DISSERTATION ON

SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN NON EMBOLIC ISCHEMIC STROKE

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THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

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for the award of the degree of

M.D. IN GENERAL MEDICINE

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THANJAVUR - 613 004

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

CHENNAI - 600 032

APRIL -2016

CERTIFICATE

This is to certify that this dissertation entitled "**SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN NON EMBOLIC ISCHEMIC STROKE**'' is the bonafide original work of **Dr.S.VISHNU PRASAD** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL - 2016. The period of the study was from June -2014 to May -2015.

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DECLARATION

I, **Dr.S.VISHNU PRASAD,** solemnly declare that dissertation titled **"SERUM URIC ACID – AN INDEPENDENT RISK FACTOR IN NON EMBOLIC ISCHEMIC STROKE".** is a bonafide work done by me at Thanjavur Medical College and Hospital during June 2014 to May 2015 under guidance and supervision of my unit chief **Prof.Dr.K.NAGARAJAN, M.D.,** Professor and head of the Department of Medicine.

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

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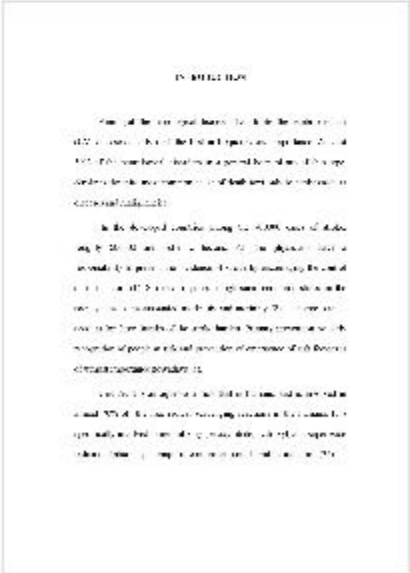

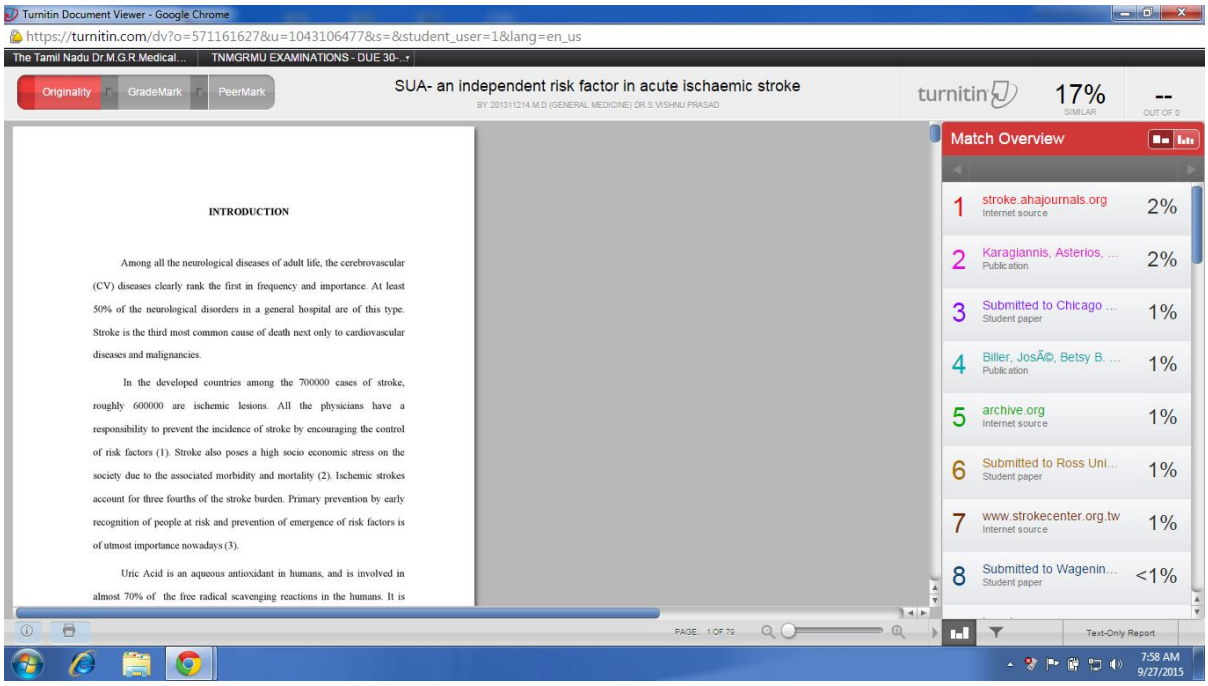
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INTRODUCTION
Among all the neurological diseases of adult life, the cerebrovascular (CV) diseases clearly rank the first in frequency and importance. At least 50% of the neurological disorders in a general hospital are of this type. Stroke is the third most common cause of death next only to cardiovascular diseases and malignancies.
In the developed countries among the 700000 cases of stroke, roughly 600000 are ischemic lesions. All the physicians have a responsibility to prevent the incidence of stroke by encouraging the control of risk factors (1). Stroke also poses a high socio economic stress on the society due to the associated morbidity and mortality (2). Ischemic strokes account for three fourths of the stroke burden. Primary prevention by early recognition of people at risk and prevention of emergence of risk factors is of utmost importance nowadays (3).
Uric Acid is an aqueous antioxidant in humans, and is involved in almost 70% of the free radical scavenging reactions in the humans. It is
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ABBREVIATIONS AND ACRONYMS

SUA	- Serum Uric Acid
HTN	- Hypertension
DM	- Diabetes Mellitus
Met S	- Metabolic Syndrome
CT	- Computerized tomography
Echo	- Echocardiogram
ECG	- Electrocardiogram
CVA	- Cerebro Vascular Accident
CV Risk	- Cardio Vascular Risk
NO	- Nitric Oxide
IR	- Insulin Resistance
IFG	- Impaired Fasting Glucose
IGT	- Impaired Glucose Tolerance

BACKGROUND AND OBJECTIVE :

Stroke is a major cause of mortality and morbidity throughout the world. Apart from the traditional risk factors of stroke many reports have suggested that hyperuricemia plays an important prognostic role in cerebrovascular accidents. The objective of this study was to evaluate the role of serum uric acid (SUA) as an independent risk factor for non-embolic ischemic stroke.

METHODOLOGY :

100 patients presenting with first episode of acute non-embolic ischemic stroke were included in the study. Patients with history of renal failure, gout, previous stroke and thiazide diuretic intake were excluded from the study. Patients presenting with hemorrhagic stroke and embolic stroke were also excluded from the study. SUA was measured using a standard analyzer. Patients were also evaluated for the presence of additional risk factors.

RESULTS :

The mean age of the study population was 59.84 years. Mean level of SUA in males was 5.39mg/dl and females was 5.51mg/dl. The mean SUA level was 6.10mgs/dl among diabetics and 4.86mgs/dl among non-diabetics showing a strong association ($p<0.05$) between SUA and diabetes mellitus. The mean SUA value for 40-49 yrs age group was 4.34 mg/dl while the elderly age group of above 70 yrs had a mean SUA value 6.65 mg/dl showing a strong association ($p<0.05$) between increasing age and SUA. A strong association was also found between SUA and cardiovascular diseases.

CONCLUSION :

This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischemic / non-embolic stroke in this study population. The association between elevated SUA and ischemic stroke may need to be considered especially when treating elderly patients, diabetics and the population with coronary artery disease. Lowering SUA level can be considered as one of the preventive modalities for stroke while treating high risk population.

KEYWORDS :

ischemic stroke, hyperuricemia, diabetes mellitus

INTRODUCTION

Among all the neurological diseases of adult life, the cerebrovascular (CV) diseases clearly rank the first in frequency and importance. At least 50% of the neurological disorders in a general hospital are of this type. Stroke is the third most common cause of death next only to cardiovascular diseases and malignancies.

In the developed countries among the 700000 cases of stroke, roughly 600000 are ischemic lesions. All the physicians have a responsibility to prevent the incidence of stroke by encouraging the control of risk factors (1). Stroke also poses a high socio economic stress on the society due to the associated morbidity and mortality (2). Ischemic strokes account for three fourths of the stroke burden. Primary prevention by early recognition of people at risk and prevention of emergence of risk factors is of utmost importance nowadays (3).

Uric Acid is an aqueous antioxidant in humans, and is involved in almost 70% of the free radical scavenging reactions in the humans. It is specifically involved in neutralizing peroxynitrite, hydroxyl, and superoxide radicals. It also plays a major role in prevention of lipid peroxidation (34).

During episodes of ischemic events and oxidative stress due to various causes the levels of local uric acid concentration elevates as a protective mechanism (64). During experimentation in animals uric acid levels were found to elevate substantially in response to adverse brain events (62). Such experiments in lab animals involving middle cerebral artery occlusion lead to a dramatic elevation of local Uric Acid levels, which remained elevated for a significant period of time following the event (63). These findings have invoked interest in the prognostic value and uses of elevated Uric Acid levels in the event of an acute ischaemic stroke.

The importance of serum uric acid (SUA) levels as an independent risk factor for stroke is being analyzed recently (4). Epidemiological research has provided substantial evidence that high SUA levels can predict the susceptibility for adverse cerebrovascular events like stroke (4-6). Recently therapeutic interventions with a SUA lowering effect have been proved to significantly decrease CV disease morbidity and mortality (8).

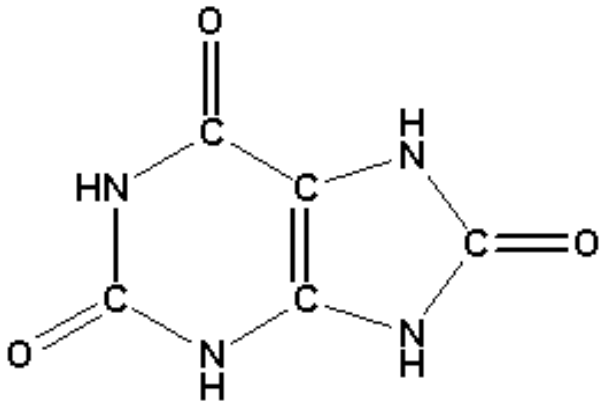
Diabetes mellitus confers a two fold to four fold higher risk of the incidence of an adverse vascular event including cerebro vascular accidents (10). This increased risk has only been partially attributed to the pathologic effects of diabetes on risk factors associated with hyperinsulinemia (10). SUA has been recently associated with insulin resistance (11). One study (10) indicates hyperuricemia is a useful predictor of cerebrovascular events in elderly diabetic patients independent of the remaining CV risk factors.

Though it has been recognised as an important risk factor for cerebrovascular events in many research studies (4-7), it is yet to be confirmed whether high SUA levels have an important role in the etiopathogenesis of Cerebrovascular disease or if it is just a co-incidental finding(12). Studies like NHANES I have provided data to support a positive association between SUA and stroke in middle age people, after accounting for other confounding factors (13).

So elevated SUA levels can be quite useful for predicting patients at risk for adverse cerebrovascular events and to start primary preventive measures(9).

REVIEW OF LITERATURE

URIC ACID



Uric Acid

Uric acid (C3H4N4O3:2,6,8 TRIOXY PURINE) is a weak organic acid ionised at position 9 with functional pKa in serum of 5.75. It is the final end product of purine metabolism in human beings. Uric acid has two forms depending on the pH. At the pH of 7.4 of most body fluids it exists as urate ion in the ratio of 50:1 to uric acid.

In acidic pH like urine at pH of 5.0 it is soluble and exist as uric acid. In serum the urate ion bind with the extracellular Na ion and forms monosodium urate.

Uric acid was first identified 200 years back. But its pathophysiologic aspects and functions in human beings is unclear.

Based on excretion of nitrogenous wastes organisms are classified as

1.ureotelic.

2.ammoniotelic.

3.uricotelic.

Ureotelic are those animals that excrete nitrogenous wastes in the form of urea. for example most of vertebrates. Ammoniotelic are the organisms that excrete NH4 ion and rely on aquatic environment for dilution of toxic substances. Uricotelic are those who excrete uric acid. For example primates,birds and reptiles.

Mammals other than primates oxidize uric acid to allantoic acid by the enzyme uricase. This allantoic acid is further processed to urea in bony fishes. This urea is still excreted in invertebrate aquatic organisms as NH4 ion.

When compared with lower invertebrate animals most of vertebrates and mammals are having high uric acid handling capacity and much increased urate level in blood. It may be a part of evolution as urate is a highly effective scavenger of reactive oxygen species and acts as an effective antioxidant. It may be one of the reasons for increased life span when compared with those of aquatic animals. Also excretion of uric acid doesn't need much of water when compared to its metabolite products. So

by excreting as such humans can conserve water. In humans the fractional excretion of uric acid is low.

Approximately 75% of uric acid is produced endogenously through cell breakdown and remaining 25% by dietary purines. Among these two third is excreted through kidney and one third through intestine.

Foods high in purine

Meat	Fish	Vegetables	Others
Liver	Anchovies	Peas	Mushrooms
Kidney	Herring	Legumes	Yeast
Heart	Sardines	Spinach	Nuts
Red meat	Mackerel	Lentils	Alcohol
Poultry	Shell fish	Beans	Beer
	Mussels	Asparagus	Wine
	Shrimp	Cauliflower	

Decreased purine intake for 10 days will reduce urate level in blood by 25% and in urine by 50%. Total serum urate level in men is 800-1500 mg and in women it is 500-1000mg. Diets rich in cow's milk and vit-c decrease uric acid.

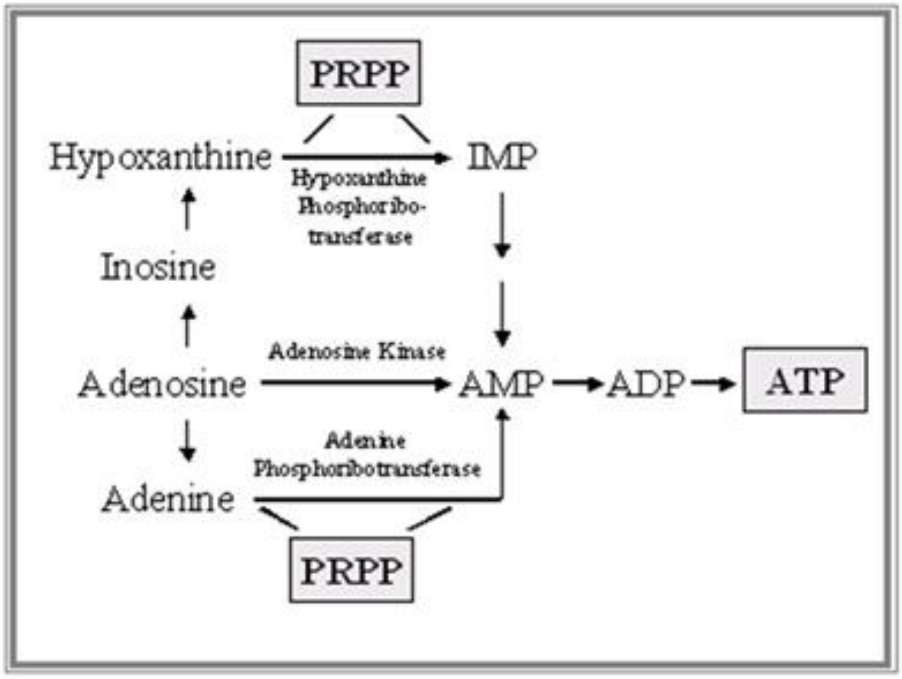
Endogenously there are two cycles of purine metabolism.

- De novo pathway
- Salvage pathway

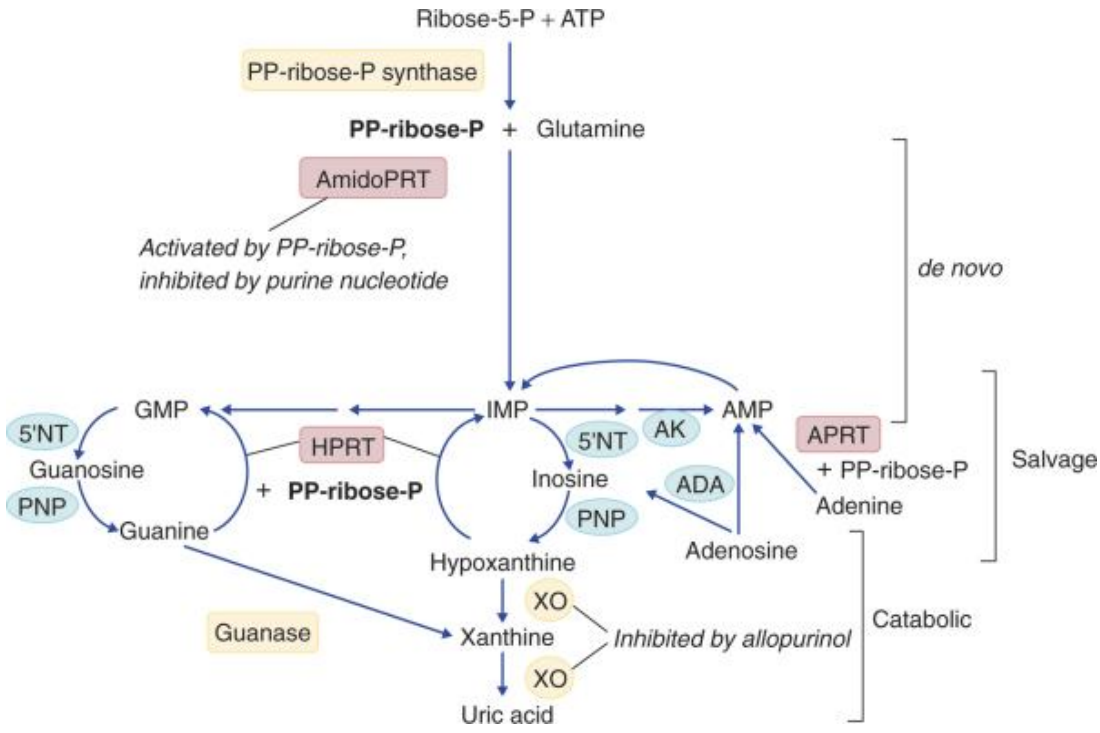
The important enzymes for clinical implications in these cycles are

1. Inosine mono phosphate
2. Adenosine deaminase
3. Hypoxanthine-guanine phosphor ribosyltransferase.

SALVAGE PATHWAY



DE NOVO PATHWAY OF PURINE SYNTHESIS



The synthesised purines are degraded by xanthine oxidase (which is the enzyme targeted by allopurinol) to uric acid. The enzyme xanthine oxidase is a molybdenum –pterin- ferrous sulphide- flavoprotein.

The formed uric acid is predominantly excreted by kidney. Uric acid undergoes 4 processes in kidney.

1.glomerular filtration

2.urate reabsorption

3.tubular secretion

4.post secretory reabsorption.

There are two important channels for urate transportation in the kidney.

Two of these transporters, glucose transporter 9 (GLUT9) and urate transporter 1 (URAT1), are members of the organic acid transporter (OAT) family and have strong effects on serum urate levels.

GLUT –9 transport:

GLUT-9 transporter is predominantly a product of SLC2A9 gene. It is a voltage dependent urate transporeter which mediates urate reabosrption.

It has two isoforms. GLUT-9L seen in basolateral side of proximal convoluted tubule and GLUT-9S in apical side. This GLUT-9 is the target for probenecid and benzbromarone and increase uric acid excretion. Different mutations of SLC2A9 cause renal hypouricemia.

As with URAT1, mediation of urate reabsorption by GLUT9 is inhibited by the uricosuric agents probenecid and benzbromarone.

GLUT9 is also expressed in the basolateral membrane of hepatocytes and regulates serum urate concentrations through dual roles in urate handling in the kidney and uptake in the liver. Mice with systemic “knockout” of GLUT9 have moderate hyperuricemia, massive hyperuricosuria, and early onset nephropathy. In contrast, specific inactivation of the GLUT9 gene in the liver of adult mice leads to severe hyperuricemia and hyperuricosuria, but without the renal disease.

GLUT9 also transports the sugars glucose and fructose, which may be pertinent to the dietary influences of these compounds on hyperuricemia and gout. A substantial role for GLUT9 in the physiologic regulation of serum or plasma urate levels is further suggested by the results of genome-wide association and candidate gene studies. Such studies show that the SLC2A9 locus and certain polymorphisms are associated with an increased risk for hyperuricemia and gout. Different mutations of SCL2A9 have also been linked with renal hypouricemia, particularly in patients with intact URAT1.

URAT-1 transporter:

This transporter is highly specific for uric acid. It can transport uric acid in both directions across the tubular membrane depending on the uric acid concentration. It is a product of SLC22A12 gene and belongs to OAT family. This channel is also seen in the apical membrane of proximal convoluted tubules. It is also inhibited by uricosuric drugs like probenecid. Mutation in the gene encoding Urat-1 transporter causes hyperuricosuria, hypouricemia

URAT1 is encoded by the SLC22A12 gene and has a typical OAT structure. URAT1 is highly specific for urate. It mediates the exchange of urate for a variety of endogenous and drug anions known to affect renal uric acid transport.

URAT1 can transport urate in either direction across the tubular cell membrane, depending on the relative concentrations of urate and other ions on each side of the membrane. Like GLUT9S, URAT1 localizes to the apical brush border membrane of proximal tubular epithelial cells.

URAT1 is important in the renal regulation of serum urate levels in normal individuals. The uricosuric drugs probenecid, benzbromarone, and lesinurad increase urate excretion by inhibiting URAT1 and other OATs. Urate transporters may also play other roles in urate metabolism, for example, in the transport of urate across hepatic cell membranes.

URAT1 interacts with the scaffolding protein PDZK1. PDZ motifs are typically involved in the protein-protein interactions that support intracellular signaling and are also present in other urate transporters, including OAT4 and NPT1 . This suggests that a more extensive multiprotein complex the “urate transportasome,” which contains transport regulatory molecules, hormone receptors, and intracellular signaling elements may be involved in regulated bidirectional transport of urate across the renal tubular epithelial cell.

Fractional renal excretion of urate (FEua = uric acid clearance/creatinine clearance × 100) in URAT1 knockout mice remains substantially less than 100%. This confirms that there are multiple mechanisms of uric acid reabsorption.

Other urate transporters:

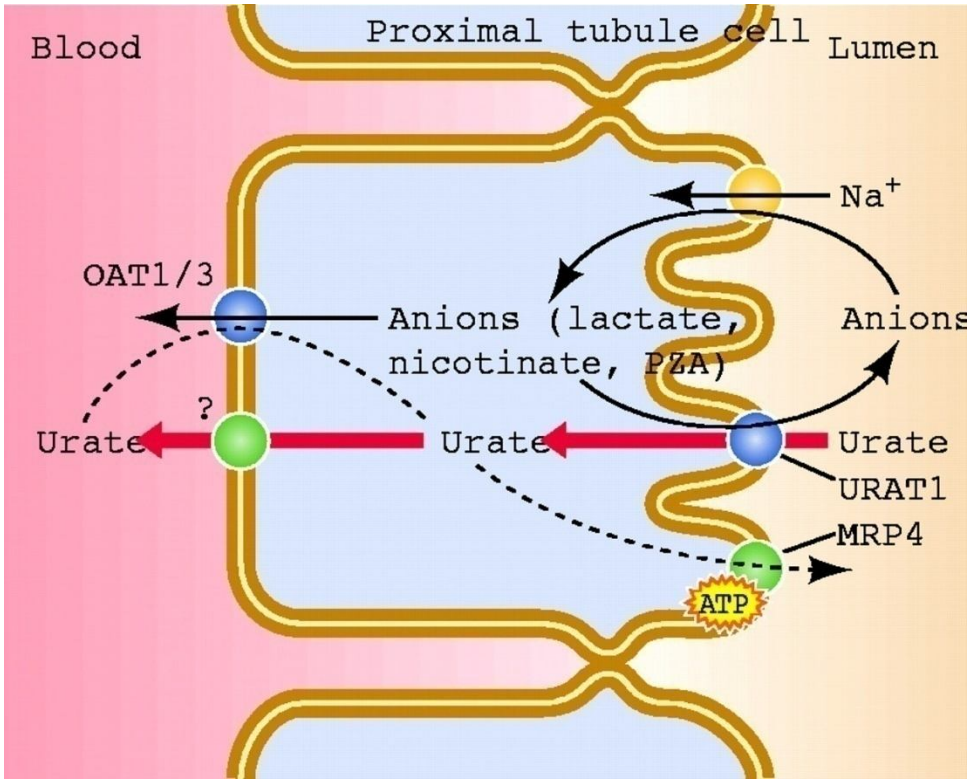
1.ABCG 2

2.NPT 1 and NPT 4

3.OAT 4

4.OAT 10.

URATE TRANSPORTERS IN THE KIDNEY



STROKE (68)

A stroke (Struck by the Hand of God) or cerebrovascular accident (CVA) is defined as the abrupt onset of a neurological deficit that is attributable to a focal vascular cause. The clinical manifestations of stroke are highly variable because of the complex anatomy of brain and its vasculature.

Cerebral ischaemia is caused by a reduction in blood flow that lasts longer than several seconds. Neurological symptoms manifest within seconds because neurons lack glycogen, so energy failure is rapid. A TIA or transient ischemic attack is a temporary sudden onset neurological deficit due to focal ischemia of brain for a duration of less than 24 hours. If the ischemia and deficit lasts for a period more than 1 hour, it may probably be due to small infarctions. Stroke has occurred if the neurological signs and symptoms last for >24hrs.

Focal ischaemia or infarction is usually caused by thrombosis of cerebral vessels themselves or by emboli form a proximal arterial source or the heart. Cerebral hemorrhage produces neurological symptoms by producing a mass effect of neural structures or from the toxic effects of blood itself.

CEREBRAL BLOOD FLOW (68)

- Gray matter – 75ml / 100gm / min
- White matter – 30 ml / 100gm / min
- Oxygen consumption – 3.5ml /100gm /min
- Glucose utilization – 5 mg / 100 gm / min

Brain store of glucose lasts only for 2 min after cessation of blood flow. The oxygen stores last only for 8 to 10 sec after cessation of blood flow.

A fall in blood flow to zero causes death of brain tissue within 4 to 10 min. Tissue surrounding the core region of infarction is ischemic but reversibly dysfunctional and is referred as the ischemic penumbra. The ischemic penumbra will eventually undergo infarction if reperfusion is not achieved and hence saving the ischemic penumbra is the goal of thrombolytic therapy.

RISK FACTORS FOR STROKE

Major risk factors (14):

The most important established risk factor for stroke is AGE, and second is probably HYPERTENSION. Additional well established risk factors are

1. Gender (male > female)	7. Carotid bruits
2. Family history	8. Smoking
3. Diabetes mellitus	9. Increased haematocrit
4. Cardiac disease	10. Elevated fibrinogen level
5. Prior stroke	11. Haemoglobinopathy
6. Transient Ischemic attacks	12. Drug abuse such as cocaine

Other risk factors (15):

1. hyperlipidemia 2. Diet 3. Oral contraceptives 4. Sedentary life style 5. Obesity 6. Peripheral vascular disease 7. Hyperuricemia 8. Infections	9. Homocystinemia 10. Migraine 11. Race 12. Geographic location 13. Season and climate 14. Type A personality 15. Alcohol consumption

Clinical presentation

Among all the neurologic diseases of adult life, stroke ranks first in frequency and importance. The common mode of expression of stroke is a relatively sudden occurrence of a focal neurologic deficit. Strokes are broadly categorized as ischemic or hemorrhagic. Ischemic stroke is due to occlusion of a cerebral blood vessel and causes cerebral infarction. The resultant neurologic syndrome corresponds to a portion of the brain that is supplied by one or more cerebral vessels.

Ischaemic and haemorrhagic stroke cannot be differentiated based on history. But haemorrhagic usually presents with features of increased intracranial tension (nausea, vomiting, and headache). Seizures can occurin up to one-fourth of hemorrhagic strokes whereas it is not as common in ischaemic stroke. Symptoms of meningeal irritation can also occur due to bleeding into the ventricles after a haemorrhagic stroke and can mimic acute meningitis . Four types of stroke syndromes are commonly seen following involvement of certain vascular distributions.

Anterior cerebral artery

ACA infarction usually presents with weakness on the contralateral side of the body predominantly involving the legs and, to a lesser extent, the arm. Such a pattern is usually seen when the hemispheric branches of ACA

are involved. The presentation of ACA infarction depends on the involved site and collateral blood flow. Other features are lack of motivation, akinetic mutism in medial frontal lobe involvement, transcortical aphasia usually when the dominant lobe is involved, deviation of the head and eyes toward the side of the lesion, paratonia (involuntary variable resistance during passive movement), disturbances of memory and emotions, loss of proprioceptive sensation in the legs, and bladder disturbances (due to paracentral lobule involvement).

Involvement of the branches supplying corpus callosum leads to apraxia, agraphia, and tactile anomia of the left hand. The artery of Heubner supplies the anterior limb of the internal capsule. Involvement of this artery can cause a pure motor weakness of the face and arm on the involved side. A Disconnection syndrome occurs when the communicating white fibres of the corpus callosum are involved and manifests as left ideomotor apraxia and left hand agraphia . Involvement of the inferior branches of ACA causes memory disturbances and behavioural abnormalities.

Middle cerebral artery

The clinical presentation of MCA territory infarct depends on whether the stem of the artery, superior branch, inferior branch, or lenticulostriate arteries are involved. Collateral circulation plays a major role in the presentation of a MCA stroke.

An MCA stem lesion and upper-division MCA infarction can be differentiated by the fact that the face and arm are more involved in the hemiparesis compared to the leg when the upper division is involved. Broaca's (motor) aphasia occurs when of the anterior branches of the upper-division are occluded resulting in disturbances of blood flow in the inferior frontal lobe.

If the stem of the MCA is involved, it causes a large hemispheric infarction. It presents clinically as hemianesthesia, homonymous hemianopia contralateral hemiplegia and horizontal deviation of the eyes ipsilaterally to the involved side. When the dominant hemisphere infarction occurs it causes global aphasia. Non-dominant lobe involvement presents as unilateral hemineglect.

When the lower-division of MCA is involved, a Wernicke's (sensory) aphasia is seen when the dominant hemisphere undergoes infarction. Occlusion of the lenticulostriate branches may cause a of pure motor hemiparesis. Such lacunar infarcts are common when the internal capsule is involved. Infarction of the nondominant lobe causes behavioural disturbances. Homonymous hemianopia can occur if the optic tracts are involved.

Gerstmann syndrome is characterized by right-left disorientation, finger agnosia, acalculia, and agraphia. It is usually seen when inferior parietal lobe (dominant) is affected. A contralateral inferior quadrantanopia can occur when either hemisphere is involved. Alexia and agraphia can

occur with angular gyrus and supra-marginal gyrus involvement usually when the left side is involved.

Posterior cerebral artery

The clinical features of PCA infarct is based on the site of occlusion. (1) P1 syndrome – when the proximal segment and its penetrating branches are involved (2) P2 syndrome – when the occlusion is distal to the site of joining of PCA with posterior communicating artery. P1 segment occlusion causes lesions in the midbrain, thalamus, and hemispheres . It mainly involves posterior choroidal and thalamogeniculate arteries. P2 segment occlusion causes temporal and occipital lobe infarction.

Involvement of the hemispheral branches causes contralateral homonymous hemianopia. It occurs because of the infarction of striate cortex, optic radiation and the lateral geniculate body. A third nerve palsy with contralateral ataxia also known as Claude's syndrome can occur. If it is associated with contralateral hemiplegia then it is known as Weber's syndrome

The Dejerine-Roussy syndrome occurring in thalamic infarction manifests as contralateral hemisensory loss and a severe burning pain in the affected areas. Bilateral proximal PCA occlusion causes extensive infarction of the midbrain and sub-thalamus leading to coma, unreactive pupils, bilateral pyramidal signs, and decerebrate rigidity.

Most common visual changes are visual hallucinations, visual and color agnosias and prosopagnosia. Anton's syndrome and Balint syndrome are seen in bilateral PCA infarcts. Ataxia and contralateral hemiballismus may also occur indicating involvement of red nucleus and subthalamic nucleus respectively.

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Vertebrobasilar artery

The vertebral artery arising from the subclavian artery has four segments. The first segment extends from its origin to the sixth transverse vertebral foramen. The second segment extends from the C6 to C2 vertebral foramen. The third segment pierces the dura at the foramen magnum. The fourth segment joins the vertebral artery of the opposite side to form the basilar artery. The various manifestation depend on the segment involved.

Superior cerebellar artery involvement causes ipsilateral cerebellar ataxia, dysarthria and loss of pain and temperature sensation over the contralateral half of the body and face (spinothalamic and trigeminothalamic tract) . Horner's syndrome and palatal myoclonus are also observed.

PICA (posterior inferior cerebellar artery) involvement causes cerebellar infarctions. When the medial branch is involved the clinical signs and symptoms are vertigo, ataxia, and nystagmus due to dysfunction of the vermis and vestibular system. When the lateral branch is involved it causes

vertigo, gait ataxia, limb ataxia, nausea, gaze palsies and dysarthria due to dysfunction of the cerebellar hemispheres.

The AICA (Anterior inferior cerebellar artery) occlusion causes ipsilateral deafness, facial weakness, tinnitus, vertigo and paresis of conjugate lateral gaze because of infarction of the vestibular nuclei present in the ventral portion of cerebellum.

Locked-in syndrome is a state of preserved consciousness with quadriplegia, aphonia, and cranial nerve involvement due to bilateral pontine or midbrain infarction.

Lateral Medullary Syndrome (Wallenberg syndrome) can be caused by occlusion of the PICA. It is characterized by pain, numbness, and impaired sensation over the ipsilateral face, ipsilateral Horner's syndrome, ipsilateral ataxia, dysphagia and loss of pain and temperature sensation in the contralateral half of the body.

Massive infarctions involving the vertebro-basilar systems can cause altered consciousness or confusion by causing cytotoxic edema and brainstem compression. Hydrocephalus and brainstem herniation are rare and fatal complications.

The Major Causes of Cerebral Vascular Occlusion and Ischemic Stroke

Two major causes of ischaemic stroke are:

1. atherosclerotic thrombotic disease of the cerebral or extracerebral vessels and
2. cerebral embolism.

Atherothrombosis :

The evolution of clinical phenomena in cerebral thrombosis, both of large intracranial (basilar, carotid) or extracranial (carotid, vertebral) and small vessels (lacunes), is more variable than that of embolism and hemorrhage.

The thrombotic stroke presents clinically in various ways. It may present completely at once or it may evolve over a period of time (minutes to hours). Such type of presentation is also called as a "stuttering" or evolving stroke. Rarely the thrombotic stroke may progress over a few days time.

Also characteristic of atherothrombotic events in many, but not all cases, is the occurrence of the stroke during sleep; the patient awakens paralyzed, either during the night or in the morning. Unaware of any difficulty, he may arise and fall helplessly to the floor with the first step.

Atheromatous plaques preferentially form at branching points and curves of the cerebral arteries. The most frequent sites are

(1) in the internal carotid artery; at its origin from the common carotid;

(2) in the cervical part of the vertebral arteries and at their junction to form the basilar artery;

(3) in the stem or at the main bifurcation of the middle cerebral arteries;

(4) in the proximal posterior cerebral arteries as they wind around the midbrain;

(5) in the proximal anterior cerebral arteries as they pass anteriorly and curve over the corpus callosum.

The last two sites are far less frequent than the first three.

Atherothrombosis may cause cerebral infarction in several ways. The most obvious is that an occlusive plaque or a thrombus formed on a plaque occupies the lumen of a major intracerebral vessel, such as the middle cerebral artery, and stops flow to the areas of the brain supplied by the vessel.

A variation of this mechanism is one of occlusion by atherosclerosis of a more proximal vessel, such as the distal carotid artery. This leads to infarction in the territory between major branches of the internal carotid circulation that are most susceptible to reduced blood flow-termed "watershed infarction."

Or, an atherothrombotic lesion in a proximal vessel may serve as the nidus for the formation of an embolus that manifests itself as a stroke in one of the territories of that vessel-called "artery-to-artery" embolism.

Cerebral Embolism

This is the most common cause of ischemic strokes Although the abruptness with which the stroke develops and the lack of prodromal symptoms point strongly to embolism, the diagnosis is based on the total clinical circumstances. Embolism always merits careful consideration in young persons, in whom atherosclerosis is less common. Only occasionally does the problem unfold more gradually, over many hours, with some fluctuation of symptoms. Possibly, in these cases the embolus initiates a propagating thrombotic process in the occluded vessel.

In most cases, the embolic material consists of a fragment that has broken away from a thrombus within the heart ("cardioembolic"). Somewhat less frequently, the source is intra-arterial from the distal end of a thrombus within the lumen of an occluded or severely stenotic carotid or vertebral artery, or a clot that originates in the systemic venous system and passes through an aperture in the heart walls, or the origin of an embolus may be from large atheromatous plaques in the aorta.

Thrombotic or infected material (endocarditis) that adheres to the aortic or mitral heart valves and breaks free are also well-appreciated sources of embolism, as are clots originating on prosthetic heart valves. Embolism caused by fat, tumor cells (atrial myxoma), fibrocartilage, amniotic fluid, or air enters into the differential diagnosis of stroke only in special circumstances

The embolus usually becomes arrested at a bifurcation or other site of natural narrowing of the lumen of an intracranial vessel. The resultant infarction is pale, hemorrhagic, or mixed; hemorrhagic infarction nearly always indicates embolism (although venous occlusion can do the same). Any region of the brain may be affected, the territories of the middle cerebral artery, particularly the superior division, being most frequently involved. The two cerebral hemispheres are approximately equally affected.

Large embolic clots can block large vessels (e.g., the carotid arteries in the neck or at their termination intracranially), while tiny fragments may reach vessels as small as 0.2 mm in diameter, usually with inconsequential effects. The embolic material may remain arrested and plug the lumen solidly, but more often it breaks into fragments that enter smaller vessels so that even careful pathologic examination fails to reveal their final location. In this instance, the clinical effects may abate. Because of the rapidity with which embolic occlusion develops, useful collateral influx does not become established. Thus, sparing of the brain territory distal to the site of occlusion is usually not as evident as in thrombosis that develops more slowly.

Several scoring systems have been developed to gauge the future likelihood of stroke from atrial fibrillation. The $CHADS_2$ and related systems are shorthand methods to quantitate the risk factors that modulate risk for stroke in a patient with atrial fibrillation. A refinement of this system, CHADS2-VASc is purported to improve these predictions but the

confidence intervals around the point estimates of predictive values in both scales are considerable and clinical judgment must be exercised in their use.

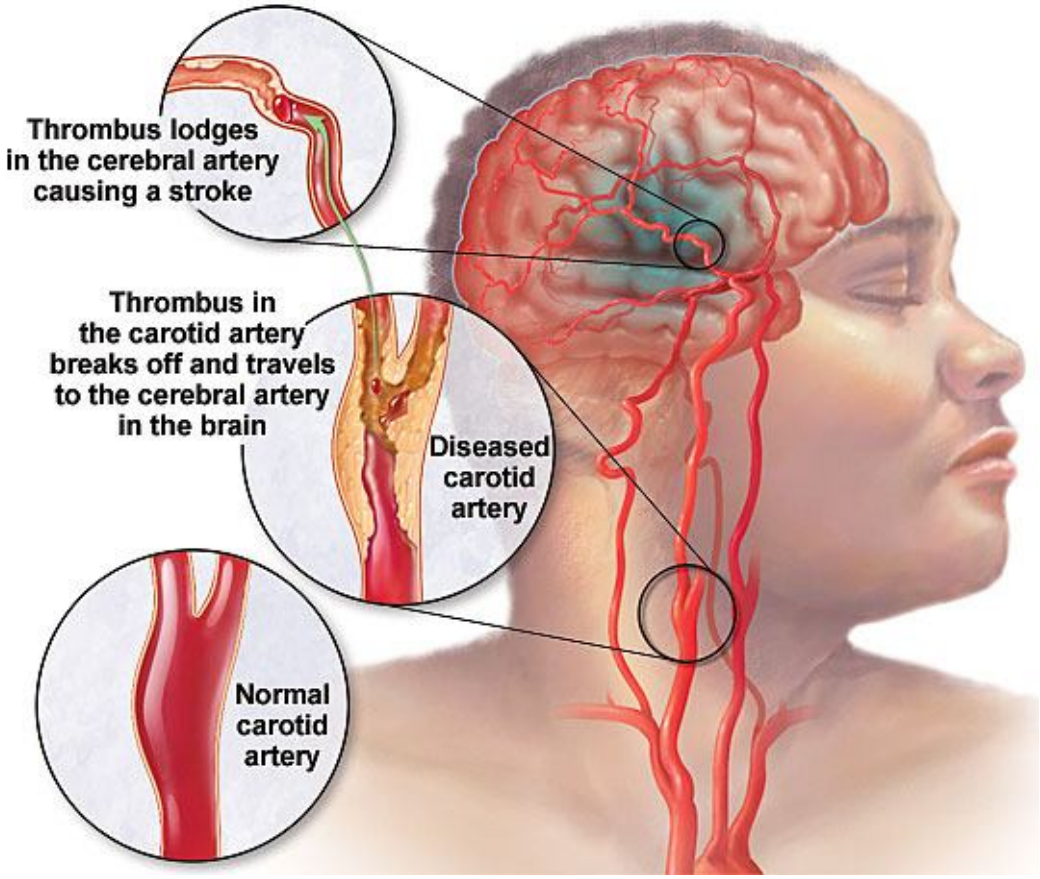
Another source of embolism is the carotid or vertebral artery, where clot forming on an ulcerated atheromatous plaque may be detached and carried to an intracranial branch (artery-to-artery embolism).

Atheromatous plaques in the ascending aorta have been recognized to be a more frequent source of embolism than had been previously appreciated. Amarenco and colleagues reported that as many as 38 percent of a group of patients with no discernible cause for embolic stroke had echogenic atherosclerotic plaques in the aortic arch that were greater than 4 mm in thickness, a size found to be associated on a statistical basis with strokes.

The migrating or traveling embolus syndrome is most evident in cases of posterior cerebral artery occlusion, either from a cardiogenic source or from a thrombus in the proximal vertebral artery ("artery-to-artery" embolism). Minutes or more before the hemianopia develops, the patient reports fleeting dizziness or vertigo, diplopia, or dysarthria, the result of transient occlusion of the origins of penetrating vessels as the clot material traverses the basilar artery.

Paradoxical embolism occurs when an abnormal communication exists between the right and left sides of the heart (particularly a patent foramen ovale [PFO]) or the alternative route of connection via a pulmonary arteriovenous fistula. Embolic material arising in the veins of the lower

extremities or pelvis or elsewhere in the systemic venous circulation bypasses the pulmonary circulation and reaches the cerebral vessels. Pulmonary hypertension (often from previous pulmonary embolism) favors the occurrence of paradoxic embolism, but these strokes occur even in the absence of pulmonary hypertension.



PATHOPHYSIOLOGY OF STROKE (1)

Cerebral infarction basically comprises two pathophysiologic processes.

1. Loss in the oxygen delivery and nutrient supply due to vascular occlusion.
2. Alterations in the metabolic processes within the neurons resulting in cell death.

Vascular Factors:

In several animal species including macaque monkeys and gerbils the critical level of cerebral blood flow was 23ml / 100gm / min; if, after short periods time, CBF is restored to higher levels the impairment of function can be reversed. Reduction of CBF below 10 to 12 ml / 100 gm / min causes infarction regardless of duration. The critical level of hypoperfusion that abolishes function and leads to tissue damage is therefore a CBF between 12 to 23 ml / 100gm / min. At this level EEG is slowed and below this level it becomes isoelectric. These biochemical abnormalities are reversed if the circulation is restored to normal level. Disturbance of calcium ion homeostasis and accumulation of free fatty acids interfere with full recovery. A CBF of 6 to 8 ml / 100 gm / min causes marked ATP depletion, increase in extra cellular $K^{+,}$ increase in intracellular calcium and cellular acidosis, leading invariably to histological signs of necrosis. Free fatty acids are activated and destroy the phospholipids of neuronal membranes.

Prostaglandins, leukotrienes and free radicals accumulate and intracellular proteins and enzymes are denatured.

Penumbra zone exists at the margin of an infarction and the degree of irreversible tissue damage is difficult to determine. The neurons in this zone is considered to be “stunned” by ischemia and this tissue is potentially recoverable if appropriate interventions are undertaken to restore blood flow. As with infarction, the duration of ischemia plays a role. Some studies show that maintaining the systolic BP or modifying the rheological flow of blood within the vascular system by haemodilution alters the perfusion in a desirable manner

Metabolic Factors:

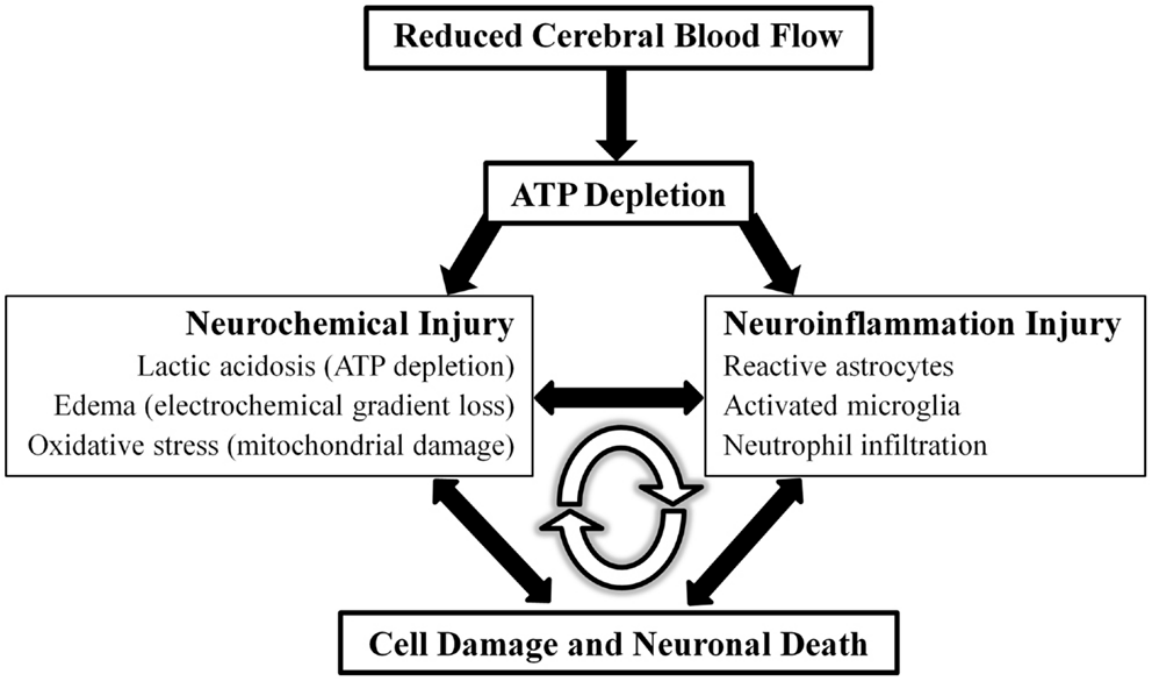
Focal cerebral infarction occurs via two ways

(1) a necrotic pathway in which cellular cytoskeletal breakdown is rapid due principally to energy failure of the cell

(2) an apoptotic pathway in which cells become programmed to die.

Ischemia produces necrosis by starving neurons of glucose and oxygen, which in turn results in failure of mitochondria to produce ATP. Without ATP, membrane ion pumps stop functioning and neurons depolarize, allowing intraıellular calcium to rise. Cellular depolarization also causes glutamate release from synaptic terminals; excess extracellular glutamate produces neurotoxicity by activating postsynaptic glutamate receptors that increase neuronal calcium influx.

Free radicals are produced by degradation of membrane lipids and mitochondrial dysfunction. Free radicals cause catalytic destruction of membranes and likely damage other vital functions of cells. Lesser degrees of ischemia, as are seen within the ischemic penumbra, favor apoptotic cellular death causing cells to die days to weeks later.



Neuroimaging in Stroke:

Plain CT Brain is done for all patients presenting with stroke to differentiate between ischaemic and hemorrhagic stroke. It is also useful to rule out intracranial mass lesions or neoplasms that can present with neurological deficits and masquerade as a stroke. When involvement of the posterior circulation is suspected in cases presenting with brainstem and cerebellar symptoms, CT should include fine cuts through the posterior fossa.

MRI is better than CT in detecting cerebral vascular diseases. MRI is superior particularly in cases involving the posterior circulation and lacunar infarcts. Another notable advantage is that MRI can rapidly detect the "ischemic penumbra" and guide decisions regarding therapeutic intervention.

The tissue water content is very useful to differentiate infarction from other lesions. Diffusion weighted images help in differentiating between acute and chronic stroke.

Features of an Early Stroke in CT Scan:

- Loss of gray/white-matter differentiation (insular-ribbon sign)
- Dense MCA sign (the horizontal part of MCA appears dense)
- Obscuration of the lentiform nucleus,
- Effacement of the sylvian fissure
- Midline shift because of cerebral oedema

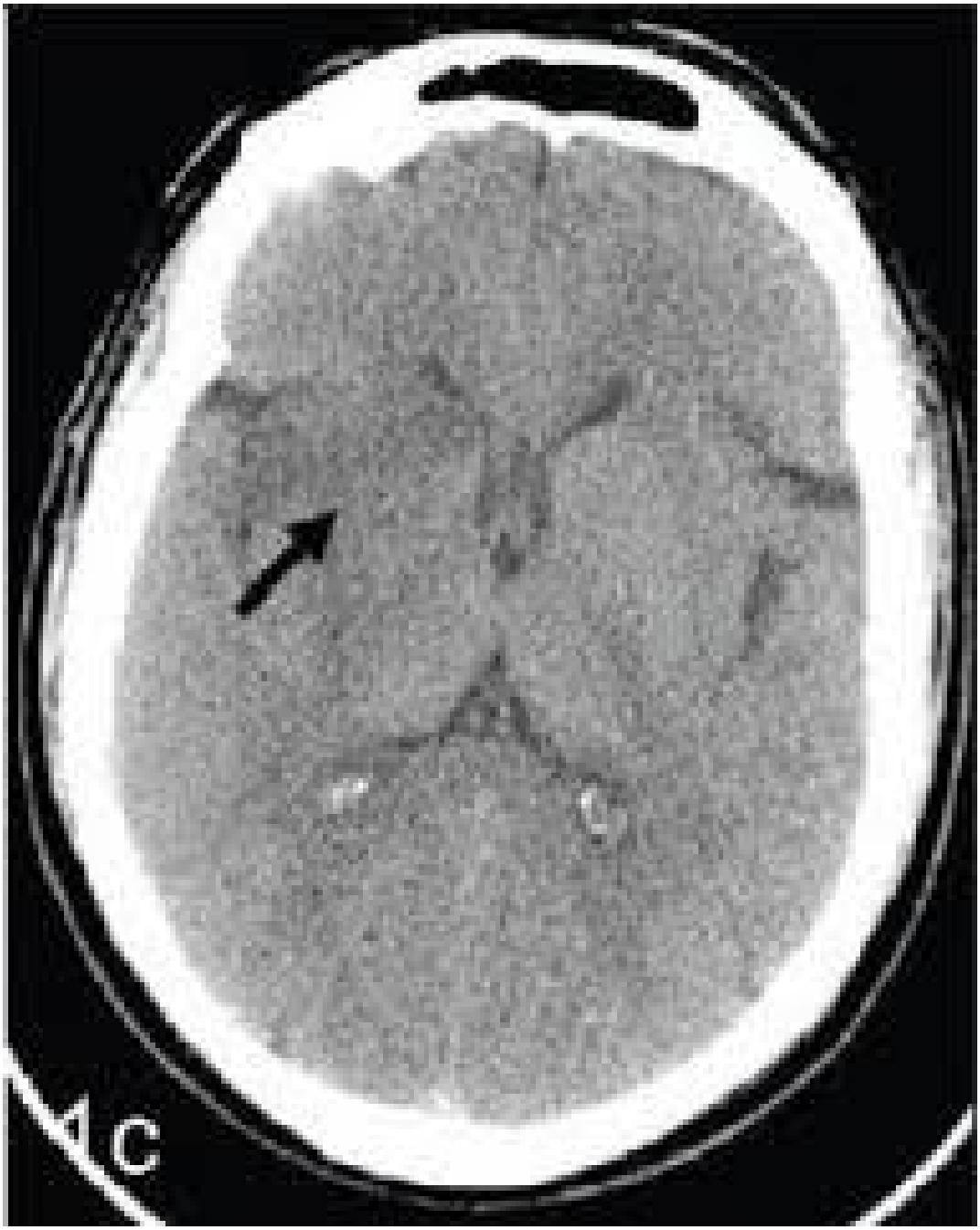


Fig 1: CT scan showing insular ribbon sign

Black arrow shows the loss of grey/white matter differentiation at the insula

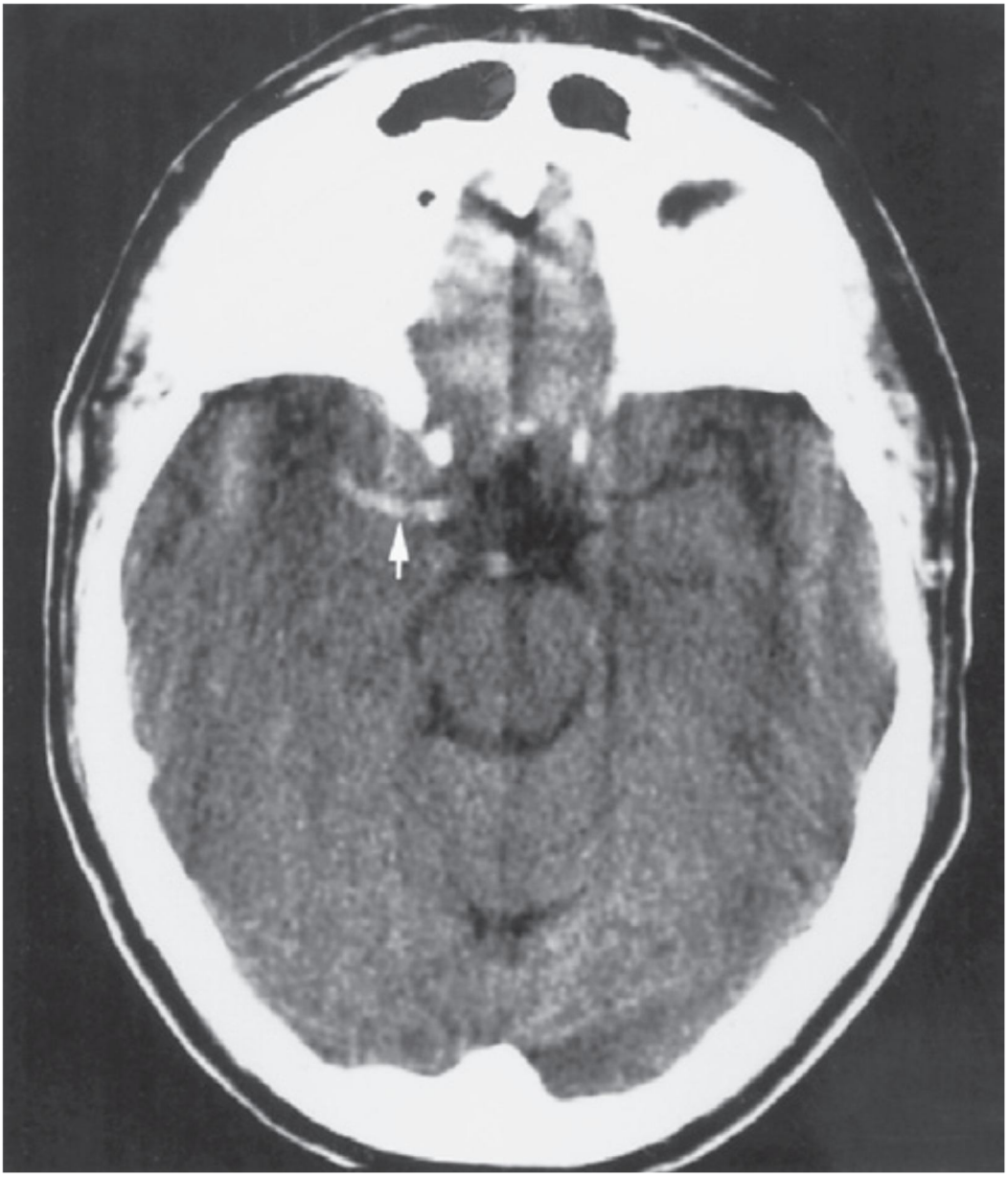


Fig 2: CT scan showing hyperdense MCA sign

White arrow shows the hyperdense horizontal portion of middle cerebral artery

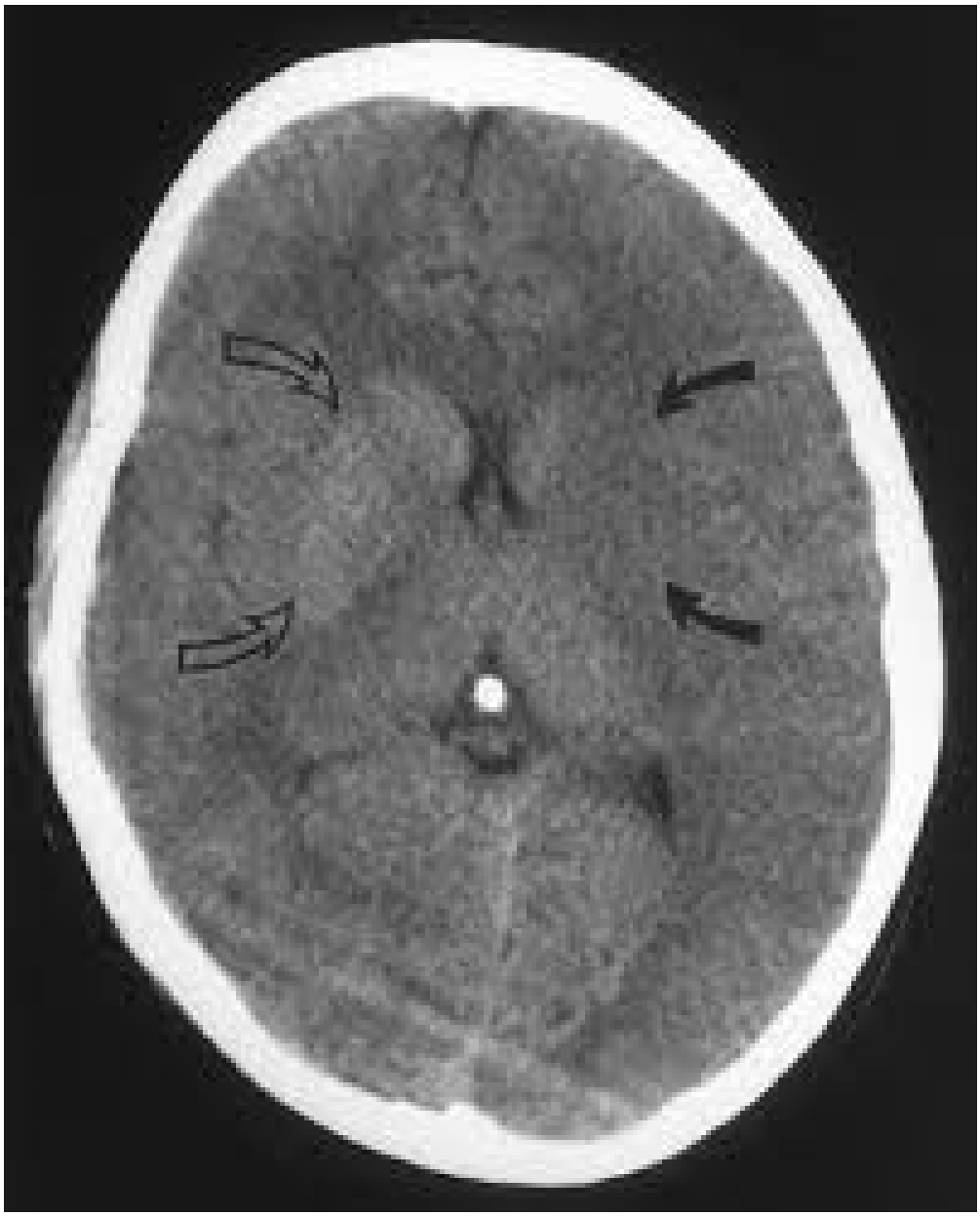


Fig.3 CT scan showing obscuration of lenticular nucleus

The filled black arrows show the ill-defined borders of the lenticular nucleus

SUA AND PATHOGENESIS OF STROKE

The mechanism by which uric acid causes stroke could be explained by experimental evidences. The possible mechanisms are as under.

SUA AND HYPERTENSION:

1. Increased SUA level precedes hypertension in one-fourth of newly diagnosed hypertension cases (21).
2. Hypertension leads to low renal perfusion which in turn causes uric acid reabsorption thereby leading to hyperuricemia (22).
3. Increased uric acid levels also caused elevated blood pressure in rats by a mechanism linked to inhibition of nitric oxide (NO), activation of rennin – angiotensin system, and development of renal arteriosclerosis (23). Once the renal arteriosclerosis develops, the kidney plays a major role in the maintenance of hypertension, and lowering the UA is no longer protective (24).
4. High uric acid level in rats cause kidney damage by mechanisms other than crystal deposition (23) and worsen pre-existing kidney damage (25).
5. UA also increases the production of cytokines like monocyte chemoattractant protein – 1 (MCP-1) from smooth muscle cells in the

blood vessels (26) and is a precursor for chemotaxis and inflammation in the blood vessels leading to atherosclerosis (27).

SUA AND FREE RADICAL MEDIATED OXIDATIVE DAMAGE – CEREBRAL ISCHEMIA

1. Cerebral infarction leads to multiple pathogenic processes in the surrounding tissue and free – radical – mediated oxidative damage plays a key role in the pathogenesis of cerebral ischemia (28). Free radicals are liberated from a variety of sources, including inflammatory cells, dysfunctional mitochondria and excitotoxic mechanisms stimulated by increased glutamate and aspartate concentrations (29).
2. Hydroxyl radicals, peroxy-nitrite and superoxide, are free radicals that can cause lipid peroxidation, a self – propagating chain reaction that irreversibly damages plasma and mitochondrial membranes (30). Products of lipid peroxidation irreversibly disrupt enzymes, receptors, and membrane transport mechanisms. The generation of local oxidants augments local injury and increases infarct size (28).
3. UA is the most abundant aqueous antioxidant in humans and may serve a protective physiologic role by preventing lipid peroxidation (34). It might therefore be expected that having elevated SUA levels during a stroke would be beneficial. Stroke is associated with a rapid decrease in serum antioxidants (31,32) and patients with lower plasma antioxidants

at the time of acute stroke have a poorer outcome (33). However, only one study has reported that high SUA levels may be neuroprotective in patients with acute stroke (35), three other large series found the opposite (6,7,9).

A probable explanation for this is that UA which usually functions as an aqueous antioxidant becomes pro-oxidant in conditions where other antioxidants like ascorbic acid are reduced (36). So a fall in ascorbic acid levels can cause SUA to become a pro-oxidant in patients affected by stroke. This hypothesis is proved by the observation that poor prognosis is observed in stroke patients with high SUA and low ascorbic acid levels (37).

SUA AND ENDOTHELIAL DYSFUNCTION:

Experimental research provides evidence that hyperuricemia causes endothelial dysfunction leading to atherosclerosis. UA was found to cause endothelial dysfunction when it was experimentally injected directly into the blood vessels(38). UA also caused oxidation of low density lipoproteins (39) and promoted neutrophil chemotaxis around blood vessels (40).

Moreover elevation of circulating pro-inflammatory markers have also been related to increased SUA levels (41-43). UA also accumulates as crystals in the atherosclerotic plaques (44).

SUA AND METABOLIC SYNDROME (MET S):

SUA also increases the risk of stroke by its relationship with Met S (45,46). SUA levels are consistently high in patients with Met S (47-49).

1. Hyperuricemia and Met S both have a common underlying mechanism which is the Insulin Resistance (IR). It is closely associated with increased SUA levels (45,50).
2. Insulin – induced UA excretion is defective in patients with MetS. This could be a cause for elevated UA levels (45).
3. Insulin Resistance also increases purine synthesis and turnover thereby causing elevated UA levels (45,50).
4. SUA adversely affects endothelial function by inhibiting nitric oxide synthesis (38). Nitric Oxide is necessary for insulin mediated glucose uptake. So hyperuricemia indirectly causes IR (51).
5. Recent studies have shown a significant association between hyperuricemia and the risk factors of Met S (48,52). Met S itself is an independent risk factor for cerebro vascular accidents (53-56).
6. Elevated SUA levels has a prognostic value independent of all the other entities of Met S, showing a positive correlation between SUA levels and poor prognosis in stroke (57).

REDUCTION OF SUA AND PROTECTION AGAINST STROKE:

Beyond xanthine oxidase inhibitors like allopurinol and other uricosuric drugs (probenecid, sulfinpyrazone), some drugs like losartan and fenofibrate can decrease the SUA level(58).

Statins markedly reduce SUA levels (59) and protects kidney functions (60) and these effects independently augment their protection from vascular events (49).

Thus reduction of SUA could also adds to the beneficial effects of statins against cerebrovascular accident (61).

The findings of LIFE study (Losartan Intervention for Endpoint Reduction in hypertension study) suggest that losartan causes a fall in SUA and confers protection against stroke (8).

REFERENCE STUDIES

1. Circ J 2007: 71: 1121-1128

Serum Uric Acid an Independent Predictor of Death After Acute Stroke – Asterios Karagiannis, MD*; Dmitri Mikhailidis. MD*; Konstantinos Tziomalos, MD*;

Conclusions: Elevated levels of SUA are independently associated with an high risk of early mortality in acute stroke.

2. Stroke, 2006; 37: 1503-1507

Uric Acid a Risk Factor for Myocardial Infarction and Stroke – The Rotterdam Study: Michael J. Bos, MD, MSc; Peter J. Kodstaal, MD, PhD; Albert Hoffman, MD, PhD;

Conclusions – Uric acid is a strong risk factor for myocardial infarction and stroke.

3. Atherosclerosis, 2006 Aug; 187(2): 401-7: Serum uric acid and risk of ischemic stroke: The ARIC study – Hozawa A., Folsom AR, Ibrahim H

Conclusion: UA is an independent predictor of ischemic stroke among subjects not using diuretics, but that high SUA level itself may not cause ischemic stroke.

4. Diabetes Metab Res Rev. 2006 Jan – Feb; 22(1): 79-82: Elevated serum uric acid levels independently predicts prognosis of stroke in diabetic patients - Newman E, Rahman F, Les KR

Conclusion: Increased SUA levels is significantly and independently associated with high risk of adverse vascular events in diabetic stroke patients.

5. Journal of Internal Medicine 2005; 258: 435-441: Serum uric acid levels and risk for acute ischaemic nonembolic stroke in the aged – H Milonis, K.. Kalatzi, J. Goudvenos, K. Saferidis

Conclusion: Elevated SUA is associated with an increased risk for acute ischaemic / nonembolic stroke in individuals aged more than 70 independent of other risk factors. .

6. Int J Cardiol, 2005 Mar 18; 99(2): 269-75: Risk factors for acute ischemic non – embolic stroke in elderly patients – Milonis HJ, Liberpoulos E, Goudvenos J.

Conclusion: SUA and Diabetes mellitus are impotant riskfactors for ischemic stroke

7. Stroke 2003; 34; 1956-1957: Editorial comment – Elevated Uric Acid and Ischemic Stroke: Accumulating Evidence That it is Injurious and Not Neuroprotective – John Kanellis and Richard J. Johnson

Concclusion: High SUA during an acute episode of stroke is harmful, more so if the level of vitamin-c is low,

8. Stroke, 2003; 34: 1951-1957: Serum Urate as an Independent Predictor of Poor Outcome and Future Vascular Events After Acute Stroke – Christopher J. Weir, PhD; Scott W. Muir, MBChB, MRCP;

Conclusions – Independent of other risk factors, higher serum urate levels predicted poor outcome and higher vascular event rates..

9. Di Yi Jun Y; Da XueXueBao. 2002 Jan; 22(1): 70-1 Serum uric acid in type 2 diabetic patients complicated by stroke. – Guan MP, Xue YM. Shen J.

Results: Male diabetic patients with stroke had significantly higher mean levels of serum uric acid than simple diabetic patients

10. Stroke. 2000; 31:2295-2300: Antioxidant Profile and Early Outcome in Stroke Patients – Antonio Cherubini, MD; Maria Cristina Polidori, MD; Mario Bregnocchi, MD

Conclusion:Patients with the worst early outcome had higher vitamin A and uric acid plasma levels and lower vitamin C levels and erythrocyte SOD activity than those who remained functionally stable.

11. International Journal of Cardiology Volume 71, Issue 1, 30 September 1999, Pages 17-22: Is hyperuricemia a risk factor of stroke and coronary heart disease among Africans? – B. Longo – Mbenza, E. LukokiLuila, PhanzuMbete and E. Kintoki Vita

Conclusion: Our results indicate that hyperuricemia among African patients is a strong predictor of myocardial infarction in men, stroke in both sexes and all causes of mortality in women.

12. Stroke, 1998; 29: 635-639: Serum Uric Acid is a Strong Predictor of Stroke in Patients with Non-Insulin – Dependent Diabetes Mellitus – SeppoLehto, MD; Leo Niskanen, MD; TapaniRo'nnemmaa, MD; MarkkuLaakso, MD

Conclusions – Our results indicate that hyperuricemia is a strong predictor of stroke events in middle – aged patients with NIDDM.

AIMS OF THE STUDY

The study is conducted to study the association between Serum Uric Acid (SUA) and acute ischaemic nonembolic stroke and to assess its risk factor potential using statistical analysis.

To also study the association between Serum Uric Acid (SUA) and other risk factors namely hypertension, Diabetes mellitus, CAD and adverse lipid profile.

MATERIALS AND METHODS

Inclusion criteria:

1. Patients who were admitted in our hospital with first – ever – in life time acute ischaemic nonembolic stroke with or without CT scan evidence of infarction within 24hrs of onset of stroke.

Exclusion criteria:

1. Patients with previous history of TIA /CVA
2. Patients who are on thiazide diuretics
3. Patients who are known cases of gout or show clinical evidences of gout.
4. Patients with chronic renal failure
5. Patients whose CT scan showing haemorrhage or other space occupying lesions other than infarct.
6. Patients who were of known cardiac diseases which could be sources of emboli or whose echocardiogram shown sources of emboli.
7. Patients with haemotological abnormalities like leukemia or other myeloproliferative disorders.

A total of 100 patients (49 males and 51 females) with acute stroke who met the criteria, admitted in TMCH Thanjavur from 01.06.2014 to 31.05.2015 were randomly selected and included in this study.

All subjects gave informed consent and the study protocol was approved by the Ethical Committee.

The blood samples were taken within 24hrs of onset of stroke and sent for biochemical analysis and were analyzed in our Biochemical Laboratory using standard analyzer. The patients were further evaluated for the presence of additional risk factors as follows, using the below mentioned parameters.

1. HYPERTENSION:

a) Known case of hypertension
b) Blood pressure more than 140mm of Hg systolic and / or more than 90mm of Hg diastolic (62)

2. DIABETES MELLITUS:

a) Known case of diabetes mellitus
b) Random or postprandial blood sugar more than 200mgs / dl and / or fasting blood sugar more than 126mgs / dl (63)
c) The patients with blood sugar values of IFG or IGT were not included as diabetics in this study.

3) CORONARY ARTERY DISEASE:

Patients with ECG evidence of old infarction or Echocardiogram showing regional wall motion abnormalities.

4. ADVERSE LIPID PROFILE (64):

- Total cholesterol - more than 200mgs/dl
- Triglycerides - more than 150mgs / dl
- LDL – C - more than 130mgs/dl
- HDL – C - less than 40mgs / dl

5. SMOKING AND ALCOHOLISM:

History of smoking and alcoholism within the last 5 years have been taken as smokers and alcoholics.

Statistical Tools

The information collected throughout the study period was recorded in a Master Chart.. Data analysis was done with the help of a computer using Statistical Package for Social Sciences software (SPSS version 22).

Using this software, frequencies, percentage, mean, standard deviation, x^2 and 'p' values were calculated. A 'p' value less than 0.05 is taken to denote significant relationship.

OBSERVATIONS AND RESULTS

The observations made in this study are categorized, analyzed and tabulated as under:

1. AGE DISTRIBUTION:

In this prospective study, 41 to 83 yrs old patients are included.

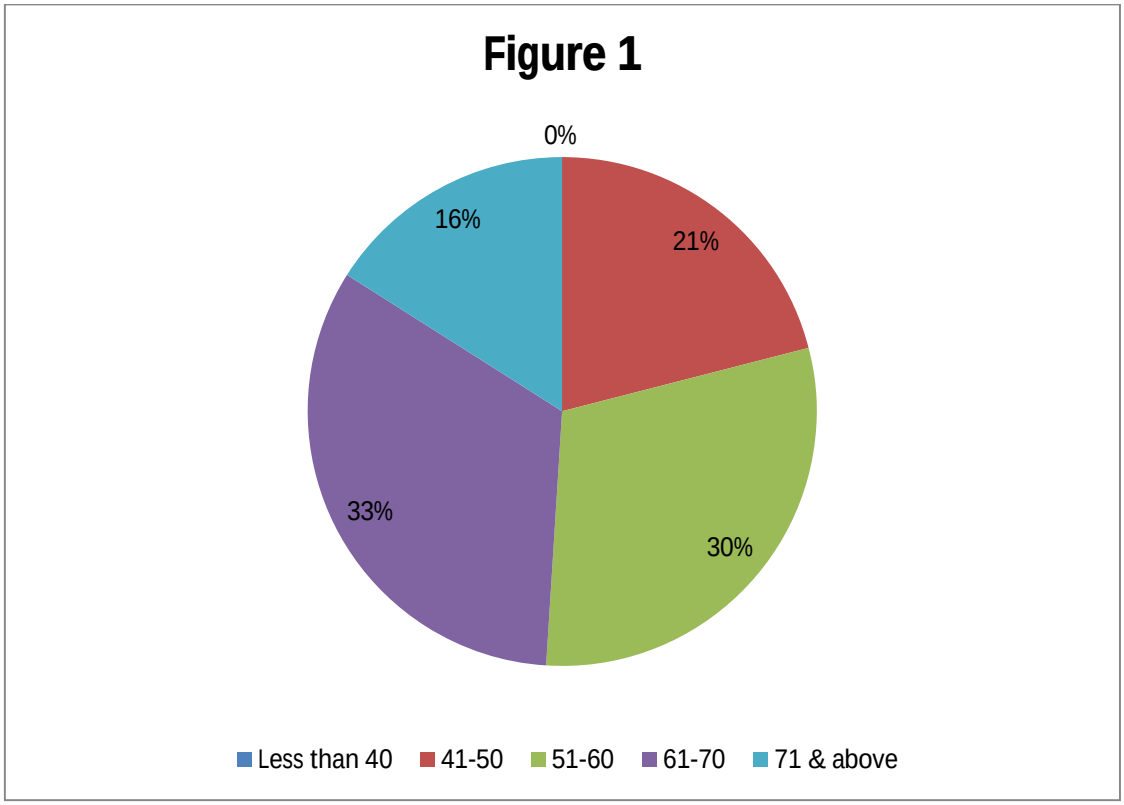
Table 1.1: Age Distribution

Age in years	**Cases**	
	No	**%**
Less than 40	-	-
41-50	21	21
51-60	30	30
61-70	33	33
71 yrs & above	16	16
Total	100	100
Mean S.D	59.84 yrs 10.47	

Above 71 yrs old constitute 16% of the population with 8 males and 8 females.

Figure 1

AGE DISTRIBUTION



- People aged 41-50 constitute 21% of the study population with 10 males and 11 females
- People aged over 60 (elderly) constitute 49% of the population

Table 1.2: Age Distribution according to sex

Age in years	Cases			
	Males		Females	
	No.	%	No.	%
Less than 40	-	-	-	-
41-50	10	20.4	11	21.6
51-60	21	42.9	9	17.6
61-70	10	20.4	23	45.1
71 & above	8	16.3	8	15.7
Total	49	100	51	100
Mean S.D	59.1 10.2		60.5 11.1	
'p'	0.238 Not significant			

The mean age of the male population is 59.1 yrs and of the female population is 60.5 yrs. The overall mean age of the study population is 59.84yrs.

2. RISK FACTORS:

Table 2.1: Risk Factors

Risk Factor	Cases	
	No	**%**
a) Hypertension		
Present	66	66
Absent	34	34
b) DM		
Present	52	52
Absent	48	48
c) Smoking		
Present	34	34
Absent	66	66
d) CAD		
Present	33	33
Absent	67	67
e) Dyslipidemia		
Present	34	34
Absent	66	66
f) Alcoholism		
Alcoholic	20	20
Non alcoholic	80	80

Hypertension is the most common risk factor found in this study population.

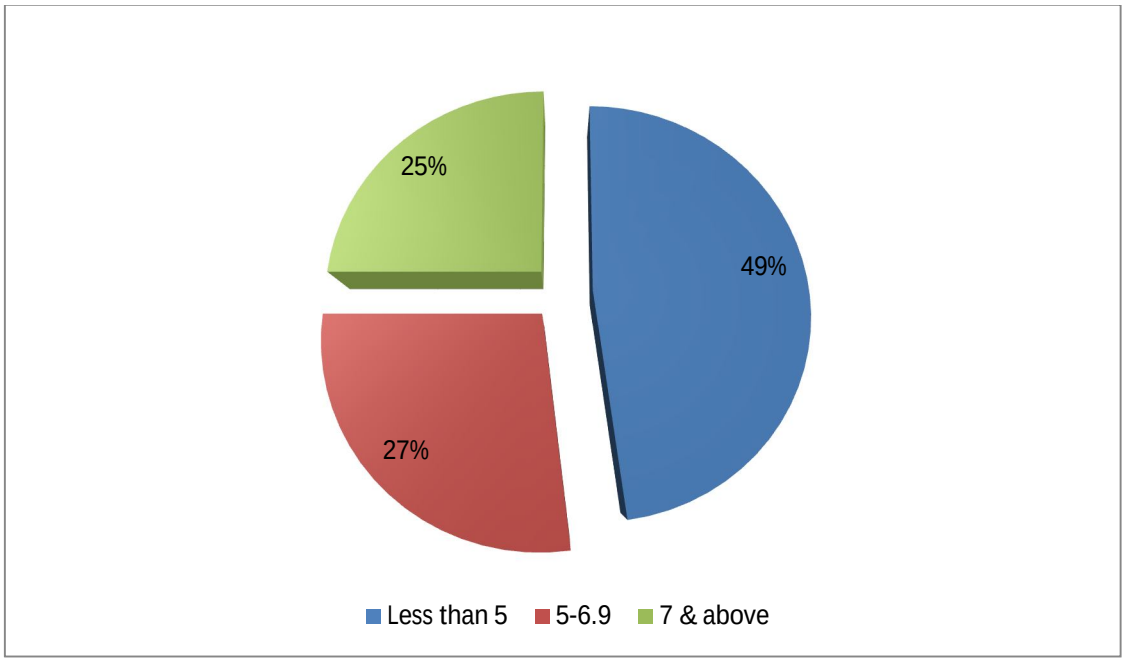
- Hypertension constitutes the major risk factor in this stroke population as 66% of the population is hypertensive. 33 males and females are hypertensives and form 67% and 64% in their respective population.
- Diabetes mellitus ranks second as a risk factor, constitute 52% of the study population with 29 (59%) males and 23 (45%) females.
- Coronary Artery Disease is associated in 33% of the population with 14 (28%) males 19 (37%) females.
- 34% of the stroke population has adverse lipid profile and both sexes share equal number of patients with abnormal lipid profile (17 each).

Table 2.2: Risk Factors according to sex

Risk Factor	Cases			
	Males		Females	
	No.	%	No.	%
a) Hypertension				
Present	33	67.3	33	64.7
Absent	16	32.7	18	35.3
b) DM				
Present	29	59.2	23	45.1
Absent	20	40.8	28	54.9
c) Smoking				
Present	34	68	-	-
Absent	16	32	50	100
d) CAD				
Present	14	28.6	19	37.3
Absent	35	71.4	32	62.7
e) Dyslipidemia				
Present	17	34.7	17	33.3
Absent	32	65.3	34	66.7
f) Alcoholism				
Alcoholic	18	36.7	2	3.9
Non Alcoholic	31	63.3	49	96.1

- Among the male population, 34 (68%) are smokers and 18 (36%) are alcoholics.

FIG: 3 URIC ACID DISTRIBUTION



- Uric acid levels above and equal to 7mg / dl – 25% (12 males and 13 females)

3.Uric acid levels and their association with risk factors:

The distribution of uric acid levels in the study population are as under:

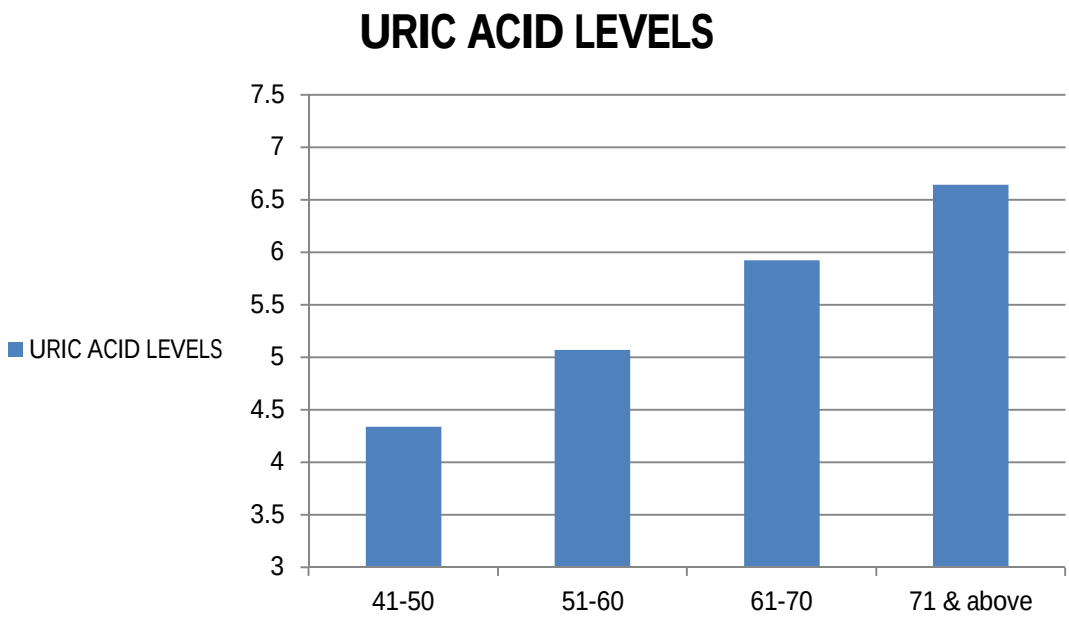
- Less than 5mg / dl – 48% (25 males and 23 females)
- Between 5 – 6.9 mg / dl – 27% (12 males and 15 females)
- Above and equal to 7mg / dl – 25% (12 males and 13 females)

Table 3.A. : Uric Acid (mg/dl)

Uric Acid (mg/dl)	**Cases**			
	Males		**Females**	
	No.	**%**	**No.**	**%**
Less than 5	25	51	23	45.1
5-6.9	12	24.5	15	29.4
7 & Above	12	24.5	13	25.5
Total	49	100	51	100
Mean S.D	5.390 1.89		5.513 1.50	
'p'	0.736 Not significant			

FIG 3.1.1

AGE AND URIC ACID LEVELS



Mean uric acid level in males is 5.39mg /dl and in females it is 5.51 mg/dl.

3.1. AGE AND URIC ACID:

Table 3.1.1: Age and uric acid

Age group	Uric Acid mg/dl	
	Mean	**S.D**
41-50	4.342	1.16
51-60	5.076	1.44
61-70	5.930	1.67
70& above	6.656	1.81
'p'	0.0001 (Significant)	

Age wise distribution of uric acid is found statistically significant. As age advances the uric acid level also rises with the 'P' value of 0.0001. This significance is maintained even when male and female populations are considered separately. ('P' of 0.0056 for males and 0.0077 for females).

Table 3.1.2: Age and uric acid according to sex

Age group	Uric Acid			
	Males		Females	
	Mean	S.D	Mean	S.D
41-50	4.21	1.54	4.46	0.71
51-60	5.05	1.50	5.12	1.38
61-70	5.92	2.03	5.93	1.53
71 & above	7.12	1.92	6.18	1.68
'p'	0.0056 Significant		0.0077 Significant	

The mean uric acid value for 40-49 yrs group is 4.34 mg/dl while the elderly age group of above 70 yrs has the mean value 6.65 mg/dl.

3.2: SEX AND URIC ACID:

Table 3.2.1: Sex and uric acid level

Sex	**Uric acid (mg/dl)**	
	Mean	**S.D**
Males	5.39	1.89
Females	5.51	1.50
'p'	0.736 (Not significant)	

There is no statistically significant association found in this study between sex and uric acid. The mean uric acid level among male population is 5.39mg/dl and among female population it is 5.51 mg/dl.

3.3: HYPERTENSION AND URIC ACID:

Table 3.3.1: Hypertension and uric acid

Hypertension	**Uric acid (mg/dl)**	
	Mean	**S.D**
Present	5.66	1.66
Absent	5.07	1.68
'p'	0.756 (Not significant)	

This study does not show any significant association between hypertension and uric acid. The mean uric acid level in hypertensive population is 5.66 mg/dl and in non hypertensive population is 5.07 mg/dl.

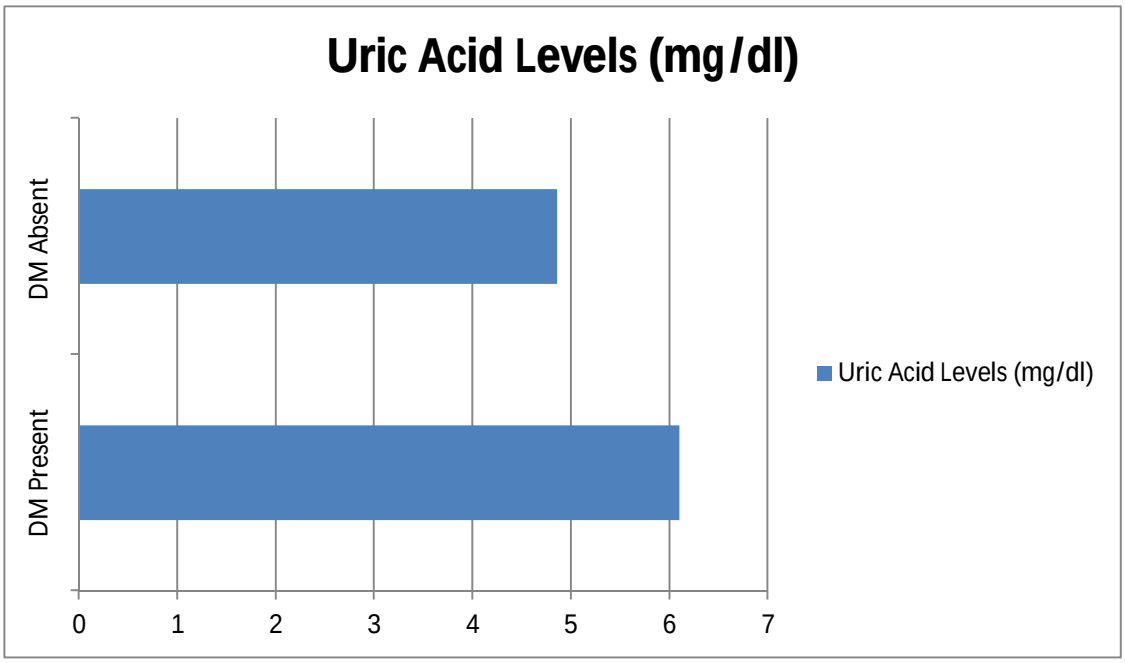
Table 3.3.2: Hypertension and uric acid – sex wise

Hypertension	**Uric acid (mg/dl)**			
	Males		**Females**	
	Mean	**S.D**	**Mean**	**S.D**
Present	5.45	1.78	5.86	1.55
Absent	5.27	2.17	4.87	1.20
'p'	0.370 Not significant		0.023 Significant	

There is a significant association found, also when males and females are considered separately. The mean uric acid levels for male hypertensives is 5.45 mg/dl (non hypertensive males 5.27mg/dl) and in females is 5.86 mg/dl (non hypertensive females – 4.87 mg/dl). So hypertensive females have a higher incidence of hyperuricemia.

Figure 3.4

DIABETES MELLITUS AND URIC ACID



Among diabetics the mean uric acid is 6.10 mg/dl while among non diabetics it is 4.86 mg/ dl.

3.4: DIABETES MELLITUS AND URIC ACID:

Table 3.4.1: DM and uric acid

DM	Uric Acid (mg/dl)	
	Mean	**S.D**
Present	6.10	1.62
Absent	4.86	1.56
'p'	0.0006 (Significant)	

There is a statistically significant association (p value – 0.0006) found between the level of uric acid and Diabetes mellitus. Among diabetics the mean uric acid is 6.10 mg/dl while among non diabetics it is 4.86 mg/ dl.

Table 3.4.2: DM and uric acid according to sex

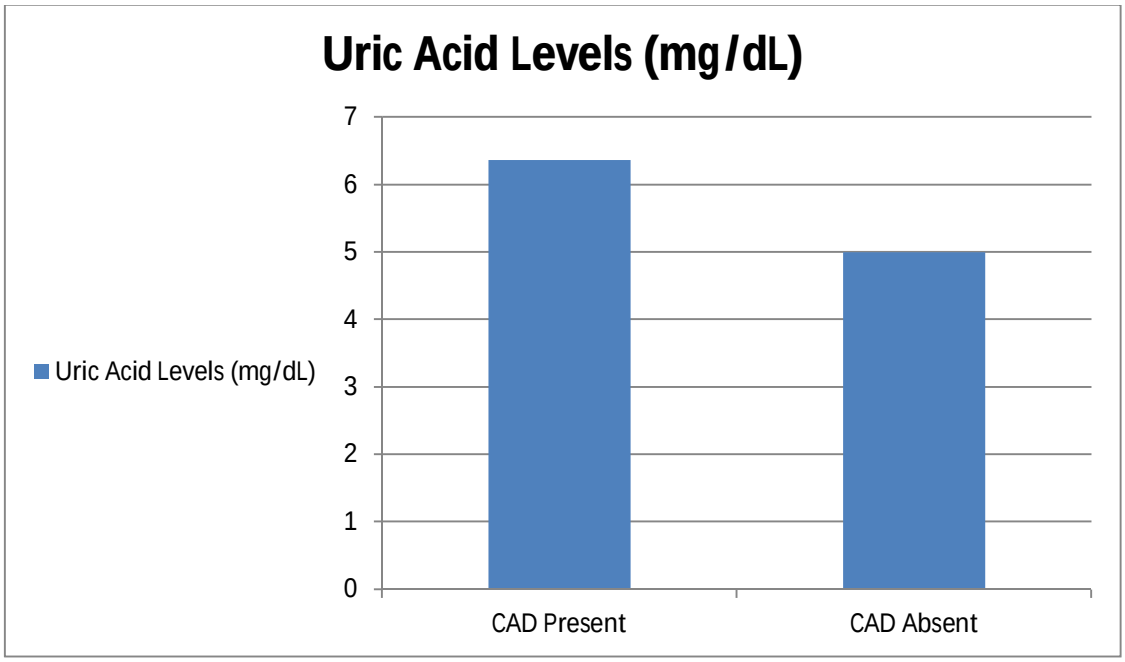
DM	Uric Acid (mg/dl)			
	Male		Female	
	Mean	**S.D**	**Mean**	**S.D**
Present	6.35	1.89	5.91	1.42
Absent	4.73	1.62	5.02	1.49
'p'	0.002 Significant		0.033 Significant	

This association is more significant among males (p value – 0.002) among whom the diabetics have 6.35 mg/dl as mean uric acid level compared to non diabetics, 4.73 mg/dl as mean value.

This association is also found significant in female population. The mean uric acid level in diabetic women is 5.91 mg/dl when compared to non diabetic women is 5.02 mg/dl.

Fig 3.5.1

CAD AND URIC ACID LEVELS



Mean uric acid level in this stroke population with CAD is 6.37 mgs/dl and in those without CAD is 5.00 mgs/dl

3.5: CAD and Uric acid:

Table 3.5.1: CAD and Uric acid

CAD	Uric Acid (mg/dl)	
	Mean	**S.D**
Present	6.37	1.88
Absent	5.00	1.41
'p'	0.0004 (significant)	

In this study, mean uric acid level in this stroke population with CAD is 6.37 mgs/dl and in those without CAD is 5.00 mgs/dl and thus establishes a statistically significant relationship ('p' 0.0004).

Table 3.5.2: CAD and Uric acid according to sex

CAD	Uric Acid (mg/dl)			
	Males		Females	
	Mean	S.D	Mean	S.D
Present	7.02	1.80	5.90	1.84
Absent	4.74	1.52	5.28	1.24
'p'	0.0003 Significant		0.1559 Not significant	

When males and females are considered, males have a significant association with a 'p' values of 0.0003. Female population does not show such association. (See table)

3.6: Hyperlipidemia and uric acid:

Table 3.6.1: Hyperlipidemia and Uric acid

Hyperlipidemia	Uric Acid (mg/dl)	
	Mean	**S.D**
Present	5.76	1.89
Absent	5.29	1.58
'p'	0.260 (Not significant)	

Mean uric acid level in hyperlipidemic stroke population is 5.76 mgs/dl and compared to 5.29 mgs / dl mean uric acid level in patients without hyperlipidemia do not show any statistical significance.

Table 3.6.2: Hyperlipidemia and Uric acid according to sex

Hyperlipidemia	**Uric Acid (mg/dl)**			
	Males		**Females**	
	Mean	**S.D**	**Mean**	**S.D**
Present	5.68	2.16	5.85	1.64
Absent	5.24	1.76	5.34	1.42
'p'	0.451 Not significant		0.260 Not significant	

There is no statistically significant relationship even when males and females are analysed separately.

3.7: Smoking and uric acid:

Table 3.7.1: Smoking and Uric acid

Smoking	**Uric Acid (mg/dl)**	
	Mean	**S.D**
Present	5.16	1.80
Absent	5.60	1.64
'p'	0.215 Not significant	

Mean uric acid level in smokers is 5.16mg / dl and among non-smokers is 5.60 mgs /dl. Thus in this study there is no statistically significant relationship between smoking and uric acid.

4. **RISK FACTORS IN POPULATION WITH HIGH URIC ACID LEVEL** (ie..>7mgs / dl)

Table 4.1 : Risk factors and uric acid levels </> 7 mgs / dl

Risk Factors	**Uric acid**			
	< 7mg/dl		**> 7mg/dl**	
	No.	**%**	**No.**	**%**
a) Hypertension				
Present	46	61	20	80
Absent	29	39	5	20
'P'	0.108 Not significant			
b) DM				
Present	44	59	8	32
Absent	31	41	17	68
'P'	0.001 **Significant**			
c)Smoking				
Present	27	36	7	28
Absent	48	64	18	72
'P'	0.523 Not significant			
d) CAD				
Present	16	21	17	68
Absent	59	79	8	32
'P'	**0.0001 Significant**			

Risk Factors	Uric acid			
	< 7mg/dl		> 7mg/dl	
	No.	%	No.	%
e) Dyslipidemia				
Present	22	29.3	12	48
Absent	53	70.7	13	52
'P'	0.145 Not significant			
f) Alcoholism (among males)				
Alcoholic	14	18.6	6	24
Non Alcoholic	61	81.3	19	76
'P'	0.696 Not significant			
No risk factor	7	9.3	2	8
At least one risk factor	68	90.7	23	92
'P'	0.6008 Not significant			
Age				
>65	11	42.3	15	57.7
<65	64	86.5	10	13.5
'p'	**0.0001 Significant**			

Further analysis is done to analyse the relationship between uric acid levels less than and more than 7mgs/dl and the risk factors. This analysis shows age more than 65 yrs, Diabetes mellitus and CAD have statistically significant relationship with uric acid level.

DISCUSSION

In this prospective study of 100 stroke patients, males and females are almost equal in number and hence there is no sex bias. Further analysis shows the mean age, (males – 59.1yrs, females 60.5yrs) and mean level of uric acid (males – 5.39mgs/ dl, females – 5.51mgs / dl) are similar. Distribution of risk factors also is of in more or less similar pattern (Hypertension: males – 33, females – 33; Diabetes mellitus: males – 29, females 23; CAD: males – 14 females – 19; Hyperlipidemia; males – 17, females – 17). Different studies (9, 12) show high mean uric acid level in the study population which is not found in this study.

But, in elderly population, both sexes show high level of uric acid which has statistical significance. Regarding the association between risk factors and both sexes, CAD is significantly associated with high uric acid levels in both sexes whereas DM is also associated with high uric acid levels in both sexes.

In this study, most of the population belongs to anterior circulation territory, especially of middle cerebral artery region with commonest presentation being hemiplegia, except in two patients with cerebellar infarction evidenced in MRI scan. As most of the posterior circulation strokes have masquerading clinical presentations and often lack CT scan evidences of infarction, they are not included in this study to avoid inclusion bias.

Age is the most common non-modifiable risk factor for the development of stroke (14). In this study, 16% of the populations are above 71yrs with 8 males and 8 females. One pilot study (9) of 163 patients above 70yrs studied the association of SUA and stroke and concludes that SUA is associated with an increased risk for acute ischaemic / nonembolicstroke in elderly patients independent of concurrent metabolic derangements. This study also shows evidences for a significant association between SUA and stroke in the elderly population, and the association was maintained even when both sexes are considered separately. Thus this study supports the association of high SUA and acute ischaemic / nonembolic stroke.

Hypertension is the most common modifiable risk factor for stroke (14). SUA is also commonly associated with hypertension (65,66). Elevated SUA level is an independent predictor of hypertension in 25% of patients with new onset, untreated primary hypertension (21). In this study, Hypertension constitutes the major risk factor as 66% of the stroke population is hypertensive. The mean uric acid level of hypertensive population is 5.66 mgs/dl and of non hypertensives 5.07 mgs/ dl and thus this study does not show any statistically significant relationship between SUA and hypertension.

Diabetes mellitus ranks second as a risk factor in this study, constitute 52% of the study population. One population based study (6) involving 1017 person with NIDDM, concludes that hyperuricemia is a strong predictor of stroke events in middle aged persons with NIDDM, independent of other CV risk factors. SUA levels are often increased in subjects with MetS (47-49). In this study, with the mean SUA level of 6.10mgs/dl among diabetics and 4.86mgs/dl among non-diabetics there is a strong association between SUA and DM. Further analysis shows this association is more stronger among males (mean SUA in male diabetics – 6.35 mgs/dl vs non-diabetic males – 4.73 mgs/dl) than females. Thus this study strongly favours for an association between SUA and acute ischaemic/ nonembolic stroke in diabetic population.

SUA is significantly associated with cardiovascular mortality in certain epidemiological studies (13). One population based cohort study (67), with a follow up of 8.4yrs, comprising 4385 participants of the Rotterdam study concludes that SUA is a strong risk factor for myocardial infarction and stroke. In this study CAD is found in 33% of the patients with 14 males and 19 females. The mean SUA level in this CAD population is 6.37mgs /dl comparing this to patients without CAD is 5.00mgs/dl which shows a strong statistical significance. Among those 33 stroke patients with

CAD 17 have SUA >7mgs/dl. This also shows a strong statistical significance with a ‘p’ value of 0.0001. Hence this study strongly favours Rotterdam study and suggests SUA is a strong risk factor for myocardial infarction and stroke.

Several prospective studies (69,70) have shown that higher levels of total cholesterol increase the risk of ischaemic stroke. Furthermore a meta-analysis of 90000 patients (61) showed that administration of statins reduces the risk of stroke among patients with CAD and that this risk reduction is primarily related to the extent to which LDL – C levels are lowered. In some studies (71.72) relating Met S and SUA, increased SUA levels correlated with low HDL – C levels.

In our study, Hyperlipidemia is considered separately and not as a part of Met S. Moreover, most of our patients in this study population are from low socio-economic group and are not found obese. In this study, the mean uric acid level hyperlipidemic patients is 5.76mgs / dl and in patients without hyperlipidemia is 5.29mgs/dl and does not show any significant association between these variables. Out of 34 patients with hyperlipidemia in this study, only 12 are found to have SUA > 7mgs /dl.

Among the other risk factors like smoking and alcoholism, they are not considered as separate risk factors in many pilot studies of this kind. This study also fails to show any statistically significant relationship between SUA and these risk factors when considered separately.

Further analysis between < 7mgs /dl and > 7mgs / dl SUA groups also maintain the association between high SUA and the risk factors namely age and CAD.

CONCLUSION

1) This study shows that elevated SUA is strongly associated with an increased risk for the development of acute ischaemic / non-embolic stroke in this study population.
2) The association between elevated SUA and ischaemic stroke may need to be considered especially when treating elderly patients, diabetics and the population with coronary artery disease.
3) Elevated SUA can be considered as one of the risk factor for acute ischaemic non – embolic stroke.
4) Lowering SUA level can be considered as one of the preventive modalities for stroke while treating high risk population.
5) It is also suggested that further studies are required to assess whether lowering of SUA level with drugs can actually reduce the risk of ischaemic stroke.

BIBLIOGRAPHY

1. Adam and Victor's principles of Neurology – 8th edition; Chapter 34; page 660-669.
2. Bonita R. Epidemiology of stroke. Lancer 1992; 339: 342-4.
3. Buckley BM. Healthy ageing: ageing safely. Eur Heart J 2001; (Suppl. 3): N6 – 10.
4. Daskalopoulou SS, Athyros VG, Elisaf M, Mikhailidis DP. Uric acid levels and vascular disease. Curr Med Res Opin 2004; 20: 951-4.
5. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971-1992, JAMA 2000; 283: 2404-10.
6. Lehto S, Niscanen L, Ronnemaa T, Laasko M. Serum uric acid is a strong predictor of stroke in patients with non-insulin dependent diabetes mellitus. Stroke 1998; 29: 635-9.
7. Weir CJ, Muir SW, Walters MR, Lees K.R. Serum urate as an independent predictor of poor outcome and future vascular events after acute stroke. Stroke 2003; 34: 1951-6.
8. Hoieggen A, Alderman MH, Kjeldsen SE et al., LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004; 65: 1041 – 9.
9. Milionis HJ, Kalantzi KJ, Goudevenos JA, Seferiadis K, Mikhailidis DP, Elisaf MS. Serum uric acid levels and risk for acute ischaemic non-embolic stroke in elderly subjects. *J Intern Med* 2005; 258: 435-441.

10. Lehto S, Niscanen L, Ronnemaa T, Laasko M. Serum uric acid is a strong predictor of stroke in patients with non-insulin dependent diabetes mellitus. Stroke 1998; 29: 635-9.
11. Rathmann W, Funkhouser E, Dyer AR, Roseman JM. Relations of hyperuricemia with the various components of the insulin resistance syndrome in young black and white adults: The CARDIA study [Coronary Artery Risk Development in Young Adults]. *Ann Epidemiol* 1998; 8: 250-261.
12. Waring WS. Uric acid: an important antioxidant in acute ischaemic stroke. QJ Med 2002; 95: 691-3.
13. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow – up study, 1971-1992. JAMA 2000; 283: 2404-10.
14. Epidemiology and stroke risk factors – office practice of Neurology, New York Churchill Livingstone 1996 pp: 224-237.
15. Risk factors of stroke – Neurology Secrets 2nd edition pp: 230.
16. Uric acid and hyperuricemia– pages form e – medicine.
17. Jossa F, Farinaro E, Panico S et al. serum uric acid and hypertension: the Olivetti Heart Study. J Hum Hypertens1994; 8: 677-81.
18. Sevanian A, Davies KJ, Hochstein P. Serumurate as an antioxidant for ascorbic acid. Am J ClinNutr 1991; 54: 1129-34.
19. Waring WS. Uric acid: an important antioxidant in acute ischaemic stroke. QJ Med 2002; 95: 691-3.
20. DeFronzo RA, Ferranini E. Insulin resistance: a multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic vascular disease. *Diabetes Care.* 1991; 14: 173-194.

21. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966; 275: 457-464.
22. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: An indicator of renal vascular involvement. *Ann Intern Med* 1980; 93: 817-821.
23. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, et al. elevated uric acid increases blood pressure in the rate by a novel crystal – independent mechanism. Hypertension 2001; 38: 1101-1106.
24. Watanabe S, Kang DH, Feng L, Nakagawa T, Kanellis J, Lan H, et al. Uric acid, hominoid evolution, and the pathogenesis of salt – sensitivity. Hypertension 2002; 40: 355-360.
25. Kang DH, Nakagawa T, Feng L, Watanabe S, Han L, Mazzali M, et al. A role for uric acid in the progression of renal disease. J Am SocNephrol 2002; 13: 2888-2897.
26. Kanellis J, Watanabe S, Li JH, Kang DH, Li P. Nakagawa T, et al. Uric acid stimulates monocyte chemoattractantprotein – 1 production in vascular smooth muscle cells via mitogen – activated protein kinase and cyclooxygenase – 2. Hypertension 2003; 41: 1287-1293.
27. Gu L, Okada Y, Clinton SK, Gerard C, Sukhova GK, Libby P, et al. Absence of monocyte chemoattractantprotein – 1 reduces atherosclerosis in low density lipoprotein receptor – deficient mice. Mol Cell 1998; 2: 275-281.
28. Love S. Oxidative stress in brain ischemia. Brain Pathol 1999; 9: 119-131.
29. Sun AY, Chen YM. Oxidative stress and neurodegenerative disorders. J Biomed Sci 1998; 5: 401-414.

30. Maxwell SR, Lip Gy. Free radicals and antioxidants in cardiovascular disease. Br J ClinPharmacol 1997; 44: 307-317.
31. Gariballa SE, Hutchin TP, Sinclair AJ. Antioxidant capacity after acute ischaemic stroke. Q J Med 2002; 95: 685-690.
32. Spranger M, Krempien S, Sehwab S, Donneberg S, Hacke W. Superoxide dismutase activity in serum of patients with acute cerebral ischemic injury: Correlation with clinical course and infarct size. Stroke 1997; 28: 2425-2428.
33. Leinonen JS, Ahonen JP, Lonnrot K, Jehkonen M, Dastidar P, Molnar G, et al. Low plasma antioxidant activity is associated with high lesion volume and neurological impairment in stroke. Stroke 2000; 31: 33-39.
34. Squadrito GL, Cueto R, SplenserAE, Valavanidis A, Zhang H, Uppu RM, et al. Reaction of uric acid with peroxynitrite and implications for the mechanism of neuroprotection by uric acid. Arch BiochemBiophys 2000; 376: 333-337.
35. Chamorro A, Obach V, Cervera A, Revilla M, Deulofeu R, Aponte JH. Prognostic significance of uric acid serum concentration in patients with acute ischemic stroke. Stroke 2002; 33: 1048-1052.
36. Abuja PM. Ascorbate prevents prooxidanteffects of urate in oxidation of human low density lipoprotein. FEBS Lett1999; 446: 305-308.
37. Cherubini A, Polidori MC, Bregnocchi M, Pezzuto S, Cecchetti R, Ingegni T, et al. Antioxidant profile and early outcome in stroke patients. Stroke 2000; 31: 2295-2300.
38. Waring WS, Webb DJ, Maxwell SRJ. Effect of local hyperuricaemia on endothelial function in the human forearm vascular bed. Br J ClinPharmacol 2000; 49: 511P.

39. Bagnati M, Perugini C, Cau C, Bordone R, Albano E, Bellomo G. When and why a water – soluble antioxidant becomes pro-oxidant during copper – induced low – density lipoprotein oxidation: A study using uric acid. Biochem J 1999; 340: 143-152.
40. Boogaerts MA, Hammerschmidt DE, Roelant C, VerwilghenRl, Jacob HS. Mechanisms of vascular damage in gout and oxalosis: Crystal induced, granulocyte mediated, endothelial injury. ThrombHaemost 1983; 50: 576-580.
41. Duff GW, Atkins E, Malawista SE. The fever of gout: Urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. Trans Assoc Am Physicians 1983; 96: 234-245.
42. Nakanishi N, Shiraishi T, Wada M. C- reactive protein concentration is more strongly related to metabolic syndrome in women that in men: The Minoh Study. Circ J 2005; 69: 386-391.
43. Kondo N, Nomura M, Nakaya Y, Ito S, Ohguro T. Assocation of inflammatory marker and highly sensitive C – reactive protein with acrobic exercise capacity, maximum oxygen uptake and insulin resistance in healthy middle – aged volunteers. Circ J 2005; 69: 452-457.
44. Patetsios P, Rodino W, Wisselink W, Bryan D, Kirwin JD, Panetta TF. Identification of uric acid in aortic aneurysms and atherosclerotic artery. Ann NY AcadSci 1996; 800: 243 – 245.
45. Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS. Elevated serum uric acid levels in metabolic syndrome: An active component or an innocent bystander? Metabolism 2006; 55: 1293-1301.

46. Ishizaka N, Ishizaka Y, Toda El, Nagai R, Yamakado M. Association between serum uric acid, metabolic syndrome, and carotid atherosclerosis in Japanese individuals. ArteriosclerThrombVascBiol 2005; 25: 1038-1044.
47. Schmidt M1, Duncan BB, Watson RL, Sharrett AR, Brancati FL, Heiss G. A metabolic syndrome in whites and African – Americans: The Atherosclerosis Risk in Communities baseline study. Diabetes Care 1996; 19: 414-418.
48. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, et al. Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. Circ J 2005; 928 – 933.
49. Athyros VG, Mikhailidis DP, Liberopoulos EN, Kakafika Al, Karagiannis A, Papageorgiou AA, et al. Effect of statin treatment on renal function and serum acid levels and their relation to vascular events in patients with coronary heart disease and metabolic syndrome: A subgroup analysis of the GREek Atorvastatin and Coronary heart disease Evaluation (GREACE) Study. Nephrol Dial Transplant 2007; 22: 118-127.
50. Modan M, Halkin H, Karasik A, Lusky A. Elevated serum uric acid: A facet of hyperinsulinaemia. Diabetologia 1987; 30: 713-718.
51. Nakagawa T, Hu H, Zharikov S, Tuttle KR, Short RA, Glushakova O, et al. A causal role for uric acid in fructose – induced metabolic syndrome. Am J Physiol Renal Physiol 2006; 290: 625-631.
52. Onat A, Uyarel H, Hergenc G, Karabulut A, Albayrak S, Sari I, et al. Serum uric acid is a determinant of metabolic syndrome in a population – based study. Am J Hypertens 2006; 19: 1055 – 1062.

53. Milionis HJ, Rizos E, Goudevenos J, SeferiadisK, Mikhaildis DP, Elisaf MS. Components of the metabolic syndrome and risk for firstever acute ischemic nonembolic stroke in elderly subjects. Stroke 2005; 36: 1372-1376.
54. Kurl S, Laukkanen JA, Niskanen L, Laaksonen D, Sivenius J, Nyyssonen K, et al. Metabolic syndrome and the risk of stroke in middle – aged men. Stroke 2006; 37: 806-811.
55. Chen HJ, Bai CH, Yeh WT, Chiu HC, Pan WH. Influence of metabolic syndrome and general obesity on the risk of ischemic stroke. Stroke 2006; 37: 1060-1064.
56. Koren – Morag N, Goldbourt U, Tanne D. Relation between the metabolic syndrome and ischemic stroke or transient ischemic attack: A prospective cohort study in patients with atherosclerotic cardiovascular disease. Stroke 2005; 36: 1366-1371.
57. Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; 285: 2486-2497.
58. Daskalopoulou SS, TzovarasV, Mikhailidis DP, Elisaf M. Effect on serum uric acid levels of drugs prescribed for indications other than treating hyperuricaemia. Curr Pharm Des 2005; 11: 4161-4175.

59. Athyros VG, Elisaf M, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al; GREACE Study Collabarative Group. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: A subgroup analysis of the GREek Atorvastatin and Coronary – heart – disease Evaluation (GREACE) study. Am J Kidney Dis 2004; 43: 589 – 599.
60. Athyros VG, Mikhailidis DP, Papageorgiou AA, Symeonidis AN, Pehlivanidis AN, Bouloukos VI, et al. The effect of statins versus untreated dyslipidaemia on renal function in patients with coronary heart disease: A subgroup analysis of the Greek atorvastatin and coronary heart disease evaluation (GREACE) study. J ClinPathol 2004; 57: 728-734.
61. Amarenco P, Labreuche J, Lavallee P, Touboul P-J. Statins in stroke prevention and carotid atherosclerosis. Systematic review and metaanalysis. Stroke 2004; 35: 2902-2909.
62. Tayag EC, Nair SN, Wahhab S, Katsetos CD, Lighthall JW, Lehmann JC. Cerebral uric acid increases following experimental traumatic brain injury in rat. Brain Res 1996; 733: 287-91.
63. Kanemitsu H, Tamura A, Kirino T, Karasawa S, Sano K, Iwamoto T, Yoshiura M, Iriyama K. Xanthine and uric acid levels in rat brain following focal ischemia. J Neurochem 1988; 51: 1882-5.
64. Nieto FJ, Iribarren C, Gross MD, Comstock GW, Cutler RG. Uric acid and serum antioxidant capacity: a reaction to atherosclerosis? Atherosclerosis 2000; 148: 131-9.

65. Sundstrom J, Sullivan L, D' Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric acid to longitudinal blood pressure tracking and hypertension incidence in the Framingham Heart Study. Hypertension 2005; 45: 28-33.
66. Masuo K, Kawaguchi H, Mikami H, OgiharaT, Tuck ML. Serum uric acid and plasma nore4pinephrine concentrations predict subsequent weight gain and blood pressure elevation. Hypertension 2003; 42: 474-480.
67. Bos MJ, Koudstaal PJ, Hofman A, WittemanJC, Breteler MM. Uric acid is a risk factor for myocardial infarction and stroke. The Rotterdam study. Stroke 2006; 37: 1503-1507.
68. Cerebrovascular diseases – Harrison's principles of Internal Medicine – 16th edition. Pages 2372-74.
69. Zhang X, Patel A, Horibe H, We Z. Asia Pacific Cohort Studies Collaboration. Cholesterol, coronary artery disease and stroke in the Asia Pacific Region. Int J Epidemiol2003; 32: 563-572.
70. Horestein RB, Smit DE, Mosca L. Cholesterol predicts stroke mortality in the Women's Pooling Project. Stroke 2002; 33c: 1863-1868.
71. AstriosKargiannis MD, Dimitri P Mikhalidis MD, KonstantinosTziomalos MD. Uric acid independently predicts early death after stroke. Circulation Journal 2007; 71: 1120-1127.
72. Gain MP, Xue YM, Shan J, Zhou L. SUA in type 2 diabetic patients complicated by stroke. Di Yi Jun Yi Da XueBao 2002; Jan ;22(1):

PROFORMA

CASE NO

Name :

Age : Sex: M/F

Address:

Occupation: Income:

Socioeconomic status: Handedness: R / L

DOA: DOD:

PRESENT COMPLAINTS:

H / O Present Illness:

Duration -

Seizures: Y / N

ICT Features: Y / N

H / O LOC : Y / N

S / O higher functions abnormality:

s/o cranial nerve lesions:

s/o motor system abnormalities:

s/o sensory involvement:

s/o cerebellar involvement:

s/o EPS involvement:

PAST HISTORY

HTN - Y / N DM – Y/N CAD-Y/N

CVA-Y/N TIA-Y/N

GOUT – Y/N Hyperlipidemia – Y / N

PERSONAL HISTORY

SMOKING - ALCOHOLISM

Diet – Veg/Non veg / Mixed

DRUG INTAKE – Thiazide diuretic

FAMILY HISTORY

DM - ; HTN ; CAD ; TIA ;CVA GOUT

CLINICAL EXAMINATION:

(a) VITALS: Pulse - /mt; BP- mm of Hg

(b) Higher functions: Consciousness;

Memory :

Speech :

Behavior :

(c) Cranial nerves :

(d) SPINOMOTOR SYSTEM: R L

Bulk of muscle	UL	
	LL	
Tone	UL	
	LL	

		R	L
Power	UL		
	LL		
DTR	UL		
	LL		
Plantar			

(e) SENSORY SYSTEM

(f) CEREBELLUM:

(g) EPS :

(h) SPINE / CRANIUM:

OTHER SYSTEMS:

(a) CVS :

(b) RS :

(c) P / A :

Diagnosis – CVA - Anterior circulation

Posterior circulation

Territory – ACA / MCA

INVESTIGATIONS:

1. Blood : TC - cells/cu.mm 2. Urine: Alb –
DC – P L E % Sug-
Hb - gms/dl Dep-

3. Blood: Sugar - mgsdl Urea – mg/dl
Creatinine mg/dl

4. Lipid profile – TGL mgs/dl LDL
TC HDL

5. Serum uric acid –

6. ECG in all leads –

7. CT Brain Plain INFARCT REGION –
INFARCT SIZE –

8. CARDIAC EVALUATION –

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR .S.VISHNU PRASAD,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :
Date :

Signature of participant

SI.NO	AGE	SEX	HTN	DM	SMOKING	CAD	DYSLIPIDEMIA	ALCOHOLISM	DIET		URIC ACID	
										<5	5-6.9	>7
1	46	Male	Absent	Absent	Yes	Absent	Present	Yes	Mixed	3.5	-	-
2	79	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	-	-	8.3
3	48	Male	Absent	Absent	Yes	Absent	Present	Yes	Mixed	2.7	-	-
4	51	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	4.1	-	-
5	54	Male	Present	Present	Yes	Absent	Present	No	Mixed	-	6.3	-
6	57	Female	Absent	Absent	No	Absent	Absent	No	Mixed	4.2	-	-
7	79	Male	Present	Present	No	Present	Absent	No	Mixed	-	-	8.2
8	64	Female	Absent	Present	No	Present	Present	No	Mixed	4.7	-	-
9	59	Male	Present	Absent	No	Absent	Present	No	Mixed	4.4	-	-
10	63	Female	Absent	Absent	No	Absent	Absent	No	Mixed	3.8	-	-
11	77	Female	Absent	Present	No	Absent	Absent	No	Veg	-	5.5	-
12	41	Female	Absent	Absent	No	Absent	Absent	No	Mixed	4.1	-	-
13	62	Male	Absent	Present	No	Absent	Absent	No	Mixed	-	6.1	-
14	53	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	-	5.3	-
15	51	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	3.5	-	-
16	62	Female	Present	Present	No	Absent	Absent	No	Veg	-	5.5	-
17	68	Male	Absent	Present	No	Absent	Absent	Yes	Mixed	-	6.4	-
18	49	Male	Present	Absent	No	Absent	Absent	No	Mixed	4.1	-	-
19	76	Male	Absent	Present	No	Present	Present	No	Mixed	-	-	8.5
20	69	Female	Present	Absent	No	Present	Absent	Yes	Mixed	-	-	7.4
21	63	Female	Present	Present	Yes	Present	Absent	Yes	Mixed	-	6.2	-
22	59	Female	Present	Absent	No	Absent	Absent	No	Mixed	4.6	-	-
23	72	Female	Absent	Absent	No	Absent	Absent	No	Mixed	-	-	7.2
24	82	Male	Present	Present	No	Absent	Absent	No	Mixed	-	5.4	-
25	48	Male	Absent	Absent	No	Absent	Absent	No	Mixed	3.9	-	-
26	72	Female	Present	Present	No	Present	Present	No	Veg	-	-	8.9
27	60	Female	Present	Absent	No	Absent	Absent	No	Mixed	4.5	-	-

SI.NO	AGE	SEX	HTN	DM	SMOKING	CAD	DYSLIPIDEMIA	ALCOHOLISM	DIET		URIC ACID	
28	71	Male	Present	Present	No	Absent	Absent	No	Mixed	-	5.1	-
29	62	Male	Present	Absent	Yes	Present	Absent	Yes	Mixed	-	-	8.7
30	41	Female	Absent	Absent	No	Absent	Absent	No	Mixed	3.6	-	-
31	46	Male	Absent	Present	No	Absent	Present	No	Veg	4.9	-	-
32	53	Male	Present	Absent	Yes	Absent	Absent	Yes	Mixed	4.1	-	-
33	61	Male	Present	Absent	No	Absent	Absent	Yes	Mixed	2.7	-	-
34	56	Male	Absent	Present	Yes	Present	Present	Yes	Mixed	-	-	8.1
35	55	Male	Present	Absent	Yes	Present	Absent	Yes	Veg	-	6.4	-
36	59	Female	Present	Absent	No	Present	Absent	No	Mixed	-	-	7.4
37	61	Female	Absent	Present	No	Present	Present	No	Mixed	-	6.7	-
38	58	Male	Present	Absent	Yes	Absent	Absent	Yes	Mixed	-	5.7	-
39	52	Male	Absent	Absent	Yes	Absent	Absent	Yes	Mixed	3	-	-
40	43	Male	Present	Absent	Yes	Absent	Present	No	Mixed	4.2	-	-
41	57	Male	Present	Absent	Yes	Absent	Absent	Yes	Mixed	3.8	-	
42	75	Male	Present	Present	No	Present	Absent	No	Mixed	-	-	9.1
43	59	Male	Present	Present	Yes	Present	Present	No	Veg	-	-	8.3
44	64	Female	Absent	Present	No	Absent	Absent	No	Mixed	-	5.9	-
45	65	Female	Present	Present	No	Absent	Absent	No	Mixed	-	-	7.1
46	42	Female	Absent	Absent	No	Absent	Present	No	Mixed	3.7	-	-
47	56	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	4	-	-
48	60	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	-	5.5	-
49	54	Male	Present	Absent	Yes	Absent	Absent	Yes	Mixed	4.5	-	-
50	74	Male	Present	Absent	Yes	Absent	Absent	Yes	Mixed	4.1	-	-
51	48	Male	Present	Present	Yes	Absent	Present	Yes	Mixed	-	-	8.1
52	57	Male	Present	Present	No	Present	Present	No	Veg	-	-	7.4
53	70	Female	Present	Absent	No	Absent	Absent	No	Mixed	-	-	8.3
54	55	Male	Present	Present	No	Present	Absent	No	Mixed	-	5.1	-
55	65	Female	Present	Present	No	Absent	Absent	No	Mixed	-	5.6	-

SI.NO	AGE	SEX	HTN	DM	SMOKING	CAD	DYSLIPIDEMIA	ALCOHOLISM	DIET		URIC ACID	
56	69	Female	Present	Present	No	Absent	Present	No	Mixed	4.8	-	-
57	41	Female	Present	Present	No	Present	Absent	No	Mixed	3.7	-	-
58	49	Female	Present	Absent	No	Absent	Absent	No	Mixed	4.3	-	-
59	83	Female	Present	Present	No	Present	Absent	No	Mixed	4.2	-	-
60	42	Female	Present	Absent	No	Absent	Absent	No	Mixed	-	5.5	-
61	63	Male	Present	Absent	No	Absent	Absent	No	Veg	4.7	-	-
62	70	Male	Absent	Absent	No	Absent	Absent	No	Mixed	-	-	9.2
63	66	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	-	5.1	-
64	51	Female	Present	Absent	No	Absent	Absent	No	Mixed	3.5	-	-
65	55	Male	Present	Present	Yes	Absent	Absent	No	Mixed	4.6	-	-
66	69	Female	Present	Present	No	Absent	Present	No	Mixed	-	-	7.3
67	64	Female	Absent	Absent	No	Absent	Absent	No	Mixed	4.8	-	-
68	62	Male	Present	Present	Yes	Present	Present	Yes	Mixed	3.8	-	-
69	64	Female	Present	Absent	No	Absent	Absent	No	Mixed	-	5.3	-
70	41	Male	Absent	Absent	Yes	Present	Present	No	Mixed	3.9	-	-
71	80	Male	Present	Present	Yes	Present	Present	Yes	Mixed	-	-	8.3
72	50	Male	Absent	Absent	Yes	Absent	Absent	No	Mixed	4.3	-	-
73	46	Male	Present	Present	Yes	Absent	Present	No	Mixed	2.5	-	-
74	65	Female	Absent	Absent	No	Present	Absent	No	Mixed	2.7	-	-
75	73	Female	Present	Absent	No	Present	Absent	No	Veg	4.1	-	-
76	71	Female	Present	Absent	No	Absent	Absent	No	Mixed	-	-	7.1
77	70	Female	Present	Present	No	Present	Absent	No	Mixed	-	-	7.5
78	63	Female	Present	Present	No	Absent	Present	No	Mixed	-	6.3	-
79	61	Male	Present	Present	Yes	Present	Present	Yes	Mixed	-	-	7.1
80	60	Male	Present	Absent	Yes	Absent	Present	No	Mixed	4.6	-	-
81	68	Male	Present	Absent	Yes	Present	Absent	No	Mixed	-	5.4	-
82	62	Female	Present	Present	No	Absent	Present	No	Veg	-	6.3	-
83	58	Female	Present	Present	No	Present	Present	No	Veg	-	-	7.5

SI.NO	AGE	SEX	HTN	DM	SMOKING	CAD	DYSLIPIDEMIA	ALCOHOLISM	DIET		URIC ACID	
84	80	Female	Present	Absent	No	Absent	Absent	No	Mixed	-	5.3	-
85	67	Female	Present	Present	No	Present	Present	No	Mixed	-	-	8.7
86	56	Female	Absent	Present	No	Absent	Present	No	Mixed	4.7	-	-
87	63	Female	Present	Present	No	Present	Present	No	Mixed	3.7	-	-
88	44	Female	Absent	Absent	No	Absent	Absent	No	Mixed	-	5.4	-
89	45	Female	Absent	Present	No	Absent	Present	No	Mixed	4.3	-	-
90	65	Female	Present	Absent	No	Absent	Absent	No	Mixed	4.1	-	-
91	74	Female	Present	Present	No	Present	Absent	No	Mixed	-	-	7.2
92	56	Male	Present	Present	Yes	Absent	Absent	Yes	Mixed	3.8	-	-
93	63	Female	Present	Present	No	Present	Present	No	Mixed	-	-	7.1
94	47	Female	Present	Present	No	Present	Absent	No	Mixed	4.8	-	-
95	56	Female	Present	Absent	No	Present	Absent	No	Mixed	4.6	-	-
96	51	Female	Present	Present	No	Present	Present	No	Veg	-	5.1	-
97	57	Male	Present	Absent	Yes	Absent	Absent	No	Mixed	3.7	-	-
98	48	Female	Absent	Present	No	Absent	Present	No	Mixed	-	5.4	-
99	65	Female	Absent	Present	No	Absent	Absent	No	Mixed	-	6.7	-
100	48	Female	Absent	Present	No	Absent	Present	No	Mixed	4.3	-	-