“CORRELATION OF SERUM URIC ACID LEVELS & LIPID LEVELS IN PATIENTS WITH ISCHAEMIC CEREBROVASCULAR ACCIDENT - A ONE YEAR CROSS SECTIONAL STUDY”

REG NO. BG0111008

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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ENDORSEMENT

This is to certify that the dissertation entitled **"CORRELATION OF SERUM URIC ACID LEVELS & LIPID LEVELS IN PATIENTS WITH ISCHAEMIC CEREBROVASCULAR ACCIDENT - A ONE YEAR CROSS SECTIONAL STUDY"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0111008.**

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LIST OF ABBREVIATIONS USED

3D TOF	-	3-dimensional time of flight
ABC	-	Airway, breathing, and circulation
ACE-I	-	Angiotensin-converting enzyme inhibitor
AF	-	Atrial fibrillation
AHA	-	American Heart Association
AMI	-	Acute myocardial infarction
ANA	-	Antinuclear antibody
APLA	-	Antiphospholipid antibody
ASA	-	American Stroke Association
ATP	-	Adenosine triphosphate
BMI	-	Body mass index
BP	-	Blood pressure
CAD	-	Coronary artery disease
CBF	-	Cerebral flow
CEMRA	-	Contrast-enhanced magnetic resonance angiography
CHD	-	Coronary heart disease
CHF	-	Congestive heart failure
CI	-	Confidence interval
CKD	-	Chronic kidney disease
CLRD	-	Chronic lower respiratory diseases
CNS	-	Central nervous system
CT	-	Computed tomography
CVD	-	Cardiovascular disease
CVT	-	Cerebral venous thrombosis
DALY	-	Disability adjusted life-year

DWI	-	Diffusion-weighted imaging
e.g.	-	For example
g	-	Gram
GABA	-	Gamma-aminobutyric acid
GSH	-	Glutathione
HDL-C	-	High density lipoprotein-cholesterol
HOMA	-	Homoeostatic model assessment
i.e.	-	That is
IMT	-	Intima-media thickness
IR	-	Insulin resistance
LDL	-	Low-density lipoprotein
LOC	-	Level of consciousness
MCA	-	Middle cerebral artery
MetS	-	Metabolic syndrome
Mg	-	Magnesium
MI	-	Myocardial infarction
mL	-	Milli litre
MRA	-	Magnetic resonance angiography
MRFIT	-	Multiple risk factor interventional trial
MRI	-	Magnetic resonance imaging
n	-	Total number
NCCT	-	Noncontrast computed tomography
NCEP	-	National Cholesterol Education Program
NIHS	-	National Institutes of Health Stroke
NIHSS	-	National Institutes of Health Stroke Scale
NMDA	-	N -methyl-D-aspartate
NO	-	Nitric oxide

OAT	-	Organic ion transporters
OC	-	Oral contraceptives
p	-	Probability
PC	-	Phase-contrast
PCA	-	Posterior cerebral artery
PTA	-	Phosphotungistic acid
PWI	-	Perfusion-weighted imaging
r	-	Pearson’s correlation coefficient
RF	-	Radiofrequency
ROS	-	Reactive oxygen species
RPR	-	Rapid plasma reagent
rTPA	-	Recombinant tissue plasminogen activator
rt-PA	-	Recombinant tissue-type plasminogen activator
SD	-	Standard deviation
SPECT	-	Single photon emission computed tomography
TIAs	-	Transient ischemic attacks
URAT1	-	Urate transporter 1
US	-	United states
VLDL	-	Very low density lipoprotein
vs	-	Versus
XDH	-	Xanthine dehydrogenase
XO	-	Xantine oxidase
XOR	-	Xanthine oxidoreductase

ABSTRACT

Background and objectives

Stroke is the third common cause of death in the world after coronary heart disease and cancer. The present study was aimed to assess serum uric acid levels in patients with ischemic cerebrovascular accident, its utility as a prognostic marker and to correlate between serum uric acid levels and lipids in patients with ischemic cerebrovascular accident.

Methodology

This study was conducted on a total of 100 patients with ischemic cerebrovascular accident from January 2012 to December 2012 at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. Uric acid level was measured with photometry using the diagnostic kit for quantification of uric acid prepared by ELITech Clinical Systems.

Results

In this study 54% of the patients were females compared 46% males with male to female ratio of 1.1:1. The commonest age group was more than 60 years present in 41% of patients. The history of hypertension and diabetes was present in 59% and 30% and smoking and alcohol consumption was noted in 51% and 32% respectively. Of the 54 women history of menopause was reported by 40 patients. Very severe NHSS score were noted in 18% patients. Serum creatinine was raised in 14% of the patients. Lipids, viz. cholesterol, HDL, LDL and triglycerides were abnormal in 83%, 86%, 52% and 80% respectively. Raised

serum uric acid levels were noted in 69% of the patients and the mean serum uric acids levels were 7.72 ± 1.22.

Conclusion and interpretation

Serum uric acid levels in patients with acute ischemic stroke are on the higher side. Higher serum uric acid levels were consistently found in patients with very severe and severe ischemic stroke assessed by NIHS score. Stroke mortality in our study was significantly correlated with high serum uric acid levels. Positive association was found between raised serum uric acid levels and sex, age, history of hypertension and diabetes mellitus, personal history of smoking and alcohol consumption and history of menopause in women.

Keywords

Ischemic cerebrovascular accident; Lipid profile; Serum uric acid;

CONTENTS

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Chapter 1

Introduction

INTRODUCTION

Stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Strokes are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke.

According to a recent report, about 780000 Americans experience a new or recurrent stroke each year, on average, one stroke every 40 seconds.[1] Stroke is the third most common cause of death worldwide after coronary heart disease and cancer especially in the elderly.[2,3] The mortality rate of stroke in the acute phase is as high as 20% and it remains higher for several years after the acute event in stroke patients than in the general population.[2]

Stroke is the second most common cause of disability and dementia in adults aged ≥ 65 years worldwide: close to 25% of stroke survivors develop dementia.[4] Stroke is also an important cause of morbidity and long term disability: up to 40% of survivors are not expected to recover their independence and self-care.[2]

It has been noted that the incidence of stroke varies considerably from country to country, furthermore in some areas or within or some racial and ethnic groups, strokes incidence may be unusually high. Based on the review of available information in India, the prevalence of stroke was estimated as 203 per 100,000 population above 20 years, amounting to a total of about 1 million cases. Upto 85% of all strokes are of ischaemic origin.

Atherosclerosis of the arteries, large and small, that supply the brain is the most common cause of ischaemic stroke. Atherosclerosis of the proximal aorta is also a source of atherogenic brain emboli. Large artery atherosclerotic infarction occurs when there is an impediment to normal perfusion, usually caused by a severe arterial stenosis or occlusion due to atherosclerosis and coexisting thrombosis or artery to artery embolism. Microatheroma, lipohyalinosis, and other occlusive diseases of the small penetrating brain arteries are the most frequent causes of small, sub-cortical "lacunar" infarcts. About 20% of ischaemic strokes are due to cardiogenic embolism, most commonly from atrial fibrillation. A variety of other occlusive disorders may be the .primary cause or variably contribute to stroke pathogenesis.[5]

Stroke is one of the most common and the most fatal and debilitating neurologic disease. Numerous risk factors are involved in the development of stroke, such as hypertension, cigarette smoking, hyperlipidemia and diabetes.[6] Recent studies indicate that there may be other factors influencing the development or course of the disease like serum levels of uric acid.[5]

Uric acid is the ultimate catabolite of purine metabolism in human and higher primates.[8] It exists in the extracellular compartment as sodium urate, and it is cleared from the plasma through the kidney.[9] Uric acid levels are influenced by age and sex. Prior to puberty, the average serum uric acid is 3.6 mg/dl for males and females. Following puberty, value rises to adult levels with women typically 1 mg/dl less than men. This lower level in women apparently reflects estrogen related enhancement of renal urate clearance.[8]

It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome.[9,10] On the other hand uric acid has been known to exert neuroprotective effects by acting as a free radical scavenger.[9,11] In humans, approximately one half the antioxidant capacity of plasma comes from uric acid.[11,12] The role of urate in ischemic stroke is poorly understood.

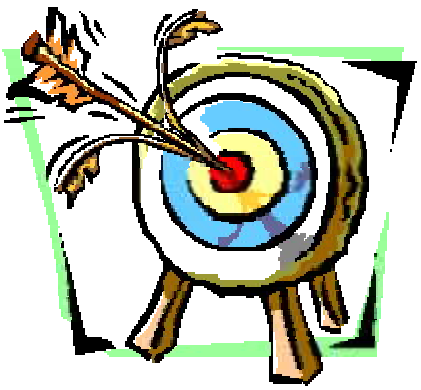
A retrospective analysis of hospitalization data of 2495 patients in Glasgow suggested that higher serum urate on admission predicted poor outcome (dead or in care) and higher vascular event rate following ischemic stroke.[13] By contrast a prospective hospital-based study involving 881 patients found that higher level of serum urate predicted better outcomes following stroke, suggesting that serum urate may be beneficial and protect against poor outcomes.[14] In addition an experimental study showed that uric acid administered early after thromboembolic stroke is neuroprotective in the rat brain and it extends the benefits of recombinant tissue plasminogen activator (rTPA).[15]

Therefore the role of uric acid as a risk factor for vascular disease and acute stroke is controversial as some of the studies have found that uric acid predicts the development of stroke, whereas others have failed to identify uric acid as a significant and independent risk factor after controlling for other atherosclerotic risk factors.[16-18] Also, there is little information available on the role of uric acid in ischemic stroke especially in Indian context. Considering these facts, the present study was planned to assess serum uric acid levels in patients with ischaemic cerebrovascular accident and to correlation between

serum uric acid levels and lipids in patients with ischaemic cerebrovascular accident.

Chapter 2

Objectives



OBJECTIVES

The objectives of the study were;

1. To study serum uric acid levels in patients with ischaemic cerebrovascular accident.

2. To study correlation between serum uric acid levels and lipids in patients with ischaemic cerebrovascular accident.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

The term “Stroke” or “Cerebrovascular accidents” has come to signify the abrupt impairment of brain function caused by a variety of pathological changes involving one (focal) or several (multifocal) intracranial or extracranial blood vessels.[19]

The concept of stroke was first noted from 460 to 370 before the Common Era by Hippocrates. At this time, the symptoms of convulsions and paralysis were referred to as apoplexy. Over the next several hundred years, scholars focused on physical symptoms and potential causes. It was not uncommon for patients to be treated with enemas and bloodletting. As technology advanced, physicians and scholars began to evaluate pathophysiological changes. These changes noted by scholars such as Thomas Willis and Jakob Wepfer led to medical interventions. Nurses' main focus was to help patients cope with and adjust to their disabilities. Within the last decade, the magnitude of research has grown exponentially. The term apoplexy has faded, and the term stroke has become common place in the medical setting.[20]

EPIDEMIOLOGY

Prevalence

Worldwide

The Centers for Disease Control and Prevention recently released mortality data indicating that in 2008, stroke declined from the third to the fourth

leading cause of death in the United States after heart disease, cancer, and chronic lower respiratory diseases (CLRD).[21]

For stroke health professionals, this demotion is a welcome indignity, and an important occasion to reflect on historical trends in stroke-specific mortality and the drivers of mortality reduction and also to highlight persisting challenges, including race–ethnicity, sex, and geographic disparities in stroke mortality; the ongoing burden of stroke disability; the expanding obesity epidemic and aging of the US population; and the epidemic of cerebrovascular disease worldwide, where stroke remains the second leading cause of death after heart disease.[22]

Despite improvements in stroke mortality in the United States, stroke remains the second leading cause of death worldwide. Over two thirds of stroke deaths worldwide occur in developing countries.[23]

The World Health Organization estimates for 2001 indicate that 4.61 million people died from cerebrovascular disease, accounting for 9.5% of deaths.[24]

Although rates of stroke mortality and burden vary greatly among countries, low-income countries are the most severely affected. There has been a 42% decrease in stroke incidence in high-income countries and >100% increase in low- to middle-income countries.[25]

The progress in prevention and mortality achieved in developed world urgently need to be translated to middle- and lower-income societies.[22]

Prevalence and incidence of stroke in India

For India, the overall age adjusted prevalence rate for stroke is estimated to lie between 84-262/100,000 in rural and between 334-424/100,000 in urban areas.[26]

The crude prevalence rate appears to be higher in urban compared to rural populations. The Parsi population in Mumbai appears particularly at risk, compared with the Indian population. The Parsi people migrated from Iran in the 7th century to India. It is argued that they are ethnically distinct from the Indian population.[26]

Whilst marriage outside their community is prohibited, the rates for prevalence and incidence of stroke are similar to that of developed countries.[26]

Morbidity and Mortality associated with Stroke

Global Stroke estimates[26]

- 400-800 strokes per 100,000.
- 5.7 million Deaths.
- 16 million new acute strokes every year.
- 28,500,000 DALYs (disability adjusted life-year).
- 28-30 day case fatality ranges from 17%-35%.

Stroke Morbidity and Mortality in India[26]

- Prevalence 90-222 per 100,000.
- 102,620 million deaths.

- 1.44-1.64 million cases of new acute strokes every year.
- 6,398,000 DALYs.
- 12% of strokes occur in the population aged <40 years
- 28-30 day case fatality ranges from 18-41%.

Classification of stroke[27]

Broadly, strokes are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke.[28]

There are many classifications according to etiology vascular territory and by time course etc.

1. Classification by time course:
    a. Transient ischaemic attack.
    b. Reversible ischaemic neurological deficit.
    c. Stroke in evolution.
    d. Completed stroke.
2. By arterial territory:
    a. Internal carotid artery territory.
    b. Vertebrobasilar territory.
    c. Lenticulo-striate.

3. By underlying pathology:

    a. Atheromatous occlusion of vessels.

    b. Atheroembolism.

    c. Lipohylinoid necrosis.

    d. Charcot Bouchard aneurysm rupture.

4. According to cause:[27]

    a. Atherosclerosis.

    b. Embolism of cardiac origin.

    C. Vasculitis: Primary CNS, PAN, Collagen Vascular Disease, temporal arteritis, infectious vasculitis.

    d. Hematological Disorders: Hemoglobinopathies, hyperviscosity syndrome, hypercoagulability states, protein C and S deficiency, APLA syndrome.

    e. Drugs: Cocaine, alcohol, amphetamines, OC pills.

    f. Others: MoyaMoya, migraine, fibromuscular dysplasia.

    g. Cerebral Venous Thrombosis.

    h. Intracerebral haemorrhage.

ISCHAEMIC STROKE

Thrombotic cerebral infarction results from the atherosclerotic obstruction of large cervical and cerebral arteries, with ischemia in all or part of the territory of the

occluded artery. This can be due to occlusion at the site of the main atherosclerotic lesion or to embolism from this site to more distal cerebral arteries.

Embolic cerebral infarction is due to embolism of a clot in the cerebral arteries coming from other parts of the arterial system, for example, from cardiac lesions, either at the site of the valves or of the heart cardiac cavities, or due to rhythm disturbances with stasis of the blood, which allows clotting within the heart as seen in atrial fribrillation.

Lacunar cerebral infarctions are small deep infarcts in the territory of small penetrating arteries, due to a local disease of these vessels, mainly related to chronic hypertension.

Several other causes of cerebral infarction exist and are of great practical importance for patient management. As they are relatively rare they can be ignored for most epidemiological purposes.

Etiology[29]

Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombosis embolism, thrombosis in situ, or relative hypoperfusion. As blood flow decreases, neurons cease functioning, and irreversible neuronal ischemia and injury begin at blood flow rates of less than 18 mL/100 g of tissue/min.

Risk factors[29]

Risk factors for ischemic stroke include modifiable and nonmodifiable etiologies. Identification of risk factors in each patient can uncover clues to the

cause of the stroke and the most appropriate treatment and secondary prevention plan.

Nonmodifiable risk factors include the following:

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Sickle cell disease
- Fibromuscular dysplasia
- Heredity

Modifiable risk factors include the following:

- Hypertension
- Diabetes mellitus
- Cardiac disease - Atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right to left shunting, such as a patent foramen ovale and atrial and ventricular enlargement
- Hypercholesterolemia
- Transient ischemic attacks (TIAs)
- Carotid stenosis
- Hyperhomocystinemia
- Lifestyle issues - Excessive alcohol intake, tobacco use, illicit drug use, obesity, physical inactivity

- Oral contraceptive use

Among the types of cardiac disease that increase stroke risk are atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right-to-left shunting, such as a patent foramen ovale and atrial and ventricular enlargement.

TIA is a transient neurologic deficit with no evidence of an ischemic lesion on neuroimaging. Roughly 80% resolve within 60 minutes.[30]

TIA can result from the aforementioned mechanisms of stroke. Data suggest that roughly 10% of patients with TIA suffer stroke within 90 days and half of these patients suffer stroke within 2 days.[31,32]

Antipsychotic medications

An analysis of 14,584 stroke patients who had at least 1 antipsychotic prescription during the year before their first hospitalization for stroke indicated that in the first few weeks of use, antipsychotics are associated with an increased stroke risk. Dosage size, older age and/or the presence of dementia, and the use of antipsychotics with a high binding affinity for alpha-2-adrenergic and M1-muscarinic receptors contributed to the stroke risk.[33]

According to the investigators, the stroke risk in persons taking antipsychotic medications was 1.6-fold higher in the 2 weeks before the stroke occurred. However, this association was observed only in the initial 28 days of antipsychotic use, after which the drugs were no longer a contributing factor in stroke.[29]

Genetic and inflammatory mechanisms[29]

Evidence continues to accumulate to suggest important roles for inflammation and genetic factors in the process of atherosclerosis and, specifically, in stroke. According to the current paradigm, atherosclerosis is not a bland cholesterol storage disease, as previously thought, but a dynamic, chronic, inflammatory condition caused by a response to endothelial injury. Traditional risk factors, such as oxidized low-density lipoprotein (LDL) and smoking, contribute to this injury. It has been suggested, however, that infections may also contribute to endothelial injury and atherosclerosis.

Host genetic factors, moreover, may modify the response to these environmental challenges, although inherited risk for stroke is likely multigenic. Even so, specific single-gene disorders with stroke as a component of the phenotype demonstrate the potency of genetics in determining stroke risk.

Flow disturbances[29]

Stroke symptoms can result from inadequate cerebral blood flow due to decreased blood pressure (and specifically, decreased cerebral perfusion pressure) or as a result of hematologic hyperviscosity due to sickle cell disease or other hematologic illnesses, such as multiple myeloma and polycythemia vera. In these instances, cerebral injury may occur in the presence of damage to other organ systems.

Large-artery occlusion[29]

Large-artery occlusion typically results from embolization of atherosclerotic debris originating from the common or internal carotid arteries or from a cardiac source. A smaller number of large-artery occlusions may arise from plaque ulceration and in situ thrombosis. Large-vessel ischemic strokes more commonly affect the MCA territory with the ACA territory affected to a lesser degree.

Lacunar strokes[29]

Lacunar strokes represent 13-20% of all ischemic strokes. They occur when the penetrating branches of the MCA, the lenticulostriate arteries, or the penetrating branches of the circle of Willis, vertebral artery, or basilar artery become occluded. Causes of lacunar infarcts include microatheroma, lipohyalinosis, fibrinoid necrosis secondary to hypertension or vasculitis, hyaline arteriosclerosis and amyloid angiopathy. The great majority are related to hypertension.

Embolic strokes[29]

Cardiogenic emboli may account for up to 20% of acute strokes. Emboli may arise from the heart, the extracranial arteries, or, rarely, the right-sided circulation (paradoxical emboli) with subsequent passage through a patent foramen ovale. The sources of cardiogenic emboli include the following:

- Valvular thrombi (eg, in mitral stenosis or endocarditis or from use of a prosthetic valve)

- Mural thrombi (eg, in myocardial infarction [MI], atrial fibrillation [AF], dilated cardiomyopathy, or severe congestive heart failure [CHF])

- Atrial myxoma

MI is associated with a 2-3% incidence of embolic strokes, of which 85% occur in the first month after MI.[35] Embolic strokes tend to have a sudden onset, and neuroimaging may demonstrate previous infarcts in several vascular territories or calcific emboli.

Risk factors include atrial fibrillation and recent cardiac surgery. Cardioembolic strokes may be isolated, multiple and in a single hemisphere, or scattered and bilateral; the latter 2 types indicate multiple vascular distributions and are more specific for cardioembolism. Multiple and bilateral infarcts can be the result of embolic showers or recurrent emboli. Other possibilities for single and bilateral hemispheric infarctions include emboli originating from the aortic arch and diffuse thrombotic or inflammatory processes that can lead to multiple small-vessel occlusions.[35,36]

Thrombotic strokes[29]

Thrombogenic factors may include injury to and loss of endothelial cells, exposing the subendothelium, and platelet activation by the subendothelium, activation of the clotting cascade, inhibition of fibrinolysis, and blood stasis. Thrombotic strokes are generally thought to originate on ruptured atherosclerotic plaques. Arterial stenosis can cause turbulent blood flow, which can increase the risk for thrombus formation, atherosclerosis (ie, ulcerated plaques), and platelet

adherence; all cause the formation of blood clots that either embolize or occlude the artery.

Intracranial atherosclerosis may be the cause in patients with widespread atherosclerosis. In other patients, especially younger patients, other causes should be considered, including[37,38] Hypercoagulable states (antiphospholipid antibodies, protein C deficiency, protein S deficiency, pregnancy), sickle cell disease, fibromuscular dysplasia, arterial dissections and vasoconstriction associated with substance abuse.

Watershed infarcts

Vascular watershed, or border-zone, infarctions occur at the most distal areas between arterial territories. They are believed to be secondary to embolic phenomenon or due to severe hypoperfusion, such as in carotid occlusion or prolonged hypotension.[39]

Risk factors with special emphasis in India[26]

There is a paucity of population based data about the coexistent proportions of risk factors for stroke in South Asians. Three transitions have contributed to the emergence of the stroke epidemic in India: demographic, lifestyle and socioeconomic. The demographic shift is characterised by increased life expectancy, lifestyle by a shift in food consumption and less physical activity and socioeconomic status with raising living standards by an urban elite who adopt western lifestyles. The resulting effect of these transitions increases risk factors for stroke, many of which are modifiable.

Non-modifiable stroke risk factors include, age, sex, low birth weight, ethnicity and genetic factors. In a recent study conducted in Gujarat, It was found that modifiable risk factors such as hypertension (40%), alcoholism (35%), smoking (28%) and hyperlipidemia (17%) are the commonest cause of stroke among the elderly; and smoking, alcoholism, increased BMI, diabetes and hypertension are significantly associated with strokes among young people.

Hyperlipidemia and diabetes are known to be the risk factor for large artery atherosclerotic and small vessel occlusive disease.

Short term risk of stroke and other vascular events are high among patients with transient ischaemic attack and minor ischaemic stroke.

The presence of coronary artery disease and large artery atherosclerosis are also considered the strong predictors of a new vascular event among the stroke survivors.

Heart disease and smoking appear to be greater risk factors for the Indian compared with the US population.

A recent hospital based multicenter prospective stroke registry in India with an objective to identify and recruit 10,000 acute stroke patients from 100 hospitals within India conducted an interim analysis to determine etiologies, clinical management and outcome with 5301 patients. Analysis found that patients with stroke had high rates of risk factors including high alcohol consumption, tobacco consumption, diabetes, hypertension and dyslipidemia. In

addition to this, the study identified that the short term mortality was higher among stroke patients with increased rates of risk factors.[40]

Pathophysiology

Acute ischemic strokes are the result of vascular occlusion secondary to thromboembolic disease. Ischemia results in cell hypoxia and depletion of cellular adenosine triphosphate (ATP). Without ATP, energy failure results in an inability to maintain ionic gradients across the cell membrane and cell depolarization. With an influx of sodium and calcium ions and passive inflow of water into the cell, cytotoxic edema results.[10]

Ischemic core and penumbra[29]

An acute vascular occlusion produces heterogeneous regions of ischemia in the affected vascular territory. The quantity of local blood flow is made up of any residual flow in the major arterial source and the collateral supply, if any.

Regions of the brain with CBF lower than 10 mL/100g of tissue/min are referred to collectively as the core, and these cells are presumed to die within minutes of stroke onset.

Zones of decreased or marginal perfusion (CBF < 25 mL/100g of tissue/min) are collectively called the ischemic penumbra. Tissue in the penumbra can remain viable for several hours because of marginal tissue perfusion.

Ischemic cascade

On the cellular level, the ischemic neuron becomes depolarized as ATP is depleted and membrane ion-transport systems fail. The resulting influx of calcium leads to the release of a number of neurotransmitters, including large quantities of glutamate, which in turn activates *N* -methyl-D-aspartate (NMDA) and other excitatory receptors on other neurons. These neurons then become depolarized, causing further calcium influx, further glutamate release, and local amplification of the initial ischemic insult. This massive calcium influx also activates various degradative enzymes, leading to the destruction of the cell membrane and other essential neuronal structures.[42]

Free radicals, arachidonic acid, and nitric oxide are generated by this process, which leads to further neuronal damage.

Ischemia also directly results in dysfunction of the cerebral vasculature, with breakdown of the blood-brain barrier occurring within 4-6 hours after infarction. Following the barrier's breakdown, proteins and water flood into the extracellular space, leading to vasogenic edema. Vasogenic edema produces greater levels of brain swelling and mass effect that peaks at 3-5 days and resolves over the next several weeks with resorption of water and proteins.[43]

Within hours to days after a stroke, specific genes are activated, leading to the formation of cytokines and other factors that, in turn, cause further inflammation and microcirculatory compromise.[42]

Ultimately, the ischemic penumbra is consumed by these progressive insults, coalescing with the infarcted core, often within hours of the onset of the stroke.

Infarction results in the death of astrocytes as well as the supporting oligodendroglia and microglia cells. The infarcted tissue eventually undergoes liquefaction necrosis and is removed by macrophages with the development of parenchymal volume loss. A well-circumscribed region of cerebrospinal fluid–like low density is eventually seen, consisting of encephalomalacia and cystic change. The evolution of these chronic changes may be seen in the weeks to months following the infarction.[29]

Hemorrhagic transformation of ischemic stroke

Hemorrhagic transformation represents the conversion of a bland infarction into an area of hemorrhage. This is estimated to occur in 5% of uncomplicated ischemic strokes, in the absence of thrombolytics. Hemorrhagic transformation is not always associated with neurologic decline and ranges from small petechial hemorrhages to hematomas requiring evacuation.[29]

Proposed mechanisms for hemorrhagic transformation include reperfusion of ischemically injured tissue, either from recanalization of an occluded vessel or from collateral blood supply to the ischemic territory or disruption of the blood-brain barrier. With disruption of the blood-brain barrier, red blood cells extravasate from the weakened capillary bed producing petechial hemorrhage or more frank intraparenchymal hematoma.[41]

Hemorrhagic transformation of an ischemic infarct occurs within 2-14 days post ictus, usually within the first week. It is more commonly seen following cardioembolic strokes and is more likely with larger infarct size.[41] Hemorrhagic transformation is also more likely following administration of t-PA, with noncontrast computed tomography (NCCT) scanning demonstrating areas of hypodensity.[44]

Poststroke cerebral edema and seizures

Although significant cerebral edema can occur after anterior circulation ischemic stroke, it is thought to be somewhat rare (10-20%).[45] Edema and herniation are the most common causes of early death in patients with hemispheric stroke.

Seizures occur in 2-23% of patients within the first days after stroke.[45] Afraction of patients who have experienced stroke develop chronic seizure disorders.

Presentation

History[29]

A focused medical history for patients with ischemic stroke aims to identify risk factors for atherosclerotic and cardiac disease, including hypertension, diabetes mellitus, tobacco use, high cholesterol, and a history of coronary artery disease, coronary artery bypass, or atrial fibrillation (see Etiology). Consider stroke in any patient presenting with acute neurologic deficit or any alteration in level of consciousness. Common signs of stroke include acute

hemiparesis or hemiplegia, acute hemisensory loss, complete or partial hemianopia, monocular or binocular visual loss, or diplopia, dysarthria or aphasia, ataxia, vertigo, or nystagmus and sudden decrease in consciousness.

In younger patients, elicit a history of recent trauma, coagulopathies, illicit drug use (especially cocaine), migraines, or use of oral contraceptives.

Establishing the time at which the patient was last without stroke symptoms is especially critical when thrombolytic therapy is an option. If the patient awakens with symptoms, then the time of onset is defined as the time at which the patient was last seen to be without symptoms. Family members, coworkers, and bystanders may be required to help establish the exact time of onset, especially in right hemispheric strokes accompanied by neglect or left hemispheric strokes with aphasia.

Physical Examination[29]

The goals of the physical examination include detecting extracranial causes of stroke symptoms, distinguishing stroke from stroke mimics, determining and documenting for future comparison the degree of deficit, and localizing the lesion.

The physical examination always includes a careful head and neck examination for signs of trauma, infection, and meningeal irritation.

Stroke should be considered in any patient presenting with an acute neurologic deficit (focal or global) or altered level of consciousness. No historical feature distinguishes ischemic from hemorrhagic stroke, although nausea,

vomiting, headache, and change in level of consciousness are more common in hemorrhagic strokes. Common symptoms of stroke include abrupt onset of hemiparesis, monoparesis, or quadriparesis, hemisensory deficits, monocular or binocular visual loss, visual field deficits, diplopia, dysarthria, ataxia, vertigo, aphasia and sudden decrease in the level of consciousness.

Although such symptoms can occur alone, they are more likely to occur in combination.

A careful search for the cardiovascular causes of stroke requires examination of the ocular fundi (retinopathy, emboli, hemorrhage), heart (irregular rhythm, murmur, gallop), and peripheral vasculature (palpation of carotid, radial, and femoral pulses, auscultation for carotid bruit).

Patients with a decreased level of consciousness should be assessed to ensure that they are able to protect their airway.

The physical examination must encompass all of the major organ systems, starting with the airway, breathing, and circulation (ABC) and the vital signs. Patients with stroke, especially hemorrhagic stroke, can clinically deteriorate quickly; therefore, constant reassessment is critical. Ischemic strokes, unless large or involving the brainstem, do not tend to cause immediate problems with airway patency, breathing, or circulation compromise. On the other hand, patients with intracerebral or subarachnoid hemorrhage frequently require intervention for airway protection and ventilation.

Vital signs, while nonspecific, can point to impending clinical deterioration and may assist in narrowing the differential diagnosis. Many patients with stroke are hypertensive at baseline, and their blood pressure may become more elevated after stroke. While hypertension at presentation is common, blood pressure decreases spontaneously over time in most patients. Acutely lowering blood pressure has not proven to be beneficial in these stroke patients in the absence of signs and symptoms of associated malignant hypertension, acute myocardial infarction, CHF, or aortic dissection.

Head and neck examination

A careful examination of the head and neck is essential. Contusions, lacerations, and deformities may suggest trauma as the etiology for the patient's symptoms. Auscultation of the neck may elicit a bruit, suggesting carotid disease as the cause of the stroke.

Cardiac examination

Cardiac arrhythmias, such as atrial fibrillation, are found commonly in patients with stroke. Similarly, strokes may occur concurrently with other acute cardiac conditions, such as acute myocardial infarction and acute CHF; thus, auscultation for murmurs and gallops is recommended.

Examination of the extremities

Carotid or vertebrobasilar dissections and, less commonly, thoracic aortic dissections may cause ischemic stroke. Unequal pulses or blood pressures in the extremities may reflect the presence of aortic dissections.

Neurologic examination

With the availability of thrombolytic therapy for acute ischemic stroke in selected patients, the physician must be able to perform a brief, but accurate, neurologic examination on patients with suspected stroke syndromes. The goals of the neurologic examination include the following:

- Confirming the presence of a stroke syndrome (to be defined further by cranial computed tomography [CT] scanning).
- Distinguishing stroke from stroke mimics.
- Establishing a neurologic baseline should the patient's condition improve or deteriorate.

Essential components of the neurologic examination include the evaluation of cranial nerves, motor function, sensory function, cerebellar function, gait, and deep tendon reflexes, as well as of mental status and level of consciousness. The skull and spine also should be examined, and signs of meningismus should be sought.

Central facial weakness from a stroke should be differentiated from the peripheral weakness of Bell palsy. With peripheral lesions (Bell palsy), the patient is unable to lift the eyebrows, wrinkle the forehead, or or close the eye on the affected side.

A useful tool in quantifying neurological impairment is the National Institutes of Health Stroke Scale (NIHSS).[46] The NIHSS is used mostly by stroke

teams. It enables the consultant to rapidly determine the severity and possible location of the stroke. A patient's score on the NIHSS is strongly associated with outcome, and it can help to identify those patients who are likely to benefit from thrombolytic therapy and those who are at higher risk of developing hemorrhagic complications of thrombolytic use.

This scale is easily used and focuses on the following 6 major areas of the neurologic examination including level of consciousness, visual function, motor function, sensation and neglect, cerebellar function and language.

The NIHSS is a 42-point scale, with minor strokes usually being considered to have a score less than 5. An NIHSS score greater than 10 correlates with an 80% likelihood of visual flow deficits on angiography. However, discretion must be used in assessing the magnitude of the clinical deficit; for instance, if a patient's only deficit is being mute, the NIHSS score will be 3. Additionally, the scale does not measure some deficits associated with posterior circulation strokes (ie, vertigo, ataxia).

NIH Stroke Scale

	Category	Description	Score
1a	level of consciousness (LOC)	Alert	0
		Drowsy	1
		Stuporous	2
		Coma	3
1b	LOC questions (month, age)	Answers both correctly	0
		Answers 1 correctly	1
		Incorrect on both	2
1c	Answers both correctly Answers 1 correctly Incorrect on both	Obeys both correctly	0
		Obeys 1 correctly	1
		Incorrect on both	2
2	Best gaze (follow finger)	Normal	0
		Partial gaze palsy	1
		Forced deviation	2
3	Best visual (visual fields)	No visual loss	0
		Partial hemianopia	1
		Complete hemianopia	2
		Bilateral hemianopia	3
4	Facial palsy (show teeth, raise brows, squeeze eyes shut)	Normal Minor	0
		Partial Complete	1
5	Motor arm left* (raise 90°, hold 10 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
6	Motor arm right* (raise 90°, hold 10 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4

	Category	Description	Score
7	Motor leg left* (raise 30°, hold 5 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
8	Motor leg right* (raise 30°, hold 5 seconds)	No drift	0
		Drift	1
		Cannot resist gravity	2
		No effort against gravity	3
		No movement	4
9	Limb ataxia (finger-nose, heel-shin)	Absent	0
		Present in 1 limb	1
		Present in 2 limbs	2
10	Sensory (pinprick to face, arm, leg)	Normal	0
		Partial loss	1
		Severe loss	2
11	Extinction/neglect (double simultaneous testing)	No neglect	0
		Partial neglect	1
		Complete neglect	2
12	Dysarthria (speech clarity to "mama, baseball, huckleberry, tip-top, fifty-fifty")	Normal articulation	0
		Mild to moderate dysarthria	1
		Near to unintelligible or worse	2
13	Best language** (name items, describe pictures)	No aphasia	0
		Mild to moderate aphasia	1
		Severe aphasia	2
		Mute	3
	Total		0-42

* For limbs with amputation, joint fusion, etc, score 9 and explain.
** For intubation or other physical barriers to speech, score 9 and explain. Do not add 9 to the total score.

Middle cerebral artery stroke[29]

MCA occlusion commonly produces contralateral hemiparesis, contralateral hypesthesia, ipsilateral hemianopsia, and gaze preference toward the side of the lesion. Agnosia is common, and receptive or expressive aphasia may result if the lesion occurs in the dominant hemisphere. Neglect, inattention, and extinction of double simultaneous stimulation may occur in nondominant hemisphere lesions. Since the MCA supplies the upper extremity motor strip, weakness of the arm and face is usually worse than that of the lower limb.

Anterior cerebral artery stroke[29]

ACA occlusions primarily affect frontal lobe function and can result in disinhibition and speech perseveration, producing primitive reflexes (eg, grasping, sucking reflexes), altered mental status, impaired judgment, contralateral weakness (greater in legs than arms), contralateral cortical sensory deficits gait apraxia, and urinary incontinence.

Posterior cerebral artery stroke[29]

PCA occlusions affect vision and thought, producing contralateral homonymous hemianopsia, cortical blindness, visual agnosia, altered mental status, and impaired memory.

Vertebrobasilar artery occlusions are notoriously difficult to detect because they cause a wide variety of cranial nerve, cerebellar, and brainstem deficits. These include vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypesthesia, syncope, ataxia.

A hallmark of posterior circulation stroke is that there are crossed findings: ipsilateral cranial nerve deficits and contralateral motor deficits. This is contrasted to anterior stroke, which produces only unilateral findings.

Lacunar stroke[29]

Lacunar strokes result from occlusion of the small, perforating arteries of the deep subcortical areas of the brain. The infarcts are generally from 2-20 mm in diameter. The most common lacunar syndromes include pure motor, pure sensory, and ataxic hemiparetic strokes. By virtue of their small size and well-defined subcortical location, lacunar infarcts do not lead to impairments in cognition, memory, speech, or level of consciousness.

Diagnosis

Approach

Laboratory evaluation of the patient with ischemic stroke should be driven by comorbid illnesses as well as the potential acute stroke. Additional laboratory tests are tailored to the individual patient. They may include rapid plasma reagent (RPR), toxicology screen, fasting lipid profile, sedimentation rate, pregnancy test, antinuclear antibody (ANA), rheumatoid factor, and homocysteine.[29]

CT is the most commonly used form of neuroimaging in the acute evaluation of patients with apparent acute stroke. MRI with magnetic resonance angiography (MRA) has been a major advance in the neuroimaging of stroke;

MRI not only provides great structural detail but also can demonstrate impaired metabolism.[29]

Carotid duplex scanning is one of the most useful tests in evaluating patients with stroke. Increasingly, it is being performed earlier in the evaluation, not only to define the cause of the stroke but also to stratify patients for either medical management or carotid intervention if they have carotid stenoses.[29]

Digital subtraction angiography is considered the definitive method for demonstrating vascular lesions, including occlusions, stenoses, dissections, and aneurysms.[29]

Complte Blood Cell Count

CBC count serves as a baseline study and may reveal a cause for the stroke (eg, polycythemia, thrombocytosis, thrombocytopenia, leukemia) or provide evidence of concurrent illness (anemia).[29]

Basic Chemistry Panel

Chemistry panel serves as a baseline study and may reveal a stroke mimic (eg, hypoglycemia, hyponatremia) or provide evidence of concurrent illness (eg, diabetes, renal insufficiency).[29]

Coagulation Studies

Coagulation studies may reveal a coagulopathy and are useful when thrombolytics or anticoagulants are to be used. In patients who are not anticoagulated and in whom there is no suspicion for coagulation abnormality,

administration of recombinant tissue-type plasminogen activator (rt-PA) should not be delayed awaiting laboratory studies.[29]

Cardiac Biomarkers

Cardiac biomarkers are important because of the association of cerebral vascular disease and coronary artery disease. Additionally, several studies have indicated a link between elevations of cardiac enzyme levels and poor outcome in ischemic stroke.[29]

Toxicology Screening

Toxicology screening may be useful in selected patients in order to assist in identifying intoxicated patients with symptoms/behavior mimicking stroke syndromes. Urine pregnancy test should be obtained for all women of childbearing age with stroke symptoms. The agent rt-PA is Pregnancy Class C.[29]

Arterial Blood Gas Analysis

Although infrequent in patients with suspected hypoxemia, arterial blood gas defines the severity of hypoxemia and may detect acid-base disturbances. If considering thrombolytics, arterial punctures should be avoided unless absolutely necessary.[29]

Imaging in Stroke

Imaging in ischemic stroke can involve several types of MRI, several types of CT scanning, angiography, ultrasonography, radiology, echocardiography, and nuclear imaging studies.[29]

Magnetic resonance imaging

Conventional MRI may take hours to produce discernable findings, well after the diffusion-weighted images have become positive. For this reason, many centers always include diffusion-weighted images in their standard brain MRI protocol. Diffusion-weighted MRI can detect ischemia much earlier than can standard CT scanning or MRI and provides useful data in stroke and TIA patients outside of the initial management window.[45]

The most commonly used technique for perfusion MRI is dynamic susceptibility, which involves generating maps of brain perfusion by monitoring the first pass of a rapid bolus injection of contrast through the cerebral vasculature. Susceptibility-related T2 effects create signal loss in capillary blood vessels and parenchyma perfused by contrast that can be measured and is proportional to the CBV.

An evidence-based guideline from the American Academy of Neurology recommends that diffusion-weighted imaging (DWI) is more useful than noncontrast CT for the diagnosis of acute ischemic stroke within 12 hours of symptom onset and should be performed for the most accurate diagnosis of acute ischemic stroke (level A). No recommendations were made regarding the use of perfusion-weighted imaging (PWI) in diagnosing acute ischemic stroke, as evidence to support or refute its value in this setting is insufficient.[47]

A study by Bhattacharya et al concluded that the early use of MRI helps to prevent emergency departments from misdiagnosing ischemic stroke in young adults presenting with signs of stroke. Reviewing a prospective database of

patients aged 16-49 years with ischemic stroke, the investigators found that the chance of misdiagnosis was lower in patients who had undergone MRI within 48 hours.[48]

The study also found that, in general, there is a particular risk that emergency departments will misdiagnose ischemic stroke in patients younger than 35 years, indicating that early MRI studies would be especially beneficial in young adults with signs of stroke.

Intra-arterial contrast enhancement may be seen secondary to slow flow during the first or second day after onset of infarction and has been correlated with increased infarct volume size.[49]

The 3 different techniques used to produce MRA images are 3-dimensional time of flight (3D TOF), phase-contrast (PC), and contrast-enhanced MRA (CEMRA). Three-dimensional TOF takes advantage of the higher signal from protons in flowing blood, compared with protons in stationary tissue, which become partially saturated and lose signal when exposed to a radiofrequency (RF) pulse. Areas of signal loss and narrowing correspond to stenosis and occlusions. PC involves tagging the spins of moving protons using bidirectional gradients and marking their changes in position when each gradient is applied. PC is exquisitely sensitive to flow, which the operator can choose the velocity threshold for, and gives excellent background suppression. CEMRA utilizes the intraluminal signal produced by a timed bolus of paramagnetic contrast material to evaluate vessel patency. Images may be single phase (i.e. arterial) or time resolved.

CT scanning

Imaging with computed tomography (CT) scanning has multiple logistic advantages for patients with acute stroke. CT scanning is able to more rapidly acquire images than MRI, allowing for assessment with an examination that includes noncontrast CT scanning, CT angiography, CT perfusion scanning in less than 10 minutes. Expedient acquisition is of the utmost importance in acute stroke imaging because of the narrow window of time available for definitive ischemic stroke treatment with pharmacologic agents and mechanical devices. CT scanning can also be performed in patients who are unable to tolerate an MR examination or who have contraindications to MRI, including pacemakers, aneurysm clips, or other ferromagnetic materials in their bodies. Additionally, CT scanning is more easily accessible for patients who require special equipment for maintaining and monitoring life support.[50,51]

The 2011 AHA/ASA CVT statement notes that MRI is more sensitive for the detection of CVT than CT. However, these modalities do not always accurately reveals positive findings of intraluminal thrombus, which is key to the diagnosis of CVT. Therefore, although a plain CT or MRI is useful in the initial evaluation, a negative finding should not rule out CVT.[52]

Other imaging studies in ischemic stroke

Transcranial Doppler ultrasonography is useful for evaluating more proximal vascular anatomy through the infratemporal fossa, including the MCA, intracranial carotid artery, and vertebrobasilar artery.[53]

Echocardiography is obtained in all patients with acute ischemic stroke in whom cardiogenic embolism is suspected.

Chest radiography has potential utility for patients with acute stroke. However, obtaining a chest radiograph should not delay the administration of recombinant tissue-type plasminogen activator (rt-PA); these radiographs have not been shown to alter the clinical course or decision-making in most cases.[54]

The use of SPECT scanning in stroke is still relatively experimental and available only at select institutions; it can theoretically define areas of altered regional blood flow.

Conventional angiography is the gold standard in evaluating for cerebrovascular disease as well as for disease involving the aortic arch and great vessels in the neck; it also provides for less invasive endovascular interventions. Conventional angiography can be performed to clarify equivocal findings or to confirm and treat disease seen on MRA, CTA, transcranial Doppler or ultrasonography of the neck.

Lumbar Puncture

A lumbar puncture is required to rule out meningitis or subarachnoid hemorrhage when the CT scan is negative but the clinical suspicion remains high.

SERUM URIC ACID LEVELS IN ISCHAEMIC STROKE

Uric acid is a weak organic acid, the end product of purine nucleotides degradation. Source of purine nucleotides are ingestion, endogenous synthesis of

purines from nonpurine precursors, and reutilization of preformed purine compounds. Degradation of purine nucleotides starts with nucleotidase activity in reaction which releases phosphate from nucleotides and produces nucleosides, adenosine and guanosine. Adenosine is than deaminated into inosine in reaction catalyzed by adenosine deaminase. Purine nucleotide phosphorilase hydrolyses ribose group from inosine and guanosine to produce xypoxantine and guanine, respectively. Guanine is deaminated to xsantine. Xantine oxidoreductase is widely distributed enzyme. It oxidases hypoxantine to xsantine, and finally xantine to uric acid in the liver, gut, lung, kidney, heart, brain and plasma.[55]

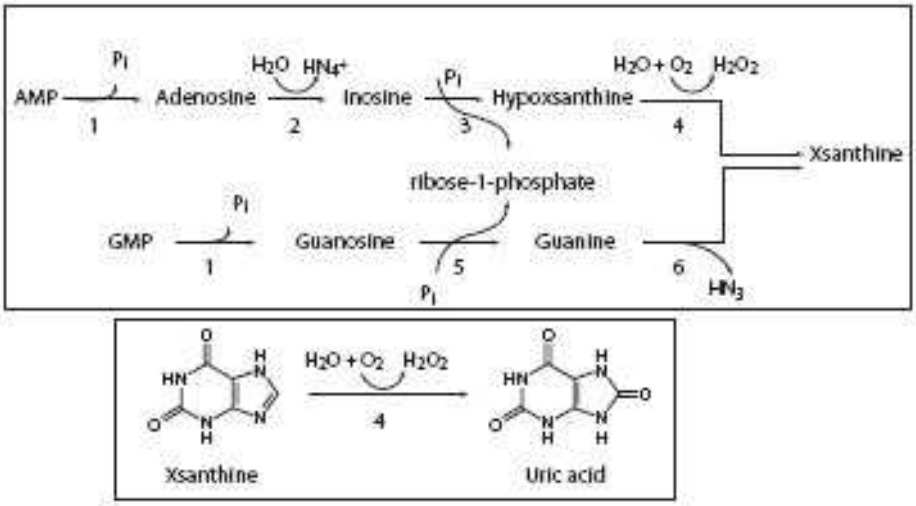


Figure 1. Degradation of purine nucleotides and formation of uric acid. 1 - Nucleotidase; 2 - Adenosine deaminase; 3 - Inosine phosphorilase; 4 - Xsanthine oxidase; 5 - Purine nucleosidase phosphorilase; 6 - Guanine deaminase.[55]

Determination of uric acid concentration includes phosphotungistic acid methods, uricase methods (in wide usage), high-performance liquid chromatograpy methods (reference methods) and dry chemistry systems.[55]

Under the steady-state conditions the production of uric acid is in balance with the uric acid disposal. The enzymes involved in uric acid production are responsible for oxidative stress and it was evidenced that SUA might be dependently or independently related to different multifactorial disorders. Elevated SUA positively correlates with development and progression of cardiovascular diseases. There is an evidence of positive association between SUA and risk of major coronary heart disease events. SUA is significantly positive correlated with hypertension and renal diseases. Nephrolithiasis of uric acid origin, as well as hyperuricemia, is more common among patients with the metabolic syndrome (MetS) and obesity.[55]

There is also a controversial opinion about prooxidative and antioxidant properties of uric acid. Uric acid is a powerful free radical scavenger in humans but it also represents a marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity. Because of all mentioned facts, it is reasonable to determinate SUA concentrations in different conditions.[55]

Uric acid and oxidative stress

Oxidative stress is considered to be one of the main reasons of cells function impairment. It is a condition of excessive production of free radicals and reactive oxygen species (ROS), as well as reduced antioxidative system, due to decreased intake of antioxidants or their excessive consumption.[55]

It is also a condition in which oxido-reductive processes in cells are turned in favor of oxidation due to excessive formation of free radicals and reactive oxygen species (ROS). Uric acid is a product of purine nucleotides

catabolism in the process catalyzed by liver enzyme xanthine oxidoreductase (XOR), which enables the oxidation of hypoxanthine to xanthine and its further oxidation to uric acid. During the production of uric acid catalyzed by xsanthine-oxidase, ROS are generated as by product,which have a significant role in the increased vascular oxidative stress.[55]

XOR is a hepatic enzyme which catalyzes the production of uric acid, nitric oxide, and reactive oxygen species, which potentially damage deoxyribonucleic acid, ribonucleic acid and proteins, inactivate enzymes, oxidize amino acids and convert poly-unsaturated fatty acids to lipids. XOR exists in two inter-convertible forms: XO-xantine oxidase and XDH-xanthine dehydrogenase. Humane XOR exists in vivo as the dehydrogenase form but is easily converted to XO by oxidation of the sulfhydryl residues or by proteolysis. There is the difference in substrate affinity of XO and XDH subforms. XDH preferentially reduces NAD^+, whereas XO cannot reduce NAD^+, preferring molecular oxygen (28).Reduction of molecular oxygen by either form of the enzyme yields superoxide and hydrogen peroxide, Uric acid is recognized as a marker of oxidative stress, but also as a protective factor acting as an antioxidant.[55]

Xanthine oxidoreductase (XOR) isoforms and characteristic reactions[55]

Xanthine oxidase (XO)	Xanthine dehydrogenase (XDH)
Hypoxanthine + H_2O +$2O_2$ →Xanthine + O_2^- + H_2O_2 Xanthine – H_2O+$2O_2$→Uric acid + O_2^- + H_2O_2	Hypoxanthine +NAD^+ –H_2C →Xanthine + NADH + H^+ Xanthine + NAD^+ –H_2C→Uric acid+NADH+ H^+
*XDH prefers NAD^+ as oxidizing substrate but it is able to react with O_2, while XO uses only O_2	

Regarding XO role in oxidative stress and pathophysiology of CVD, most therapeutic approaches are oriented on inhibiting the XO activity and disabling free radicals accumulation as a feasible target.[55]

Some studies showed that therapeutic use of allopurinol, xanthine oxidase inhibitor, which reduces serum levels of uric acid, show protective effects in situations associated with oxidative stress,[56,57] because of decreasing of ROS.

In clinical studies, for example in coronary bypass surgery, the protective effects of allopurinol are noticed as decreasedhospital mortality rate, increased cardiac index, better postoperative recovery and reduced lipid peroxidation.[58]

In heart failure allopurinol improves myocardial contractility by restoring myocardial calcium sensitivity and β-adrenergic responsiveness.[55]

The other explanation of benefitial allopurinol effect considers the effects on vascular endothelial function. Xanthine oxidase plays a key role in mediating intermittent hypoxia-induced vascular dysfunction and administration of allopurinol might prevent it.[55]

The investigations on animal models in the most cases also confirmed the beneficial effect of allopurinol after induction of myocardial infarction[58] with reducing myocardial damage, better recovery of ventricular function, better preservation of cellular ATP levels and mitochondrial ATP generation during ischemia and prevention of the decrease in left ventricular pressure. The beneficial effects of allopurinol may be unrelated to the inhibition of the XO, and decreasing the free radicals. The effects of allopurinol action as a xanthine-

oxidase inhibitor are increasing of intermediates, hypoxanthine and xanthine, and decreasing of final product uric-acid.[55]

Taking into account that xanthine derivatives are widely used medicaments in treatment of different disease (inflammatory diseases, behavioral, neurodegenerative diseases, renal diseases, respiratory diseases, cancer pain etc, the effect of xanthine or hypoxhantine should be considered in explanations of the mechanisms involved in effects of XOR inhibition.[55]

It is well known that widely used and examinated xanthine derivative is caffeine. The biological effects of caffeine and other xanthines have many molecular targets. Xanthines are antagonists of adenosine receptors, inhibitors of phosphodiesterases, antagonists of GABA receptors and sensibilators of calcium releaseryanodine-sensitive channels in the sarcoplasmic and endoplasmic reticulum.[55]

It appeared that caffeine also has stimulatory effects on Mg-ATPase and calcium sensitivity in cardiac myofibrils. Uric acid itself also can have an impact in oxidative stress. Experimental data showed that NO- labeled 1,3-$^{15}N_2$-uric acid ($^{15}N_2$-UA) under anaerobic conditions in several different media, including human plasma and endothelial cell lysates results with production of 5-aminouracil (5-AU) and 6-aminouracil (6-AU). These findings provide a mechanism for how uric acid may inhibit endothelial function by inhibition of NO-function under conditions of oxidative stress.[55]

Recent clinical studies demonstrated that high-dose allopurinol usage was associated with a lower risk of cardiovascular events and all-cause mortality,[59]

and that profoundly reduces vascular tissue oxidative stress and improves vascular/endothelial dysfunction.[60]

Elevated serum concentration of uric acid are associated with increased risk for cardiovascular disease (CVD), but there are also evidence of their potential role as antioxidants in CVD.[55]

Uric acid acts as an ‘‘antioxidant’’ substance with acting as a free radical scavenger and a chelator of transitional metal ions which are converted to poorly reactive forms.[55]

Both *in vitro* and *in vivo* studies confirmed that uric acid is a powerful free radical scavenger in humans.[61]

Antioxidant properties of uric acid could be expected to offer a number of benefits within the cardiovascular system or other oxidative stress related disorders. Thus, the role of high uric acid levels (supportive or protective) in development of cardiovascular disease is still unclear, and the explanations lie in different approach of *in vitro* experimental studies, as well as in different design of clinical studies.

Some protective and pathogenic roles of uric acid[55]

	Protective	Pathogenic
Tissue	Serum	Intacellular milieu atherosclerotic plaque adipose tissue
	Increasing GSH in hippocampus	Mediating intermittern hypoxia-induced vascular dysfunction
	Sinergistic neuroprotection with plasmalogen	Inhibiting endothelial function by inhibition of NO function under conditions of oxidative stress
Effects	Free radical scavenger and a chelator of transitional metal ions	Surrogate marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity

The role of uric acid in cardiovascular and cerebrovascular disorders

Pathophisiology of atherosclerosis and its consequences coronary artery disease, cererebrovascular disease and finally acute myocardial infarction (AMI) and stroke are related to oxidative stress. Interrelationship between concentrations of SUA and cardiovascular or cerebrovascular diseases has been observed for a long time. Most of the cardiovascular risk factors are in potentially overlapping with SUA concentrations.[55]

The positive association of hyperuricemia with obesity, impaired glucose tolerance, hypertension and history of heart disease was observed on a large Finland cohort population (aged 40-69). The study also showed significantly higher total mortality of hyperuricemic men and women in 5 years than in normouricemics.[62]

Retrospective analysis of general Italian population (N = 10,181) showed that study subjects with hyperuricemia were characterized by significantly higher prevalence of abnormal values of fasting plasma glucose and triglycerides as compared to subjects with reference concentrations.[63]

The most important and well evidenced is possible predictive role of uric acid in predicting short-term outcome (mortality) in AMI patients and stroke.[62]

Different prospective studies exploring the interrelationship between serum uric acid and cardiovascular outcomes in various categories of subjects are summarized by Strazzullo and Puig.[64]

In general conclusions, in population samples with relatively low risk of CVD, SUA is a very weak predictor of CVD, but it is a significant independent predictor among subjects at high or very high risk.[64]

Based on the study design it has been shown that hyperuricemia might be independent factor of cardiovascular events primarily in subject groups with high cardiovascular risk (angiographically proven CHD,congestive heart failure and stroke survivors).[64]

The first large prospective study was established on 83,683 Austrian men cohort who was prospectively followed for a median of 13.6 years.[65] This investigation confirmed the independent relationship between elevated SUA and mortality from coronary heart failure and stroke, but the association of SUA with mortality from acute, subacute, or chronic forms of coronary heart disease (CHD) after adjustment for potential confounding factors was absent.

Cross-sectional population-based, follow-up study of epidemiological data (N = 5926 US-subjects, aged 25 to 74) showed that increased serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality.[66]

In cross-sectional study on 982 Turkish patients,[67] whom coronary angiography was performed for the suspicion of CAD (47), SUA concentrations wereindependently associated with the severity of coronary atherosclerotic plaques.

In 212 Spanish patients, who were hospitalized because of acute HF and left ventricular systolic dysfunction, the presence of hyperuricemia was associated with a higher risk of death and/or new hospitalizations in the long-term, independently of ventricular function, renal function and functional ability.[68]

Results of some other studies, on contrary suggest that serum concentrations of uric acid were not an independent risk factor for CVD. In retrospective study, which included 716 Korean consecutive patients who underwent coronary angiography after adjusting for age, diabetes, smoking, cholesterol, and metabolic syndrome there were no independent association of SUA.[69]

Any apparent association with these outcomes is probably due to the association of uric acid level with other risk factors.[70]

This was shown especially in thestudies of general population and studies involving patients with history of arterial hypertension, which didn't show independent association with CVD.[64]

Different investigations also indicate that uric acid does not have a causal role in the development of coronary heart disease or death from CVD. The contribution of SUA in atherosclerosis development through effects on arterial calcification was absent in the multicentre American Family Heart Study on population-based cohorts in the US, which was designed to assess risk factors for heart disease, the association between SUA and carotid atherosclerotic plaques.[71]

It is evidenced that there is no consensus about its action in cardiovascular disease, although the confirmation of active participation of uric acid in heart failure exists.[72]

However, investigation based on large prospective studies and cross sectional follow-up studies confirmed the independent association of SUA with cardiovascular diseases. On contrary, retrospective studies, studies on general population and those performed on smaller number of study participants did not always provided the similar results.[55]

Beside the study design, different observation results also might be explained on cellular level. Namely, there is a difference between uric acid in serum and intracellular uric acid or highly hydrophobic areas such are atherosclerotic plaques and adipose tissue. Antioxidant activity is evidenced in serum while it seems that intracellular uric acid contributes in pathophysiology of heart failure.[72]

It is evidenced from the literature data that these controversies are very interesting subject for discussion between different scientific groups. Conflicting conclusions of the different studies are the consequence of differences in the compositions of the population's studies (number, treatment, biochemical and clinical data), length of follow up, analysis of the different CAD-risk variables and corrections according those variables.[55]

Proctor *et al*. reported on the association between high urate levels and atherosclerosis. They state that hyperuricemia might have a protective role (antioxidant) or it could be a primary cause (pro-oxidant) in atherosclerosis.[73]

Protective role of uric acid has been established on animal model. Intraperitoneal injection of purine derivatives, caffeine or uric acid into male C57BL/6 mice significantly increased total glutathione (GSH) levels in the hippocampus. This study suggests that caffeine and uric acid induce neuronal GSH synthesis by promoting cysteine uptake, leading to neuroprotection.[74]

The clinical efficacy of uric acid as a protective antioxidant is currently under investigation in a Phase III trial because it was shown that co-administration of uric acid and recombinant tissue plasminogen activator provides synergistic neuroprotection in experimental thromboembolic models and protection of oxidative stress in patients with acute stroke.[55]

Overall, it is postulated that hyperuricemia is not directly responsible for vascular injury and increased risk for cerebrovascular disease but it simply represent a surrogate marker for high levels of damaging oxidative stress associated with increased xanthine oxidase activity. Indeed, hyperuricaemia is a

significant predictor of disease state and progression of chronic heart failure. The assessment of UA is widely available at low cost, which may be an advantage for widespread determination of this marker. As it is preferably for biomarkers to fulfill the information for the evaluation of disease severity, prognosis and treatment it is evidenced that uric acid determination is reasonable for heart failure.[55]

Manzano *et al*. have developed a novel risk model for elderly patients with heart failure which includes uric acid and left-atrial dimension and provide a reliable estimate of death or hospital admission rates over a 2-year follow-up period.[75] This might help to identify higher risk patients who may benefit from more intensive treatment.

SUA and hypertension

Hypertension and increased SUA additionally complicate the controversies of uric acid role in cardiovascular events and the factors involved in pathogenesis of atherosclerotic consequences. Many clinical studies implicate on causative role of uric acid in hypertension.[55]

There are at least two aspects of interrelationships between hypertension and uric acid, molecular mechanisms and elimination pathways of urates.[55]

For presentation of the first aspect we have reviewed a few clinical trials bellow. Randomized, double-blind, placebo-controlled, crossover trial involving 30 adolescents who had newly diagnosed, essential hypertension and SUA > 360

mmol/L and who were treated with allopurinol, resulted in reduction of blood pressure.[76]

Close association of new-onset essential hypertension in children; suggest that lowering of uric acid can lower blood pressure in some patients. SUA impacts blood pressure in pediatric hemodialysis patients, independent of volume, nutritional and weight status.[55]

The study on the Polish patients which was performed to evaluate the influence of allopurinol on blood pressure and aortic compliance in patients with arterial hypertension depending on hypotensive therapy with angiotensin-converting enzyme inhibitor (ACE-I) or thiazide diuretic, showed that allopurinol does not produce additional antihypertensive effects in patients with treated arterial hypertension.[77]

For understanding the mechanisms of uric acid roles either as a predictor or consequence, animal models has been investigated. In animal models it has been shown that induced mild hyperuricemia may contribute to endothelial dysfunction and reduction of nitric oxide (NO) levels.[78]

2645 Greece systolic heart failure patients were involved in the Beta-Blocker Evaluation of Survival Trial. The results showed that hyperuricaemia might predict poor outcomes primary as a marker of increased xanthine oxidase activity. It confirmed significant association with poor outcomes in heart failure patients without chronic kidney disease (CKD) but not in those with CKD as a consequence of decreased renal excretion of uric acid.[79]

Uric acid is primarily excreted via the urine. That excretion is dependent on a number of urate transporters, including urate transporter 1 (URAT1), organic ion transporters (OAT1 and OAT3) and ATP-dependent urate export transporters (MRP4). Urate balance depends on those transporters activities. Transporter URAT 1 is responsible for the reabsorption of urate, which is normally 90% reabsorbed after glomerular filtration.[55]

Considering the influence of uric acid on hypertension it should be pointed to all factors which might be involved. Kidney function, functionality of the transporters, genetic polymorphisms of the transporters, factors of the oxidative stress have to be included in evaluation of interrelationships between hyperuricemia and hypertension. Impaired kidney function is responsible for many mechanisms involved in pathogenesis of hypertension, so the elevation of SUA might be one of them.[55]

SUA and metabolic syndrome

It is well known that nephrolithiasis of uric acid origin is significantly more common among patients with the MetS, obesity and type 2 diabetes. Prevalence of metabolic abnormalities in Brazilian people with metabolic syndrome was associated with concentration of uric acid. After Roux-en-Y gastric bypass and consequently weight loss uric acid concentration were reduced.[55]

Lower urine pH was associated with an increase in waist circumference in over than thousand Japanese men. Waist circumference is a key feature for the metabolic syndrome and HOMA-R as an index of insulin resistance. Lower urine

pH was also associated with an increase in BMI, and an increase in serum uric acid.[80]

SUA levels were significantly and negatively correlated with HDL-C in Korean males, but not in females but SUA levels increased significantly with an increasing number of MetS components and abdominal obesity in both genders.[81]

This might be explain with the presence of increased intracellular adenosine (uric acid precursor), a derivative of higher AMP concentrations due to increased synthesis of fatty acid-acyl-CoA in peripheral tissues, and the authors propose that in early obesity increased levels of uric acid are related to elevated plasma fatty acids.[55]

Molecular base for explanations of the interrelationship between hyperuricemia and MetS, we might also provide from high dietary carbohydrates intake especially for fructose or sucrose intake. On the other hand the animal model experiments showed that fructose feed rats *vs*. glucose feed rats, had higher body weight, blood pressure, and concentrations of insulin, uric acid and triglycerides.[55]

Fructose enters hepatocytes and other cells (human and animal), where it is completely metabolized by fructokinase with the consumption of ATP, without negative regulatory mechanism to prevent the depletion of ATP like is in glucose metabolism. Lactic acid and uric acid are than generated in the process.[55]

Lowering of the urine pH is than the consequence of the organic acids accumulation. Metabolic fates of the fructose in the liver than increases the

biosynthesis of endogenous triglyceride, VLDL excretion and LDL overproduction.[55]

This also was confirmed in the clinical studies because it was shown that the reduction in serum uric acid correlated directly with the decrease in triglyceride levels.[82] Any factor that may increase biosynthetic pathway in which ATP is consumed and adenilate is produces might be involved in overproduction of uric acid.

Severe and mild hyperuricemia have been recognized as an independent risk factor for endothelial dysfunction flow-mediated vasodilatation of the brachial artery in subjects without MetS, whereas only severe hyperuricemia (but not mild hyperuricemia) appeared to exacerbate endothelial dysfunction in similar subjects with MetS in middle-aged healthy Japanese men.[83]

Measurement of uric acid concentration

Uric acid concentration might be measured in serum, plasma, urine and in exhaled breath condensate. Determination of uric acid concentration includes phosphotungistic acid methods (PTA), uricase methods (in wide usage), high-performance liquid chromatography methods (reference methods), dry chemistry systems and biosensor methods. PTA methods interfere with many endogenous and exogenous compounds. More specific and very low cost (less than 10 eurocents per analysis) are enzymatic methods with bacterial enzyme uricase, uricase- peroxidase standard method. Ascorbic acid and bilirubin interfere with urate determination, so the use of ascorbat oxidase and aminophenason is

necessary. Up-to-date biosensor methods can also be used as a low-cost alternative to conventional methods.[55]

Prior to determination of urate in urine, alkalinization of urine might be necessary, because of urate crystallize at pH lower than 5.75. It is evidenced that uric acid concentrations are significantly associated with BMI, gender, glomerular filtration rate and hypertension. Many additional factors, including exercise, diet, drugs, and state of hydration, may result in transient fluctuations of uric acid levels. According to that the reference intervals for uric acid aren't equable, and there is no clear limit for hyperuricemia. So it is very important to document well the strategy and the individuals included in the reference interval.[55]

Lipid profile and stroke

Haemorrhagic and ischaemic strokes share two common features; they arise out of *defects* in arteries and they *damage* the brain. In most other respects they differ. This probably accounts for the confusion about the role of dyslipidaemia as a risk factor when these two main stroke types are not distinguished.[84]

Atheroma lies at the root of the pathogenesis of thromboembolic stroke, extending from the diseased heart, through the atheromatous aorta and carotids to the intracranial circulation. It is therefore to be expected that dyslipidaemia should contribute to the constellation of risk factors for this disease. Surprisingly, this relationship is not clear-cut.[84]

Plasma cholesterol

The level of plasma cholesterol has not been consistently shown to be a predictor of stroke risk. A large prospective observational study of middle-aged men found no relationship between plasma total cholesterol concentration and 16.8 year incidence of fatal or non-fatal stroke.[85]

A large 10-year prospective study[86] of 14,175 middle-aged men and women, free of clinical cardiovascular disease at the outset, found a weak inconsistent relationship between low density lipoprotein-cholesterol (LDL-c) or high density lipoprotein-cholesterol (HDL-c) and ischaemic stroke.

Two large meta-analyses[87,88] aggregated studies from very large cohorts and failed to find a relationship between cholesterol and stroke.

However, in contrast, the MRFIT study[89] in 350,977 men, aged 35–57 years found that a clear relationship emerged when stroke was categorised into ischaemic (thrombotic and embolic) and haemorrhagic types, the risk of ischaemic stroke increasing with total cholesterol concentration. The relationship was close to that observed between coronary deaths and total cholesterol in the same study. Conversely, the risk of haemorrhagic stroke was highest at the lowest total cholesterol concentrations. This finding is unexpected and as yet is not satisfactorily explained.

The Honolulu Heart Program[90] also found a continuous and progressive increase in thromboembolic stroke rates with increasing cholesterol levels. The odds ratio between the highest and lowest quartiles of serum cholesterol was 1.4

(95% confidence interval (CI), 1.1–1.9) for thromboembolic stroke, not dissimilar to that for CHD 1.7 (CI 1.4–2.0).

The Women's Pooling Project[91] studied 24,343 women with a mean age of 52.0 (range 30–97) years for 13.9 years. There was a highly significant relationship between the highest quintile of plasma total cholesterol and non-haemorrhagic stroke death in women younger than 55 years, although the relationship was less consistent in middle cholesterol quintiles.

A number of factors contribute to the apparent contradiction in the results of these observational studies of stroke risk. Many studies fail to distinguish between stroke types, and thus neglect the likelihood that differences in aetiology between ischaemic and haemorrhagic events may have differing or even competing risk factors. In addition, confounding variables may distort multivariate analyses, which rarely take a comprehensive account of the many risk factors (more than 20) proposed for stroke.[84]

Many study cohorts are relatively young, whereas the main burden of stroke is in the elderly. The relative risk of stroke doubles each decade after 55 years,[92,93] the age below which many prospective cohort studies have been centred.

Therefore, information is lacking in some of the largest studies on whether dyslipidaemia may predispose to stroke in the elderly in whom it is most prevalent.[84]

HDL cholesterol

As a risk factor in atherosclerosis (in particular CHD), low HDL-c concentration might be expected to contribute to stroke risk. This is supported by a number of small case-control studies.[94-96]

A large prospective study[85] over 16.8 years in men aged 40–59 years at outset with no prior history of stroke which found that higher levels of HDL-c were associated with a significant decrease in risk of non-fatal stroke (top quintile versus lowest quintile of HDL-c; adjusted odds ratio 0.59, CI 0.39–0.90). Fatal strokes, of which there were 58 cases, were not predicted by HDL-c level. Aetiological plausibility is given to this by ultrasonographic intima-media thickness (IMT) studies in carotid arteries which show HDL-c concentrations inversely associated with atheroma burden.[97,98]

Triglycerides

Plasma triglyceride concentrations have not appeared as signif icant independent factors in the studies cited above, but these studies examined other lipids as risk factors.[84]

A follow-up cohort study of screenees for the BIP trial[99] reported triglyceride concentrations to be positively and independently predictive of stroke, but likely selection bias limits ability to generalise this to populations.

Chapter 4

Methodology

METHODOLOGY

This study was done at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was a cross sectional study.

Study period and duration

This study was conducted for the period of one year, from January 2012 to December 2012.

Place

The present study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum, a tertiary care teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

This study was comprised of patients presenting with ischemic cerebrovascular accident to the Department of Medicine and Neuromedicine under KLEs Dr. Prabhakar Kore Hospital.

Sample size

A total of 100 patients with ischemic cerebrovascular accident were studied.

Sampling procedure

$n = 4pq/d^2$

p=30, q=70, d=10

Sample size = 84

However to achieve uniform distribution, sample size of 100 patients was considered.

Selection criteria

Inclusion

- All patients with ischemic cerebrovascular accident identified based on clinical as well as laboratory and radiological evaluation that is, including computed tomography scan or magnetic resonance imaging.

Exclusion

- Age < 18 years.
- Patients with chronic intake of hyperuricemic drugs.
- Patients with conditions which alter serum uric acid levels such as;
    - Lymphoproliferative diseases
    - Polycythemia
    - Myeloproliferative disorders
    - Diabetic ketoacidosis
    - Lactic acidosis

Ethical clearance

The ethical clearance was obtained from Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Patients were screened for the eligibility and those fulfilling the selection criteria were briefed about the nature of the study. In case of comatose patients, the relatives / caretakers were informed about the study. The patients/caregivers expressing their willingness to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Method of collection of data

Demographic data such as age and sex were recorded. History of other co-morbid conditions such as, hypertension, diabetes mellitus, previous stroke, ischemic heart disease, personal history such as habits of alcohol consumption, smoking, were noted. A thorough physical examination was conducted for vitals (pulse rate, blood pressure and respiratory rate) followed by systemic examination. Evaluation of central nervous system was done based on NIHSS. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Investigations

The patients were evaluated for the tests.

- Serum creatinine

- Serum uric acid
- Lipid profile
    1. Total cholesterol
    2. High density lipoprotein
    3. Low density lipoprotein
    4. Triglycerides

Estimation of Uric Acid levels

Uric acid level was measured with photometry using the diagnostic kit for quantification of uric acid prepared by ELITech Clinical Systems.

Outcome variables

Serum uric acid

Serum uric acid levels were interpreted as below;[100]

Males: 3.5 - 7.2 Normal

Females: 2.6 – 6.0 Normal

Lipid profile

Based on NCEP (National Cholesterol Education Program) guidelines[100] normal values of lipid parameters were;

- Low density lipoprotein < 100 mg/dL.
- High density lipoprotein;
    - Female > 50 mg/dL.
    - Males > 40 mg/dL.

- Total Cholesterol < 200 mg/dL.
- Triglycerides < 150 mg/dL.

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet (Annexure III). The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test. The continuous data was expressed as mean ± standard deviation (SD) and the comparison was done using unpaired 't' test. The Pearson correlation coefficient was used to find the correlation. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

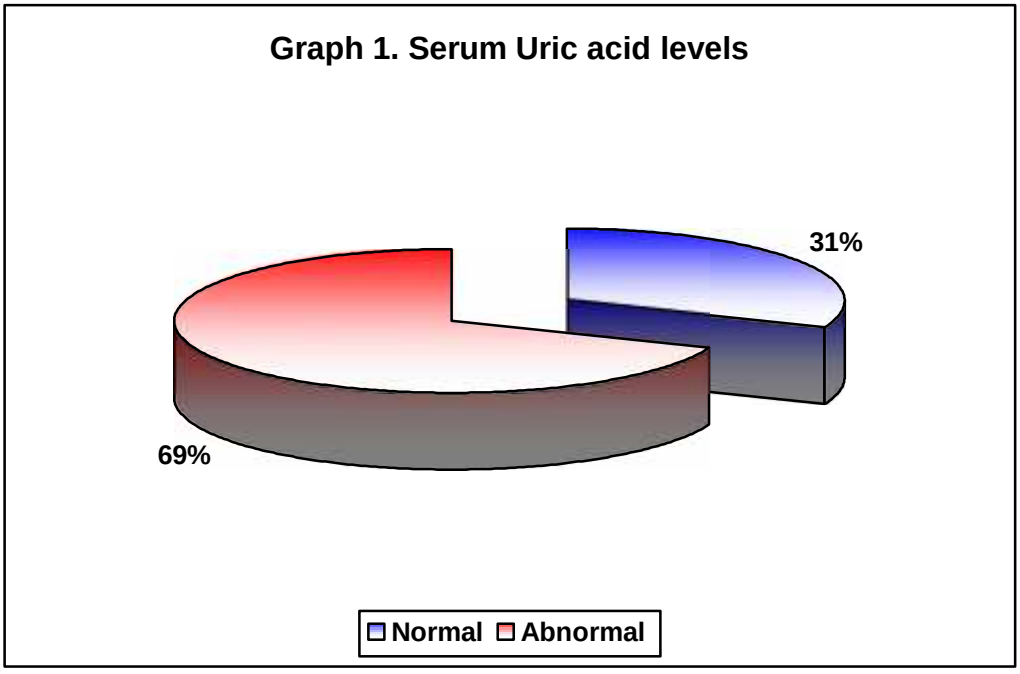
RESULTS

This study was done at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 100 patients with iscahemic cerebrovascular accident during the study period of one year from January 2012 to December 2012 were studied.

The data obtained was coded and entered into the master chart. The data was analysed and the final observations were tabulated as below.

Table 1. Serum Uric acid levels

Serum Uric acid levels	Distribution (n=100)	
	Number	**Percentage**
Normal	31	31.00
Abnormal	69	69.00
Total	**100**	**100.00**

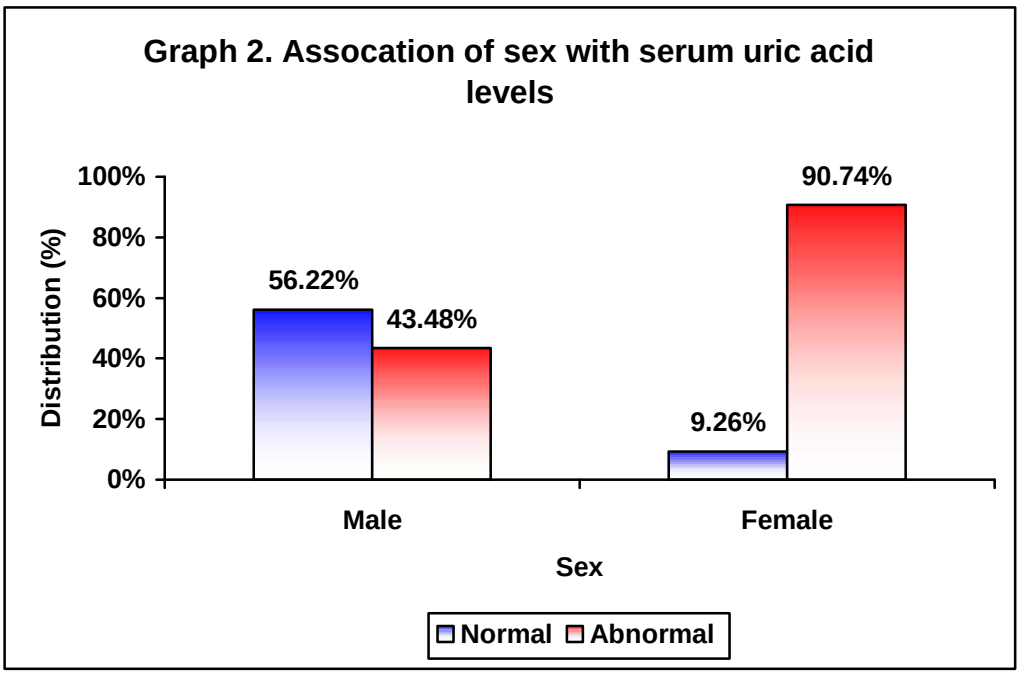


In the present study 69% of the patients had abnormal uric acid levels and in 31% the same were normal. The mean serum uric acids levels were found to be 7.72 ± 1.22

Table 2. Association of sex with serum uric acid levels

Sex	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Male	26	56.52	20	43.48	46	46.00
Female	5	9.26	49	90.74	54	54.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p < 0.001

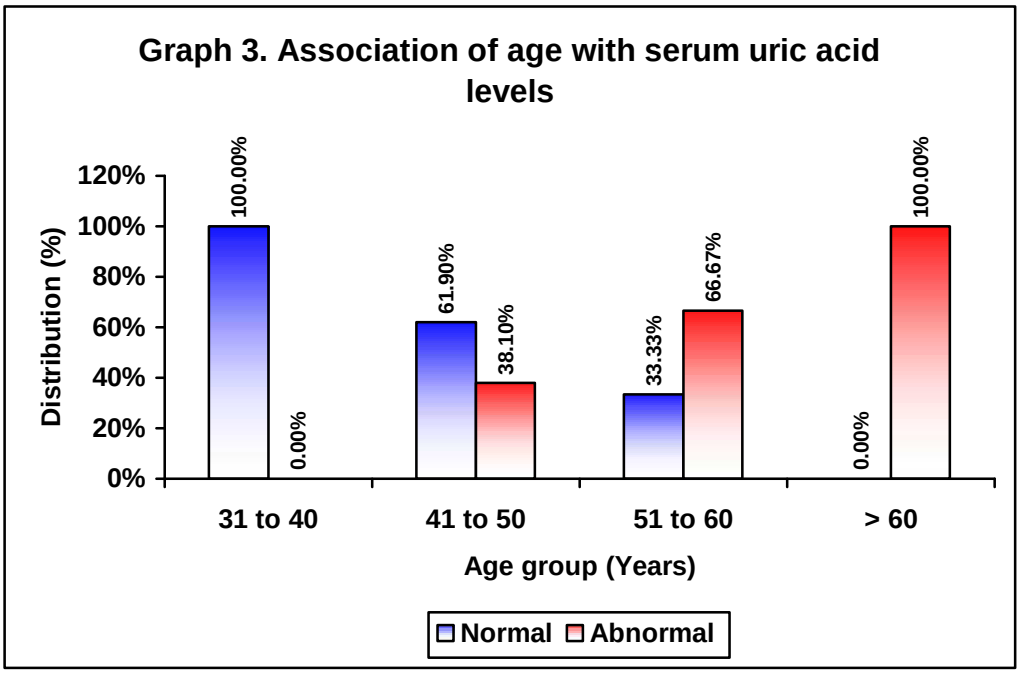


In this study 54% of the patients were females compared 46% males with male to female ratio of 1.1:1. Among the females 90.74% had abnormal uric acid levels and this difference was statistically significant (p<0.001).

Table 3. Association of age with serum uric acid levels

Age group (years)	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
31 to 40	8	100.00	0	0.00	8	8.00
41 to 50	13	61.90	8	38.10	21	21.00
51 to 60	10	33.33	20	66.67	30	30.00
> 60	0	0.00	41	100.00	41	41.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p < 0.001



In the present study the commonest age group was more than 60 years accounting for 41% of all the patients. Among them all (100%) had raised uric acid levels. This difference was statistically significant (p<0.001).

Table 4. History

History	Distribution (n=100)	
	Number	**Percentage**
Hypertension	59	59.00
Diabetes mellitus	30	30.00
Stroke	18	18.00
Ischaemic heart disease	18	18.00

In this study history of hypertension was present in 59% of the patients and diabetes was reported by 30% patients. However, 18% of the patients each reported history of previous stroke and ischaemic heart disease.

Table 5. Personal history

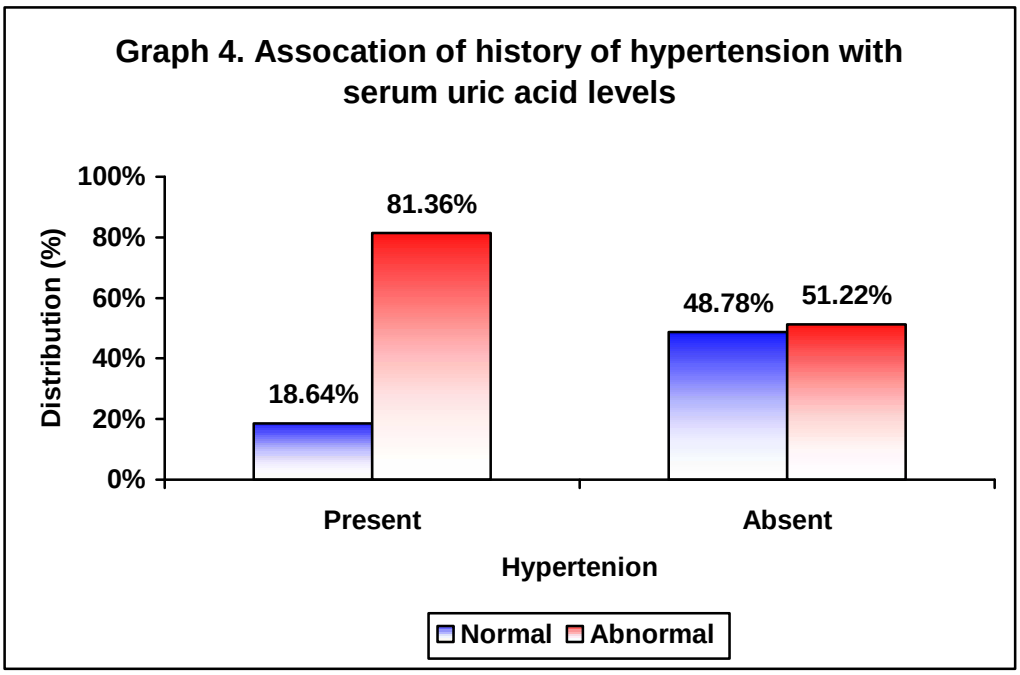
History	Distribution (n=100)	
	Number	**Percentage**
Smoking	22	22.00
Alcohol consumption	32	32.00

In the present study history of smoking and alcohol consumption was noted in 22% and 32% of the patients respectively.

Table 6. Association of history of hypertension with serum uric acid levels

Hypertension	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	11	18.64	48	81.36	59	59.00
Absent	20	48.78	21	51.22	41	41.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.001

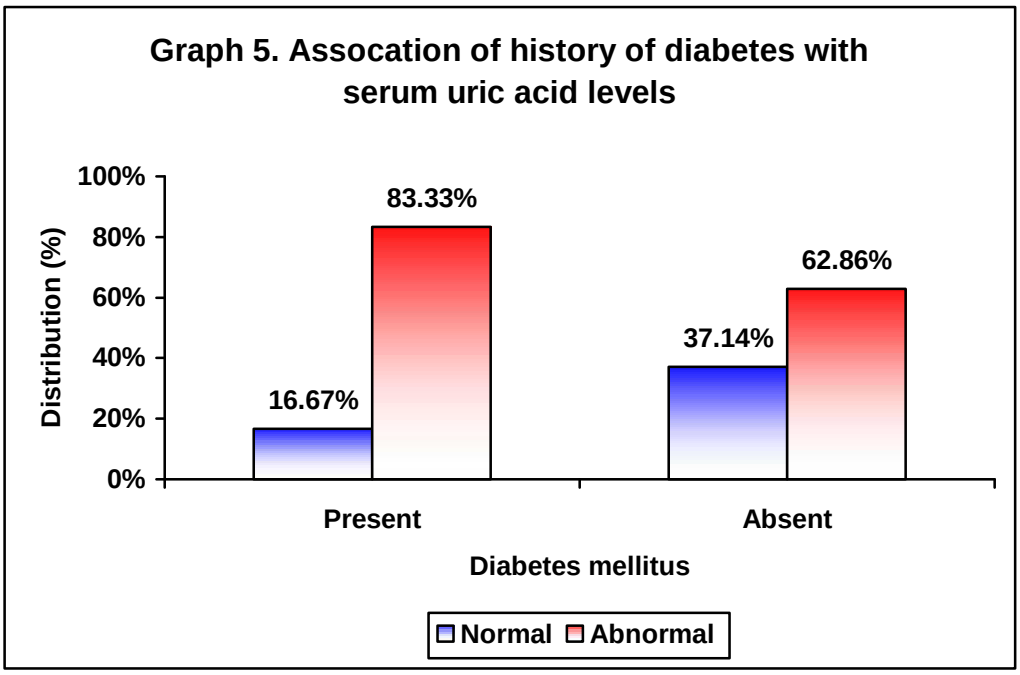


In the present study of the 59% of the patients with hypertension 18.64% had normal serum uric acid levels compared to 81.36% with abnormal. This difference was statistically significant (p=0.001).

Table 7. Association of history of diabetes mellitus with serum uric acid levels

Diabetes mellitus	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	5	16.67	25	83.33	30	30.00
Absent	26	37.14	44	62.86	70	70.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.042

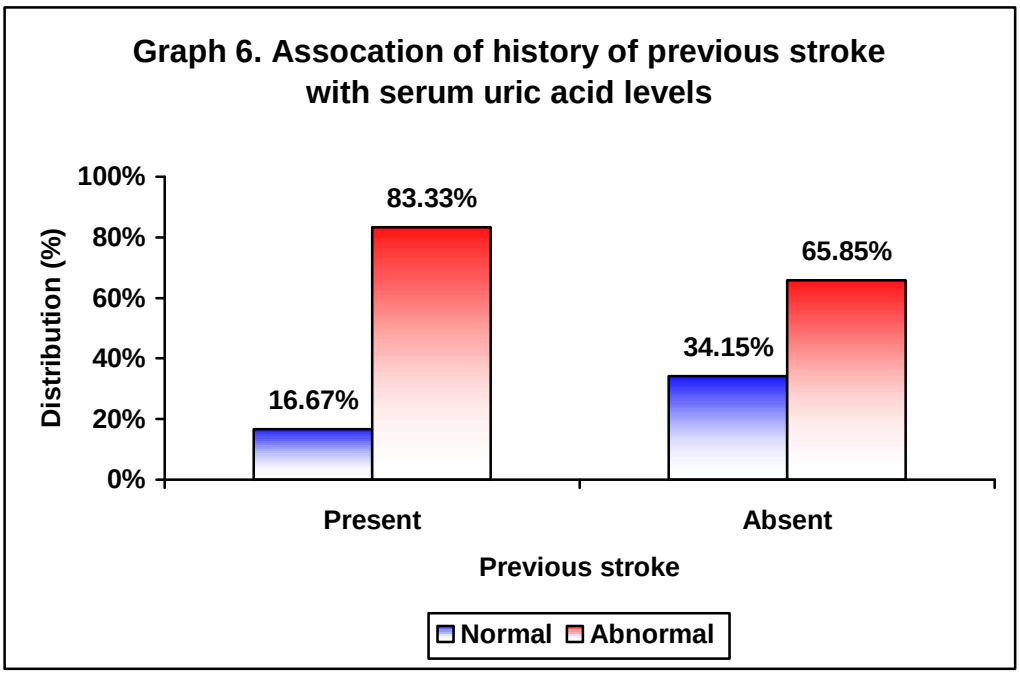


In this study history of diabetes was noted in 30% of the patients. Of these, 83.33% of the patients had raised uric acid levels (p=0.042).

Table 8. Association of history of previous stroke with serum uric acid levels

Previous stroke	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	3	16.67	15	83.33	18	18.00
Absent	28	34.15	54	65.85	82	82.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.146



In the present study history of previous stroke was present in 18% of the patients. Out of which, 83.33% of the patients had raised uric acids levels compared to 65.85% of the patients who had raised uric acid levels but no prior stroke history. This difference was statistically not significant (p=0.146).

Table 9. Association of history of ischaemic heart disease with serum uric acid levels

Ischaemic heart disease	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	5	27.78	13	72.22	18	18.00
Absent	26	31.71	56	68.29	82	82.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

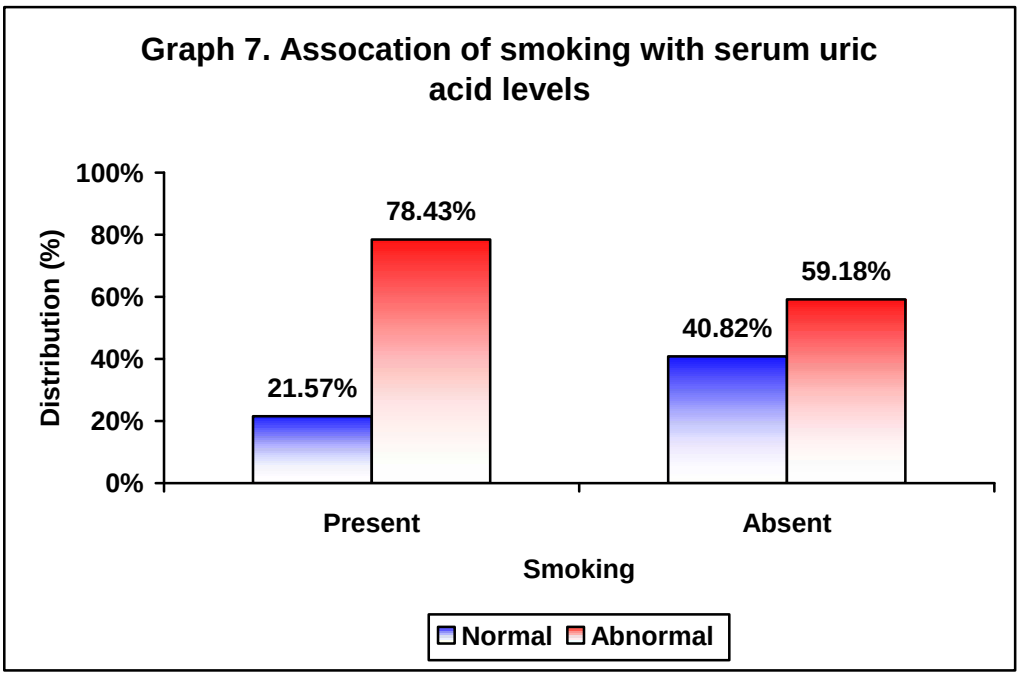
p = 0.744

In the present study history of ischaemic heart disease was noted in 18% of the patients. Out of which, 72.22% had raised uric acids levels compared to 68.29% of the patients among whom the history of ischaemic heart disease was absent. But this difference was statistically not significant (p=0.744).

Table 10. Association of smoking with serum uric acid levels

Smoking	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	11	21.57	40	78.43	51	51.00
Absent	20	40.82	29	59.18	49	49.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.037

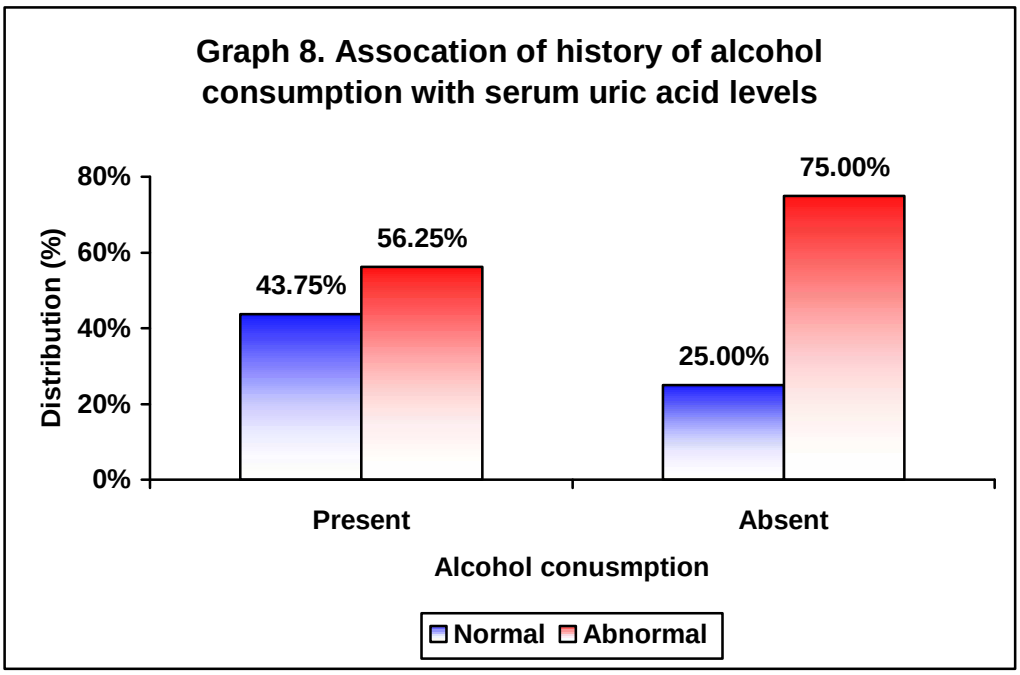


In the present study significantly higher number of patients who gave history of smoking had abnormal uric acids levels (78.43%) compared to those who were non smokers (59.18%) (p=0.037).

Table 11. Association of alcohol consumption with serum uric acid levels

Alcohol consumption	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Present	14	43.75	18	56.25	32	32.00
Absent	17	25.00	51	75.00	68	68.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.059



In this study, of the 32 patients with history of alcohol consumption 56.25% of the patients had raised uric levels. However, this difference was statistically not significant (p=0.059).

Table 12. Association of menopause with serum uric acid levels

Menopause	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	**%**	**No**	**%**	**No**	**%**
Present	0	0.00	40	100.00	40	40.00
Absent	5	35.71	9	64.29	14	14.00
Total	**5**	**5.00**	**49**	**49.00**	**54**	54.00

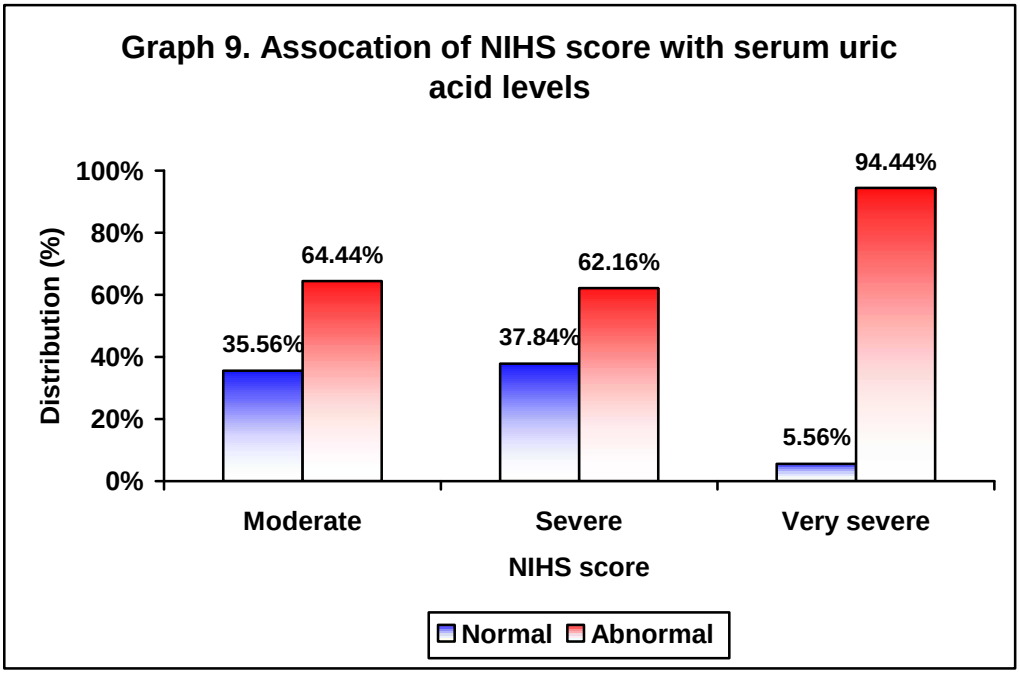
p < 0.001

In the present study, of the 54 women history of menopause was reported by 40 patients and all of them were found to have raised raised uric levels. This difference was statistically significant (p<0.001).

Table 13. Association of NIHS score with serum uric acid levels

NIHS Score	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Moderate	16	35.56	29	64.44	45	45.00
Severe	14	37.84	23	62.16	37	37.00
Very severe	1	5.56	17	94.44	18	18.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.035

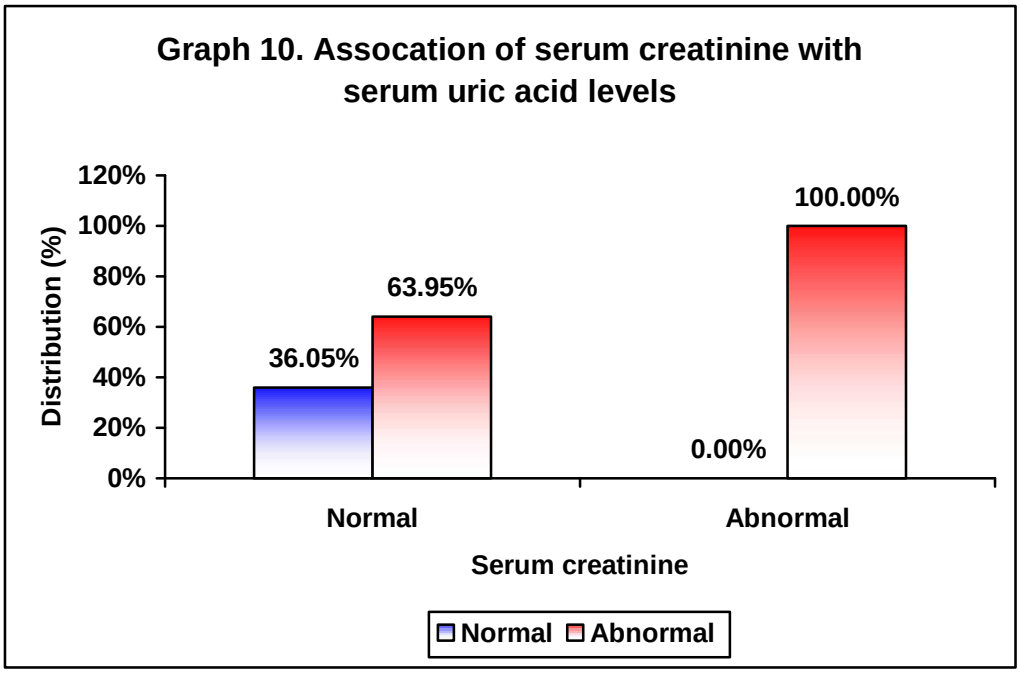


In this study 18 patients had very severe NIHS scores. Among these, 94.44% of the patients had raised uric levels (p=0.035).

Table 14. Association of serum creatinine with serum uric acid levels

Serum creatinine	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Normal	31	36.05	55	63.95	86	86.00
Abnormal	0	0.00	14	100.00	14	14.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.007

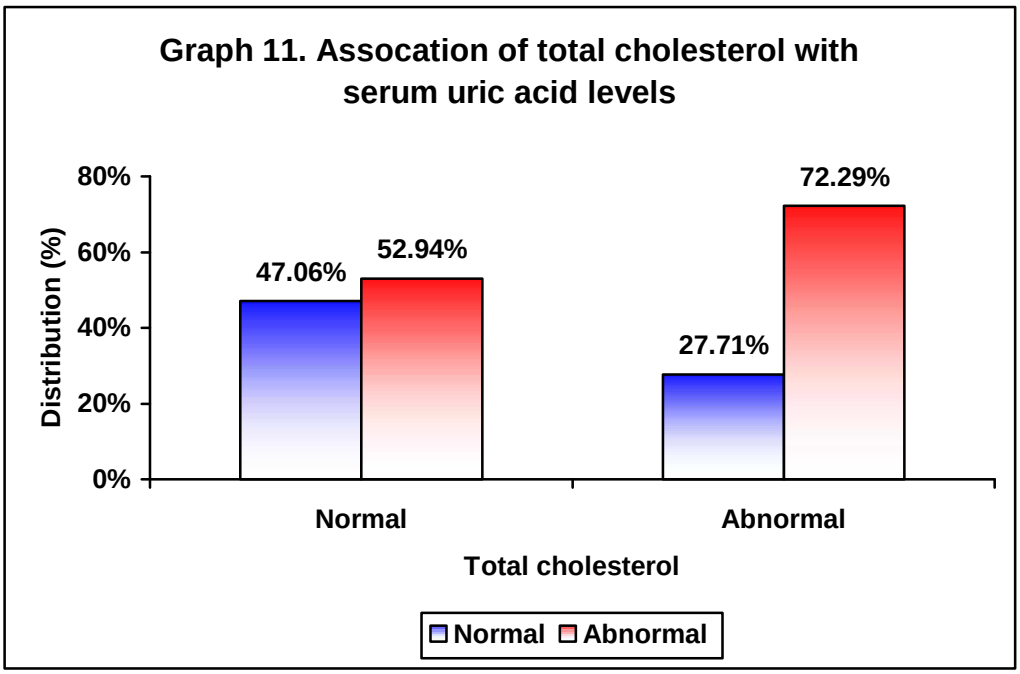


In the present study all the patients with raised serum creatinine (100%) had raised uric acid levels (p=0.007).

Table 15. Association of total cholesterol with serum uric acid levels

Total cholesterol	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Normal	8	47.06	9	52.94	17	17.00
Abnormal	23	27.71	60	72.29	83	83.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.116

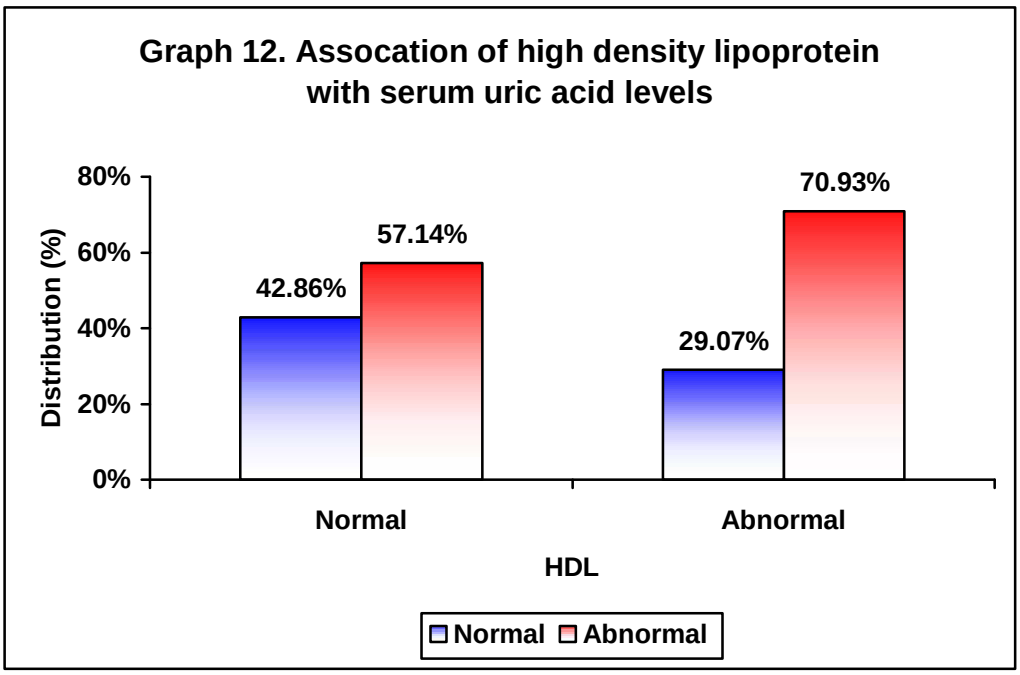


In the present study, of the 83 patients with raised cholesterol levels, 72.29% had raised uric acid levels compared to 27.71% with normal uric acids levels. However, this difference was statistically not significant (p=0.116).

Table 16. Association of high density lipoprotein with serum uric acid levels

HDL	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Normal	6	42.86	8	57.14	14	14.00
Abnormal	25	29.07	61	70.93	86	86.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.301

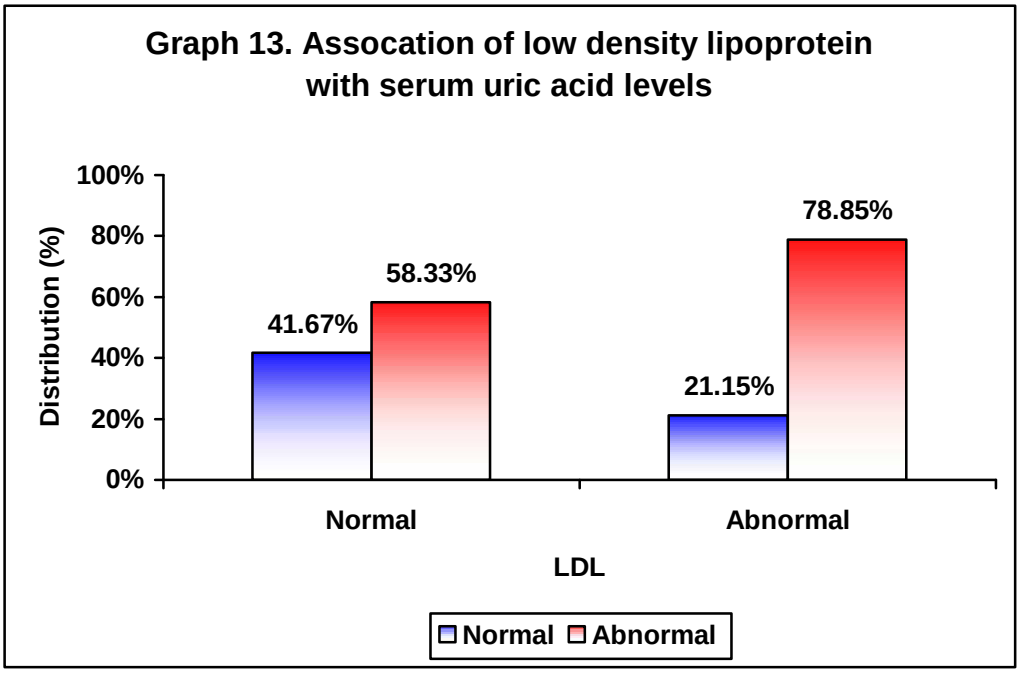


In the present study, of the 86 patients with abnormal HDL levels, 70.93% had raised uric acid levels compared to 29.07% with normal uric acids levels. However, this difference was statistically not significant (p=0.301).

Table 17. Association of low density lipoprotein with serum uric acid levels

LDL	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Normal	20	41.67	28	58.33	48	48.00
Abnormal	11	21.15	41	78.85	52	52.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0. 027

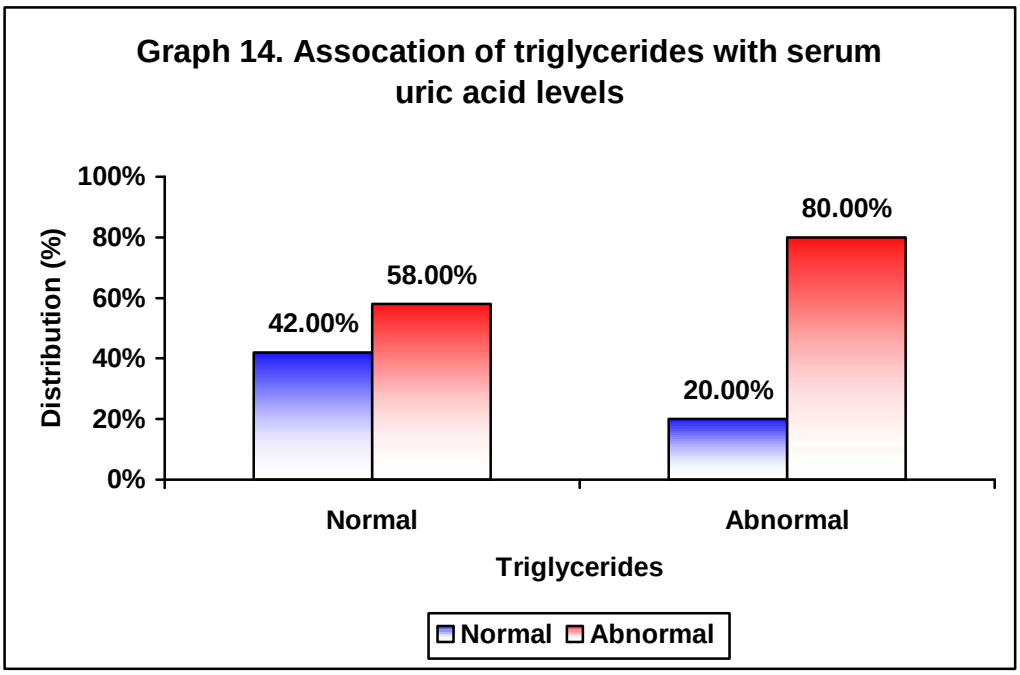


In the present study, LDL was found to be abnormal in 52 patients. Of these, significantly higher number of patients (78.75%) had raised uric acid levels (p=0.027).

Table 18. Association of triglycerides with serum uric acid levels

Triglycerides	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Normal	21	42.00	29	58.00	50	50.00
Abnormal	10	20.00	40	80.00	50	50.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p = 0.017

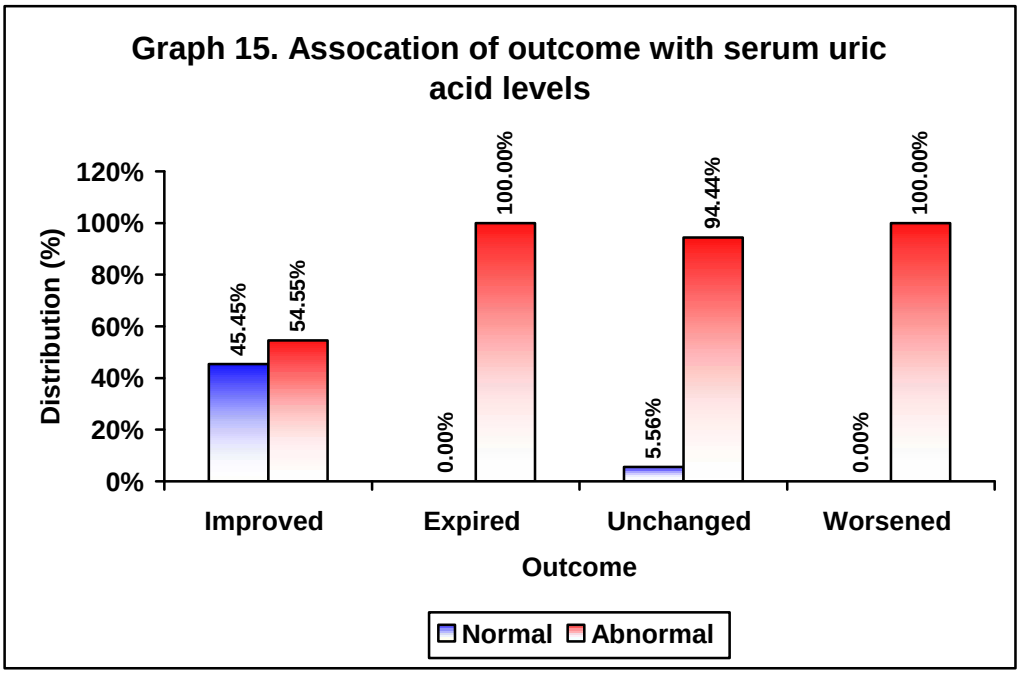


In this study significantly higher number of patients with abnormal triglyceride levels had raised uric acid levels (80% vs 20%; p=0.017)

Table 19. Association of outcome with serum uric acid levels

Outcome	Serum uric acid levels				Total	
	Normal		Abnormal			
	No	%	No	%	No	%
Improved	30	45.45	36	54.55	66	66.00
Expired	0	0.00	14	100.00	14	14.00
Unchanged	1	5.56	17	94.44	18	18.00
Worsened	0	0.00	2	100.00	2	2.00
Total	**31**	**31.00**	**69**	**69.00**	**100**	100.00

p < 0.001

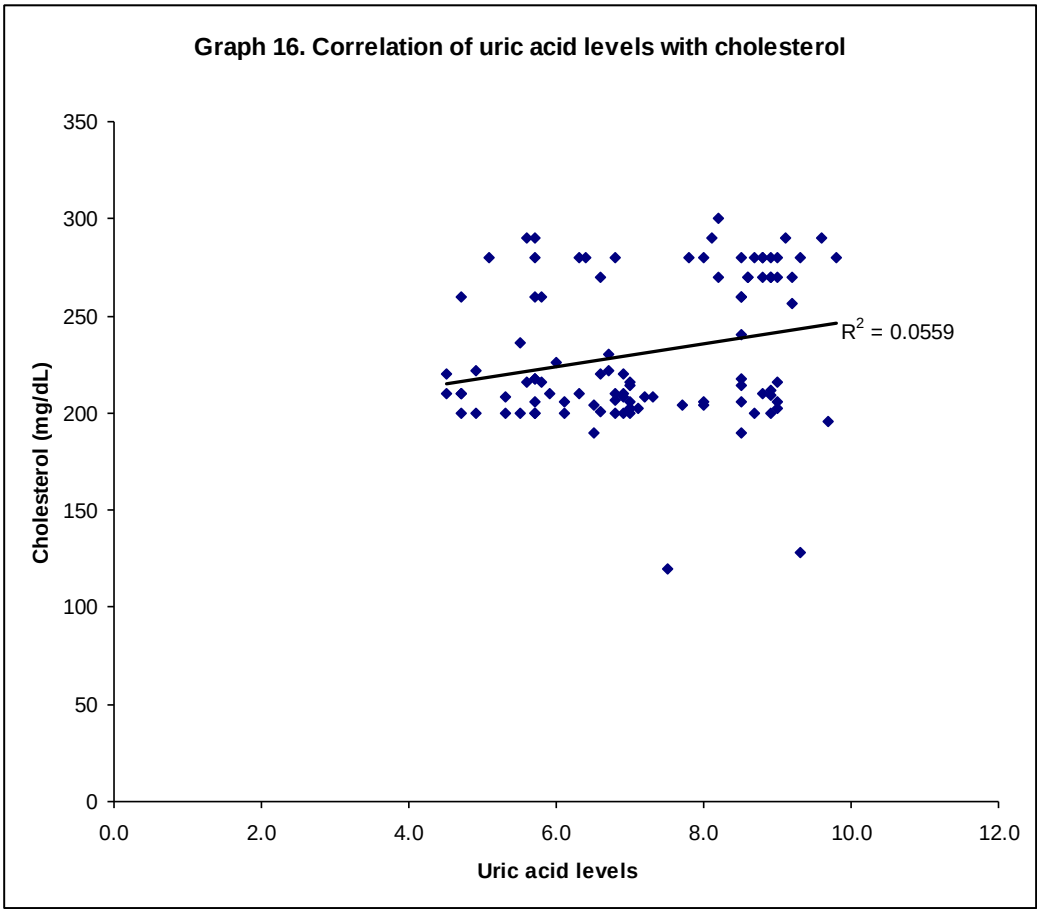


In this study 14% of the patients expired and all of them had raised serum uric acid levels (100%). This difference was statistically significant (p<0.001).

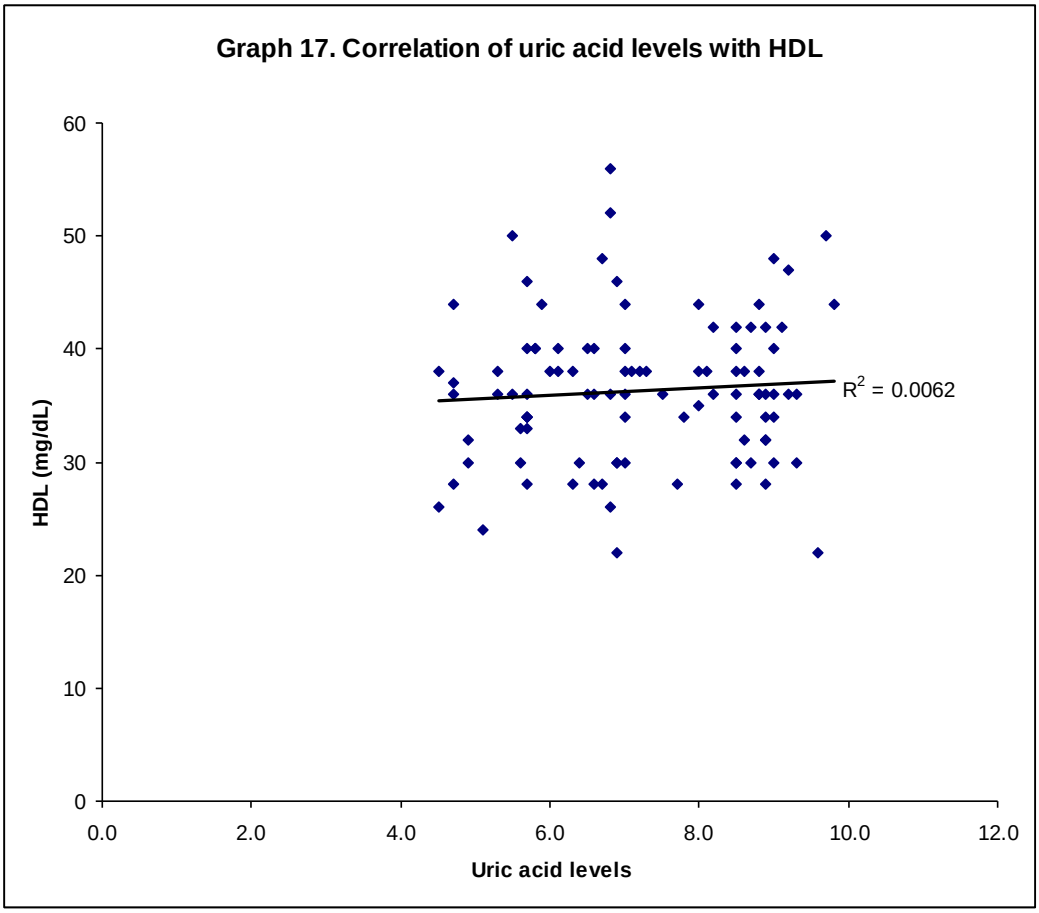
Table 20. Comparison of study variables in patients with normal and abnormal serum uric acid levels

Variables	Serum uric acid levels				p
	Normal		Raised		
	Mean	SD	Mean	SD	
Age (Years)	47.45	7.86	64.64	10.46	**<0.001**
PR (/min)	74.87	2.84	74.94	2.84	0.908
RR (/min)	16.52	2.61	17.30	2.45	0.160
SBP (mm Hg)	132.58	12.92	134.93	12.60	0.401
DBP (mm Hg)	70.74	5.25	74.04	6.11	**0.007**
NHSS score	14.94	6.42	18.06	9.98	0.064
SSS Score	26.19	10.75	26.80	9.96	0.792
Sr. creatinine (mg/dL)	0.62	0.09	1.14	0.76	**<0.001**
Sr. uric acid	5.75	0.85	7.90	1.19	**<0.001**
Cholesterol	220.58	28.37	236.25	39.53	**0.027**
HDL (mg/dL)	34.32	6.34	37.23	6.40	**0.039**
LDL (mg/dL)	158.10	27.12	175.42	35.01	**0.009**
Triglycerides (mg/dL)	151.48	39.95	182.83	54.61	**0.002**

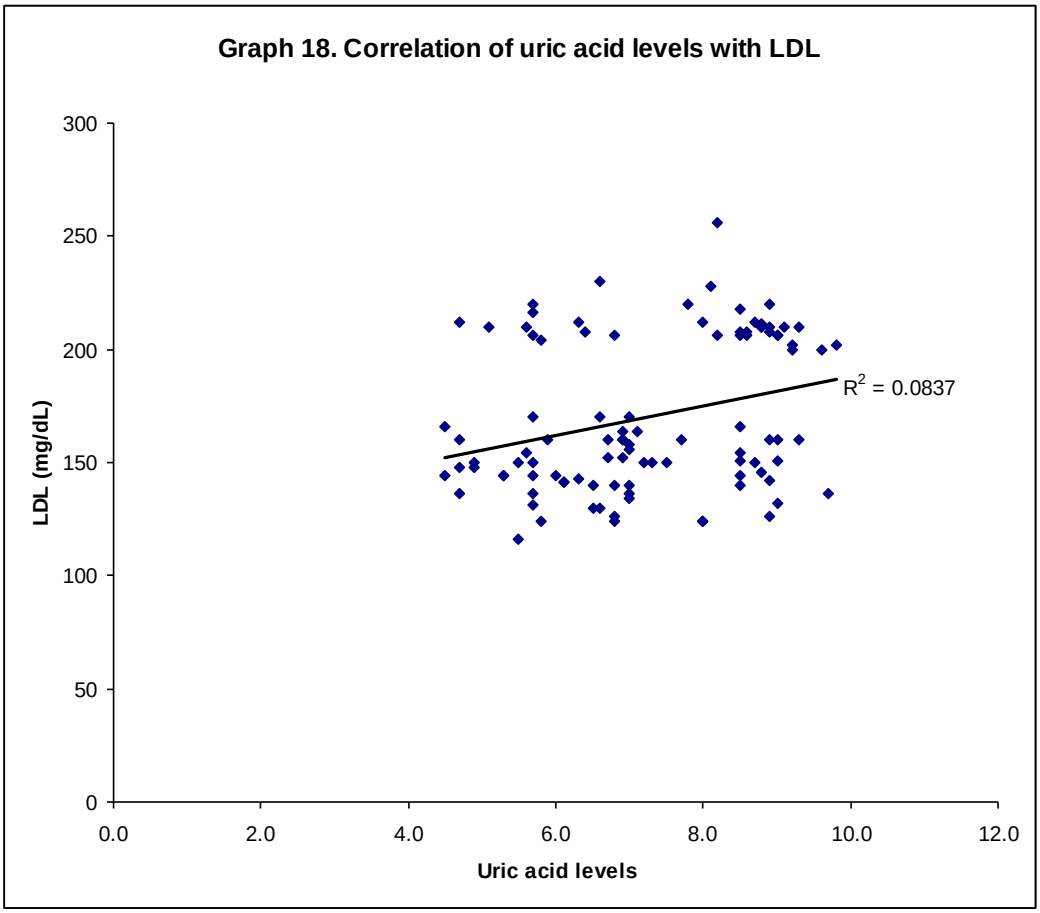
Table 20 shows characteristics of study population in patients with normal and raised serum uric acid levels. Statistically significant difference was observed with patients mean age, diastolic blood pressure, serum creatinine, cholesterol, HDL, LDL and triglycerides levels ($p<0.050$).



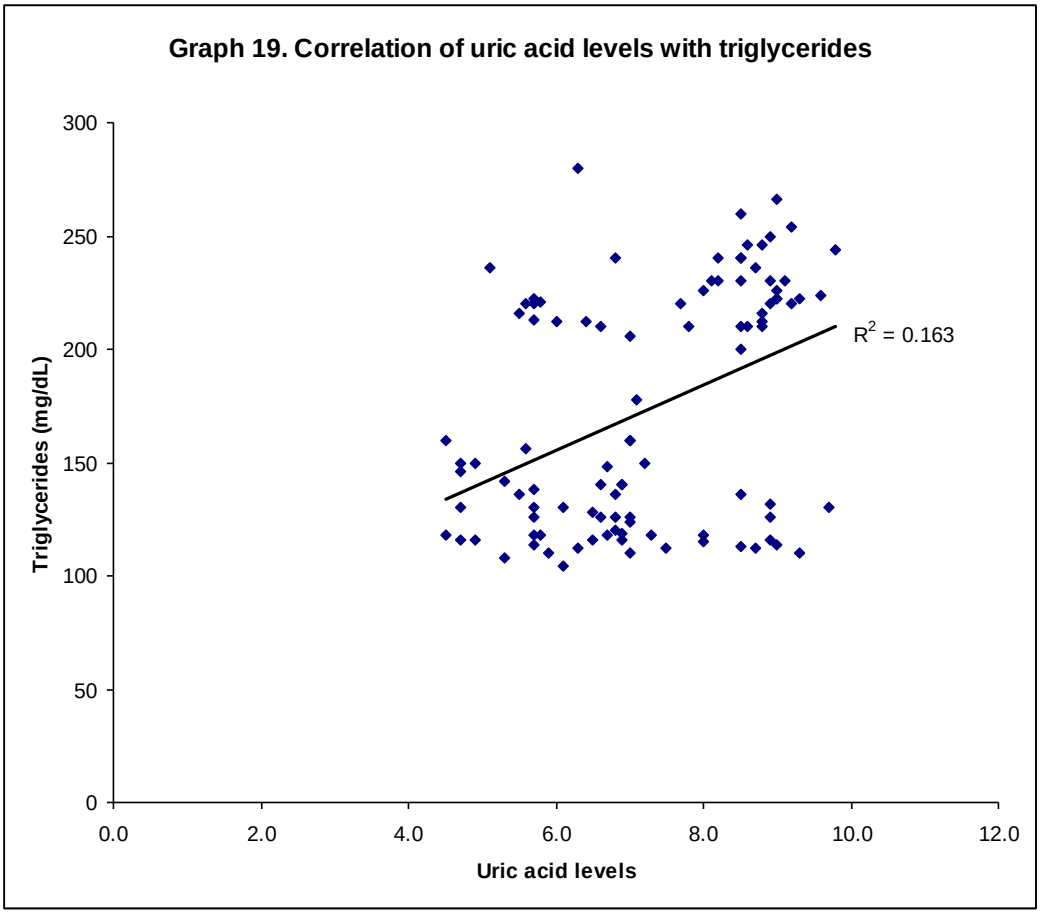
Graph 16 shows correlation of uric acid levels with total cholesterol. The value of Pearson's correlation coefficient r was 0.24. The value of R^2, the coefficient of determination, is 0.06. Although there was a positive correlation, the relationship between uric acid levels and total cholesterol was weak as r was nearer to the value of zero.



Graph 17 shows correlation of uric acid levels with HDL. The value of Pearson's correlation coefficient r was 0.08. The value of R^2, the coefficient of determination, was 0.01. Although there was a positive correlation, the relationship between uric acid levels and HDL was weak as r was nearer to the value of zero.



Graph 18 shows correlation of uric acid levels with LDL. The value of Pearson's correlation coefficient r was 0.29. The value of R^2, the coefficient of determination, was 0.08. Although there was a positive correlation, the relationship between uric acid levels and LDL was weak as r was nearer to the value of zero.



Graph 19 shows correlation of uric acid levels with LDL. The value of Pearson's correlation coefficient r was 0.4. The value of R^2, the coefficient of determination, was 0.16. Although there was a positive correlation, the relationship between uric acid levels and triglycerides was weak as r was nearer to the value of zero.

Chapter 6

Discussion

DISCUSSION

Cerebrovascular accidents are showing an increasing trend. According to a recent report, about 780000 Americans experience a new or recurrent stroke each year, on average, one stroke every 40 seconds. Stroke is the third common cause of death in the world after coronary heart disease and cancer especially in the elderly. The mortality rate of stroke in the acute phase is as high as 20% and it remains high for several years after the acute event as compared to the general population.[102]

Stroke is the second most common cause of disability and dementia in adults aged ≥ 65 years worldwide: close to 25% of stroke survivors develop dementia. Stroke is also an important cause of morbidity and long term disability: up to 40% of survivors are not expected to recover their independence with self-care and 25% become unable to walk independently.[102]

Uric acid is the ultimate catabolite of purine metabolism in humans and higher primates. It exists in the extracellular compartment as sodium urate, and it is cleared from the plasma through the kidney. Uric acid levels are influenced by age and sex. Prior to puberty, the average serum uric acid is 3.6 mg/dl for males and females. Following puberty, value rises to adult levels with women typically 1 mg/dl less than men. This lower level in women apparently reflects estrogen related enhancement of renal urate clearance. It has been reported that increased levels of uric acid are associated with established cardiovascular risk factor such as elevated serum triglyceride and cholesterol concentration, hypertension, obesity, insulin resistance and metabolic syndrome. On the other hand uric acid

has been known to exert neuroprotective effects by acting as a free radical scavenger. In humans, approximately one half the antioxidant capacity of plasma comes from uric acid.[102]

However, the role of urate in ischemic stroke is poorly understood. The role of uric acid as a risk factor for vascular disease and acute stroke is controversial and there is little data about it. Hence, the present study was planned to assess serum uric acid levels in patients with ischemic cerebrovascular accident and to find the correlation, if any, between serum uric acid levels and lipids in patients with ischemic cerebrovascular accident.

The present cross sectional study was done at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on a total of 100 patients with ischemic cerebrovascular accident from January 2012 to December 2012.

In the present study raised serum uric acid levels were noted in 69% of the patients and the mean serum uric acids levels were also found to be raised above the normal limits that is, 7.72 ± 1.22. These findings suggest that serum uric acid levels in patients with acute ischemic stroke are on higher side. Similar findings were reported in a recent study from Iran where mean serum uric acid level was 5.94 (±1.70) mg/dl and about half of the patients with acute stroke were hyperuricemic.[102] According to a large 10 years follow up study, the prevalence of hyperuricemia in United States was 20.1%.[103] Recently, another large study in Bangkok showed prevalence of hyperuricemia as 24.4%.[104] According to these

studies[102-104] prevalence of hyperuricemia was significantly higher in patients with acute stroke than normal population.

Stroke is the one of the main clinical manifestations of CVD and studies investigating the relation between the uric acid and stroke have been inconsistent. Some studies[102-104] reported a positive independent relationship between uric acid and stroke whereas others demonstrated that uric acid did not relate significantly to stroke occurrence.[105]

Bansal et al[106] studied 50 patients with ischemic thrombotic cerebrovascular disease: thirty percent of the cases showed hyperuricemia and they concluded that elevated serum uric acid level may be a playing a role in the causation of ischemic thrombotic cerebrovascular disease in general and especially in patients below 40 years of age.

Kim et al conducted a systematic review and metaanalysis of 16 prospective cohort studies including 238449 adults to assess the association between hyperuricemia and risk of stroke incidence and mortality. They found that hyperuricemia may modestly but statically significant increase the risk of both stroke incidence and mortality.[107]

According to results of Milionis et al[108] study, elevated serum uric acid levels were associated with increased risk of acute ischemic stroke in the elderly. On the other hand in the Syst-Eur trial that included patients with isolated systolic hypertension, no significant relationship was detected between serum uric acid levels and fatal and non fatal strokes.[109]

Moreover, in a Japanese middle-aged population, hyperuricemia was not associated with stroke mortality in 108284 person years of follow up.[110] Goldberg et al[111] studied middle aged men and followed them for 20 years and they did not show a significant correlation between serum uric acid and thromboembolic stroke.

Cazzato et al.[112] reported no difference in uric acid level between patients with stroke and control group and their results demonstrated that hyperuricemia was not a high risk factor in cerebrovascular disease.

Recently Chen et al[113] studied 226 hemodialysis patients and followed them for 18 months, 43 patients experienced acute ischemic stroke; serum uric acid was inversely related to acute ischemic stroke morbidity in hemodialysis patients in their study.

The possible explanations for the discrepancies observed in these studies could be attributed to the study design, the population studied (different ethnicities with different CVD risk) and the confounders measured.[105]

In this study, an almost equal distribution of sex was observed with 54% of the patients being females and 46% being males with male to female ratio of 1.1:1. Among the females 90.74% had abnormal uric acid levels and this difference was statistically significant ($p<0.001$). These findings were consistent with the previous studies in the literature. A study from developing country reported the prevalence of hyperuricemia is 35.2% in men and 8.7% in women.[114] In contrast, other studies showed significant differences in uric acid level

between men and women but there was no difference in prevalence of hyperuricemia between men and women.[115]

In this study, 40 of the 54 women reported history of menopause and all (100%) of them were found to have raised uric levels ($p<0.001$). These results were in accordance with the previous study of Galvan et al.[116] who stated that uric acid levels are higher in postmenopausal females as oestrogen hormone is uricosuric, since it stimulates urinary urate excretion.

In the present study 41% of the patients were aged more than 60 years. Of these, all (100%) had raised uric acid levels. This difference was statistically significant ($p<0.001$). Also, the mean age in patients with raised serum uric acids levels was significantly higher (64.64 ± 10.46 years) compared to those with normal serum uric acid levels (47.45 ± 7.86 years; $p<0.001$). Similar findings were reported in a study where there was a weak but significant positive association between age of patients and their serum uric acid levels.[114] In contrast, a recent study from Iran reported significant negative correlation between age of patients and their serum uric acid levels.[102]

In this study history of hypertension and diabetes was reported by 59%, and 30% while 18% each reported history of previous stroke and ischemic heart disease. Further significantly higher number of patients with history of hypertension (81.36%; $p=0.001$) and diabetes (83.33%, $p=0.042$) had raised uric acid levels whereas no statistically significant difference was observed in patients with history of previous stroke ($p=0.146$) and ischemic heart disease ($p=0.744$). These findings indicate that, patients with diabetes and hypertension having

raised serum uric acid levels have higher chances of ischemic cerebrovascular accident. Previous studies also reported significant association between insulin resistance, systolic and diastolic blood pressure and serum uric acid levels.[117] In contrast, a recent study from Iran reported no significant association between serum uric acid level and diabetes mellitus and hypertension. Chammaro et al.[14] assessed prognostic significance of serum uric acid concentration in patients with acute ischemic stroke and they reported that diabetics had lower uric acid concentration than other patients and uric acid concentration was inversely associated with fasting blood glucose.[14]

In the present study, the personal history of smoking and alcohol consumption was noted in 22% and 32% of the patients respectively. It was observed that, of the 51 patients with smoking history and 32 patients with alcohol consumption, 78.43% and 56.25% of the patients had raised serum uric acids levels suggesting statistically significant association of smoking and alcohol consumption with serum uric acid levels ($p=0.037$ and $p=0.059$ respectively). A study by Bonora et al showed that there was no significant association between smoking and uric acid level.[117]

Hyperuricemia also has been found to accelerate renal disease in the remnant kidney models[118] and to accelerate experimental cyclosporine nephropathy.[119] In the present study 14% of the patients had raised serum creatinine. Of these, all the patients (100%) had raised serum uric acid levels ($p=0.007$). In the past few years, there has been increasing evidence that hyperuricemia may be a true renal risk factor.[120] Epidemiological studies have found that hyperuricemia is an independent risk factor for renal dysfunction in

normal population.[121] Hyperuricemia also has been found to accelerate renal disease in the remnant kidney models[118] and to accelerate experimental cyclosporine nephropathy.[119] The main pathophysiologic mechanism by which uric acid causes these conditions involves an inhibition of endothelial nitric oxide bioavailability,[122] activation of rennin angiotensin system,[119] and direct actions on endothelial cells and vascular smooth muscle cells.[123] The importance of these pathways is suggested by a recent prospective study in which lowering uric acid in individuals with hyperuricemia and renal dysfunction was associated with improved BP control and slower progression of renal disease ($p = 0.021$).[124]

In the present study cholesterol, HDL, LDL and triglycerides were abnormal in 83%, 86%, 52% and 80% respectively. It was observed that a significant number of patients with raised LDL (78.75%; p=0.027) and triglyceride levels (80%; p=0.017) also had raised serum uric acid levels. Whereas, in those with abnormal HDL and cholesterol levels, no statistically significant corelation was observed with respect to uric acids levels (p=0.301 and p=0.116 respectively). However, all the lipid variables, that is, the mean cholesterol (236.25 ± 39.53 vs 220.58 ± 28.37l p=0.027), HDL (37.23 ± 6.40 vs 34.32 ± 6.34; p=0.039), LDL (175.42 ± 35.01 vs 158.10 ± 27.12; p=0.009) and triglycerides (182.83 ± 54.61 vs 151.48 ± 39.95; p=0.002) were found to be abnormal in patients with raised serum uric acid levels. Fang and Alderman (2000)[125] also stated that higher serum uric acid levels were associated with increasing cholesterol levels. Chamorro et al.[14] documented that serum uric acid is directly associated with serum triglycerides ($p = 0.0001$).

Metabolic syndrome is defined as a syndrome of truncal obesity, insulin resistance, elevated BP, hypertriglyceridemia, and hyperuricemia.[126] Recently, uric acid was found to have a causal role in the metabolic syndrome that was induced experimentally by fructose.[120] Fructose rapidly raises uric acid as a consequence of activation of fructokinase with ATP consumption, intracellular phosphate depletion, and stimulation of AMP deaminase.[127] Lowering uric acid in fructose-fed rates ameliorate much of the metabolic syndrome, including a reduction in BP, serum triglycerides, hyperinsulinemia, and weight gain.[120]

Overall, the present study showed that, serum uric acid levels in patients with ischemic cerebrovascular accident were high and showed a strong correlation with stroke severity based on NIHSS. Further correlation between serum uric acid levels and lipids showed that in patients with raised LDL and triglycerides serum uric acid levels were significantly raised while no statistically significant difference was noted in patients with raised cholesterol and abnormal HDL but the mean serum uric acid levels in patients with abnormal lipid levels, that is, cholesterol, LDL, HDL and triglycerides were significantly raised. However, this study had few limitations viz, small sample size and serum uric acid levels in different acute ischemic stroke sub-types could not be assessed due to the small sample size. Further studies on larger sample sizes considering different acute ischemic stroke sub-types would further explore the role of serum uric acid precisely.

Chapter 7

Conclusion

CONCLUSION

In the present study more than two third patients (69%) with acute ischemic stroke had raised serum uric acid levels. Also, the mean serum uric acids levels were found to be raised above the normal limits (7.72 ± 1.22). Statistically significant association was found between raised serum uric acid levels and NIHS score as also between uric acid and sex, age, history of hypertension and diabetes mellitus, personal history of smoking and alcohol consumption and history of menopause in women.

Further, the quantitative analysis of lipids showed significantly raised serum uric acid levels in patients with raised LDL and triglycerides and, significantly raised mean serum uric acid levels were found in patients with abnormal cholesterol, LDL, HDL and triglycerides.

Chapter 8

Summary

SUMMARY

Stroke is the third common cause of death in the world after coronary heart disease and cancer. The present study was aimed to assess serum uric acid levels in patients with ischemic cerebrovascular accident, its utility as a prognostic marker and to correlate between serum uric acid levels and lipids in patients with ischemic cerebrovascular accident.

This study was conducted on a total of 100 patients with ischemic cerebrovascular accident from January 2012 to December 2012 at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

In this study 54% of the patients were females compared 46% males with male to female ratio of 1.1:1. The commonest age group was more than 60 years present in 41% of patients. The history of hypertension and diabetes was present in 59% and 30% and smoking and alcohol consumption was noted in 51% and 32% respectively. Of the 54 women history of menopause was reported by 40 patients. Very severe NHSS score were noted in 18% patients. Serum creatinine was raised in 14% of the patients. Lipids, viz. cholesterol, HDL, LDL and triglycerides were abnormal in 83%, 86%, 52% and 80% respectively. Raised serum uric acid levels were noted in 69% of the patients and the mean serum uric acids levels were 7.72 ± 1.22.

Based on the findings of this study, it may concluded that, serum uric acid levels in patients with acute ischemic stroke are on the higher side. Higher serum uric acid levels were consistently found in patients with very severe and severe

ischemic stroke assessed by NIHS score. Stroke mortality in our study was significantly correlated with high serum uric acid levels. Positive association was found between raised serum uric acid levels and sex, age, history of hypertension and diabetes mellitus, personal history of smoking and alcohol consumption and history of menopause in women. No significant relationship could be detected between serum uric acid levels and history of prior stroke. On quantitative analysis, higher number of patients had raised serum uric acid levels with raised LDL and triglycerides while quantitative analysis showed, significantly raised mean serum uric acid levels in patients with raised cholesterol, LDL, HDL and triglycerides.

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

"CORRELATION OF SERUM URIC ACID LEVELS & LIPID LEVELS IN PATIENTS WITH ISCHAEMIC CEREBROVASCULAR ACCIDENT - A ONE YEAR CROSS-SECTIONAL STUDY"

Objective and purpose of the study

This research is intended to estimate the Serum Uric acid and lipid levels in patients with ischaemic cerebrovascular accident. The principal investigator of the study is Dr. *** ***** under the guidance of Dr. **** *******

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood sample and get a chest x ray done for the same study.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from your arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn. You may also face some radiation hazards while getting an x ray done.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part you can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsorer may

stop your participation in this study any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

VOLUNTARY PARTICIPATION/ WITHDRAWAL

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about my rights as a participant you may call Dr. **** *****, Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number **** *******.

CONSENT FORM

I voluntarily agree to take part in this study by signing on the line below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicated that I have read this entire consent form or it has been read to me, and has been explained to me in my vernacular language and had all my questions answered. I will be given a copy of this consent form.

Signature/Left Thumb print of the Participant or legally authorized representative.

Participant's Name/ : …….

Signature/ Left Thumb

Impression of the participant's : …….

Name of the legally authorized : …….

representative/ Guardian

Signature/ Left Thumb Impression. : …….

Witness's Name : …….

Signature/ Left Thumb Impression. :…….

Investigators name and Signature : …….

Date and Place : …….

Dr. *** ********.**
Associate Professor,
Dept. of Medicine, J. N. Medical College,
K.L.E. University, Belgaum 10.
Ph.No. ***** ********
Ext. ****

Dr. ***** *******
Post-Graduate,
Department of Medicine,
J.N. Medical College,
Belgaum
Ph.No. ***** ******
Ext. ****

Annexures

Annexure II

ANNEXURE II – PROFORMA

Patient Name: I.P number:

Age: Sex:

Address: Occupation:

Date of admission: Date of discharge:

SYMPTOMS :

1. Fever Yes/No
2. preceding delivery Yes/No
3. preceding convulsions Yes/No
4. preceding headache Yes/No
5. unconsciousness Yes/No
6. right sided hemiplegia Yes/No
7. right sided hemiparesis Yes/No
8. left sided hemiplegia Yes/No
9. left sided hemiparesis Yes/No
10. faciaj palsy Yes/No
11. monoplegia Yes/No

TREATMENT HISTORY:

Chronic diuretic use Yes/No

Chronic salicyclate use Yes/No

Use of any other drug altering uric acid level-

PERSONAL HISTORY:

Habits: h/o smoking Yes/No

H/o Alcohol consumption Yes/No

Hypertensive Yes/No

Diabetic Yes/No

PAST HISTORY:

Any medical disease affecting uric acid levels-

Prior stroke history

PHYSICAL EXAMINATION:

GENERAL CONDITION:

Pallor: Yes/No

Icterus: Yes/No

Lymphadenopathy: Yes/No

Cyanosis: Yes/No

Clubbing: Yes/No

Edema: Yes/No

VITALS:

Temperature:

Pulse:

Respiratory rate:

Blood pressure:

Pt condition on discharge Improved/ Worsened

/Same/ Expired

SYSTEMIC EXAMINATION:

C.N.S.:

C.V.S.:

P.A.:

R. S:

LABORATORY INVESTIGATIONS:

- RBS
- Serum Creatinine
- Lipid Profile
- Urine routine
- Chest X-ray
- ECG
- CT/ MRI brain as appropriate
- Serum Uric Acid

DIAGNOSIS:

Annexures

Annexure III

ANNEXURE III – MASTER CHART

-	-	Absent
+	-	Present
BP	-	Blood pressure
bpm	-	Beats per minute
E	-	Expired
F	-	Female
I	-	Improved
mg/dL	-	Milligram per deciliter
mm Hg	-	Millimeter of mercury
M	-	Male
N	-	Normal
NIHS	-	National Institutes of Health Stroke
S	-	Unchanged
W	-	Worsened