DISSERTATION ON

A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND STROKE SEVERITY

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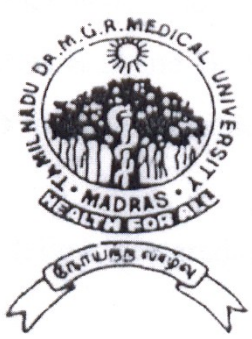

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CERTIFICATE

This is to certify that this dissertation entitled **"A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND STROKE SEVERITY"** submitted by **Dr. RAMESH KUMAR A. C** appearing for Part II M.D. Branch I General Medicine Degree examination in September 2006 is a bonafide record of work done by him under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India

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DECLARATION

I solemnly declare that the dissertation titled "A STUDY ON CORRELATION BETWEEN SERUM CORTISOL AND STROKE SEVERITY" is done by me at Madras Medical College & Govt. General Hospital, Chennai during 2004-2005 under the guidance and supervision of Prof. V. Sundaravadivelu, M.D.

The dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree (Branch I) in General Medicine.

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CONTENTS

INTRODUCTION

A stress response consisting of increased levels of cortisol and catecholamines in the first weeks after acute stroke has been known since the 1950s[1-4], and a failure of dexamethasone suppression of cortisol levels indicated a dysregulation of the hypothalamic pituitary adrenal (HPA) system[1].The cortisol response has been identified in both cerebral infarction and intracerebralhaemorrhage[1-4]. High s-cortisol levels have been related to poor outcome [2, 6]. It is, however, not known whether this adrenal glucocorticoid stress response is beneficial or harmful to the damaged brain.

The cortisol response is related positively to blood glucose [8] a parameter that increases after severe stroke [6-9] possibly resulting from the stress response. It has been reported that cortisol correlated positively to white blood cell count, fibrinogen, and other markers of the inflammatory response after stroke[10] as well as IL-6[11], and it was suggested that cytokines modulate the cortisol response after acute stroke[11] by stimulating the HPA axis leading to increased levels of cortisol in the periphery[12]. Some researchers suggested that the association between high stress hormone levels and less favourable outcome could be related to cardiac abnormalities resulting from the increased levels of stress-hormones[2, 3]. In one study, the degree of sympathetic activation was associated with the extent of the damage to the insula, which is assumed to be involved in the regulation of the autonomic nervous system[13]. Insular damage in experimental stroke has also been shown to result in an increase in the circulating

levels of catecholamines suggesting this as a mechanism for the cardiac complications associated with stroke[14].

It has also been observed that the normal circadian rhythm of cortisol is suspended during acute stroke as equal levels of cortisol were found round the clock[15].

Whether the stress response is just an epiphenomenon to stroke severity or independently contributes to prognosis remains uncertain. Furthermore, the stress response has not yet been put in perspective by evaluation in the context of parameters generally assumed to be of importance in acute stroke.

AIM

1. The aim of the study was to investigate if a single serum cortisol determination related to stroke severity.

2. If cortisol is related to paraclinical parameters in acute stroke in order to gain knowledge of the relations between cortisol and other paraclinical variables of known relevance to stroke.

REVIEW OF LITERATURE

A *stroke* (previously known as a cerebrovascular accident) is rapidly developing clinical symptoms and/or signs of focal, and at times global (applied to patients in deep coma and to those with subarachnoid haemorrhage) loss of brain function, with symptoms lasting more than 24 hours or leading to death, with no apparent cause other than that of vascular origin[17]. There is a wide range of severity, from recovery in a few days, through persistent disability, to death.

A *transient ischaemic attack* (TIA) is an acute loss of focal brain or monocular function with symptoms lasting less than I 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply as a result of arterial thrombosis, embolism, or low flow, associated with arterial, cardiac, or haematological disease[18]. About 80 per cent of all strokes are ischaemic, 10 per cent are due to primary intracerebral haemorrhage, about 5 per cent are due to subarachnoid haemorrhage.

After coronary heart disease and all cancers, stroke is the third most common cause of death in the world, causing-about 4 million deaths in 1990, three-quarters of them in developing countries[19]. A typical estimate of stroke prevalence is about 5/1000 population, but clearly the exact figure depends on the population age and sex structure, and becomes about 50/1000 in men and 25/1000 in women aged 65-74[20].

South Asian populations have a high prevalence of coronary heart disease, central obesity (i.e. high waist-to-hip ratio), insulin resistance, non-insulin-dependent diabetes, and hypertension[21], and a high stroke mortality, but there is no good information on incidence[22]. This seems to be due partly to genetic susceptibility (high serum lipoprotein (a) levels) in these people, potentiated by dietary- and lifestyle-induced changes in lipid levels [23].

Risk factors for ischaemic stroke

- Age
- Male sex
- Increasing blood pressure
- Cigarette smoking
- Blood lipids
- Diabetes mellitus
- Increasing plasma fibrinogen
- Raised factor VII coagulant activity
- Raised tissue plasminogen activator antigen
- Low blood fibrinolytic activity
- Raised von Willebrand factor

- Raised haematocrlt
- Atrial fibrillation
- Sex hormones
- Excess alcohol consumption
- Obesity and diet
- Physical Inactivity
- Raised white blood cell count
- Recent Infection
- Hyperhomocysteinaemia
- Snoring
- Corneal arcus
- Psychological factors
- Vasectomy
- Low serum albumin
- Diagonal earlobe crease
- Impaired ventilatory function
- Family history of stroke
- Social deprivation
- Evidence of pre-existing vascular disease
- Myocardial infarction/angina

- Cardiac failure
- Left ventricular hypertrophy
- Peripheral vascular disease
- Cervical arterial bruit and stenosis
- Transient Ischaemic attacks

Age

Age is the strongest risk factor for ischaemic stroke, primary intracerebral hemorrhage, and subarachnoid hemorrhage[24].

Sex

There is a small excess of males, which is most prominent in middle to old age, disappearing in the very elderly and probably absent in the young.

Blood pressure

In healthy populations, in both sexes and allowing for the association with age, increasing blood pressure is strongly associated with subsequent stroke risk, and probably with all the main pathological types[24]. Although most of the information comes from consideration of the diastolic blood pressure, the relationship with systolic blood pressure is similar and possibly stronger, and evens 'isolated' systolic hypertension is associated with increased risk[25].

The association between increasing blood pressure and stroke is less in the elderly than in middle age. What is not quite so clear is whether hypertension is still a risk factor in the very elderly, where stroke may be associated with low pressures, perhaps because low pressures are a reflection of pre-existing cardiovascular and other disease [26]. Hypertension probably increases stroke risk by increasing the extent and severity of atheroma[27] and the prevalence of small vessel disease in the perforating arteries within the brain.

Cigarette smoking

Cigarette smoking has been better accepted as a risk factor for coronary heart disease than stroke. However, there is no doubt of an association with stroke, there is a dose-response relationship, males and females are equally affected, the association seems to become weaker in the elderly, and there is perhaps an association with passive smoking[28]. Although smoking is a strong risk factor for subarachnoid haemorrhage and for ischaemic stroke there appears to be less association with primary intracerebral haemorrhage[28, 29]. Ex-cigarette smokers have a sustained excess risk of stroke for some years

Blood lipids

Any relationship between blood lipids and stroke is much weaken, if it exists at all[30, 31], although perhaps Increased serum lipoprotein (a) is predictive, Some attempts to relate atheroma in the extra and intracranial circulation to blood lipid concentrations have suggested an association.

Diabetes mellitus

Diabetes mellitus has long been recognised as a risk factor for vascular disease and about doubles the risk of stroke compared with non-diabetics, probably independently of any association with other risk factors such as hypertension.[32, 33]

Pathophysiology of acute cerebral ischaemia

The brain normally derives its energy from the oxidative metabolism of glucose. Because there are negligible stores of glucose in the brain, when CBF falls and the brain becomes ischaemic, a series of neurophysiological and functional changes, which are dependent on the oxidative metabolism of glucose to provide energy in the form of ATP, occur at various thresholds of flow before cell death. Different mechanisms are responsible for reversible loss of cellular function, and for irreversible cell death, and there are differences between the mechanisms that cause death of neurons, glia, and endothelial cells, and perhaps between white matter and grey matter[34, 35]

Cerebral ischaemia causes not only reversible and then irreversible loss of brain function, but also cerebral oedema[36] Ischaemic oedema it partly 'cytotoxic' and partly 'vasogenic'. Cytotoxic oedema starts within minutes of stroke onset, and affects the grey more than the white matter, with damaged cell membranes allowing intracellular water to accumulate.

Vasogenic oedema, which starts rather later, within hours of stroke onset affects the white matter more than the grey the damaged blood-brain barrier allowing plasma constituents to enter the extracellular space, Ischaemic cerebral oedema when its maximum in 2-4 days and then subsides over a week or two.

Hyperglycemia is associated with a poor outcome after stroke, either because the consequences of ischaemia are exacerbated in the presence of high blood glucose concentrations, perhaps mediated by excess lactate production[37], or because hyperglycemia reflects the stress response, and so the severity of the initial stroke[38, 39]. Clearly, trials of glucose lowering need to be done to sort this out.

Fever is associated with a worse outcome and hypothermia with a better outcome in stroke but, like blood sugar, it is not clear whether this association represents a causal relationship, and therefore whether any intervention would be worthwhile. Dehydration, increasing haematocrit, and raised whole blood viscosity are further potential exacerbating factors.

The causes of stroke

Cerebral ischaemia and infarction are usually caused by sudden occlusion of an artery supplying the brain or, less often, by low flow distal to an already occluded or highly stenosed artery. Occlusion or stenosis can be the result of disease of the arterial

wall; embolism from the heart; haematological disorders; and various rare, but sometimes treatable, conditions which are proportionately more common in young stroke patients (where degenerative arterial disease is unusual) but which can still be a cause of stroke in the elderly.

Causes of ischaemia and infarction

- Arterial wall disorders
    - Atheroembolism
    - Intracranial small vessel disease
    - Trauma
    - Dissection
    - Fibromuscular dysplasia
    - Congenital arterial anomalies
    - Moyamoya syndrome
    - Embolism from arterial aneurysms
    - Leukoaraiosis
    - Irradiation
    - Infection
- Embolism from the heart

- Haematological disorders
- Miscellaneous conditions
- Pregnancy/puerperium
- Oral contraceptives and other female sex hormones
- Drug abuse

- Cancer
- Perioperative
- Migraine
- Inflammatory bowel disease
- Homocystinaemia
- Fabry's disease
- Mitochondrial cytopathy
- Hypoglycaemia
- Fibrocartilaginous embolism
- Snake bite
- Fat embolism
- Epidermal naevus syndrome
- Susac's syndrome
- Nephrotic syndrome

Atheroma seems to be an almost inevitable accompaniment of ageing, at least in developed countries. It is by far the most common arterial disorder and, when complicated by thrombotic or embolism, Is the most frequent, but by no means only, cause of cerebral ischaemia and infarction.

The approximate relative frequency of the main causes of ischaemic stroke and TIA

Atherothrombosis affecting large and medium-sized arteries between the heart and the brain	50%
Intracranial small vessel disease	25%
Embolism from the heart	20%
Rare disorders	5%

Distribution of atheroma

Atheroma mainly affects large and medium-sized arteries at places of arterial branching, tortuosity , and confluence[40]. These are sites of haemodynamic sheer stress and thus endothelial trauma; boundary layer separation, blood stagnation, and the accumulation of platelets; and of turbulence, all of which are likely to promote thrombosis[41] .Atheroma starts in childhood, it is thought in response to endothelial injury[42]. The plaques are complicated by platelet adhesion, activation, and aggregation,

which inmates blood coagulation and subsequent thrombosis.

Causes of dissection of the extra- and Intracranial arteries

- Traumatic
    - Penetrating injury
    - Non-penetrating Injury
- Spontaneous
    - Fibromuscular dysplasia
    - Cystic medial necrosis
    - Marfan's syndrome
    - Ehlers-Danlos syndrome
    - Pseudoxanthoma elasticum
    - Inflammatory arterial disease
    - Infective arterial disease (e.g. syphilis)

Spontaneous intracranial haemorrhage

Spontaneous intracranial haemorrhage occurs within the brain (primary intracerebral haemorrhage), into the subarachnoid space (subarachnoid haemorrhage), sometimes into the ventricles (intraventricular haemorrhage), and rarely into the subdural space (subdural haemorrhage). The exact site of origin may not necessarily be immediately obvious because, for example, a saccular aneurysm can rupture into the brain as well as into the subarachnoid space, or disruption of a small perforating artery

can cause intraventricular haemorrhage as well as a basal ganglia haematoma. Even at post-mortem, there may be uncertainty because the source of the haemorrhage may well have been destroyed, particularly if small (e.g. a tiny intracranial vascular malformation). The causes of intracranial haemorrhage are much the same, whatever the primary site of the bleeding, although their relative frequency varies somewhat with the site.

Causes of spontaneous Intracranial haemorrhage.

- Hypertension
- Aneurysms
  - Saccular
  - Atheromatous
  - Mycotic
  - Myxomatous
  - Dissecting
- Cerebral amyloid angiopathy
- Intracranial vascular malformations
  - Arteriovenous (cerebral, dural)
  - Venous
  - Cavernous
  - Telangiectasis
- Haemostatic failure
  - Haemophilia and other coagulation disorders

        - Thrombocytopenia
        - Thrombotic thrombocytopenic purpura
        - Anticoagulation
        - Therapeutic thrombolysis
        - Antiplatelet drugs
        - Polycythaemia rubra vera
        - Essential thrombocythaemia
        - Paraproteinaemias
        - Disseminated intravascular coagulation
        - Renal failure
        - Liver failure
        - Snake bite
    - Inflammatory vascular disease
    - Haemorrhagic transformation of cerebral infarction
    - Intracranial venous thrombosis
    - Sickle-cell disease/trait
    - Moyamoya syndrome
    - Carotid endarterectomy
    - Posterior fossa and other intracranial surgery
    - Delayed post-traumatic 'spat-apoplexie'

- Alcoholic binge
- Wernicke's encephalopathy
- Vascular tumours
- Melanoma
- Choriocarcinoma
- Malignant astrocytoma
- Oligodendroglioma
- Medullobiastoma
- Haemangioblastoma
- Choroid plexus papilloma
- Hypernephroma
- Endometrial carcinoma
- Bronchogenic carcinoma
- Drug abuse
- Infections
    - Herpes simplex
    - Leptospirosis
    - Anthrax
    - Chronic meningitis
    - Scorpion bite

- Silastic dural substitute

Primary Intracerebral haemorrhage

Primary intracerebral haemorrhage (PICH) is somewhat more frequent than subarachnoid haemorrhage, the incidence increases with age. It is most commonly due to intracranial small vessel disease associated with hypertension, cerebral amyloid angiopathy, and intracranial vascular malformations, but there is usually a combination of different factors operating in any one individual, e.g. hypertension and cerebral amyloid angiopathy, therapeutic thrombolysis and a vascular malformation, etc.[43]Less common causes include saccular aneurysms; haemostatic defects, particularly induced by anticoagulation[44], therapeutic thrombolysis, perhaps with cerebral amyloid angiopathy, and possibly antiplatelet drugs; cerebral vasculitis and drug abuse.

The site of PICH, shown on CT, provides some clue to the cause; 'hypertensive' haemorrhages tend to occur slightly more in the basal ganglia, thalamus, and pons, while lobar haemorrhages (i.e. superficial in cerebrum) tend to be somewhat more often due to cerebral amyloid angiopathy, vascular malformations, and haemostatic failure. Occasionally PICHs occur in different parts of the brain simultaneously, or over a short period of time. Rarely, PICH is familial.

Spontaneous subarachnoid haemorrhage

The incidence of spontaneous subarachnoid haemorrhage (SAH) increases with age and is about 5-10/100 000 population/annum, being somewhat more frequent in women than men. A ruptured saccular aneurysm is by far the most common cause[45]. Some SAHs are due to bleeding from an intracranial vascular malformation, a few are due to rarities, and depending on the intensity of investigation in about 15 per cent no cause can be identified in life [46].Primary intraventricular haemorrhage is very unusual, except in premature babies. In adults, a cause is not always found. Some may be due to a vascular malformation in the ventricular wall[47]. The clinical features are so similar to SAH that it can only be differentiated on CT, or at post-mortem.

Subdural haemorrhage is more often traumatic, or due to ventricular decompression for hydrocephalus, than spontaneous (but remembering that trauma can so easily be ignored or forgotten). Rupture of a vascular malformation in the dura or of a very peripheral aneurysm (mycotic much more likely than saccular), a haemostatic defect (particularly therapeutic anticoagulation), or a peripheral cerebral tumour can be responsible. It is also a very rare complication of lumbar puncture.

Transient ischaemic attacks

About 15 per cent of first stroke patients have had earlier TIAs, but only about half of them consult a doctor. Therefore, the incidence of TIAs presenting to medical attention (about 0.5 per 1000 population per annum) must be an underestimate of the real situation[18, 48]. By definition, the symptoms last less than 24 hours, but a few patients have

residual neurological signs of no functional significance, e.g. reflex asymmetry. About 25 per cent have focal hypodensity on CT, relevant to the symptoms in about half and therefore perhaps representing recent infarction[49].

An even higher proportion has focal lesions on MRI[50]. However, the diagnosis depends *not* on either neurological signs or imaging but essentially on the nature and duration of the symptoms in the right 'vascular' milieu (elderly, vascular risk factors, absent pulses, and bruits, etc.). Fortunately, in general, there is less inter observer disagreement about symptoms, which are remembered, than signs which are likely to attenuate and disappear[51]. The main use of brain imaging is to rule out the very occasional structural lesion causing 'transient focal neurological attacks'.

Causes of transient focal neurological attacks

- Focal cerebral ischaemia (i.e. TIA)
- Migraine with aura
- Partial epileptic seizures
- Structural intracranial lesions
- Tumour
- Chronic subdural haematoma
- Vascular malformation

- Giant aneurysm
- Multiple sclerosis
- Labyrinthine disorders
- Peripheral nerve or root lesion
- Metabolic
    - Hypoglycaemia
    - Hyperglycaemia
    - Hypercalcaemia
    - Hyponatremia
- Psychological

Symptoms of T I A

- Unilateral weakness, heaviness, or clumsiness
- Unilateral sensory symptoms
- Dysarthria
- Transient monocular blindness
- Dysphasia
- Unsteadiness/ataxia

- Bilateral simultaneous blindness
- Vertigo
- Homonymous hemianopia
- Diplopia
- Bilateral motor loss
- Dysphagia
- Crossed sensory and motor loss

Clinical features.

The diagnosis of stroke is straightforward if there is a clear history of focal brain dysfunction which started suddenly, or was first noticed on waking, particularly if the patient has not had a previous stroke, is over the age of 50, and has vascular risk factors or disorders. There may be some progression over the first few minutes or hours, but usually the deficit stabilizes by 12-24 hours and, if the patient survives, recovery starts within a few days in most cases. The severity ranges from a trivial deficit, which is gone in a day, through a persistent deficit with or without disability, to death within hours of onset.

If the history is clear-cut, the chance of a CT or MRI brain scan showing anything other than an infarct or haemorrhage (or being normal if done early in the case of

infarction or the lesion is very small) is under five per cent[52]. If there is doubt about the speed of onset of a focal deficit, then the diagnosis is rather more likely to be an intracranial mass lesion, such as a tumour or chronic subdural haematoma. If the onset was clearly sudden, but there was no obvious focal deficit, then brain imaging may show a thalamic or cerebellar infarct or haemorrhage. Clinical clues to an intracranial tumour are recent headaches, seizures, papilledema, a worsening deficit over days or weeks, and any suggestion of a primary tumour out with the brain. Clues to a chronic subdural haematoma are head injury in the previous few weeks; more drowsiness, confusion and headache than anticipated from the severity of the neurological deficit; a fluctuating course; and a patient on anticoagulants.

Other diagnoses are usually but not necessarily obvious: multiple sclerosis (young age); peripheral nerve or root lesion (clinical signs); post-seizure hemiparesis (history); metabolic encephalopathy (global rather than focal neurological features); somatization and hysteria (young age, signs); encephalitis (fever, clinical symptoms and signs, diffusely abnormal EEG); and intracranial abscess (fever and predisposing cause such as sinusitis, congenital heart lesion, etc.)[53]. Occasionally, head injury causing intracerebral haemorrhage can be missed if the patient is amnesic for the injury itself and has an unmarked scalp; while ischaemic stroke shortly after an obvious head injury may be due to neck artery dissection.

Haemorrhagic strokes causing a fall and so head injury can be equally confusing if

the CT scan shows ‘primary intracerebral haemorrhage' or 'subarachnoid haemorrhage' and the circumstances at the onset are unclear[54]. If there are persisting signs from a previous stroke, and the patient then falls ill for some other reason such as an infection, or has an epileptic seizure, the old signs may appear to worsen and so mimic stroke recurrence.

Determining the site of the lesion depends on classical clinicoanatomical correlation[55]. A simple system, which does not require great neurological skill, divides stroke patients first into four main clinical syndromes: total anterior circulation syndrome (TACS), partial anterior circulation syndrome (PACS), lacunar syndrome (LACS), and posterior circulation syndrome (POCS). Occasionally one has to put the patient in an uncertain category. This division depends entirely and only on the symptoms and signs, which are accessible to everyone, irrespective of the availability or standard of any technology.

Next, based on brain CT or perhaps MRI, patients with primary intracerebral haemorrhage are separated off. The rest, where the scan is either normal or shows infarction in a relevant area, can then be divided into: total anterior circulation infarct, about 15 per cent of the total in community-based studies (TACI); partial anterior circulation infarct, 35 per cent (PACI); lacunar infarct, 25 per cent (LACI); and posterior circulation infarct, 25 per cent (POCI)[56].These categories provide some prognostic

information for survival, residual disability, and recurrence, and an indication of the cause of the stroke[57]

Total anterior circulation syndrome (TACS)

A large haematoma in one cerebral hemisphere, or an infarct large enough to affect the cortex, basal ganglia, and internal capsule, causes a characteristic clinical syndrome of contralateral hemiparesis, with or without a sensory deficit, involving the whole of at least two of the three body areas (face, upper limb, lower limb), a homonymous visual field defect, and new higher cerebral or 'cortical' dysfunction (dysphasia, neglect, visuospatial problems, etc., depending on cerebral dominance). Total anterior circulation infarcts. (TACIs) ate usually due to acute occlusion of the internal carotid artery (normally atherothrombotic), or embolic occlusion of the proximal middle cerebral artery from a cardiac or proximal arterial source[58].

Partial anterior circulation syndrome (PACS)

A lobar haemorrhage, or a cortical infarct, causes a more restricted clinical syndrome consisting of only two of the three components of the total anterior circulation syndrome; or just isolated higher cortical dysfunction such as dysphasia; or a pre-dominantly proprioceptive deficit in one limb; or a motor/ sensory deficit restricted to one body area or part of one body area[59]. If the 'cortical' signs are rather subtle (dressing apraxia, neglect, dysphasia mistaken for dysarthria, etc.),the patient may be misclassified as 'lacunar'.

Partial anterior circulation or cortical infarcts (PACIs) are caused by occlusion of a

branch of the middle cerebral artery, or rarely the trunk of the anterior cerebral artery, usually as a consequence of embolism from the heart or proximal atherothrombosis, in the same ways as TACIs. Anterior cerebral artery infarcts cause contralateral weakness, predominantly of the lower limb, perhaps with some cortical sensory loss, and aphasia if in the dominant hemisphere.

Lacunar syndrome (LACS)

Lacunar syndromes are defined clinically and are highly predictive of small, deep lesions affecting the motor and/or sensory pathways, i.e. in the corona radiata, internal capsule, thalamus, cerebral peduncle, and pons[59, 60].

The four main lacunar syndromes are most reliably defined if there has been no previous stroke and if the patients are examined at the time of their maximal deficit

1pure motor stroke

2 pure sensory stroke

3 sensorimotar stroke

4 ataxic hemiparesis

Posterior circulation syndrome (POCS)

Brainstem, cerebellar, thalamic, or occipital lobe signs normally indicate infarction in the distribution of the vertebrobasilar (i.e. posterior) circulation[61], or a localized haemorrhage. A combination of brainstem and occipital lobe signs is highly suggestive of infarction due to thromboembolism within the basilar and posterior cerebral artery (PCA) territories. Occasionally, proximal PCA occlusion causes enough temporal, thalamic and

perhaps midbrain infarction to cause some contralateral hemiparesis and sensory loss. A marked cognitive deficit such as aphasia, as well as the expected homonymous hemianopia, and so be confused with occlusion of the middle cerebral artery or one of its branches[62]; this is the so-called 'walking total anterior circulation syndrome (TACS)' because although it fulfils the definition of a TACS, the motor loss is mild. The causes of infarction in the vertebrobasilar territory are rather heterogeneous and, in individual.

Investigations of stroke

Apart from routine investigations

- Full blood count
- ESR
- Electrolytes
- Urea
- Plasma glucose
- Plasma cholesterol
- Urine analysis
- Electrocardiogram

C T Brain.

When it is essential to exclude PICH, there is no alternative to a CT scan, preferably within hours of stroke onset before any haematoma has vanished.

Ischaemic stroke, the CT scan is normal immediately after onset, and if the lesion is small (less than about 0.5 cm in diameter), or in the posterior fossa, the scan may remain normal. With larger infarcts, a diffuse low-density area begins to appear, due to increasing brain water content, within a few hours. This may be accompanied by subtle effacement of sulci and loss of the normal grey-white matter differentiation, loss of the insular ribbon, loss of outline of the lentiform nucleus, and compression of the adjacent ventricle[63].

When the lesion is large, more obvious infarct swelling, brain shift, and herniation may be seen a few days after onset. In addition, CT can show haemorrhagic transformation, either asymptomatic or symptomatic, and although this tends to occur a few days after stroke onset in large infarcts, it can happen within hours and the haemorrhagic area can look very like a primary haemorrhage [64.] MRI is more sensitive but less specific than C T.

Primary intracerebral haemorrhage (PICH) appears at once on CT as a well-demarcated high-density round or oval area, with or without rupture into the ventricles or on to the surface of the brain. Lesions as small as 0.5cm in diameter can be picked up. Mixed-density haemorrhages, suggesting blood of different ages, is rather characteristic of amyloid angiopathy, and a blood-fluid level suggests a haemostatic defect of some

sort[65].

MRI is less; available than CT and patients have to lie still for longer, which for acute stroke makes CT the preferred immediate imaging technique, particularly since it displays intracerebral haemorrhage more reliably[66]. MRI is not necessarily superior to CT in detecting the very earliest signs of cerebral infarction [67].

Cortisol

Cortisol is the predominant corticosteroid secreted from the adrenal cortex in humans. In a healthy, unstressed person, cortisol is secreted according to a diurnal pattern under the influence of corticotropin released from the pituitary gland. Corticotropin secretion, in turn, is under the influence of hypothalamic corticotropin - releasing hormone and both hormones are subject to negative feedback control by cortisol itself. Circulating cortisol is bound to corticosteroid binding globulin, with less than 10 percent in the free, bioavailable form.

With severe infection, trauma, burns, illness, or surgery, there is an increase in cortisol production by as much as a factor, of six that is roughly proportional to the severity of the illness[68]. Diurnal variation in cortisol secretion is also lost. These effects are due to increased production of cortisol secretion is also lost. These effects are due to increased production of corticotropin - releasing hormone and corticotropin and a

reduction in negative feedback from cortisol[69]. Stimulation of the hypothalamic - pituitary - adrenal axis in this context is caused by elevated levels of circulating cytokines, among other factors[70].

Adrenal responsiveness to exogenous corticotropin is normally maintained during acute illness[71]. In addition, during critical illness, levels of corticosteroid binding globulin decrease rapidly[72], leading to increase at sites of inflammation owing to the cleavage of corticosteroid - binding globulin by neutrophil elastate, an effect that liberates cortisol[75]. In addition to having systemic actions, inflammatory metabolism[10] and can increase the affinity of glucocorticoid receptors for cortisol[11]. These changes in cortisol action appear to be important adaptive mechanisms regulating the inflammatory response[70].

During severe illness, many factors can impair the normal corticosteroid response. These factors include preexisting conditions affecting the hypothalamic - pituitary - adrenal axis[76], but corticosteroid insufficiency can also occur during the course of acute illness. Responses involving corticotropin releasing hormone and corticotropin can be impaired by head injury, central nervous system depressants, or pituitary infarction[77].

Adrenal cortisol synthesis can be impaired by multiple meachanisms[71,76]. The anesthetic agent etomidate and the antifungal agent ketoconazole inhibit the activity of enzymes involved in cortisol synthesis[78]. Adrenal hemorrhage can occur in sick patients,

especially those with septicemia and underlying coagulopathy, and adrenal insufficiency can occur when there is extensive destruction of adrenal tissue caused by tumors or infection. The high levels of inflammatory cytokines in patients with sepsis can also directly inhibit adrenal cortisol synthesis[79].

Ischaemic stroke is a stress factor triggering a complex defensive reaction called "alarm reaction" by Selye. Stress gives rise to liberation of catecholamines, dopamine beta-hydroxylase in the blood, cerebro-spinal fluid and urine. Patients with ischaemic stroke were found to have increased adrenaline, noradrenaline, and 3-metoxy-4-hydroxymandelic acid level in urine and increased cortisol level in blood serum. Patients, especially those with severe ischaemic stroke have increased concentrations of glucose metabolites in blood and cerebro-spinal fluid: pyruvate acid, lactic acid, acetylacetic acid and hydroxybutyric acid.

In acute illness, cortisol secretion increases whereas that of the adrenal androgens, and dehydroepiandrosterone sulfate declines. The period following ischemic stroke can be considered as a reaction to a stressful event. Changes in cortisol secretion are one of the indicators of stress reaction

Increased levels of glucocorticoids (GCs) released from the adrenal cortex during stress have negative effects on many organ systems and may impair the immune system, myocardial function and affect carbohydrate, protein and fat metabolism. *In vitro* and *in vivo* studies have demonstrated neurotoxic effects of GCs, including exacerbation of

hypoxic injury to neurones[80]. Experimental ischaemic injury to neurones is thus potentiated by high physiological levels of GCs and attenuated after adrenalectomy[81-83].

Prolonged sustained exposure to GCs may also influence cognition and mood[84]. Central for these effects is the hippocampal formation, important for mood and cognition and with a high density of corticosteroid receptors[85, 86]. However, adrenalectomy *per se* can also induce neuronal injury and adequate circulating GC levels are essential for maintaining body homeostasis[87].

Acute stroke is associated with increased activity in the hypothalamic-pituitary-adrenal axis resulting in increased cortisol production and elevated circulating cortisol level[88-90]. Previous research have shown that excessive cortisol levels after stroke is associated with cognitive dysfunction[89-91], severity of hemiparesis[89,92] and may predict stroke outcome and the later development of depression[93] . In contrast, low circulating cortisol levels have been associated with poor outcome after burns and septicemia[94-97], stressing the importance of cortisol for the maintenance of vital functions.

During the first few days after stroke, there is an initial rise of ACTH and cortisol but a subsequent, rapid decline of ACTH with a persisting increase of cortisol. This dissociation between ACTH and cortisol is most likely due to a cortisol-induced depression of ACTH levels combined with an increased responsiveness at the adrenal levels[88, 90].

Another factor likely to contribute to the altered adrenal steroid production is an

increased cytokine drive in stroke patients[98], i.e. release of interleukin (IL)-1, IL-6 and tumour necrosis factor alpha, which act on several levels of the HPA axis[99-100]. Thus, an increased cytokine drive may be partially responsible for the observed cortisol/adrenal dissociation.

Increased cortisol levels may induce cognitive dysfunction[101] and in experimental studies GCs in conjunction with ischaemia exert a toxic effect on neurones, especially those in the hippocampus[81, 102], where it can induce hippocampal pyramidal neurone degeneration. Hippocampal stimulation during surgery in man is known to inhibit the cortisol axis, and the hippocampus is suggested to be important for the feedback regulation for the cortisol axis[84, 103]. Hippocampal dysfunction may thus lead to hypercortisolism that, in turn, may aggravate existing damage, resulting in a vicious circle.

Even minor doses of exogenously administered cortisol cause a decreased cognitive performance[101], suggesting that the increases seen in the present report may contribute to the observed disorientation. Furthermore, disorientation may be an important contributor to, and predictor of, the outcome in acute stroke[104, 105].

MATERIALS AND METHODS

Patients

The study included 60 patients with acute stroke in the study within 24 h of stroke onset after informed consent. The patients were recruited from medical wards in government general hospital. Of them, 13 patients we excluded as per exclusion criteria. The remaining 47 patients were selected for the study.

Exclusion criteria

1. Pregnancy
2. Liver disease
3. Age <18
4. Patients who are taking following drugs
    a.phenytoin
    b. rifampicin
    c. ketaconazole
    d. steroids

Methodology

Blood pressure, pulse rate, body temperature, and Scandinavian Stroke Scale (SSS) were recorded in all patients at their arrival in hospital. Diagnosis of cerebral infarction or intracerebral haemorrhage was based on clinical findings and CT-scan in all patients. Blood samples are taken for total count, blood sugar, and serum cortisol.

Single-measurement serum cortisol was chosen as a previous study has shown that a circadian rhythm cannot be demonstrated in acute stroke(15).

Scandinavian stroke Scale

(Scandinavian Stroke Study Group, 1985)

Consciousness: fully conscious - **6**, somnolent, can be awaked to full consciousness - **4**, reacts to verbal command, but is not fully conscious - **2**, coma - **0**;

Orientation: correct for time, place and person - **6**, two of these - **4**, one of these - **2**, completely disorientated - **0**;

Speech: no aphasia - **10**, impairment of comprehension or expression disability - **6**, more than yes/no, but not longer sentences - **3**, only yes/no or less - **0**;

Eye movement: no gaze palsy - **4**, gaze palsy present - **2**, forced lateral gaze - **0**;

Facial palsy: none/dubious - **2**, present - **0**;

Gait: > walks 5 m without aids - **12**, walks with aids - **9**, with help of another person - **6**, without support - **3**, bedridden/wheelchair - **0**;

Arm, motor power (assessed only on affected side): raises arm with normal strength - **6**, raises arm with reduced strength - **5**, raises arm with flexion in elbow - **4**, can move, but not against gravity - **2**, paralysis - **0**;

Hand, motor power (assessed only on affected side): normal strength - **6**, reduced strength in full range - **4**, some movement, fingertips do not reach palm - **2**, paralysis - **0**;

Leg, motor power (assessed only on affected side): normal strength - **6**, raises straight leg with reduced strength - **5**, raises leg with flexion of knee - **4**, can move, but not against gravity - **2**, paralysis - **0**;

Foot paresis: none - **2**, present - **0**.

Serum cortisol

Serum cortisol is estimated by competitive immunoenzymatic calorimetric method (DiaMetra kit). The analyzing laboratories were blinded to all clinical information about patients.

Cortisol (antigen) in the sample competes with horseradish peroxidase-cortisol (enzyme labeled antigen) for binding on to the limited number of anti-cortisol (antibody) sites on the microplates (solid phase). After incubation, bound/free separation is

performed by a simple solid phase washing. The enzyme substrate (H2O2) and the TMB-substrate are added. After an appropriate time is elapsed for maximal color development, the enzyme reaction is stopped and absorbances are determined. Cortisol concentration in the sample is based on a series by a set of standard. The color intensity is inversely proportional to the cortisol concentration in the sample.

Statistical analysis

Statistical analysis was performed by SPSS 11.5 for Windows. Normal distribution was assessed by Kolmogorov Smirnov's one-sample test. Spearman's - correlation was applied in testing correlations in not continuous variables. Student's *t* test was used in comparing means of independent, normally distributed, continuous variables. Stratifications were based on the median of SSS score. Univariate logistic regression analysis and variables reaching a significance level of 0.1 in univariate analysis were done.

A significance level of 0.05 was selected for the final model. Stroke severity as assessed by SSS and blood glucose, body temperature, pulse rate, total WBC count, systolic and diastolic blood pressure were correlated with serum cortisol. Statistical significance were taken when the P value is < 0.05 (95% confidence interval)

OBSERVATIONS

Table No. 1

Patient characteristics

Patient characteristics N=47	Percentage or Median with quartiles
Age	60 yrs (50-65)
Male sex	55.3 %
H/o Hypertension	42.6%
H/o Diabetes	27.7%
H/o CAD	14.9%
H/o Alcoholism	25.0%

Table No.2

Patient profile on admission

Patient indicators	Mean	Standard deviation
SBP	158.21	15.59
DBP	93.45	11.00
Pulse rate	85.45	8.35
Temperature	99.6	1.21
Total count	8348	1873.4
Blood sugar	103.36	21.29
Serum cortisol	33.52	11.20
SSS	27.55	8.56

Table No.3

Levels of correlation with SSS

Factor	**Correlation coefficient**	Significance P value
SBP	-0.166	0.266
DBP	-0.108	0.469
Pulse	-0.057	0.703
Temperature	-0.292	0.046
TC	-0.161	0.279
Blood sugar	-0.171	0.251
Serum cortisol	-0.437	0.002

Table No.4

Levels of correlation with Serum cortisol

Factor	**Correlation coefficient**	Significance P value
SBP	0.282	0.055
DBP	0.167	0.262
Pulse	0.423	0.003
Temperature	0.312	0.001
TC	0.248	0.032
Blood sugar	0.248	0.093
SSS	-0.437	0.002

Data from 47 patients participated in this study is finally entertained for analysis of which 26 patients are males (55.3%). The mean age of presentation is 58.21 yrs as shown in Table 1.

The mean duration of presentation i.e. from the time of onset of stroke and presentation to the hospital is 13.62 hours. Of the 47 patients enrolled for the study, 13 persons were known diabetics (27.7%) and 20 persons were known hypertensives (42.6%).

Of the 47 patients enrolled for the study, 8 (17%) patients were having hemorrhagic stroke and the remaining were suffering from ischemic strokes. The most common site for ischemic stroke was MCA territory including its lenticulostriate branches.

Of the 47 patients, 12 persons (25.5%) were alcoholics and 17 persons were smokers (36.2%). Alcoholism and smoking were exclusively seen in males.

On admission, almost all the patients were having systolic blood pressure more than 140 mmHg. 29 patients (61.7%) were having diastolic blood pressure more than 90 mmHg. The average temperature is about 99.6 degree F and the mean pulse rate is about 85.45.

The investigations showed total WBC count of about 8400 cells/cu.mm as an average. Blood sugar estimation revealed an average blood sugar of 103.36 mg/dL.

Serum cortisol measured as the time of admission showed a mean of about 33.52 mg/dL and a standard deviation of about 11.20 mg/dL. The value varied between 11.6 to 52.8 mg/dL.

The Scandinavian stroke scale assessment at the time of admission ranged from 7 to 41 in our patients for a total of 60. The mean SSS score is about 27.55 with standard deviation is about 8.56.

The correlation between SSS and serum cortisol were analyzed. The correlation coefficient (rho ρ) is about -0.437 with a P value of 0.002.

The relationship between SSS score and other parameters were also analyzed. The correlation coefficient was more for body temperature (-0.292) with a P value of 0.045. The correlation coefficients for other parameters were depicted in Table 3 with corresponding P values

To analyse the relationship of serum cortisol and the important parameters correlation coefficients were computed. The highest magnitude of correlation was obtained for SSS score as depicted above. There is also good correlation between serum cortisol and body temperature. The other parameters are depicted in Table 4.

CHARTS AND GRAPHS

Fig.1 Age distribution

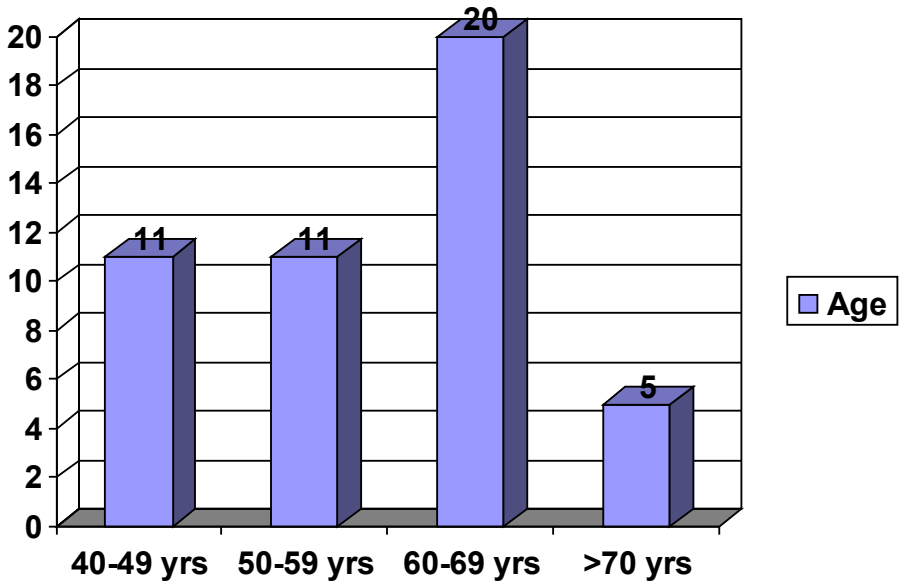


Fig.2 Sex distribution

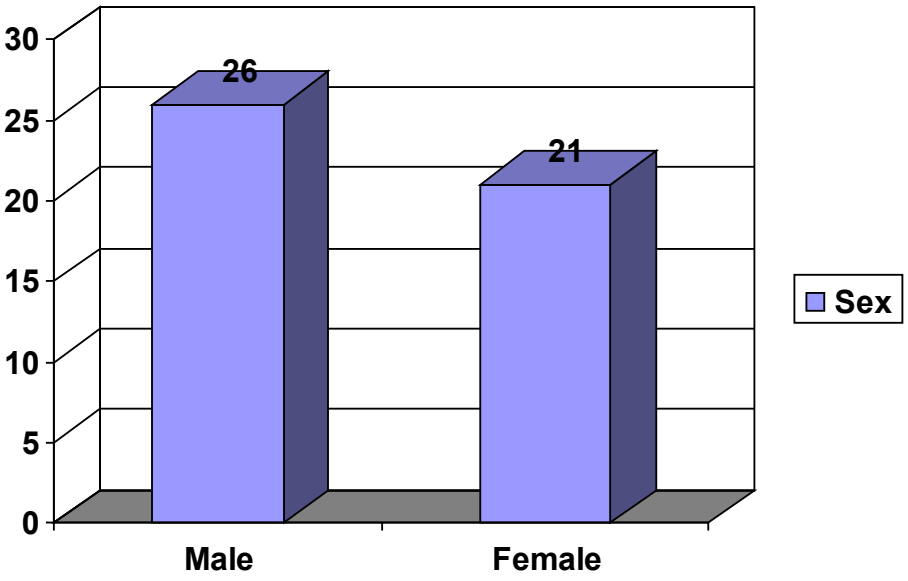


Fig.3 Duration of presentation

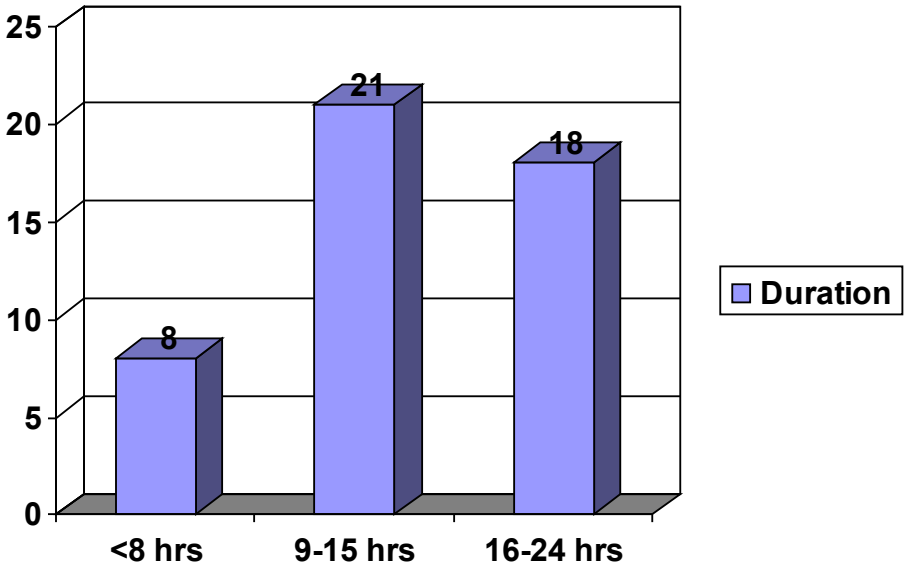


Fig.4 Stroke severity - SSS

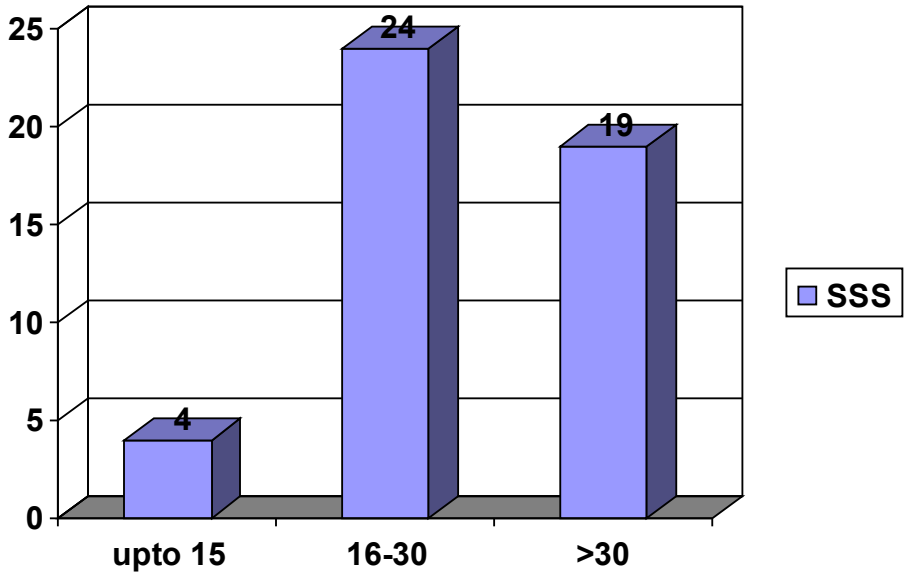


Fig.5 Type of stroke

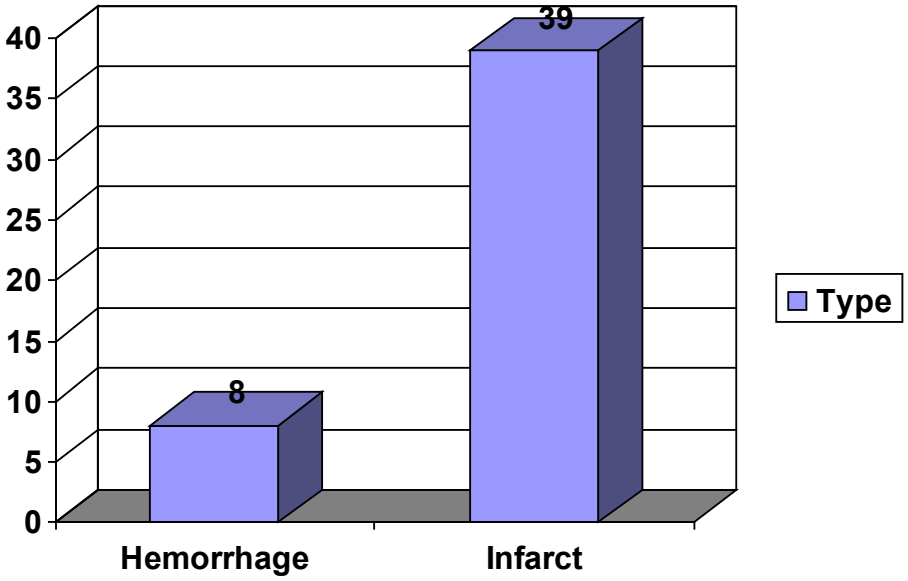


Fig. 6 Correlation between SSS and Serum cortisol levels

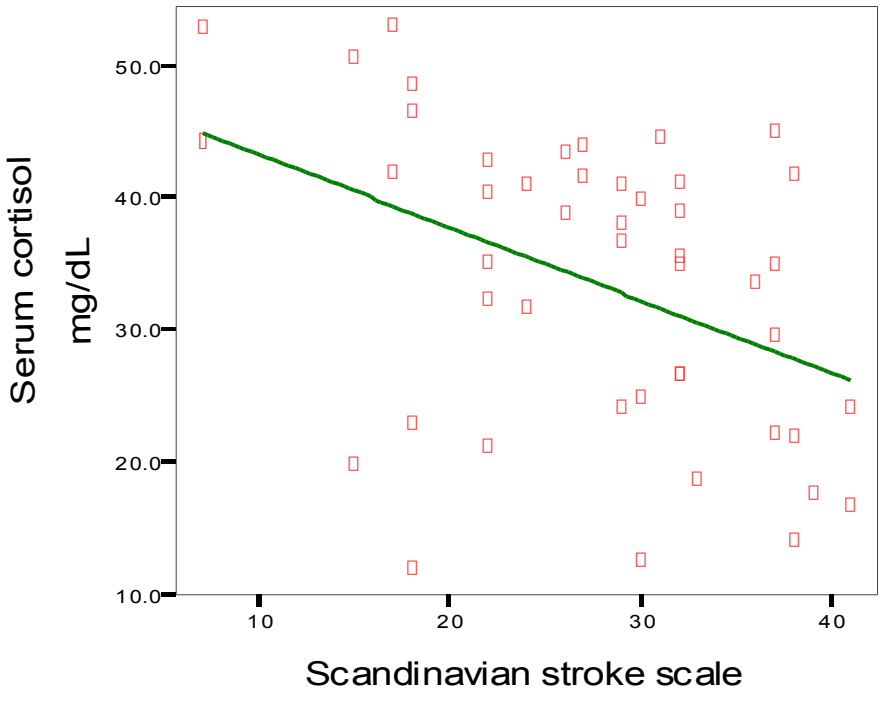


Fig.7 Correlation between SSS and Blood sugar

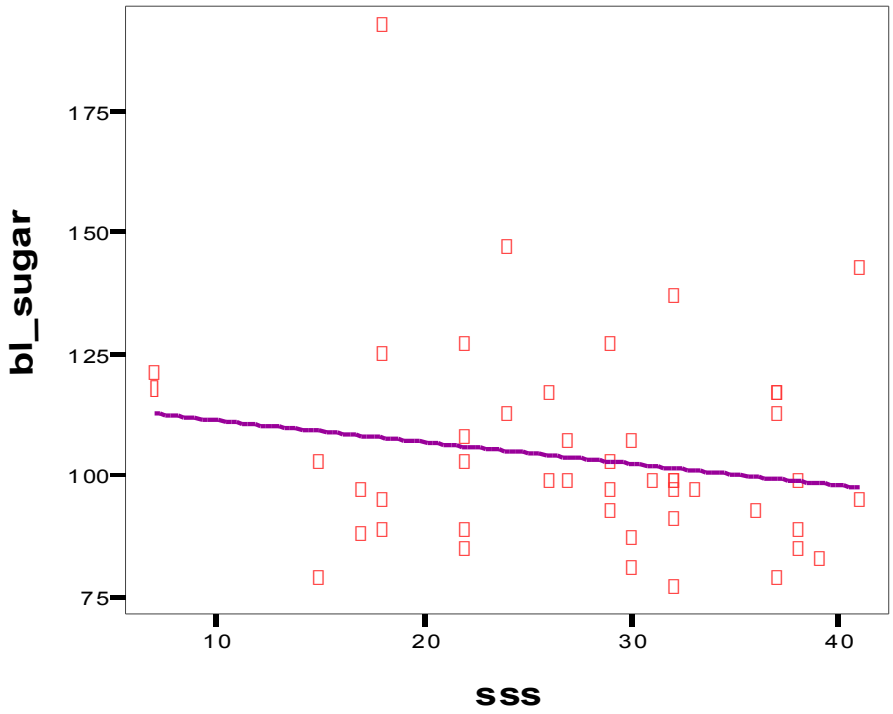


Fig.8 Correlation between SSS and Total count

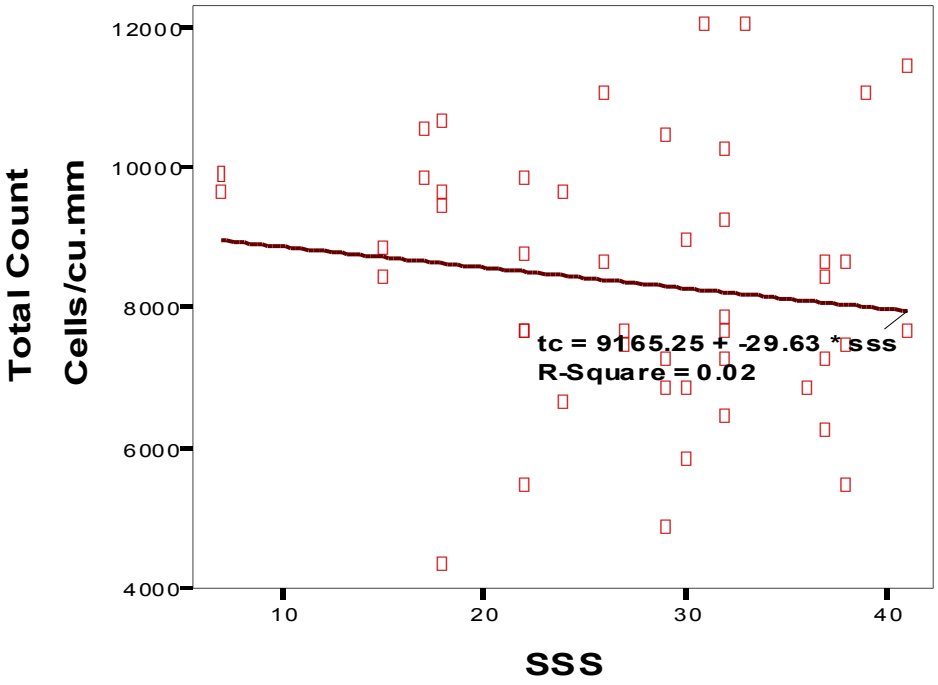


Fig.9 Correlation between Systolic blood pressure and SSS

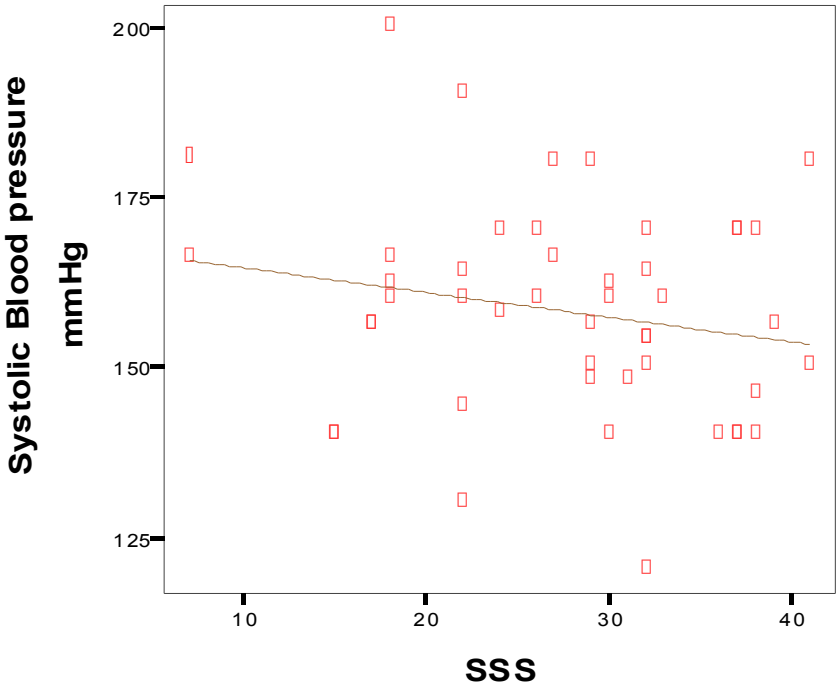


Fig.10 Correlation between Diastolic blood pressure and SSS

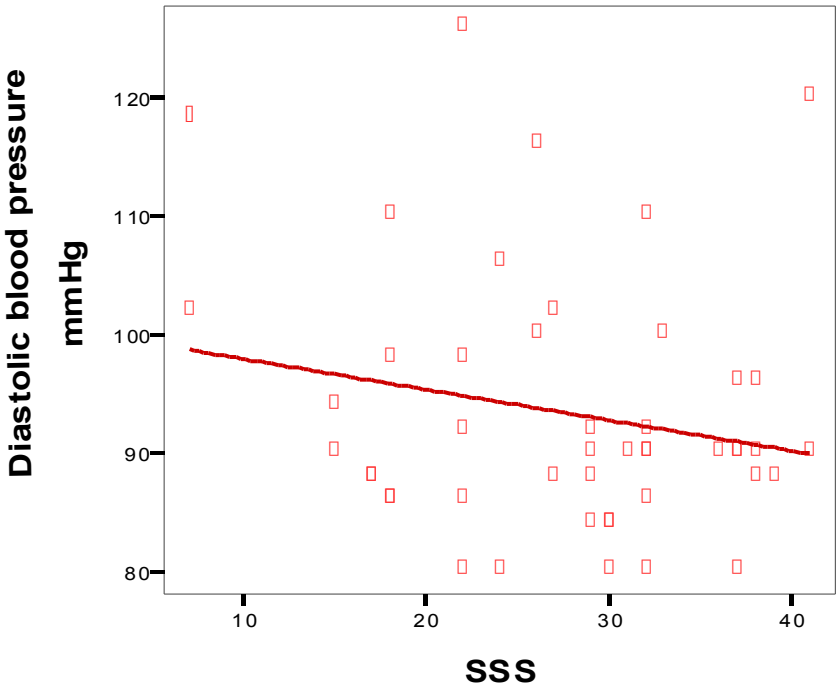


Fig.11 Correlation coefficients compared for SSS

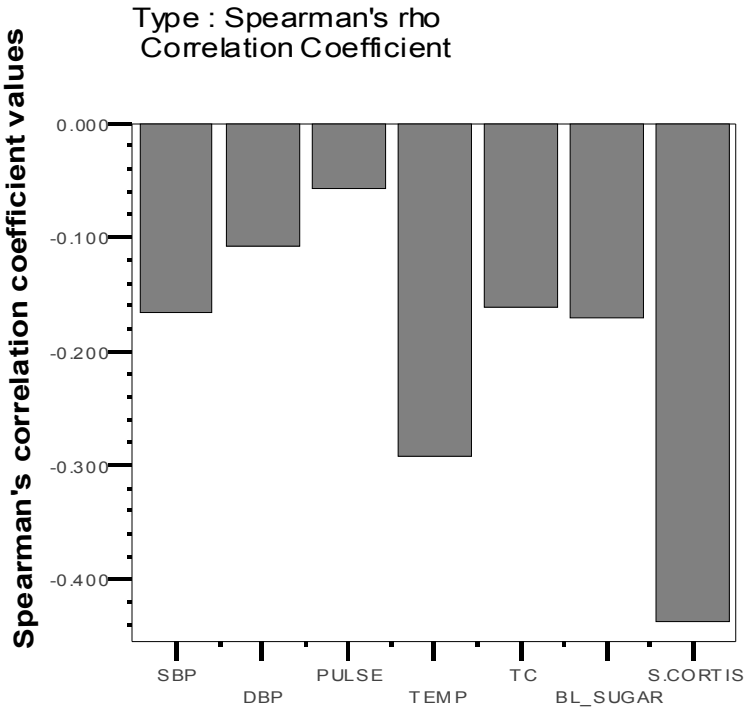
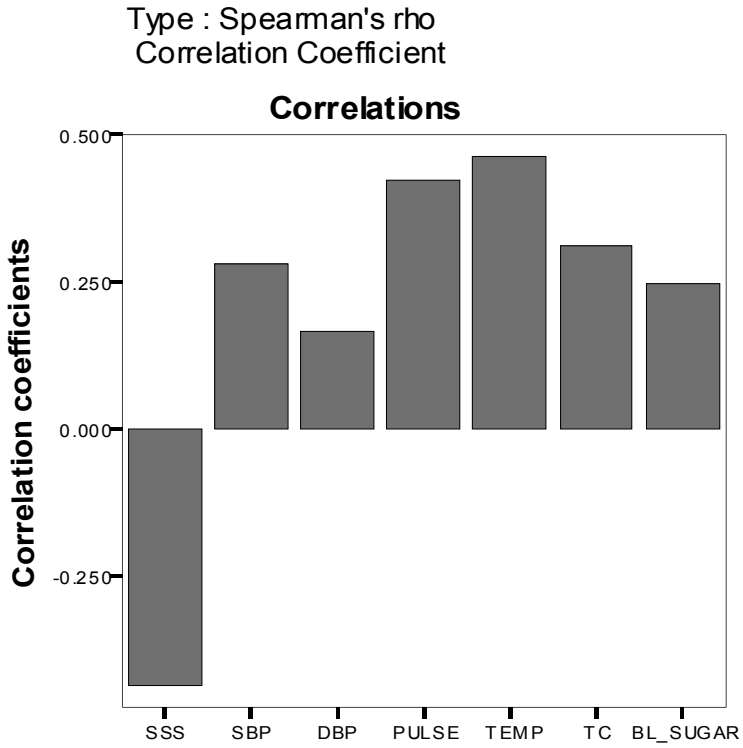


Fig.12 Correlation coefficients for Serum cortisol



DISCUSSION

In this study on Indian population involving 47 patients with stroke, we evaluated the relationship between serum cortisol level and stroke severity as assessed by Scandinavian stroke scale score. This study shows a statistically significant correlation between serum cortisol and stroke severity ($P<0.05$).

Earlier studies have shown that elevated serum cortisol is an indirect indicator of stroke severity. This is evident from our study that showed an inverse correlation between SSS scores which is inversely related to the stroke severity and increasing serum cortisol.

We also tried to show correlation between serum cortisol and other clinical and paraclinical parameters of relevance in stroke. The most significant correlation is between serum cortisol and temperature ($P=0.001$). There is also statistically significant correlation between serum cortisol with total WBC count ($P=0.032$) and pulse rate ($P=0.003$)

Eventhough earlier studies showed that blood glucose is related significantly to stoke severity and serum cortisol, in our study there is no significant correlation.

Although there is a direct correlation between stroke severity and both

systolic and diastolic blood pressure, statistical significance was not obtained (P= 0.266 and 0.469 respectively).

The limitation in our study is that ACTH, nor-adrenaline and adrenaline and other hormones involved in the stress response is not measured.

CONCLUSION

The following conclusions were derived from our study

1) High serum cortisol correlated with severity of stroke

2) High serum cortisol also correlated with pulse rate, body temperature and WBC count.

SCOPE OF FUTURE STUDIES

This study conducted in Indian population has significant observations and potential therapeutic implications. Still few questions remain unanswered. Although serum cortisol has been convincingly proved an independent indicator of severity of stroke, the exact pathophysiological mechanism of relationship has to be elucidated by further studies.

Estimation of other harmones involved in stress response such as ACTH, epinephrine, cytokines can be undertaken to correlate the severity of stroke.

Serum cortisol and stroke severity

Proforma

Name: Age&Sex: IP No.

Time duration: Presenting complaints:

LOC: Seizures: Fever: Others:

History

HTN DM PT BA IHD

CVA Seizures Smoking Alcoholism

General Examination

GCS: BP: PR: JVP: Temperature:

Cranial nerves: VII

CNS examination

SSS:

1. Consciousness
2. Orientation
3. Speech
4. Eye movements
5. Facial palsy
6. Gait
7. Arm power
8. Hand power

9. Leg power
10. Foot paresis

Investigations:

Blood Hb: TC: DC: ESR:

Blood Sugar: Urea: Creatinine: Electrolytes:

Lipid profile:

Serum cortisol:

USG abdomen:

ECG:

ECHO:

CT Brain:

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