke event. Previous studies had demonstrated age and neurological deficit score on admission to be related to functional outcome at 30 or 90 days, but not to admission serum cortisol levels or concentration of pro-inflammatory cytokines, which were also found not to be independently predictive of dependency at these periods after stroke \(^{93, 94, 114}\).

This may be because at these stages in the illness other factors bordering on comorbidity, complications, and rehabilitation may be contributory.

g. **Cortisol and case fatality**

This study showed that serum cortisol level was significantly higher among the 28% of the patients population that died within the study period. This finding agreed to earlier studies \(^{94, 115}\). This study did not correlate serum
cortisol to 7th day mortality even though the mean cortisol levels were different for the dead and the survivors. However the serum cortisol levels correlated to the 30th and 90th day mortality. This finding however did not agree with the findings in the study in which serum cortisol correlated to 7th day mortality, but not to death at 30 days and 3 months115. The number of affected casualties recorded at the 7th day may be responsible for non significance of this difference. More over death within 7 days following acute stroke event may be caused by other factor related to cardiac, pulmonary and systemic co-morbidities or complications.

CHAPTER EIGHT

CONCLUSION

Patients who suffered acute ischaemic stroke manifested higher cortisol levels than controls and the male significantly more than the females.
They also have higher blood sugar levels than controls which may be assumed to be reactive.

The dead among the stroke patients showed higher serum cortisol levels than the survivors.

The higher admission cortisol levels correlated with the admission hyperglycaemia observed. Many studies had earlier related adverse outcome following stroke to reactive hyperglycaemia.

This study therefore demonstrated that acute ischaemic stroke is an acute stressful event, measured by high admission serum cortisol levels. The cortisol levels related significantly to admission hyperglycaemia, 30th and 90th day fatality risk, but not to dependency at 30th or 90th day after stroke.

RECOMMENDATIONS

A multicentre study with a larger sample size of patients is needed to further elucidate the findings in this study. There may also be need for intervention studies to study the effects of countering cortisol response in
patients with acute stroke. Serial cortisol estimations in the acute phase and beyond may give clearer picture on the role of cortisol in acute stroke events

LIMITATIONS OF STUDY

- Stroke diagnosis and subtyping was done using Siriraj score system with its obvious limitation.
- The access to brain C T Scan was limited by high cost of this valuable investigation even when requested.
• Cost containment: bearing the enormous cost of serum cortisol estimation.

• Sample size: The findings would be better substantiated with a larger sample size.

• Two (8%) of the control group 1 subjects were diabetic and may have influenced the findings. It would have been desirable to compare the diabetics and non diabetics among them.

REFERENCES


31. PROGRESS Collaborative group 2001: “Randomized trial of a perindopril based blood pressure lowering regimen among 6105 individuals with previous stroke or transient ischaemic attack.” *Lancet* 2001; 358; 1033 – 1041.


APPENDIX 1

I ______________________________________ of __________________________

________________________________________________________

hereby give my consent to myself/my __________________________ to be
included in the study of the Predictive value of serum cortisol level in adult
Nigerians with acute ischaemic stroke.

Dr._____________________________________________ has explained the
nature of the study with its benefits and risks to me. I understand that the study
is to be carried out solely for the purpose of medical research and I am willing
to act/allow ______________________________ as a subject for
that purpose on the understanding that I shall be entitled to withdraw this
consent at any time. I also recognize that the results or study may be of
significant benefit to mankind.

Date __________________________ Signed ________________________

__________________________________(witness to the patient’s signature) I
confirm that I have explained to the patient/_______________________ the
purpose and nature of this study and the risk involved, including the fact that
his refusal to participate will not in any way affect his normal care by me or
any other member of the institution. I know the consequences of any false
declaration on this or any other form.

Date _______________________ Doctor’s Signature _________________
APPENDIX II

STRESS RESPONSES IN ACUTE ISCHAEMIC STROKE: PREDICTIVE VALUE OF SERUM CORTISOL TO SEVERITY AND OUTCOME

STUDY QUESTIONNAIRE

Name: ___________________________________________________________

Hospital Number: ___________________ Sex: __________________________

Date of Birth (or approx age ) ____________________________

Date of Admission ___________________________________________

Date and time of onset of stroke: _________________________________

**Symptoms at Onset:**

- [ ] None
- [ ] Vomiting
- [ ] Convulsion
- [ ] Headache
- [ ] Others (specify) __________________________________________

**Level of Consciousness at Onset**

- [ ] Alert
- [ ] Impaired

**Handedness:**

- [ ] Right
  - Left hemiparesis

- [ ] Left
  - Right hemiparesis

- [ ] Quadriparesis

**Past Medical History**
[ ] Hypertension
Duration _____________

[ ] Diabetes Mellitus
Duration _____________

[ ] T.I.A
Dates _____________

[ ] SCD

[ ] Others (specify) _____________________________

**Drug History – List Drugs**

[ ] Anihypertensives _____________________________

[ ] Oral hypoglycaemie drugs _____________________________

[ ] Oral Contraceptives _____________________________

[ ] Insulin _____________________________

[ ] Others _____________________________

**Family History**

[ ] Hypertension

[ ] Diabetes mellitus

[ ] Stroke

[ ] Others (specify) _____________________________

**Social History**

Cigarette Smoking

Yes [  ]

No [  ]

If yes, quantity and duration _____________________________

Alcohol

Yes [  ]

No [  ]

If yes, quantity and duration _____________________________

**Language Disturbance**

[ ] None

[ ] Expressive dysphasia

[ ] Receptive dysphasia

[ ] Global dysphasia
Facial Palsy
[ ] Present (UMN  LMN)
[ ] Absent

Other Cranial Nerve Palsy
[ ] Absent
[ ] Present (specify cranial nerve and side) ___________________

Muscle Power on Admission
Upper _______________ Lt _______________ Rt _______________
Upper limb _____________ Lt _______________ Rt _______________

Cerebellar Signs
[ ] Present
[ ] Absent

Sririraj Stroke Score
* Siriraj Score on admission ________________________________
* WHO Score on admission ________________________________

Probable clinical type of stroke based on WHO criteria
[ ] Haemorrhagic stroke
[ ] Ischaemic Stroke

Confirmed Aetiological type of Stroke (from CT, or postmortem)
[ ] Intracerebral Haemorrhage
[ ] Cerebral infarction
[ ] Subarachnoid Haemorrhage
[ ] Not confirmed
1. **VITAL SIGNS**

<table>
<thead>
<tr>
<th></th>
<th>6 Hourly x 1 day</th>
<th>12 Hourly x 2 days</th>
<th>Daily for 14 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. **Glasgow Coma Scale daily 14 days**

3. **SSS Score on Admission**

4. **WHO Score on Admission**

5. **NIHSS Score**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
<th>3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

6. **Modified Rankin Scale**

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Day 7</th>
<th>Day 30</th>
<th>3 months</th>
<th>On Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

7. **Death. Date**

8. **Cause of death**

9. **Number of days of admission**
<table>
<thead>
<tr>
<th>Investigations</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting blood sugar</td>
<td></td>
</tr>
<tr>
<td>Random blood sugar</td>
<td></td>
</tr>
<tr>
<td>Serum Cholesterol</td>
<td></td>
</tr>
<tr>
<td>Serum triglyceride</td>
<td></td>
</tr>
<tr>
<td>EGG</td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td></td>
</tr>
<tr>
<td>CT brain scan</td>
<td></td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
</tr>
<tr>
<td>WBC Total</td>
<td></td>
</tr>
<tr>
<td>% Diff.</td>
<td>N.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>L.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>B.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>E.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>ESR</td>
<td></td>
</tr>
<tr>
<td>Hct.</td>
<td></td>
</tr>
<tr>
<td>Serum Urea</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Creatine</td>
</tr>
</tbody>
</table>
[ ]
Na+ ________________________________

[ ]
K+ ________________________________

[ ]
Cl- ________________________________

[ ]
HCO3 ________________________________

[ ] Serum Cortisol ________________________________

[ ] ________________________________

[ ] ________________________________

Complications

| [ ] | Nil ________________________________ |
| [ ] | Aspiration Pneumontis ________________________________ |
| [ ] | Pneumonia ________________________________ |
| [ ] | UTI ________________________________ |
| [ ] | Decubitus ulcer ________________________________ |
| [ ] | Septicaemia ________________________________ |
| [ ] | Depression ________________________________ |
| [ ] | ________________________________ |
| [ ] | Others (specify) ________________________________ |

Date of discharge ________________________________

Date of Death ________________________________

Cause of Death ________________________________

Muscle Power on discharge
Upper Limb
___________________                  Lt
___________________                  Rt

Lower Limb
___________________                  Lt
___________________                  Rt

**Condition on Discharge**

[  ]  Not ambulant ______________________________
[  ]  Ambulant with Support ____________________________
[  ]  Ambulant without Support ____________________________

NIHSS SCORE AT Discharge ______________ at 30 days ___________

MODIFIED RANKIN SCALE SCORE At Discharge _________________ at 30 days ___________

---

### APPENDIX III

#### NIH Stroke Scale

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Level of Consciousness (LOC)</td>
<td>Alert</td>
</tr>
<tr>
<td>1b</td>
<td>LOC questions (month, age)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Answer both correctly</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Answer 1 correctly</td>
<td>1</td>
</tr>
<tr>
<td>1c</td>
<td>IOC Command</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Open-close eyes.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incorrect on both</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Obeys both correctly</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Obeys 1 correctly</td>
<td>1</td>
</tr>
<tr>
<td>1d</td>
<td>(grip and release hand)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incorrect on both</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Partially gaze palsy</td>
<td>1</td>
</tr>
<tr>
<td>Best gaze</td>
<td>Forced deviation</td>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------</td>
<td></td>
</tr>
<tr>
<td>2 Best visual</td>
<td>Normal 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial gaze palsy 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Forced deviation 2</td>
<td></td>
</tr>
<tr>
<td>3 Best visual (visual fields)</td>
<td>No visual loss 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial hemianopia 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete hemianopia 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bilateral hemianopia 3</td>
<td></td>
</tr>
<tr>
<td>4 Facial palsy (Show teeth, raise brows, squeeze eye shut)</td>
<td>Normal 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minor 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complete 3</td>
<td></td>
</tr>
<tr>
<td>5 Motor arm left* (raise 90°, hold 10 seconds)</td>
<td>No drift 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drift 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannot resist gravity 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No effort against gravity 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No movement 4</td>
<td></td>
</tr>
<tr>
<td>6 Motor arm right* (raise 90°, hold 10 seconds)</td>
<td>No drift 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Drift 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cannot resist gravity 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No effort against gravity 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No movement 4</td>
<td></td>
</tr>
<tr>
<td>7 Motor leg left* (raise 30°, hold 5 seconds)</td>
<td>Cannot resist gravity 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No effort against gravity 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No movement 4</td>
<td></td>
</tr>
<tr>
<td>8 Motor leg right* (raise 30° hold 5 seconds)</td>
<td>Cannot resist gravity 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No effort against gravity 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No movement 4</td>
<td></td>
</tr>
<tr>
<td>9 Limb ataxia (finger-nose, heel-shin)</td>
<td>Absent 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present in 1 limb 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Present in 2 limbs 2</td>
<td></td>
</tr>
<tr>
<td>10 Sensory (pinprick to face, arm, leg)</td>
<td>Normal 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Partial loss 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe loss 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No neglect 0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(double simultaneous testing)</td>
<td>Partial neglect</td>
</tr>
<tr>
<td>---</td>
<td>--------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Dysarthria</td>
<td>Normal articulation</td>
</tr>
<tr>
<td></td>
<td>(speech clarity to “mama, baseball, huckleberry, tip-top, fifty-fifty”)</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>Best language**</td>
<td>No aphasia</td>
</tr>
<tr>
<td></td>
<td>(name items, describe pictures)</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*For limb with amputation, joint fusion, etc, score 9 and explain.*

**For intubation or other physical barriers to speech, score 9 and explain.*
## APPENDIX IV
### SUMMARY OF WHO CRITERIA

<table>
<thead>
<tr>
<th>Cerebral infarction</th>
<th>Intracerebral haemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. LOC</td>
<td>Absent</td>
</tr>
<tr>
<td>2. Headache</td>
<td>Absent</td>
</tr>
<tr>
<td>3. Vomiting</td>
<td>Absent</td>
</tr>
<tr>
<td>4. TIA</td>
<td>Present</td>
</tr>
<tr>
<td>5. HBP</td>
<td>Absent/ ↑</td>
</tr>
<tr>
<td>6. CSF</td>
<td>Clear</td>
</tr>
<tr>
<td>7. Occurrence</td>
<td>At rest</td>
</tr>
</tbody>
</table>

LOC = Loss of consciousness
TIA = Transient Ischaemic attack
HBP = Hypertension
CSF = Cerebrospinal fluid
↑ = Mild
↑↑ = Moderate
↑↑↑ = Severe

** = **
APPENDIX V
SIRIRAJ STROKE SCORE

A. Consciousness: alert = 0, drowsy/stupor = 1, semicoma/coma = 2
B. Vomiting: absent = 0, present = 1
C. Headchae: absent = 0, present = 1
D. Antheroma markers (history of DM, angina, intermittent claudication):
   absent = 0, present = 1

Score: \( (2.5 \times \text{consciousness} \ldots) + (2 \times \text{vomiting} \ldots) + (2 \times \text{headache} \ldots) + (0.1 \times \text{diastolic BP} \ldots) - (3 \times \text{atheroma marker} \ldots) - 12 = \)

\[ \ldots \]

\( > + 1 = \text{Haemorrhage} \)
\( < - 1 = \text{Infarction} \)
\( > - 1 + 1 = \text{Uncertain} \)
## APPENDIX VI
### MODIFIED RANKIN SCALE

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms, able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability, unable to carry out all previous activities, but able to look after own affairs without assistance.</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance.</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention.</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

**TOTAL (0 - 6): ____________________**
APPENDIX VII

GLASGOW COMA SCALE

Eye opening (E)
- Spontaneous 4
- To Speech 3
- To pain 2
- Nil 1

Best motor response (M)
- Obeys 6
- Localizes 5
- Withdraws 4
- Abnormal flexion 3
- Extensor Response 2
- Nil 1

Verbal Response (V)
- Oriented 5
- Confused conversation 4
- Inappropriate words 3
- Incomprehensible sounds 2
- Nil 1

Coma score $E + M + V$
Minimum –3 maximum 15
APPENDIX VIII

SAMPLE CALCULATIONS

\[ \text{Sample} = \frac{\text{CPM (sample)}}{\text{CPM (standard)}} \times 100 \]

\[ \text{1400} = \frac{20000}{20} \times 100 \]

\[ = 70\% \]

This calculation is for example only. The user must construct a standard curve each time they assay the sample.

TABLE STANDARD

<table>
<thead>
<tr>
<th>Standard</th>
<th>CPM</th>
<th>ANV CPM</th>
<th>Sample</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 pg/dl</td>
<td>20,916</td>
<td>25,254</td>
<td>24,097</td>
<td>24,107</td>
</tr>
<tr>
<td>1 pg/dl</td>
<td>22,220</td>
<td>27,110</td>
<td>25,008</td>
<td>22,160</td>
</tr>
<tr>
<td>3 pg/dl</td>
<td>20,805</td>
<td>26,109</td>
<td>10,206</td>
<td>10,409</td>
</tr>
<tr>
<td>10 pg/dl</td>
<td>14,044</td>
<td>18,313</td>
<td>18,206</td>
<td>18,313</td>
</tr>
<tr>
<td>30 pg/dl</td>
<td>9,497</td>
<td>14,790</td>
<td>9,687</td>
<td>9,602</td>
</tr>
<tr>
<td>100 pg/dl</td>
<td>5,085</td>
<td>6,480</td>
<td>5,695</td>
<td>4,865</td>
</tr>
<tr>
<td>Control</td>
<td>17,930</td>
<td>18,143</td>
<td>18,178</td>
<td>18,178</td>
</tr>
<tr>
<td>Control</td>
<td>12,964</td>
<td>18,986</td>
<td>17,964</td>
<td>17,964</td>
</tr>
<tr>
<td>Control</td>
<td>7,345</td>
<td>12,165</td>
<td>7,769</td>
<td>7,769</td>
</tr>
<tr>
<td>Control</td>
<td>7,345</td>
<td>12,165</td>
<td>7,769</td>
<td>7,769</td>
</tr>
<tr>
<td>Control</td>
<td>7,345</td>
<td>12,165</td>
<td>7,769</td>
<td>7,769</td>
</tr>
</tbody>
</table>

TABLE STANDARD CURVE

<table>
<thead>
<tr>
<th>CPM (pg/dl)</th>
<th>Control (uL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>20</td>
<td>100</td>
</tr>
<tr>
<td>30</td>
<td>200</td>
</tr>
<tr>
<td>40</td>
<td>300</td>
</tr>
<tr>
<td>50</td>
<td>400</td>
</tr>
<tr>
<td>60</td>
<td>500</td>
</tr>
<tr>
<td>70</td>
<td>600</td>
</tr>
<tr>
<td>80</td>
<td>700</td>
</tr>
<tr>
<td>90</td>
<td>800</td>
</tr>
<tr>
<td>100</td>
<td>900</td>
</tr>
</tbody>
</table>

NOTE: The curve serves only as an example. Critical values must not be derived from it.

XII. EXPECTED PHYSIOLOGICAL RANGES

The following data was obtained from one sample of patient’s samples.

MORNING SAMPLES (0500 A.M.) 7 to 24 pg/dl

AFTERNOON SAMPLES (1300 P.M.) 3 to 11 pg/dl

As with any diagnostic test, differences in physiological ranges may be encountered from laboratory to laboratory due to patient demographics, laboratory methodology, and preparation sampling. These ranges should only be used as guidelines. We recommend each laboratory establish its own ranges using a statistically significant number of characterized patient specimens in each diagnostic category.