CLINICAL PROFILE OF CEREBRAL INFARCTION AND ITS OUTCOME IN RELATION TO GLYCEMIC STATUS ON PRESENTATION – A PROSPECTIVE STUDY

By
Dr. Narone Utkarsha C.

Dissertation Submitted to the
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In partial fulfillment
of the requirements for the degree of

M.D.

In

GENERAL MEDICINE

Under the Guidance of
Dr. M.S. BIRADAR M.D. (MEDICINE)
PROFESSOR & HOD

DEPARTMENT OF GENERAL MEDICINE

B. L. D. E. A'S SHRI B. M. PATIL MEDICAL COLLEGE

HOSPITAL & RESEARCH CENTRE, BIJAPUR

2010

RAJIV GANDHI UNIVERSITY OF HEALTH SCIENCES, BANGALORE, KARNATAKA

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I hereby declare that this dissertation entitled **"CLINICAL PROFILE OF CEREBRAL INFARCTION AND ITS OUTCOME IN RELATION TO GLYCEMIC STATUS ON PRESENTATION – A PROSPECTIVE STUDY"** is a bonafide and genuine research work carried out by me under the guidance of **Dr.M.S.Biradar** $_{M.D}$ Professor and HOD., Department of Medicine.

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Dr M. S. Biradar $_{MD}$
Professor and Head of the Dept.
Dept. of Medicine
BLDEA's Shri. B. M. Patil
Medical College Hospital &
Research Centre, Bijapur.

Date:
Place: Bijapur

ENDORSEMENT BY THE H.O.D

B. L. D. E. A'S

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL

& RESEARCH CENTRE, BIJAPUR

This is to certify that the dissertation entitled **"CLINICAL PROFILE OF CEREBRAL INFARCTION AND ITS OUTCOME IN RELATION TO GLYCEMIC STATUS ON PRESENTATION – A PROSPECTIVE STUDY"** is a bonafide research work done by **Dr. Narone Utkarsha C.** under the guidance of **Dr. M. S. Biradar** $_{\text{M.D}}$ Professor and HOD., Department of Medicine.

Dr M. S. BIRADAR $_{\text{MD}}$
Professor and HOD,
Dept. of Medicine,
BLDEA's Shri. B. M. Patil
Medical College Hospital &
Research Centre, Bijapur.

Date:

Place: Bijapur

ENDORSEMENT BY THE PRINCIPAL

B. L. D. E. A'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL & RESEARCH CENTRE, BIJAPUR

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Dr. M. S. BIRADAR $_{\text{M.D.}}$
Incharge Principal
BLDEA's Shri. B. M. Patil
Medical College Hospital &
Research Centre, Bijapur.

Date:
Place: Bijapur

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Date:

Place: Bijapur **Dr. Narone Utkarsha C.**

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Date:

Place: Bijapur **Dr. Narone Utkarsha C.**

LIST OF ABBREVIATIONS

AAN	-	American Academy of Neurology
ACA	-	Anterior cerebral artery.
ACoA	-	Anterior communicating artery.
AF	-	Atrial fibrillation
AHA	-	American Heart Association
AP – 1	-	Activator Protein - 1
AVM	-	Arteriovenous malformation
BGA	-	Blood glucose on admission
CAA	-	Cerebral Amyoloid Angiopathy
Ca2+/Na+	-	Calcium – sodium exchange pump
CCA	-	Common carotid artery
CNS	-	Central nervous system
CT	-	Computer tomography
CVA	-	Cerebrovascular accident
DM	-	Diabetes mellitus
DSA	-	Digital subtraction angiography
ECA	-	External carotid artery
ECAM	-	Endothelial cell adhesion molecule
Egr 1	-	Early growth response factor 1
FDA	-	Food and Drug Administration
GS	-	Glycemic status
ICA	-	Internal carotid artery.
ICAM	-	Intercellular adhesion molecule
ICH	-	Intracerebral hemorrhage
iNOS	-	Inducible Nitric Oxide synthase
MCA	-	Middle cerebral artery
MCP	-	Monocyte chemotactic protein
MMP 9	-	Matrix metalloproteinase 9
MRI	-	Magnetic resonance imaging
NF kB	-	Nuclear factor kappa – B cells
NIHSS	-	National Institute of Health Stroke scale

NINDS	-	National Institute of Neurological Disorders and Stroke
NMDA	-	N- Methyl D – Aspartic acid
NO	-	Nitric oxide
PAI – 1	-	Plasminogen activator inhibitor 1
PARP	-	Poly (ADP ribose) polymerase
PCA	-	Posterior cerebral artery
PoCA	-	Posterior communicating artery
ROS	-	Reactive oxygen species
rtPA	-	Recombinant tissue Plasminogen activator
TCD	-	Transcranial Doppler ultrasound.
TF	-	Tissue factor
TIA	-	Transient ischemic attack
TNF	-	Tumour necrosis factor

ABSTRACT

Background and objectives: Hyperglycemia in both diabetic and non- diabetic (i.e., stress hyperglycemia) patients is associated with poor prognosis both in terms of mortality and functional recovery. The aim of this study is to correlate the clinical profile, infarct size on CT scan and clinical outcome of cerebral infraction in relation to glycemic status on presentation.

Materials and methods: 60 consecutive patients admitted with acute cerebral infarction to BLDEA,s Sri B. M. Patil Medical College Hospital and Research Centre, Bijapur from Nov 2007 - Nov 2008 were studied. Random Blood Glucose levels were done on hospital admission and were clinically scored based on NIHSS on day 1, at the time of discharge and then again on day 30 wherever feasible to assess the clinical outcome.

Results: Stress hyperglycemia group had higher percentage of medium sized infarcts and Diabetes group had higher percentage of large sized infarcts. For any infarct size NIHSS score was highest in the diabetes mellitus group and least in normoglycemia group. Rate of recovery of stroke was slowest in diabetes mellitus group compared to stress hyperglycemia with good recovery in the normoglycemia group. There was higher rate of complications and mortality in hyperglycemia group, increasing in proportion with worsening of glycemic status.

Conclusion: Admission blood glucose levels and NIHSS scores correlate well with infarct size. Patients with hyperglycemia have more severe stroke, more complications with poor recovery compared to normoglycemia group.

Keywords: Cerebral infarction; glycemic status; diabetes; stress hyperglycemia; normoglycemia; NIHSS score.

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INTRODUCTION

Cerebrovascular accident (CVA) is the third most common leading cause of death worldwide, after coronary heart disease and cancer. The World Health Organisation (WHO) defines stroke as "rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting for 24 hours or longer, or leading to death with no apparent cause other than of vascular origin".[1]

Among 80% of all CVAs are ischemic, rest being due to haemorrhage. There are many factors which alter the outcome of stroke.

Acute hyperglycemic response to stress has been recognized since Claude Bernard's observations more than a century ago.[2] This "diabetes of injury" exemplifies the obligatory metabolic rearrangements required to cope with critical stress. The concept evolved as glucose became identified as metabolic mirror of the severity and outcome of critical illness.

Stress hyperglycemia has been defined as hyperglycemia in previously euglycemic patients that corrects once the acute process resolves. Hyperglycemia occurs in 60% of the cases with acute stroke and in 12- 53% cases without the prior diagnosis of diabetes. It imposes a range of adverse effects like abnormal immune function [3], hemodynamic and electromyocardial disturbances and increased infection rate [4]. Various studies have shown a direct relationship between the extent of stress hyperglycemia and severity and outcome of stroke, including mortality. Hyperglycemia in both diabetic and non- diabetic (i.e., stress hyperglycemia) patients is associated with poor prognosis both in terms of mortality and functional recovery, irrespective of patient's age, severity of condition or stroke sub- type. [5]

There are only few Indian studies on glycemic status and its influence on stroke outcome. The present study was conducted in a tertiary referral hospital to study the admission glycemic status and its effect on infarct size and severity using the NIHS scale in cases of cerebral infarction.

AIMS AND OBJECTIVES OF THE STUDY

To study the clinical profile, infarct size on CT scan and clinical outcome of cerebral infraction in relation to glycemic status on presentation.

REVIEW OF LITERATURE

HISTORICAL REVIEW

Hippocrates was the first to give the first description of cerebral infarction as an apoplexy where it means “astonished or thunderstruck or sudden bereft of one’s sense” and applied it descriptively to stroke. He wrote in his aphorisms on apoplexy, “persons are more subject to apoplexy between the ages of forty and sixty”, and attacks of numbness might reflect “impending apoplexy”. A few hundred years after Hippocrates, Galen (131- 201 AD) described the anatomy of the brain and its blood vessels from dissections of animals.

Johann Jacob Wepfer (1620- 1695) was the first to suggest that apoplexy was caused by disease of the blood vessels of the brain. He discovered that something disrupted the blood supply in the brains of people who died from apoplexy. He recognized obstruction of the carotid and vertebral arteries as the cause of apoplexy. He was the first to show that bleeding into the brain was an important cause of apoplexy.

Thomas Willis, a neuroanatomist described the circle of anastomotic vessels at the base of the brain in his best known CEREBRAL ANATOME. He recognized transient ischemic attacks, the phenomenon of embolism and existence of the occlusion of the carotid artery. Giovanni Battista Morgagni (1682- 1771) was able to focus attention on pathology and cause of the disease.

John Abercrombie gave a detailed clinical examination of apoplexy in his general text published in 1828. He used the presence of headache, stupor and paralysis and outcome to separate apoplectics into three clinical groups. In the middle of the nineteenth century, four atlases were published, each containing plates of brain and vascular lesions – Hooper’s atlas, Crureiher’s atlas (1835-1842), Carswell’s atlas (1838) and Bright’s atlas (1831).

The general medical and neurological texts of Osler, Gowers and Wilson contained in detail descriptions of the clinical findings and prognosis of the various stroke syndromes. During the twentieth century, there was an explosive growth of interest in and knowledge about stroke. Advanced technology allowed better visualization of the anatomy and functional aspects of the brain and of vascular lesions during life. Technological revolution was brought about by the Portuguese

neurosurgeon Moniz (1874- 1955), who surgically exposed and temporarily ligated the internal carotid artery in the neck and then injected 30% solution of sodium iodide, taking skull films later at regular intervals.

Modern angiography began with the work of Seldinger in Sweden, who devised a technique by which a small catheter could be inserted into an artery over a flexible guidewire after withdrawing the needle.In the mid 1960's, Hounsfield of the research laboratories of Electrical musical instruments in Britain, originated the concept of Computed Tomography (CT). By the late 1970's third generation scanners had made CT a useful, almost indispensable, diagnostic technique. It clearly distinguished between brain ischemia and haemorrhage and defined the size and location of most brain infarcts and haemorrhages.

In the mid 1980's Magnetic Resonance Imaging (MRI) proved superior to CT in showing old hemosiderin containing haemorrhages and in imaging vascular malformations, lesions abutting on bony surfaces and posterior fossa structures.

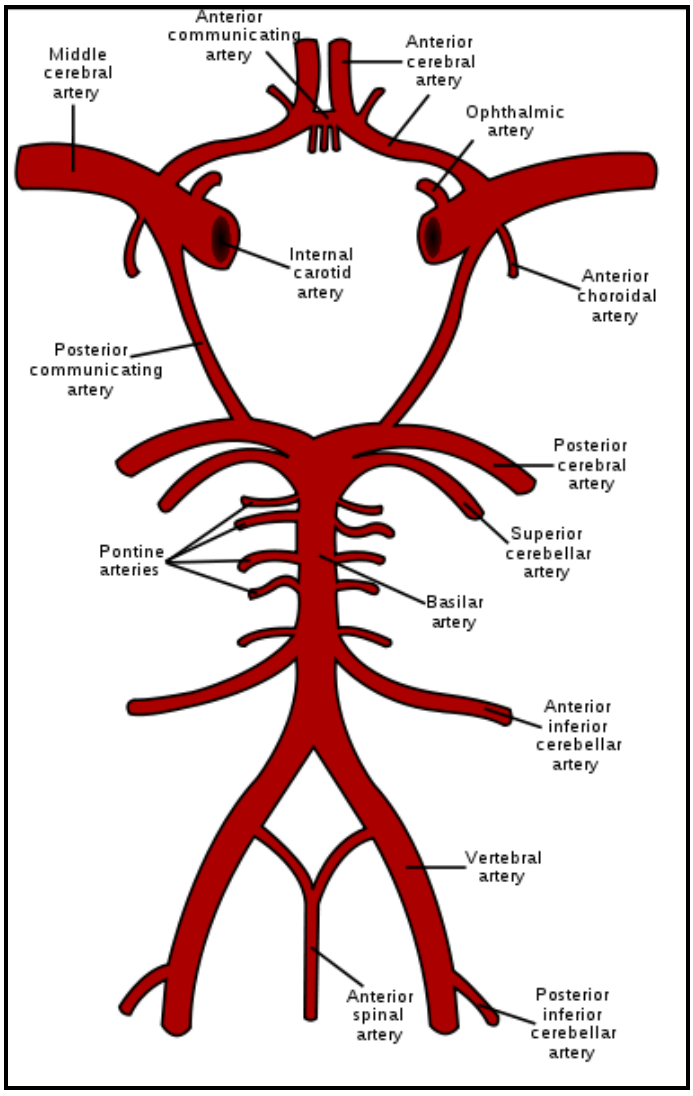
In 1961, Franklin and colleagues introduced ultrasound to medicine which imaged the extracranial carotid arteries non invasively. In 1982, Aaslid and colleagues introduced a high energy bidirectional pulsed Doppler system that used low frequencies to study intracranial arteries, termed Trans Cranial Doppler ultrasound (TCD). In the 1970's and 1980's Echocardiography and ambulatory cardiac rhythm monitoring was introduced which greatly improved cardiac diagnoses and cardiogenic sources of embolism.

By the end of twentieth century, advanced brain imaging with CT, MRI and newer MR modalities, diffusion, perfusion and functional MRI and MR spectroscopy showed the clinicians the localization, severity and potential reversibility of brain ischemia. Trans esophageal Echocardiography (TEE) studied cardiac and aortic sources of stroke. Vascular lesions were quickly and safely defined using spiral CT angiography, MR angiography, extracranial and transcranial ultrasound.[6,7]

ANATOMY OF CEREBRAL CIRCULATION

Blood supply to the brain is delivered by two internal carotid and two vertebral arteries, which anastomose at the base of the brain to form the circle of Willis.The carotid arteries supply.

Figure no. 1 : CIRCLE OF WILLIS



The anterior and the vertebrobasilar system supplies the posterior portions of the brain. At rest, the brain which is 2% of total body weight, receives 20% of cardiac output and consumes 20% of total inspired oxygen.

The Internal Carotid Artery (ICA) starts at the carotid sinus at the bifurcation of the common carotid artery (CCA) at the level of thyroid cartilage. It runs up the neck without any branches, to the base of the skull where it passes

through the foramen lacerum to enter the carotid canal of the petrous bone. It then runs through the cavernous sinus in a ‘S’ shaped curve, pierces the dura and exits just medial to the anterior clinoid process, and then bifurcates into the Anterior

Cerebral Artery (ACA) and the larger Middle Cerebral Artery (MCA).

The External Carotid Artery (ECA) also starts at the CCA bifurcation and supplies the jaw, face, scalp, neck and meninges. The Ophthalmic artery is the first branch of ICA. It supplies the eye and other structures of the orbit.

The Posterior Communicating Artery (PoCA) is the next artery to arise from the ICA. It passes back to join the first part of the Posterior Cerebral Artery (PCA). Tiny branches supply the adjacent optic chiasma, optic tract, hypothalamus, thalamus and mid brain.

The anterior choroidal artery arises from the last section of the ICA, just beyond the PoCA origin and supplies the optic tract, internal capsule, medial parts of the basal ganglia, medial parts of the temporal lobe, thalamus, lateral geniculate body, proximal optic radiation and midbrain.The Anterior Cerebral Artery (ACA) passes horizontally and medially to enter the interhemispheric fissure, anastomoses with its counterpart of the opposite side via the Anterior Communicating Artery (AoCA), curves up around the genu of the corpus callosum, and supplies the anterior and medial parts of the cerebral hemisphere.

The MCA enters the sylvian fissure and divides into 2 – 4 branches which supply the lateral parts of the cerebral hemisphere.The proximal MCA (M1 segment) gives rise to penetrating branches (lenticulostriate arteries) that supply the putamen, outer globus pallidus, posterior limb of internal capsule, adjacent corona radiate and most of the caudate nucleus. In the sylvian fissure, the MCA divides into superior and inferior divisions (M2 branches). Branches from the superior division supply the frontal and superior parietal cortex, whereas branches from the inferior division supply the inferior parietal and temporal cortex.

The vertebral artery arises from the proximal subclavian artery and ascends to pass through the transverse foramina of the sixth to second vertebrae. It unites with the opposite vertebral artery on the ventral surface of the brainstem at the pontomedullary junction to form the basilar artery, The vertebral artery gives rise to the anterior and posterior spinal arteries, the posterior inferior cerebellar artey and small penetrating arteries to the medulla. The posterior inferior cerebellar

artery supplies the inferior vermis, inferior and posterior surfaces of the cerebellar hemispheres and brainstem.

The basilar artery ascends ventral to the pons to the ponto midbrain junction in the interpeduncular cistern where it divides into two PCA. It also gives rise to the anterior inferioe cerebellar artery which supplies the rostral cerebellum, brainstem, inner ear, and the superior cerebellar artery which supplies the brainstem, superior half of cerebellar hemisphere, vermis and dentate nucleus. The PCA encircles the midbrain close to the oculomotor nerve at the level of the tentorium and supplies the inferior parts of the temporal lobe and the occipital lobe. Many small perforating arteries arise from the proximal portion of the PCA to supply the midbrain, thalamus, hypothalamus and geniculate bodies. In about 15% of the individuals, the PCA is the direct continuation of the PoCA, its main blood supply the coming from the ICA rather than the basilar artery.

Collateral Blood Supply to The Brain:

Normally the ICA provides blood to the anterior two – thirds of the ipsilateral cerebral hemisphere. There is rather little mixing of blood via the PoCA and so the posterior circulation is usually supplied by the vertebral, basilar and PCA. However there are various ways in which collateral blood supply to the brain can develop distal to the occlusion of major arteries in the neck and head. The actual pattern of collateral blood flow depends on where the major blood vessels are occluded, and on which collateral channels are anatomically available in a particular individual, and free from disease.

Collateral Blood Flow May Develop Via:

The circle of Willis, which is formed by the proximal part of the two ACAs connected by the ACoA, and the proximal part of the two PCAs, which are connected to the distal ICAs by the PoCA. However 50% of the circles have one or more hypoplastic or absent segments.

Other Areas Of Collateral Blood Flow Are :

- Around the orbit
- Leptomeningeal anastomoses
- Parenchymal anastomoses

Venous Drainage :

Venous blood flows centrally via the deep cerebral veins and peripherally via the superficial cerebral veins into the dural venous sinuses which drain into the internal jugular veins. The cerebral veins are thin walled, have no valves and the blood flow is often in the same direction as in neighbouring arteries.[8]

EPIDEMIOLOGY OF STROKE

Stroke is the third most common cause of death after ischemic heart disease and cancer in the United States. Every year there are approximately 700,000 cases of stroke—roughly 600,000 ischemic lesions and 100,000 hemorrhages with 175,000 fatalities from these causes . [9]

Stroke is also the leading cause of disability in adults. Stroke poses major socioeconomic challenge in rehabilitation of survivors after stroke. Out of the thousands of stroke survivors each year, 30% require assistance with activities of daily living, 20% require assistance with ambulation and 16% require institutional care. The human and financial cost of stroke are immense and its estimated annual economic impact in our society, both directly in health care and indirectly in lost income is approximately $41 billion.[10]

Variation in the incidence of stroke among patients aged 75 to 84 years ranged from 1054 in France to 2062 in Sweden per 1,00,000 population . In the USA, there has been a steady decline to 54% for the past 30 years . In Japan, incidence of cerebral infarction has declined to 34% and cerebral hemorrhage to 29% between the periods 1961-66 and 1972-76. In Finland two studies beginning in 1972 and 1977 found about one third reduction in stroke incidence. It was primarily thought that this reduction was due to widespread control of hypertension. Within past 10 years, the declining annual incidence rate appears to have leveled off and some epidemiologists fear that it may begin to rise. In Sweden, there was a 38% increase in stroke among women from 1975 – 78 and 1983 – 85. [11]

EPIDEMIOLOGY OF STROKE IN INDIA

In India, several cross – sectional population – based epidemiological studies have been carried out in different parts of the country since eighties. The first community based study on stroke was carried out in and around Vellore during 1969 – 71 and Rohtak during 1971 – 74.

Analysis of data from major urban university hospitals suggested that nearly 2% of all hospital cases, 4.5% of medical and 20% of neurologic admissions are from stroke. [12]

In the early 1980s, the prevalence of stroke was around 500 – 700 per 100000 in the western countries and 900 per 100000 in Asia. [13]

The annual incidence rate of stroke ranged from 105 – 262/ 100000 population with the incidence falling within the range reported in the west i.e., 100 – 300/ 100000 population. The stroke subtypes were cerebral infarcts in 68% and cerebral haemorrhage in 32%. The ratio of cerebral infarct to haemorrhage was 2.21, with more cases of cerebral haemorrhage than that observed in the western countries. [14,15]

The stroke represented 1.2% of total deaths in the country, when all ages were included with gender ratio M:F = 1.24 [16]. The proportion of stroke death increased with age and 2.4% of all deaths were in the age group of > 70 years. Diabetes mellitus, hypertension, tobacco use and low hemoglobin were the most important risk factors for ischemic stroke. [17] The prevalence of stress hyperglycemia in Indian studies ranged from 14 – 62% [18]

RISK FACTORS FOR STROKE

1) Non modifiable risk factors:
   (a) Age – It is the single most important risk factor for stroke. Risk doubles for each decade after 55 years.
   (b) Gender – Males suffer from stroke 1.25 times more commonly than females, who have greater mortality than men for stroke each year.
   (c) Race – In an increasing order Afro Carribeans > Asians > Europeans have stroke incidence.
   (d) Heredity – Increased incidence of stroke is noted in families.
   (e) Prior stroke or TIA - A person who has had one or more TIAs is almost 10 times more likely to have a stroke than someone of the same age and sex.

2) Modifiable risk factors:
   (a) Blood pressure – Hypertension It is the single most important modifiable risk factor for ischemic stroke. Prevalence of stroke is 45% at 50 years, 60% at 60 years in patients having hypertension. The incidence is approximately three times greater in persons with elevated BP (>160 mm Hg systolic) than in normal, irrespective of age and sex. In a meta analysis it is shown that every 7.5 mm Hg reduction in Diastolic

      BP causes 46% decline in stroke and treatment of isolated systolic hypertension reduces stroke risk by 36%. About 40% of strokes can be attributed to systolic blood pressure of > 140mm Hg. [17,19,20]

   (b) Smoking – The Framingham study showed three-fold increase of ischemic strokes as compared to non- smokers. The Multiple Risk Factor Intervention Trial data shows that smoking is related to all forms of stroke with about the same strength as it is to coronary heart disease. The effect was greatest at younger ages and parallel the number of cigarettes smoked. [21,22]

(c) Diabetes Mellitus – It increases the risk of stroke by 1.8 – 3.5 times. Most of the ischemic strokes in them are lacunar strokes. In addition to glucose status, hyperglycemia and increased insulin resistance are the major risk factors for ischemic stroke. In the Framingham study it was the sixth most important predictive factor for stroke. [23]

(d) Blood lipids – Dyslipidemias increase the risk of stroke by 1 – 2 times. There is a higher incidence in patients with low high density lipoproteins (HDL) and high low density lipoproteins (LDL) and triglycerides (TG) [20]. The 20 – 30% relative risk reduction in stroke that occurs within 1-2 years after institution of statins is due to its pleotropic effect which improves the endothelial function, plaque stabilization, anti thrombotic properties, diminished inflammation and improved hemorrheologic environment.

(e) Obesity – The Whitehall study showed that body mass index (BMI) was predictive of stroke in both smokers and non- smokers. It was estimated that having a BMI above 25 kg/m^2 and smoking account for 60% of strokes in men upto 65 years. [8]

(f) Cardiovascular diseases – According to the Framingham study, Electrocardiographic changes of left ventricular hypertrophy increases the risk of ischemic stroke by ten fold; non specific ST and T changes by four fold and congestive cardiac failure by nine fold [21,24] Hypertension and peripheral vascular disease, myocardial infarction, cardiac arrhythmias are the risk factors for embolic stroke. Patients with chronic atrial fibrillation are five to seven times more liable for embolic stroke than age matched population of normal cardiac rhythm. Mitral valve prolapse, prosthetic
valves, endocarditis and congenital heart diseases are all important ausative factors for embolic strokes. [25]

(g) Alcohol – The risk is variable. In low to moderate consumption it lowers overall mortality, while heavy consumption increases the risk of haemorrhage. Embolic strokes result from cardiac arrhythmias and cardiac wall motion abnormalities, hypertension, enhanced platelet

aggregation and activation of clotting cascade, which are common in alcoholics. [26]

(h) Anticoagulant therapy – Anticoagulant therapy increases the risk of intracranial haemorrhage.

(i) Illicit drug use – Use of cocaine, heroin, amphetamine, LSD, etc. has been found to be associated with increased risk for stroke.

(j) Oral contraceptives – Young women consuming oral contraceptives, have a high risk for stroke and much more in those whose estrogen content is more than 50 mcg. Cerebral infarction is more likely due to thrombotic disease secondary to enhanced platelet aggregability and alteration in clotting factors. [27]

(k) Miscellaneous – Migraine, decreased serum fibrinogen levels, polycythemia, increased homocysteine levels, etc are associated with risk of ischemic stroke.

CLASSIFICATION OF STROKE

(I) According to pathogenesis

(a) Ischemic strokes

(i) With cerebral infarction:

1. Cerebral thrombosis with or without atherosclerosis
2. Cerebral embolism
3. Cerebral venous thrombosis
4. Arteritis
5. Arterial hypotension and anoxic encephalopathy
6. Blood diseases
7. Cerebral anoxia
8. Dissecting aneurysm of brachiocephalic vessels
9. Angiographic complications
10. Infarction of undetermined cause

(ii) With cerebral ischemia

1. Transient ischemic attacks
2. Local embolism from proximal atheromatous plaques and paradoxical embolism
3. With cardiac arrhythmias
4. Arterial hypotension or hemodynamic crisis
5. Vasospasm with migraine or subarachnoid hemorrhage
6. Undetermined source
7. Idiopathic and rare types (drugs and oral contraceptives, consumption coagulopathy, cerebral malaria, Behcet's syndrome, cerebral amyloid angiopathy, hyperhomocysteinemia, hyperviscosity)

(b) Haemorrhagic stroke

1. Hypertensive cerebral hemorrhage
2. Ruptured aneurysm
3. Ruptured angioma
4. Trauma
5. Blood dyscrasias (leukemia, purpura, hyperviscosity syndromes and other bleeding diatheses)
6. Complications of anticoagulant therapy or thrombolytic therapy

7. Bleeding in brain tumours
8. Miscellanous causes (arteritis, bleeding in hemorrhagic infarct)
9. From undetermined sources

(c) Stroke of undetermined origin

1. Multi infarct dementia in lacunar sundrome or leukoariosi
2. Moyamoya disease
3. Fibromuscular dysplasia
4. Binswanger's subcortical arteriosclerotic encephalopathy
5. Winiwarter- Buerger disease
6. Aortic arch syndrome
7. Unclassified syndromes

(II) Etiological classification

1. Atherosclerotic thrombosis
2. Transient ischemic attacks
3. Embolism
4. Ruptured or unruptured saccular aneurysm or AVM
5. Arteritis
6. Cerebral thrombophlebitis
7. Hematologic disorders
8. Trauma and dissection of carotid and basilar artery
9. Amyloid angiopathy
10. Dissecting aortic aneurysm
11. Systemic hypotension with arterial stenosis
12. Complicationds of arteriography
13. Neurologic migraine with persistent deficit
14. With tentorial, foramen magnum and subfalcial herniations
15. Miscellaneous types

(III) Clinical classification

1. Arterial territories (Oxfordshire stroke subtype classification)

(a) Anterior circulation syndrome

- Anterior cerebral artery (ACA) syndrome
- Middle cerebral artery (MCA) syndrome

(b) Posterior Circulation Syndrome

- Vertebrobasilar artery syndrome

- Posterior cerebral artery syndrome

2. Clinical manifestations

   (a) TIA : Focal neurological deficit with complete recovery within 24 hours

   (b) Reversible Ischemic Neurological Deficit (RIND) : Neurological deficit with complete recovery within a period of one week.

   (c) Evolving stroke : Gradual stepwise development of neurological deficit

   (d) Complete stroke : Rapid in onset with persistent neurological deficit which does not progress beyond 96 hours. [9,17]

PATHOGENESIS OF STROKE

Cerebrovascular disorders are the result of either ischemia or haemorrhage within the central nervous system. The neurologic deficit reflects the location and size of the lesion.

Most cases of acute stroke are ischemic, usually resulting from thrombotic or embolic occlusion of a cerebral artery. An infarct is usually due to either thrombosis or atherosclerotic lesions or embolism from the heart, aorta or extracranial/ intracranial vasculature.

Atherothrombotic or thromboembolic arterial occlusions account for around 80 – 85% of all cases of stroke. Cerebral atherothromboembolism involves predominantly middle cerebral artery, followed by the posterior cerebral artery; the anterior cerebral artery and the basilar artery are involved less frequently.

Haemorrhage may be epidural, subdural, subarachnoid, intra parenchymal or intraventricular in location. Intracerebral haemorrhage is responsible for 10% of all strokes and subarachnoid haemorrhage accounts for the remainder. Haemorrhage could result from arterial hypertension, saccular aneurysm, arteriovenous malformations, blood dyscrasias, vasculitis, sympathomimetic drugs, cerebral amyloid angiopathy, trauma and neoplasms. [10,27,28]

PATHOPHYSIOLOGY OF CEREBRAL INFARCTION

The pathogenesis of brain damage from cerebrovascular occlusion can be separated into two sequential processes:

1. Vascular and hematological events that cause the initial reduction and subsequent alteration of local cerebral blood flow.
2. Ischemia induced abnormalities of cellular chemistry that produce necrosis of neurons, glia and other supportive brain cells.

The molecular consequences of brain ischemia are changes in cell signaling (neurotransmitters, neuromodulators), in signal transduction, in metabolism and in gene regulation/ expression.

In the normal adult brain, cerebral blood flow at rest is approximately 50 – 55 ml/ 100 g per minute, and the cerebral metabolic rate of oxygen is 165 mmol/ 100 g per minute. The cerebral microcirculation distributes blood to its target organ by regulating blood flow and distributing oxygen and glucose to the brain while removing by- products of metabolism. Cerebral ischemia is caused by decrease blood supply to the microcirculation. The magnitude of flow reduction is a function of collateral blood flow which depends on individual vascular anatomy as well as the site of occlusion.

Complete interruption of cerebral blood flow suppresses electrical activity within 12- 15 seconds, inhibits synaptic excitability of cortical neurons after 2 -4 minutes and inhibits electrical excitability after 4 -6 minutes. As the blood flow reduces to 18 ml/ 100 g per minute, the brain reaches a 'threshold for electrical failure'. Though these neurons are not functioning normally, they still have the potential for recovery. The 'threshold of membrane failure' occurs when blood flow reduces to 8 ml/ 100 g per minute. This can result in cell death. Fall in cerebral blood flow to zero causes death of brain tissue within 4 -10 minutes.

The upper threshold of blood flow i.e., 18 ml/ 100 g per minute and lower threshold of blood flow i.e., 8 ml/ 100 g per minute mark the limits of the ischemic penumbra. The area of misery perfusion or the ischemic penumbra, is the area of the ischemic brain between these two flow thresholds in which there are some neurons that are functionally silent but structurally intact and potentially salvageable. This ischemic penumbra will eventually infarct if blood flow is not restored. Thus saving the penumbra is the goal of thrombolytic therapy and newer

therapies under investigation. The ischemic penumbra is imaged by using perfusion – diffusion imaging with MRI. Fever dramatically worsens ischemia, as does hyperglycemia [glucose > 11.1 mmol/L (200 mg/dL)], so it is reasonable to suppress fever and prevent hyperglycemia as much as possible.

Induced moderate hypothermia to mitigate stroke is the subject of continuing clinical research.

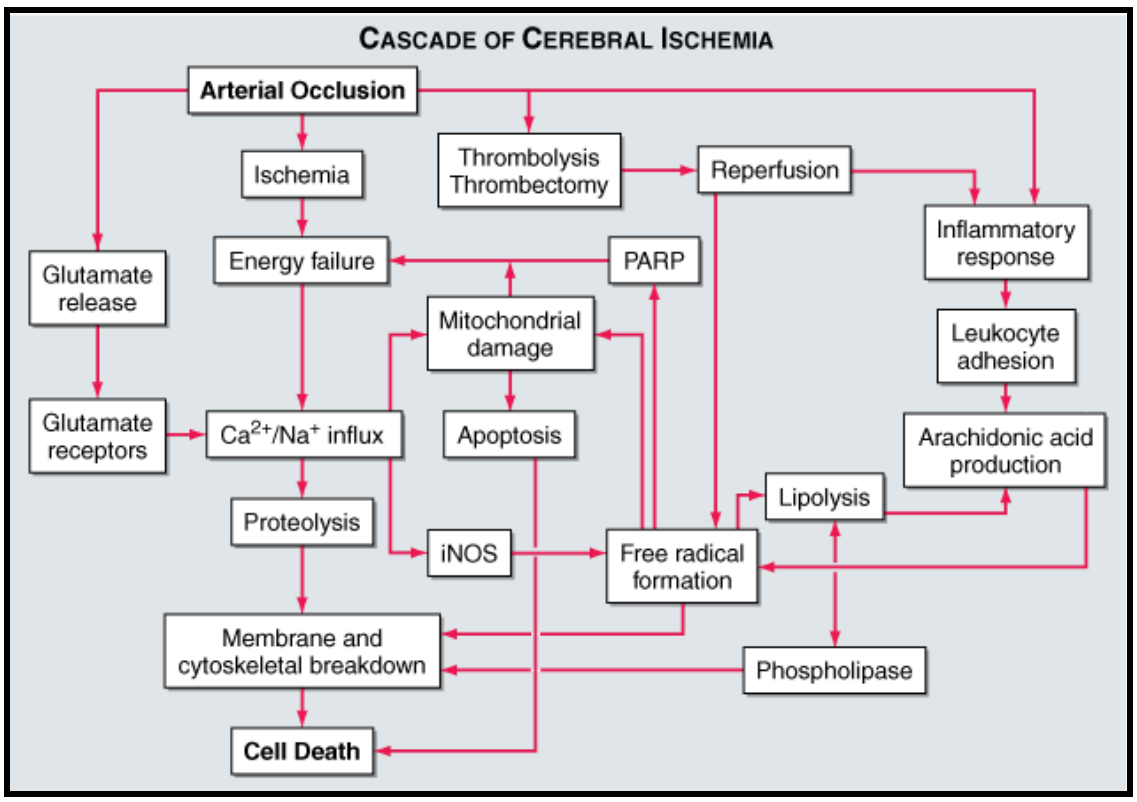
Cellular death occurs via two distinct mechanisms:

a. A necrotic pathway in which cellular cytoskeletal breakdown is rapid, principally due to energy failure of the cell.

b. An apoptotic pathway in which cells become programmed to die.

After cerebral ischemia, a cascade of complex biochemical events occurs within seconds to minutes. Ischemia causes impairment of brain energy metabolism, loss of aerobic glycolysis, intracellular accumulation of sodium and calcium ions, release of excitotoxic neurotransmitters, elevation of lactate levels with local acidosis, free radical production, cellular swelling, overactivation of lipases and proteases and cell death. Many neurons undergo apoptosis after focal brain ischemia. Ischemic brain injury is exacerbated by leucocyte infiltration and development of brain edema.

Figure no. 2 : CASCADE OF CEREBRAL ISCHEMIA



CARDIOEMBOLIC STROKE

Cardioembolism is responsible for ~20% of all ischemic strokes, primarily due to embolism of thrombotic material forming on the atrial or ventricular wall or the left heart valves. Embolic strokes are sudden in onset, with maximum neurologic deficit at once. The fragmentation of thrombus or quick lysis produces only transient ischemic attack (TIA).

Emboli from the heart most often lodge in the MCA, the posterior cerebral artery (PCA), or one of their branches; infrequently, the anterior cerebral artery (ACA) territory is involved. Emboli large enough to occlude the stem of the MCA (3–4 mm) lead to large infarcts that involve both deep gray and white matter and some portions of the cortical surface and its underlying white matter. A smaller embolus may occlude a small cortical or penetrating arterial branch. The location and size of an infarct within a vascular territory depend on the extent of the collateral circulation.

The most significant causes of cardioembolic stroke in most of the world are nonrheumatic (often called nonvalvular) atrial fibrillation, MI, prosthetic valves, rheumatic heart disease, and ischemic cardiomyopathy Artery-to-Artery Embolic Stroke

Artery- to –artery embolism appears to be the dominant vascular mechanism causing ischemia. It is secondary to distal embolisation to intracranial arteries from thrombus on atherosclerotic plaques. Carotid bifurcation atherosclerosis is the most common source of artery-to-artery embolus, and specific treatments have proven efficacy in reducing risk. Other sources are aortic arch, common carotid, internal carotid, vertebral and basilar arteries.

Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery and the carotid siphon (portion within the cavernous sinus). Male gender, older age, smoking, hypertension, diabetes, and hypercholesterolemia are risk factors for carotid disease.

Carotid atherosclerosis produces an estimated 5% of ischemic stroke, and the risk of stroke rises with increase in the degree of carotid narrowing.

Intracranial atherosclerosis produces stroke either by an embolic mechanism or by in- situ thrombosis of a diseased vessel and is more common in patients of Asian and African- American descent. It is estimated that after a stroke or TIA from intracranial atherosclerosis the risk of a second stroke is about 15% per year.

Dissection of the internal carotid or vertebral arteries or even vessels beyond the circle of Willis is a common source of embolic stroke in young (age< 45 years) patients. The dissection is usually painful and precedes the stroke by several hours or days. [9,10,28,29]

PATHOLOGY OF CEREBRAL INFARCTION

Hypotension, Hypoperfusion and Low Flow States – Global Cerebral Ischemia:

Morphology

On macroscopic examination, the brain is swollen, the gyri are widened, and the sulci are narrowed. The histopathologic changes that attend irreversible ischemic injury (infarction) are grouped into three categories.

Early changes occurring 12 to 24 hours after the insult, include the acute neuronal cell change (red neurons) characterized at first by microvacuolization, then eosinophilia of the neuronal cytoplasm, and later nuclear pyknosis and karyorrhexis. Similar acute changes occur somewhat later in astrocytes and oligodendroglia. Pyramidal cells of the Sommer sector (CA1) of the hippocampus, Purkinje cells of the cerebellum, and pyramidal neurons in the neocortex are the most susceptible to irreversible injury.

Subacute changes occurring at 24 hours to 2 weeks include necrosis of tissue, influx of macrophages, vascular proliferation, and reactive gliosis. Repair seen after 2 weeks is characterized by removal of all necrotic tissue, loss of normally organized CNS structure, and gliosis. In the cerebral cortex, the neuronal loss and gliosis produce an uneven destruction of the neocortex with preservation of some layers and involvement of others termed as pseudolaminar necrosis.

Border zone infarcts ("watershed") are wedge -shaped areas of infarction that occur in those regions of the brain and spinal cord that lie at the distal fields of arterial irrigation. In the cerebral hemispheres the border zone between the anterior and the

middle cerebral artery distribution is at greatest risk. Damage to this region produces a sickle-shaped band of necrosis over the cerebral convexity a few centimeters lateral to the interhemispheric fissure. Border zone infarcts are usually seen after hypotensive episodes.

Focal cerebral ischemia – infarction from obstruction of local blood supply

Cerebral arterial occlusion may lead to focal ischemia and ultimately if it is sustained to infarction of a specific region of CNS tissue within the territory of distribution of the compromised vessel. The size, location, and shape of the infarct and the extent of tissue damage that results from focal cerebral ischemia brought

about by occlusion of a blood vessel are determined by modifying factors, most importantly the adequacy of collateral flow.

Partial and inconstant reinforcement is available over the surface of the brain for the distal branches of the anterior, middle, and posterior cerebral arteries through cortical and leptomeningeal anastomoses. Occlusive vascular disease of severity sufficient to lead to cerebral infarction may be due to in situ thrombosis or embolization from a distant source. The majority of thrombotic occlusions are due to atherosclerosis. The evolution of arterial stenosis varies from progressive narrowing of the lumen and thrombosis, which may be accompanied by anterograde extension to fragmentation and distal embolization.

Arteritis of small and large vessels, in association wuth syphilis and tuberculosis, formerly accounted for cerebral infarcts; infectious vasculitis is now more commonly seen in the setting of immunosuppression. Embolism to the brain occurs from a wide range of origins. Cardiac mural thrombi are the most common sources.

Infarcts are subdivided into two broad groups based on their macroscopic and corresponding radiologic appearance.

(a) Hemorrhagic (red) infarction - characterized macroscopically by multiple, sometimes confluent, petechial hemorrhages, is typically associated with embolic events. The hemorrhage is presumed to be secondary to reperfusion of damaged vessels and tissue, either through collaterals or directly after dissolution of intravascular occlusive thrombus.

(b)Nonhemorrhagic (pale, bland, anemic) infarcts - associated with thrombosis.

The macroscopic appearance of a nonhemorrhagic infarct changes in time. During the first 6 hours of irreversible injury, little can be observed. By 48 hours the tissue becomes pale, soft, and swollen, and the corticomedullary junction becomes indistinct. From 2 to 10 days, the brain becomes gelatinous and friable, and the previously ill-defined boundary between normal and abnormal tissue becomes more distinct as edema resolves in the adjacent tissue that has survived. From 10 days to 3 weeks, the tissue liquefies, eventually leaving a fluid-filled cavity lined by dark gray tissue, which gradually expands as dead tissue is removed.

On microscopic examination, the tissue reaction evolves along the following sequence: After the first 12 hours ischemic neuronal change (red neurons) and both cytotoxic and vasogenic edema predominate. There is loss of the usual tinctorial characteristics of white and gray matter structures. Endothelial and glial cells mainly astrocytes swell and myelinated fibers begin to disintegrate. Up to 48 hours neutrophilic emigration progressively increases and falls off. Phagocytic cells from circulating monocytes, adventitial histiocytes, and activated microglia are evident at 48 hours and become the predominant cell type in the ensuing 2 to 3 weeks. The macrophages become stuffed with the products of myelin breakdown or blood and may persist in the lesion for months to years. As the process of liquefaction and phagocytosis proceeds, astrocytes at the edges of the lesion progressively enlarge, divide, and develop an extensive network of protoplasmic extensions. Reactive astrocytes can be seen as early as 1 week after the insult.

After several months, the striking astrocytic nuclear and cytoplasmic enlargement recedes. In the wall of the cavity, astrocyte processes form a dense feltwork of glial fibers admixed with new capillaries and a few perivascular connective tissue fibers. In the cerebral cortex, the cavity is delimited from the meninges and subarachnoid space by a gliotic layer of tissue, derived from the molecular layer of cortex. The pia and arachnoid are not affected and do not contribute to the healing process.

Venous infarcts are often hemorrhagic and may occur after thrombotic occlusion of the superior sagittal sinus or other sinuses or occlusion of the deep cerebral veins. Carcinoma, localized infections, or other conditions leading to a hypercoagulable state place patients at risk for venous thrombosis. [30]

CLINICAL FEATURES OF ISCHEMIC STROKES

Stroke Within The Anterior Circulation

The internal carotid artery and its branches comprise the anterior circulation of the brain.

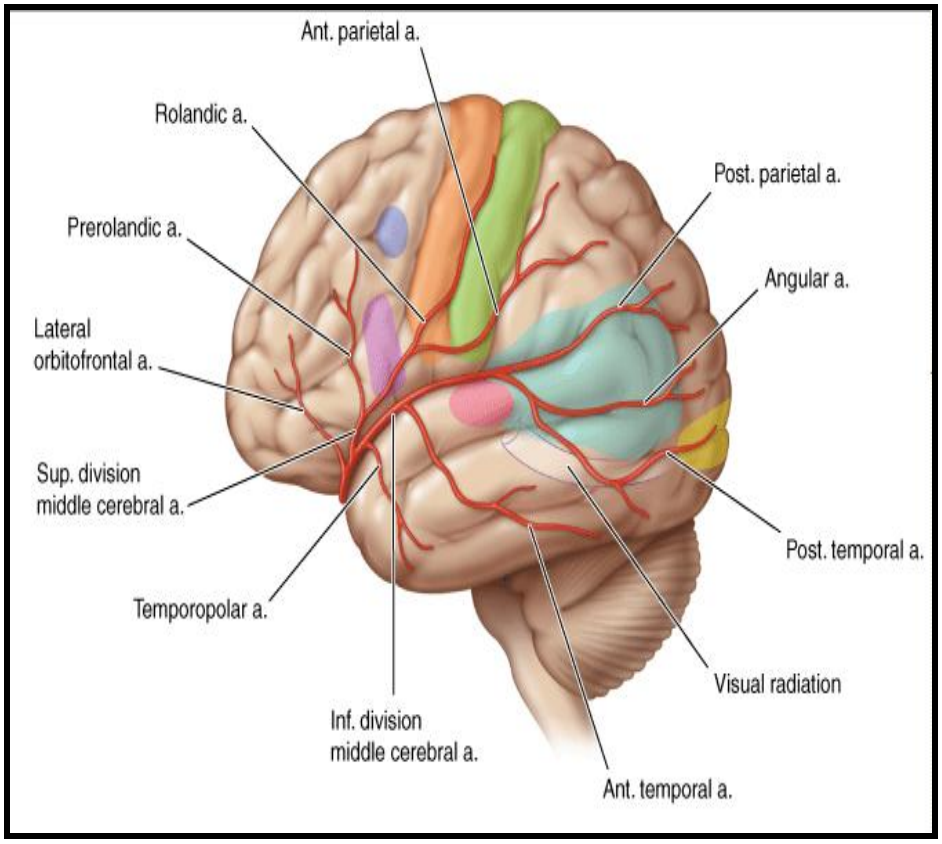
(A) Middle Cerebral Artery territory involvement

The cortical branches of the MCA supply the lateral surface of the hemisphere except for

(1) The frontal pole and a strip along the superomedial border of the frontal and parietal lobes supplied by the ACA, and

(2) The lower temporal and occipital pole convolutions supplied by the PCA.

Figure no. 3 : Diagram showing lateral aspect of cerebral hemisphere showing branches and distribution of middle cerebral artery



Signs and symptoms of MCA territory involvement

1. Somatic motor area for face and arm and the fibers descending from the leg area to enter the corona radiata and corresponding somatic sensory system:

- Paralysis of the contralateral face, arm, and leg

- sensory impairment over the same area (pinprick, cotton touch, vibration, position, two-point discrimination, stereognosis, tactile localization, barognosis, cutaneographia)

2. Motor speech area of the dominant hemisphere :

- Motor aphasia

3. Central, suprasylvian speech area and parietooccipital cortex of the dominant hemisphere :

- Central aphasia, word deafness, anomia, jargon speech, sensory agraphia, acalculia, alexia, finger agnosia, right-left confusion (the last four comprise the Gerstmann syndrome)

4. Central speech area (parietal operculum) : Conduction aphasia

5. Nondominant parietal lobe (area corresponding to speech area in dominant hemisphere)

- Apractognosia of the nondominant hemisphere, anosognosia, hemiasomatognosia, unilateral neglect, agnosia for the left half of external space, dressing "apraxia," constructional "apraxia," distortion of visual coordinates, inaccurate localization in the half field, impaired ability to judge distance, upside-down reading, visual illusions.

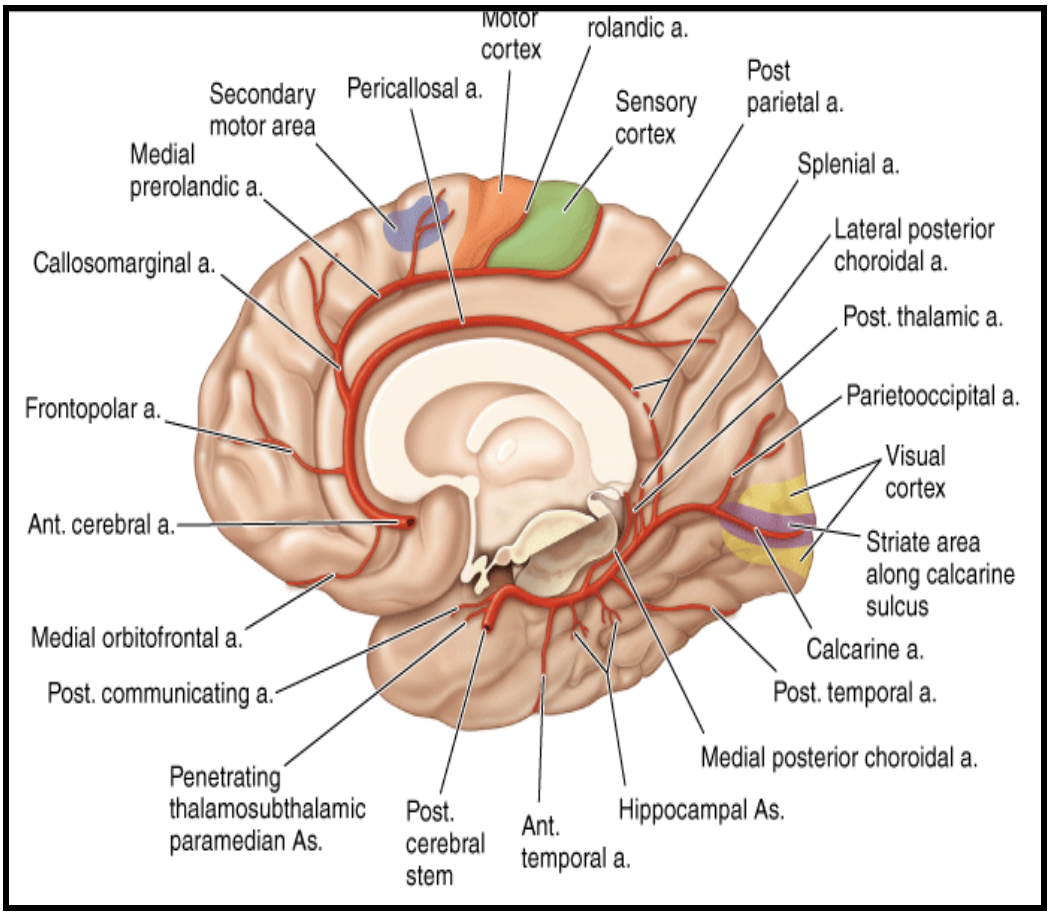
6. Optic radiation deep to second temporal convolution : Homonymous hemianopia

7. Frontal contraversive eye field or projecting fibers : Paralysis of conjugate gaze to the opposite side.

(B) Anterior Cerebral Artery (ACA) territory involvement

The ACA is divided into two segments: the precommunal (A1) circle of Willis, or stem, which connects the internal carotid artery to the anterior communicating artery, and the postcommunal (A2) segment distal to the anterior communicating artery.

Figure no. 4 : Diagram showing medial aspect of cerebral hemisphere showing branches and distribution of anterior cerebral artery



Signs and symptoms of ACA territory involvement

1. Motor leg area : Paralysis of opposite foot and leg:

2. Arm area of cortex or fibers descending to corona radiate : lesser degree of paresis of opposite arm

3. Sensory area for foot and leg : Cortical sensory loss over toes, foot, and leg:

4. Sensorimotor area in paracentral lobule : Urinary incontinence:

5. Medial surface of the posterior frontal lobe; likely supplemental motor area : Contralateral grasp reflex, sucking reflex, gegenhalten

6. Uncertain localization—probably cingulate gyrus and medial inferior portion of frontal, parietal, and temporal lobes : Abulia, slowness, delay, intermittent interruption, lack of spontaneity, whispering, reflex distraction to sights and sounds

7. Frontal cortex near leg motor area : Impairment of gait and stance

8. Corpus callosum : Dyspraxia of left limbs, tactile aphasia in left limbsAnterior Choroidal Artery territory involvement - contralateral hemiplegia, hemianesthesia (hypesthesia), and homonymous hemianopia.

Internal Carotid Artery Territory Involvement:

With a competent circle of Willis, occlusion often goes unnoticed. If the thrombus propagates up the internal carotid artery into the MCA or embolizes it, symptoms are identical to proximal MCA occlusion. Sometimes there is massive infarction of the entire deep white matter and cortical surface.

When the origins of both the ACA and MCA are occluded at the top of the carotid artery, abulia or stupor occurs with hemiplegia, hemianesthesia, and aphasia or anosognosia. When the PCA arises from the internal carotid artery (a configuration called a fetal posterior cerebral artery), it may also become occluded and give rise to symptoms referable to its peripheral territory.

Recurrent transient monocular blindness (amaurosis fugax) is seen in about 25% of symptomatic internal carotid artery disease. Ischemia or infarction of the ophthalmic artery or central retinal arteries occurs at the time of cerebral TIA or infarction.

Common Carotid Artery involvement:

All symptoms and signs of internal carotid occlusion may also be present with occlusion of the common carotid artery.

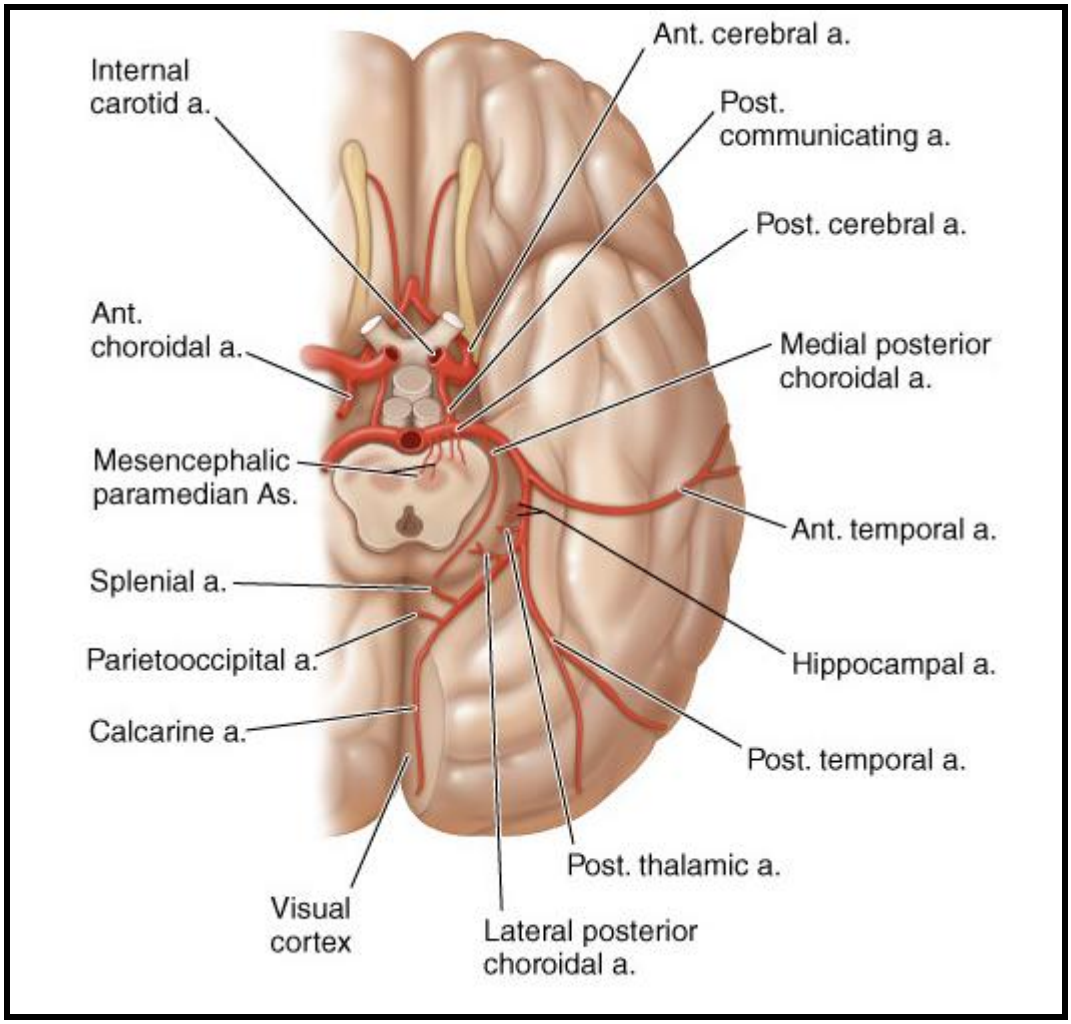
Stroke Within The Posterior Circulation

Two clinical syndromes are commonly observed with occlusion of the posterior cerebral artery involvement:

(1) P1 syndrome: midbrain, subthalamic, and thalamic signs, which are due to disease of the proximal P1 segment of the PCA or its penetrating branches (thalamogeniculate, Percheron, and posterior choroidal arteries)

(2) P2 syndrome: cortical temporal and occipital lobe signs, due to occlusion of the P2 segment distal to the junction of the PCA with the posterior communicating artery.

Figure no. 5 : Diagram showing inferior aspect of the brain with the branches and distribution of the posterior cerebral artery



Signs and symptoms of PCA territory involvement

Peripheral territory

(1) Calcarine cortex or optic radiation nearby : Homonymous hemianopia (often upper quadrantic).

(2) Bilateral occipital lobe with possibly the parietal lobe involvement : Bilateral homonymous hemianopia, cortical blindness, awareness or denial of blindness; tactile naming, achromatopia (color blindness), failure to see to-and-fro movements, inability to perceive objects not centrally located, apraxia of ocular movements, inability to count or enumerate objects, tendency to run into things that the patient sees and tries to avoid

(3) Hippocampal lesion bilaterally or on the dominant side only: Verbal dyslexia without agraphia, color anomia, Memory defect
(4) Nondominant, calcarine, and lingual gyrus lesions: Topographic disorientation and prosopagnosia
(5) Dominant visual cortex, contralateral hemisphere: Simultanagnosia, hemivisual neglect
(6) Calcarine cortex: Unformed visual hallucinations, peduncular hallucinosis, metamorphopsia, teleopsia, illusory visual spread, palinopsia, distortion of outlines, central photophobia
(7) Nondominant hemisphere: Complex hallucinations

Central Territory:

1. Posteroventral nucleus of thalamus; involvement of the adjacent subthalamus body or its afferent tracts : Thalamic syndrome: sensory loss (all modalities), spontaneous pain and dysesthesias, choreoathetosis, intention tremor, spasms of hand, mild hemiparesis
2. Dentatothalamic tract and issuing third nerve : Thalamoperforate syndrome: crossed cerebellar ataxia with ipsilateral third nerve palsy (Claude's syndrome)
3. Third nerve and cerebral peduncle : Weber's syndrome: third nerve palsy and contralateral hemiplegia.
4. Cerebral peduncle : Contralateral hemiplegia
5. Supranuclear fibers to third nerve, interstitial nucleus of Cajal, nucleus of Darkschewitsch, and posterior commissure : Paralysis or paresis of vertical eye movement, skew deviation, sluggish pupillary responses to light, slight miosis and ptosis (retraction nystagmus and "tucking" of the eyelids may be associated)
6. Dentatothalamic tract : Contralateral rhythmic, ataxic action tremor; rhythmic postural or "holding" tremor (rubral tremor)

Vertebral and Posterior Inferior Cerebellar Arteries

1. The first (V1) extends from its origin to its entrance into the sixth or fifth transverse vertebral foramen.
2. The second segment (V2) traverses the vertebral foramina from C6 to C2.
3. The third (V3) passes through the transverse foramen and circles around the arch of the atlas to pierce the dura at foramen magnum.
4. The fourth (V4) segment courses upward to join the other vertebral artery to form the basilar artery; only the fourth segment gives rise to branches that supply the brainstem and cerebellum.

The posterior inferior cerebellar artery (PICA) in its proximal segment supplies the lateral medulla and, in its distal branches, the inferior surface of the cerebellum.

Atherothrombotic lesions have a predilection for V1 and V4 segments of the vertebral artery.The first segment may become diseased at the origin of the vessel and may produce posterior circulation emboli; collateral flow from the contralateral vertebral artery or the ascending cervical, thyrocervical, or occipital arteries is usually

sufficient to prevent low-flow TIAs or stroke. When one vertebral artery is atretic and an atherothrombotic lesion threatens the origin of the other, the collateral circulation, which may also include retrograde flow down the basilar artery, is often insufficient.

Disease of the distal fourth segment of the vertebral artery can promote thrombus formation manifest as embolism or with propagation as basilar artery thrombosis. Stenosis proximal to the origin of the PICA can threaten the lateral medulla and posterior inferior surface of the cerebellum.

If the subclavian artery is occluded proximal to the origin of the vertebral artery, there is a reversal in the direction of blood flow in the ipsilateral vertebral artery. Exercise of the ipsilateral arm may increase demand on vertebral flow, producing posterior circulation TIAs, or "subclavian steal."

Although atheromatous disease rarely narrows the second and third segments of the vertebral artery, this region is subject to dissection, fibromuscular dysplasia, and, rarely, encroachment by osteophytic spurs within the vertebral foramina.

Embolic occlusion or thrombosis of a V4 segment causes ischemia of the lateral medulla. The constellation of vertigo, numbness of the ipsilateral face and contralateral limbs, diplopia, hoarseness, dysarthria, dysphagia, and ipsilateral Horner's syndrome is called the lateral medullary (or Wallenberg's) syndrome. Most cases result from ipsilateral vertebral artery occlusion; in the remainder, PICA occlusion is responsible. Occlusion of the medullary penetrating branches of the vertebral artery or PICA results in partial syndromes. Hemiparesis is not a feature of vertebral artery occlusion.

Medial medullary syndrome rarely occurs with infarction of the pyramid and contralateral hemiparesis of the arm and leg, sparing the face. Contralateral loss of joint position sense and ipsilateral tongue weakness occur when the medial lemniscus and emerging hypoglossal nerve fibres are involved.

Cerebellar infarction with edema can lead to sudden respiratory arrest due to raised ICP in the posterior fossa. Drowsiness, Babinski signs, dysarthria, and bifacial weakness may be absent, or present only briefly, before respiratory arrest ensues. Gait unsteadiness, headache, dizziness, nausea, and vomiting may be the only early symptoms and signs and should arouse suspicion of this impending complication, which may require neurosurgical decompression, often with an excellent outcome.

Small Vessel Stroke:

The term lacunar infarction refers to infarction following atherothrombotic or lipohyalinotic occlusion of a small artery (30–300 μm) in the brain, now termed as small-vessel stroke; accounts for ~20% of all strokes.

The MCA stem, the arteries comprising the circle of Willis (A1 segment, anterior and posterior communicating arteries, and P1 segment), and the basilar and vertebral arteries all give rise to 30- to 300micrometre branches that penetrate the deep gray and white matter of the cerebrum or brainstem. Each of these small branches can occlude either by atherothrombotic disease at its origin sor by the development of lipohyalinotic thickening. Thrombosis of these vessels causes small infarcts that are referred to as lacunes (Latin for "lake" of fluid noted at autopsy). They range in size from 3 mm to 2 cm. Hypertension and age are the principal risk factors.

The most common lacunar syndromes are the following:

(1) Pure motor hemiparesis from an infarct in the posterior limb of the internal capsule or basis pontis; the face, arm, and leg are almost always involved
(2) Pure sensory stroke from an infarct in the ventral thalamus
(3) Ataxic hemiparesis from an infarct in the ventral pons or internal capsule
(4) Dysarthria and a clumsy hand or arm due to infarction in the ventral pons or in the genu of the internal capsule.
(5) Pure motor hemiparesis with "motor (Broca's) aphasia" due to thrombotic occlusion of a lenticulostriate branch supplying the genu and anterior limb of the internal capsule and adjacent white matter of the corona radiata.

Transient symptoms (small vessel TIAs) may herald a small-vessel infarct; they may occur several times a day and last only a few minutes. Recovery from small-vessel strokes tends to be more rapid and complete than recovery from large-vessel strokes; in some cases, however, there is severe permanent disability. Evaluation for embolic sources (carotid and heart) is important in lacunar syndrome, as small vessel infarction may be the initial manifestation of a large vessel source (either thrombosis or embolism). [9,10,29]

Watershed Ischemic Syndromes:

Watershed infarcts occur in the border zone between adjacent arterial perfusion beds. These occur during or after cardiac surgery or after an episode of sustained or severe arterial hypotension after cardiac arrest, prolonged hypoxemia or bilateral severe carotid artery disease.

Ischemia in the border zone or junctional territory of the ACA, MCA and PCA result in bilateral parieto- occipital infarcts with a wide variety of visual manifestations, including bilateral lower altitudinal field defects, optic ataxia, cortical blindness and difficulty in judging size, distance and movement.

Unilateral watershed infarcts occur in patients with underlying severe arterial stenosis or occlusion when there is some degree of hemodynamic failure in these patients. It can also be caused by microembolism or hyperviscosity states.

Ischemia between the territories of the ACA and MCA bilaterally result in bibrachial cortical sensori motor impairment (man-in-a-barrel) and impaired saccadic eye movements caused by compromise of the frontal eye fields. Ischemia between the territories of the MCA and PCA result in bilateral parieto trmporal infarctions with cortical blindness, dyslexia, dyscalculia, dysgraphia and memory defects for verbal and non verbal material.

Watershed infarcts are also recognized between the territorial supply of the PICA, AICA and SCA> Watershed infarcts may also involve the internal watershed region in the centrum semi ovale adjacent to and slightly above the body of the lateral ventricles [9,10,28,29]

INITIAL ASSESSMENT OF A STROKE PATIENT:

(A) Immediate evaluation

1. Stabilisation of airway, breathing and circulation
2. Neurologic examination to define the neurologic deficits to classify the event into one of the clinical stroke syndromes
3. Stroke mimics like hypoglycemia, conversion disorded, hypertensive encephalopathy, seizures, etc. to be excluded
4. Secondary assessment of the neurological deficits and possible comorbidities
5. Other conditions requiring immediate intervention to be excluded.
6. Potential causes of the stroke to be determined for early secondary prevention.

(B) History taking

1. Time of onset – The time of stroke onset is when the patient was last seen to be symptom free.
2. Circumstances around the development of the neurological symptoms.
3. History of features of other potential causes of the symptoms
4. History of use of medications, especially oral anticoagulants and antiplatelet agents
5. Determine risk factors for cardiac disease, arteriosclerosis, drug abuse, migraine, seizure or pregnancy
6. Determine eligibility for therapeutic intervention like revascularization. [31]

(C) Systemic examination

1. Assessment of airway, breathing and circulation including pulse oximetry, blood glucose and body temperature
2. Head and neck examination to see for signs of trauma, carotid disease (bruits), seizure activity (contusions, tongue bite), congestive heart failure (distension of jugular vein)
3. Cardiovascular system examination to identify valvular diseases, irregular rhythm, associated ischemic heart disease, etc
4. Examination of skin and extremities to detect coagulopathies, platelet disorders, etc.

5. The initial NIHSS score provides important prognostic information. Approximately 60% to 70% of patients with an acute ischemic stroke and a baseline NIHSS score <10 will have a favorable outcome after 1 year as compared with only 4% to 16% of those with a score >20. In the NINDS trial of rtPA, those with a score of 20 or greater on the NIHSS had a 17% chance of intracranial hemorrhage, whereas the risk of bleeding was only 3% among those with a score <10. [32]

(D) Investigations

1. Basic work-up to be done in all patients of acute ischemic stroke:

- Complete blood count
- Prothrombin time, bleeding and clotting profile, partial thromboplastin time
- Plasma glucose level
- Blood urea nitrogen and serum creatinine
- Lipid profile
- Urine analysis
- Chest X-ray
- Electrocardiogram

2. Non enhanced cranial CT (computed tomography)

- primary diagnostic brain imaging study for evaluation of stroke. [33,34]

(a) Hyperacute infarcts (<12 hours)

Early CT signs of ischemic stroke in MCA territory: loss of grey- white matter differentiation, sulcal effacement, effacement of the sylvian fissure and obscuration of the lentiform nucleus.Horizontal part of the MCA may be hyperdense (dense MCA sign) before infarction becomes visible.

(b) Subacute infarcts

After the first 24-48 hours, most large vessel infarcts are visivle on non enhanced CT as wedge- shaped areas of decreased attenuation that involve both grey and white matter in a typical vascular distribution. Initially mass effect increases then begins to diminish in 7-10 days.

(c) Chronic infarcts

Focal well delineated encephalomalacic areas appear on CT scans. Adjacent sulci become prominent and ipsilateralventricle enlarges. Enhancement disappears after 8-10 weeks. Dystrophic calcification can occur very rarely.

"Scan negative infarcts" usually occur with lower brainstem infarcts, lacunar infarcts, early scans (60% cases within 12 hrs of ictus may not pick up the lesion), scans done afte 2^{nd}-3^{rd} week may not show or may underestimate the size of the infarct.[35,36]

Figure No. 6 : CT showing Hyper dense MCA sign - high attenuation within the expected location of the right MCA (arrows), consistent with an acute thrombus

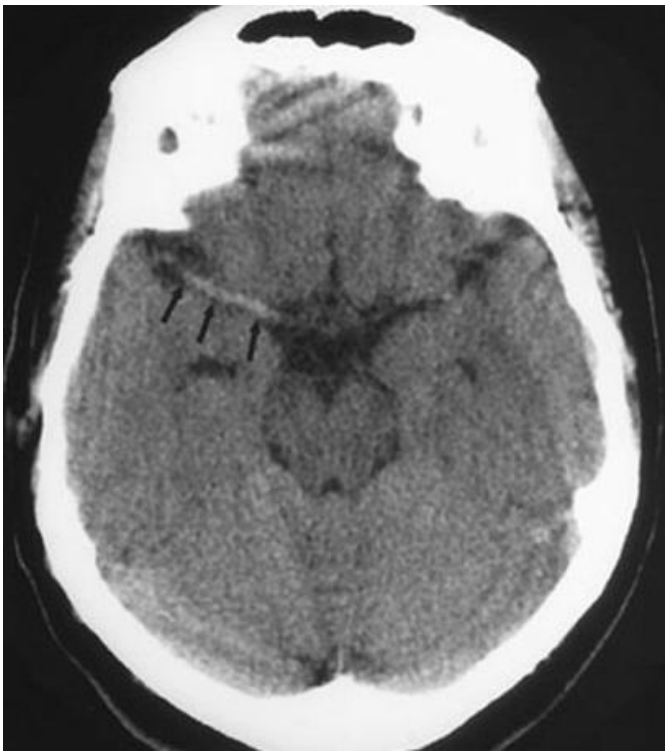


Figure No. 7 : CT Showing Left Basal Ganglia Infarction

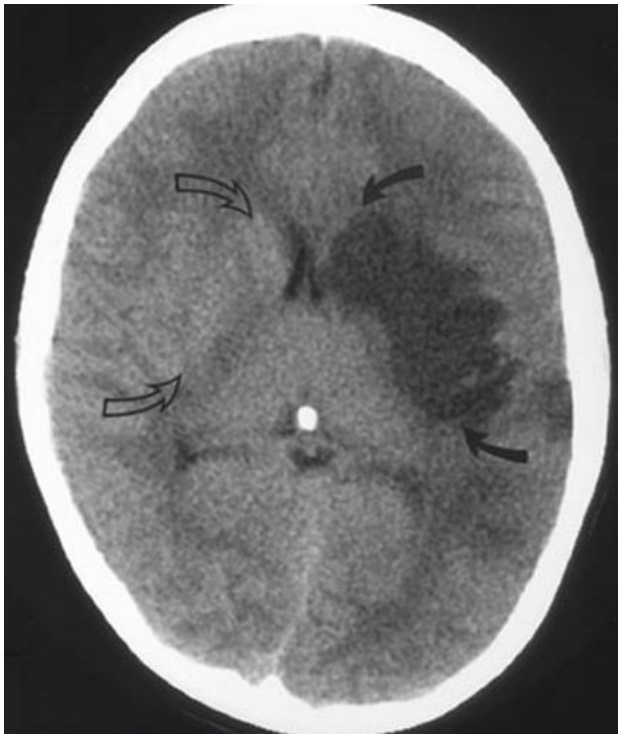
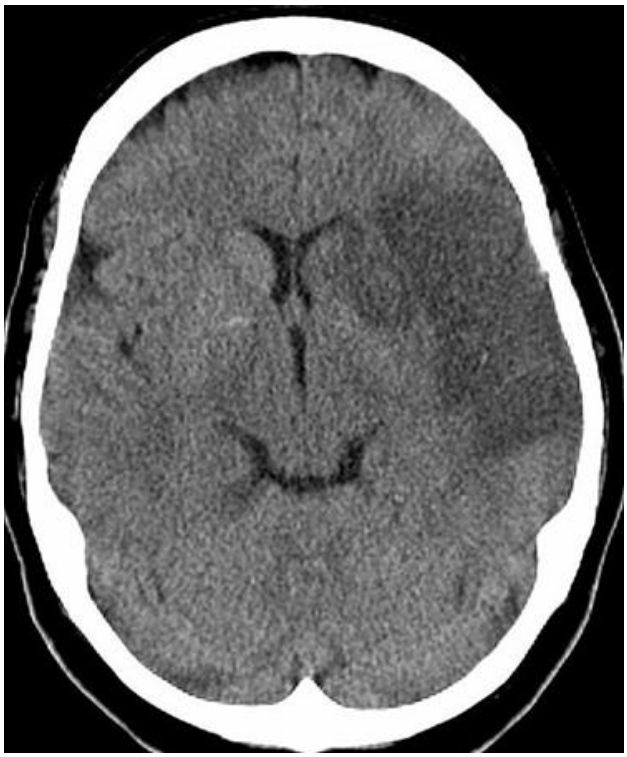


Figure No. 8 : CT Showing Left MCA Territory Infarction



3.Multimodal CT

i. Whole brain perfusion CT – gives a map of cerebral blood volume and areas of hypoattenuation representing the ischemic core.

ii.Dynamic perfusion CT – provides absolute measures of cerebral blood flow, mean transit time and cerebral blood volume.

iii.Helical CT angiography – rapidly and non invasively assesses the vasculature both intracranially and extracranially and provides information regarding vessel occlusion or stenosis.

4. Magnetic Resonance Imaging (MRI)

- Superior to CT for detecting cerebral ischemia.
- It reveals flow voids and hemosiderin and also alterations resulting from ischemic necrosis and gliosis.

5. Multimodal MRI

ii. Diffusion weighted MRI (DWI) – allows detection of ischemic regions within minutes of symptom onset and early identification of the lesion size, site and age.

iii. Perfusion weighted MRI (PWI) – provides relative measures of cerebral hemodynamics The ischemic penumbra is approximated on MRI as region sof perfusion change without a corresponding diffusion abnormality (diffusion-perfusion mismatch). [37]

6. MRI angiography

Delineates blood flow and vascular lesions, including atheromatous plaques in the carotid and vertebrabasilar systems. Useful in identifying acute proximal large-vessel occlusions but cannot identify reliably distal or branch occlusions.

7. Other brain imaging methods

i. Oxygen-15 positron-emission tomography (PET) can quantify regional brain perfusion and oxygen consumption. PET provided the first evidence of a penumbra in stroke patients by identifying regions of decreased cerebral blood flow and increased oxygen extraction fraction with relatively preserved oxygen metabolism. [38]

ii. Xenon-enhanced CT provides a quantitative measurement of CBF by employing inhaled xenon. Perfusion CT measures CBF by mapping the appearance of a bolus of iodinated contrast. Both can be used to screen for thresholds of reversible or irreversible ischemia among patients with acute stroke. [39]

iii. Single photon-emission computed tomography (SPECT) identifies thresholds for reversible ischemia and could be helpful in predicting outcomes or monitoring responses to treatment. [40]

iv. Duplex Doppler ultrasonography

For detection of > 50% diameter stenosis, sensitivity is 87-96% and specificity is 81-96%. Can detect atheromatous plaque and stenosis of large vessels especially carotids.

v. Transcranial Doppler sonography Evaluates blood flow velocity and patency of the main intracranial arteries and in identification of igh intensity transient microembolic signals. [41]

vi. Conventional angiography or Digital Subtraction Angiography (DSA) – determines extent of vascular disease, size and ,ocation of atherosclerotic lesions and collateral circulation.

8. Cardiac imaging studies like Echocardiography to assess potential causes of TIA or evolving stroke. [42]

Treatment Of Acute Ischemic Stroke:

(A) General supportive care

a. Maintaining adequate tissue oxygenation is important to prevent hypoxia and potential worsening of the neurological injury. Patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level of ≥95%. [43]

b. Fever - Increased body temperature in the setting of acute ischemic stroke has been associated with poor neurological outcome, possibly due to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production. [44]

Measures can include antipyretic medications and cooling devices. Hypothermia has been shown to be neuroprotective after experimental global and focal hypoxic brain injury. [45]

c. Arterial hypertension An elevated blood pressure can result from the stress of the stroke, a full bladder, pain, preexisting hypertension, a physiological response to hypoxia, or increased intracranial pressure. In most circumstances, the blood pressure should generally not be lowered, except in hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction. [46] Antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg.

d. Arterial Hypotension Correction of hypovolemia and optimization of cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement with normal saline and correction of arrhythmias—such as slowing ventricular response to rapid atrial fibrillation. If these measures are ineffective, vasopressor agents such as dopamine may be used.

e. Hypoglycemia As hypoglycemia can cause focal neurological signs rapid correction of a low serum glucose concentration is important.

f. Diabetes mellitus - Hyperglycemia is associated with poor outcomes- [47]

(B) Measures to Restore or Improve Perfusion

(i) Thrombolytic therapy

The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg max; 10% as a bolus, then the remainder over 60 min) within 3 h of onset resulted in good functional outcome though incidence of hemorrhage increased after thrombolsis Those with NIHSS score < 20) had the greatest possibility for a favorable response to treatment.[48] In ECASS-II, intravenous rtPA was not more effective than placebo in improving neurological outcomes at 3 months after stroke. [49]

In the multicentre acute stroke trial Europe study group (MAST-E), streptokinase in the dose of 1.5 million units over one hour was associated with hemorrhagic transformation of ischemic infarct and hence not recommended. [50]

Intra-arterial thrombolysis is an option for treatment of selected patients with major stroke of <6 hours' duration due to large vessel occlusions of the middle cerebral artery. [51] It is not FDA approved.

(ii) Anticoagulants

According to the Joint Guideline Statement from the AHA and AAN, urgent routine anticoagulation with the goal of improving neurological outcomes or preventing early recurrent stroke is not recommended as it is associated with increased risk of bleeding complications [52]

(iii) Antiplatelet Agents

a) Aspirin

The International Stroke Trial (IST) demonstrated a significant reduction in recurrent ischemic events by aspirin within the first 2 weeks, but acute mortality was not reduced At 6 months, patients assigned aspirin had a significantly lower incidence of death and dependency. [53]

The Chinese Acute Stroke Trial (CAST) showed that mortality was ignificantly reduced with aspirin, but the rates of long-term complete recovery or death and disability were not significantly improved.[54]

A combined result suggested that aspirin was effective in reducing recurrent ischemic stroke, death, or dependency.

b) Ticlopidine

In the ticlopidine aspirin stroke study, the risk of non fatal stroke or death from any cause at 3 years was lower in ticlopidine group as compared to aspirin group (17% vs 19%). The 3 year risk of fatal or non fatal risk was also lower (10% vs 13%). Thus it was concluded that ticlopidine was more effective than aspirin. The Canadian American ticlopidine study concluded that an exclusive benefit cannot be claimed for ticlopidine over aspirin in treating patients with stroke. [55]

c) Clopidogrel

It is a theinopyridine derivative which is a potent inhibitor of platelet aggregation caused by ADP. In a trial recent stroke/TIA patients were randomized to receive clopidogrel 75 mg/ day vs clopidogrel 75 mg/day with low dose aspirin 75 mg/day, showed no statistically significant difference in outcome between the two treatment groups. Clopidogrel can be given to patients allergic to aspirin. [56]

(C) Neuroprotective agents

Hypothermia is probably the most powerful neuroprotectant. (6) Various drugs have been tried like calcium channel antagonists (nicardipin, nimodipine), NMDA receptor agonist (selfolate, eliprodil), ICAM – I antibodies (Enlimomab), GABA

nergic antagonists (Diazepam, Clomethiozole), glutamate antagonists (leleluzole), free radical scavengers (tirilazed, dihydrolipoate), lipid peroxidation inhibitors (Ebselen). Many of these drugs are in experimental stages and further studies are required before routine use .[57]

(3) Surgical Interventions

The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) single-arm trial investigated endovascular thrombectomy to restore patency of occluded intracranial vessels within 8 h of ischemic stroke symptoms. Recanalization of the target vessel occurred in 48% of treated patients and in 60% following use of adjuvant endovascular methods, and successful recanalization at 90 days correlated well with favorable outcome. [28] The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) evaluated patients with symptomatic stenosis of carotid arteries found a substantial benefits in patients with a stenosis of > 70%. [55]

(4) Treatment of Acute Neurological Complications

(a) Brain Edema and Increased Intracranial Pressure The goals of management of brain edema are to

(1) reduce intracranial pressure

(2) maintain adequate cerebral perfusion to avoid worsening of the brain ischemia

(3) prevent secondary brain injury from herniation.

Osmotherapy and hyperventilation are recommended for patients whose condition is deteriorating secondary to increased intracranial pressure. Corticosteroids are not recommended.Surgical decompression and evacuation of large cerebellar infarctions that are leading to brain stem compression and hydrocephalus is recommended. Though it is life saving, survivors have severe residual neurological impairments. [58]

(b) Seizures

These are likely to occur within 24 hours of stroke and are usually partial with or without secondary generalization. Recurrent seizures develop in approximately 20% to 80% of patients.

There are no data about the utility of prophylactic administration of anticonvulsants after stroke.

(c) Hemorrhagic Transformation

The use of all antithrombotics, but especially anticoagulants and thrombolytic agents, increases the likelihood of serious hemorrhagic transformation. The early use of aspirin also is associated with a small increase in the risk of clinically detectable hemorrhage.[52,53]

Management of patients with hemorrhagic infarction depends on the amount of bleeding and its symptoms.

MOTOR RECOVERY FROM STROKE

Most stroke recovery occurs in the first 2-3 months. At 2-3 years, greater than 90% of recovery has occurred. Measures of functional recovery at 1 year poststroke conclude that 75-85% of patients are ambulatory, 48-58% regain independence in performance of activities of daily living and 10-29% require nursing home care.

Factors associated with less favorable outcomes are medical comorbidities (eg, diabetes mellitus [DM], cardiac disease, ECG abnormalities), prior stroke, prior functional dependence, sensory and visual deficits, severe motor deficits, loss of consciousness, cognitive deficits, and incontinence.

Recovery of arm movement is less complete than recovery of leg movement, perhaps because arm paresis usually is greater than leg paresis and because the arm requires finer movements to perform skilled activities. The lack of initial movement or measurable grip strength by 4 weeks following onset is associated with a less favorable prognosis for return of useful arm function.

Language does not improve evenly across all components. In most studies, comprehension skills demonstrate the best recovery. The different types of aphasia also have differing prognoses for recovery; the worst is global aphasia and the best is anomic aphasia. Recovery from aphasia appears to occur independently of recovery from hemiparesis.

Neurophysiologic mechanisms for recovery from stroke

Recovery often is attributable to the resolution of edema and return of circulation to the ischemic penumbra; however, as noted by Brodal, these mechanisms cannot account for recovery occurring beyond 4-6 weeks following stroke.

Factors contributing to brain reorganization after stroke are improved synaptic transmission, loss of perilesional GABA-ergic inhibition, increased glutamatergic activity, changes in neuronal-membrane excitability, and removal of inhibition. Collectively, these mechanisms give rise to the concept of neuroplasticity.

Several clinical observations illustrate the bilaterality of the brain. Perhaps the most dramatic of these observations are the reports of remarkable return of function following hemispherectomy. Papanicolaou demonstrated greater right hemisphere activity in a recovering aphasic patient, as compared to controls. He concluded that the right hemisphere was taking over some of the language function of the damaged left hemisphere.

Cortical reorganization through synaptogenesis and unmasking (formation of new synapses and release from inhibition, respectively) may account for a considerable portion of the recovery seen following stroke. This reorganization may occur both locally and remotely from the lesion.

Immediate reorganization may take place through unmasking of previously inactive synapses, a process thought to take place through disinhibition, through the development of denervation

hypersensitivity, or by rerouting of impulse traffic as a result of a rapidly acting feedback mechanism. The slower recovery may be explained by axonal or dendritic sprouting.

Many reports document the ability of CNS neurons to sprout; however, neuronal sprouting and synaptogenesis can be maladaptive, leading to spasticity, memory dysfunction, and seizures. Evidence suggests that dendritic development depends on repetitive functional demand or training in specific activities. Early training may be particularly beneficial.

The redevelopment of adequate inhibition following stroke may play an important role in recovery. Mass movements and pathologic reflexes reflect a loss of inhibitory mechanisms. The development of inhibition may be responsible for the reappearance of fine coordinated movements.

Neurotransmitter alterations

The following drug classes are thought to have a positive effect on motor recovery: cholinergic and anticholinesterases, norepinephrine, amphetamines, L-dopa, and phenylpropanolamine. Conversely, drugs that antagonize the norepinephrine system (eg, haloperidol, phenoxybenzamine) have been shown to retard recovery of motor function when given early after injury. In addition, drugs commonly prescribed following stroke (eg, benzodiazepines, anticonvulsants, alpha-blocking antihypertensives) also may interfere with recovery. Gamma-aminobutyric acid (GABA) and serotonin are major inhibitory transmitters in the CNS. Levels of both are elevated following brain ischemia. However, several studies have shown that early GABA- ergic activation improves stroke outcomes and that benzodiazepine use just before stroke may have potentially positive effects on reperfusion after an embolic infarct. [59]

NATIONAL INSTITUTE OF HEALTH STROKE SCALE (NIHSS)

The National Institute of Health Stroke Scale (NIHSS) is a systematic assessment tool that provides a quantitative measure of stroke – related neurologic deficit. The examination evaluates motor functions, visual fields, ataxia, speech, language, cognition and sensory impairments. Points are given for levels of functioning in each of these areas, which are then combined for a toal score. The higher the score, greater the neurological deficits present.

The score can be correlated with the patient's clinical presentation. It is a clinical assessment tool to evaluate and document neurological. The scale is valid for predicting lesion size and can be used as a measure of stroke severity. It serves for planning patient care and provides a common language for information exchange among health care providers.

The NIHSS is a 15- item neurologic examination stroke scale used to evaluate the effect of acute cerebral infarction on the levels of consciousness, language, neglect, visual – field loss, extraocular movement, motor strength, ataxia, dysarthria and sensory loss. Scores < 5 indicate mild neurological impairment, between 5 and 15 indicate mild to moderately severe impairment, between 15 to 25 indicates severe impairment and scores > 25 indicate very severe impairment.

Initiall stroke severity as measured by baseline NIHSS score strongly predicts mortality and functional outcome. One additional point on the baseline decreased by 24% the likelihood of survival and excellent outcome at 7 days and by 17% at 3 months. For excellent outcome as determined by the NIHSS score </= 1 at 3 months, the baseline NIHSS score, small vessel infarct, history of previous stroke, history of diabetes, history of pre stroke disability and infarct volume at 7 to 10 days were all significant predictors. For very poor outcome, only infarct volume was a significant predictor of NIHSS score of ≥ 20 or death at 3 months. [60]

Table No. 1 : NATIONAL INSTITUTE OF HEALTH STROKE SCALE

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—alert
		1—drowsy
		2—obtunded
		3—coma/unresponsive
1B	Orientation questions (two)	0—answers both correctly
		1—answers one correctly
		2—answers neither correctly
1C	Response to commands (two)	0—performs both tasks correctly
		1—performs one task correctly
		2—performs neither
2	Gaze	0—normal horizontal movements
		1—partial gaze palsy
		2—complete gaze palsy
3	Visual fields	0—no visual field defect
		1—partial hemianopia
		2—complete hemianopia
		3—bilateral hemianopia
4	Facial movement	0—normal
		1—minor facial weakness
		2—partial facial weakness
		3—complete unilateral palsy
5	Motor function (arm)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 10 seconds
		3—no effort against gravity
		4—no movement
6	Motor function (leg)	0—no drift
	a. left	1—drift before 5 seconds

	b. right	2—falls before 5 seconds
		3—no effort against gravity
		4—no movement
7	Limb ataxia	0—no ataxia
		1—ataxia in one limb
		2—ataxia in two limbs
8	Sensory	0—no sensory loss
		1—mild sensory loss
		2—severe sensory loss
9	Language	0—normal
		1—mild aphasia
		2—severe aphasia
		3—mute or global aphasia
10	Articulation	0—normal
		1—mild dysarthria
		2—severe dysarthria
11	Extinction or inattention	0—absent
		1—mild (loss 1 sensory modality)
		2—severe (loss 2 modalities)

HYPERGLYCEMIA AND STROKE

Hyperglycemia is common in patients with acute stroke, occurring in up to 60% of patients overall [61,62] and approximately 12- 53% of acute stroke patients without a prior diagnosis of diabetes [63]. Hyperglycaemia predicts higher mortality and morbidity after acute stroke independently of other adverse prognostic factors, such as older age, type and severity of stroke, and non-reversibility of the neurological deficit.[64]

Several explanations may account for the observed association between hyperglycemia and poor prognosis after ischemic stroke:

(1) Hyperglycemia may be directly toxic to the ischemic brain. Accumulation of lactate and intracellular acidosis in the ischemic brain (produced through anaerobic cerebral glucose metabolism) [65] promotes and accelerates ischemic injury by enhancing lipid peroxidation and free radical formation,[66] and impairing mitochondrial function. [67] These neurotoxic effects may be particularly important in the ischemic penumbra where neurons are injured but still viable [68]. Hyperglycemia facilitates the development of cellular acidosis in the ischemic penumbra and results in a greater infarct volume, thus promoting the recruitment of potentially salvageable neurons into the infarction.

(2) Hyperglycemic patients are relatively deficient in insulin. This leads to both reduced peripheral uptake of glucose (increasing the amount of glucose available to diffuse into brain) and increased circulating free fatty acids. Free fatty acids may impair endothelium-dependent vasodilation [69].

(3) Stress hyperglycemia patients are likely to have dysglycemia (ie, blood glucose level above the normal range but below the threshold for diabetes [70] or undiagnosed diabetes when not stressed. These patients have a higher risk of vascular disease than patients with normal blood glucose level. [71] These patients could sustain more ischemic damage at the time of infarction as a result of more extensive underlying cerebral vasculopathy compared with those who do not develop stress hyperglycemia. Hyperglycemia is an important determinant of the widespread changes in both small cerebral blood vessels [72] and large extracranial vessels [73] seen in diabetic patients.

(4) Hyperglycemia may disrupt the blood-brain barrier [74] and promote hemorrhagic infarct conversion. [75]. Higher admission serum glucose level is associated with a

higher risk of hemorrhagic conversion of the infarct, with a substantial rise in risk with levels >8.4 mmol/L.[76]

(5) Stress hyperglycemia may be a marker of the extent of ischemic damage in patients with stroke. Patients with severe or fatal strokes might develop hyperglycemia because of greater release of "stress hormones" such as cortisol and norepinephrine. Strength of the positive association between hyperglycemia and mortality lessened after accounting for the severity of stroke (as indicated by decreased level of consciousness and weakness score at the onset of stroke).[77] Stress hyperglycemia is of pathophysiological significance in patients with stroke and is not simply an epiphenomenon of the stress response to stroke.

(6) Hyperglycemia-Associated Reduction in Perfusion Hyperglycemia causes 24% reduction in regional blood flow, reduction in blood circulation to the marginal ischemic areas and converts ischemic penumbra to infarct.[78] CO_2-induced increase in cerebral blood flow is decreased in diabetics.[79] CO_2-induced cerebral vasodilatation is mediated through NO, and diabetics are known to have decreased endothelial NO production.

(7) Hyperglycemia-Associated Impaired Calcium Homeostasis Excitatory amino acids, notably glutamate, play a central role in neuronal death by activation of postsynaptic glutamate receptors, particularly NMDA receptors. This leads to an excessive influx of calcium through ion channels, mitochondrial injury, and eventual cell death. Thus, hyperglycemia, by increasing the availability of glutamate, may induce calcium-mediated neuronal cell death. Hyperglycemia may also be harmful to calcium recovery during the early perfusion period after focal cerebral ischemia, thereby increasing intracellular calcium for a longer time. [80]

(8) Inflammation and Free Radical–Associated Injury Hyperglycemia is known to be associated with inflammation and oxidative stress. Glucose intake results in comprehensive inflammation as reflected in an increase in nuclear factor κB (NF-κB) binding and a decrease in inhibitor kappa B (IκB) expression. [81] NF-κB is a nuclear transcription factor that normally stays in the cytoplasm in association with IκB.[82]

In response to an inflammatory stimulus, there is an increase in IκB kinase-α and IκB kinase- ß, which phosphorylate IκB and result in its ubiquitination and proteosomal degradation. Degradation of IκB results in release of NF-κB and in its translocation from the cytoplasm to the nucleus, where it stimulates the

transcription of proinflammatory cytokines. Activation of NF-κB and superoxide generation have been shown to be involved in tissue injury after occlusion of middle cerebral artery. NF-κB activation leads to increased production of inflammatory cytokines and chemokines such as tumor necrosis factor-α and monocyte chemoattractant protein (MCP-1). This attracts leukocytes to the ischemic area. Superoxide radicals can cause direct cell damage through lipid peroxidation, protein carbonylation, and DNA damage. Superoxide also neutralizes NO produced by endothelium by converting NO to peroxinitrite. NO is critical in maintenance of blood flow to the ischemic brain tissue by causing vasodilatation of arteries.

Glucose intake also causes an increase in the other proinflammatory transcription factors:

Activator protein-1 (AP-1) and early growth response-1 (Egr-1). AP-1 regulates the transcription of matrix metalloproteinases (MMPs), whereas Egr-1 modulates the transcription of tissue factor (TF). Thus, glucose intake increases the expression of MMP-2 and MMP-9 as well as that of TF.

MMP-9, also involved in the process of central spreading depression after an acute stroke, plays a significant role in brain damage by increasing brain edema. Central spreading depression is characterized by neuronal and glial depolarization, which is followed 3 to 6 hours later by an increase in the expression of MMP-9 initially in the cortical blood vessels, spreading later to neuronal layers and finally to the pia and the arachnoid. [83,84]

The increase in MMP-9 results in a reduction of laminin, endothelial barrier antigen, and the zona occludens. [84] These 3 proteins are important in the maintenance of blood–brain barrier.

The decrease in their concentration affects the integrity of the blood–brain barrier and an increase in the permeability of the barrier, resulting in edema with the leakage of plasma proteins and inflammatory cells. Stroke patients with hyperglycemia indeed develop more pronounced cerebral edema. [85]

(9) Hyperglycemia and thrombosis Multiple studies have identified a variety of hyperglycemia-related abnormalities in hemostasis, favoring thrombosis [86]. Human studies in patients with type 2 diabetes have shown platelet hyperactivity indicated by increased thromboxane biosynthesis Hyperglycemia-induced

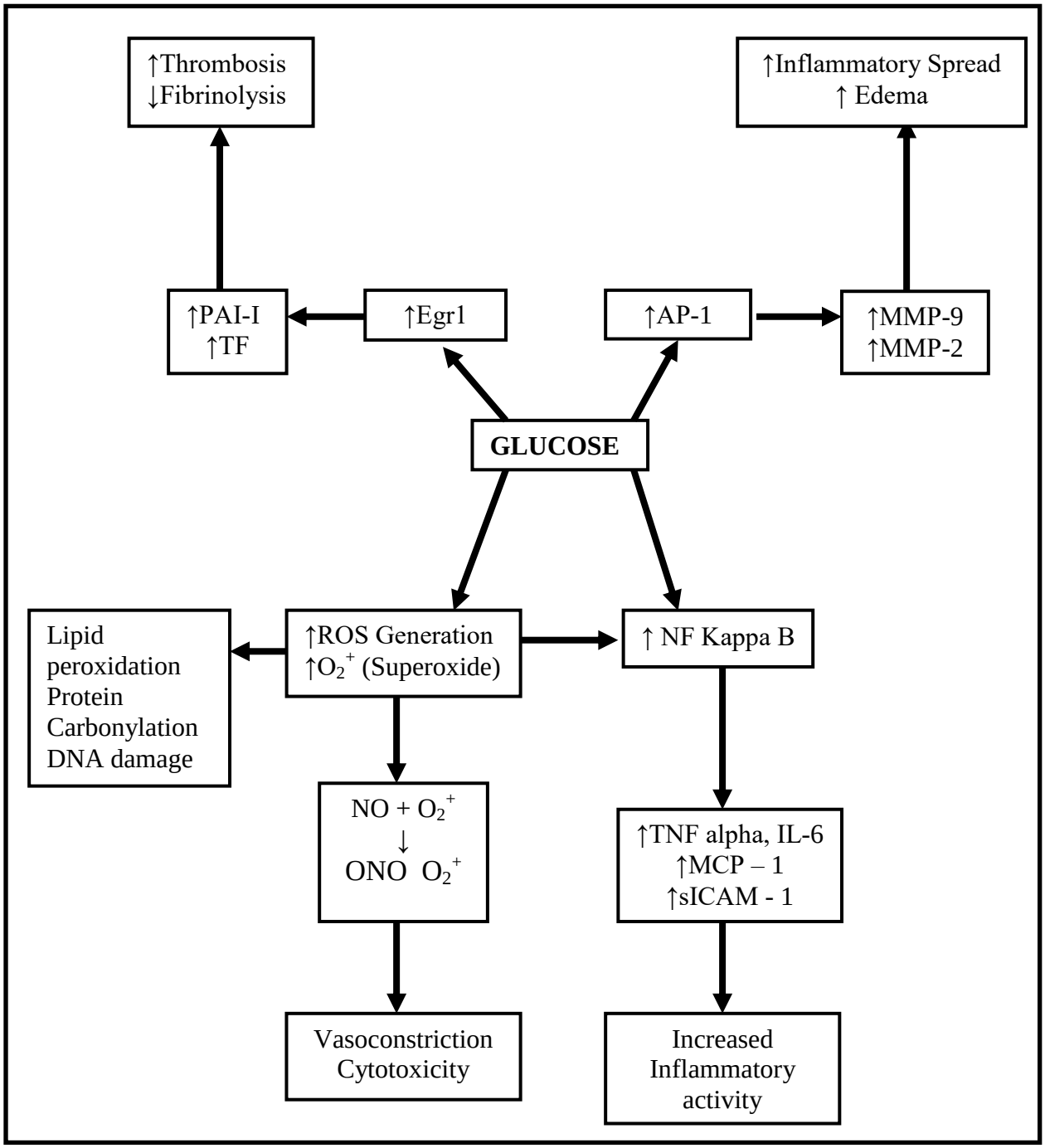
elevations of interleukin (IL)-6 levels have been linked to elevated plasma fibrinogen concentrations and fibrinogen mRNA. [87,88]

(10) Increased platelet activation as shown by shear-induced platelet adhesion and aggregation on extracellular matrix has been demonstrated in patients with diabetes. [86]

(11) Hyperglycemia and endothelial cell dysfunction

In the healthy state, the vascular endothelium maintains the vasculature in a quiescent, relaxant, antithrombotic, antioxidant, and antiadhesive state. Acute hyperglycemia may directly alter endothelial cell function by promoting chemical inactivation of nitric oxide [89], triggering production of reactive oxygen species (ROS) or activating other pathways.

Figure No. 9: Glucose Mediated Pro-inflammatory and Pro-Coagulant Effects



INSULIN TREATMENT IN ACUTE ISCHEMIC STROKE

(1) Insulin therapy reduces ischemic brain damage and can be neuroprotective. Insulin reduced neuronal necrosis regardless of its effect on glucose levels. [90] In addition, insulin, and to a lesser extent insulin-like growth factor-1, reduced ischemic damage when injected directly into the brain ventricles. [91]

a) Insulin has recently been shown to possess a potent anti-inflammatory effect in vitro and in vivo. It suppresses several proinflammatory transcription factors, such as NF-κB, Egr-1, and AP-1, and the corresponding genes regulated by them that mediate inflammation.

b) Insulin suppresses ROS generation. [92] In addition to its inhibitory effect on AP-1 and Egr-1, insulin suppresses their regulated gene products as indicated by a fall in plasma concentration of MMP-9, TF, and PAI-1, [93] an effect diametrically opposite to that of glucose. MMP-9 is a cardinal mediator and a reduction in its activity or expression by insulin could be a rational therapeutic approach in the prevention or the limitation of ischemia-related damage to the brain.

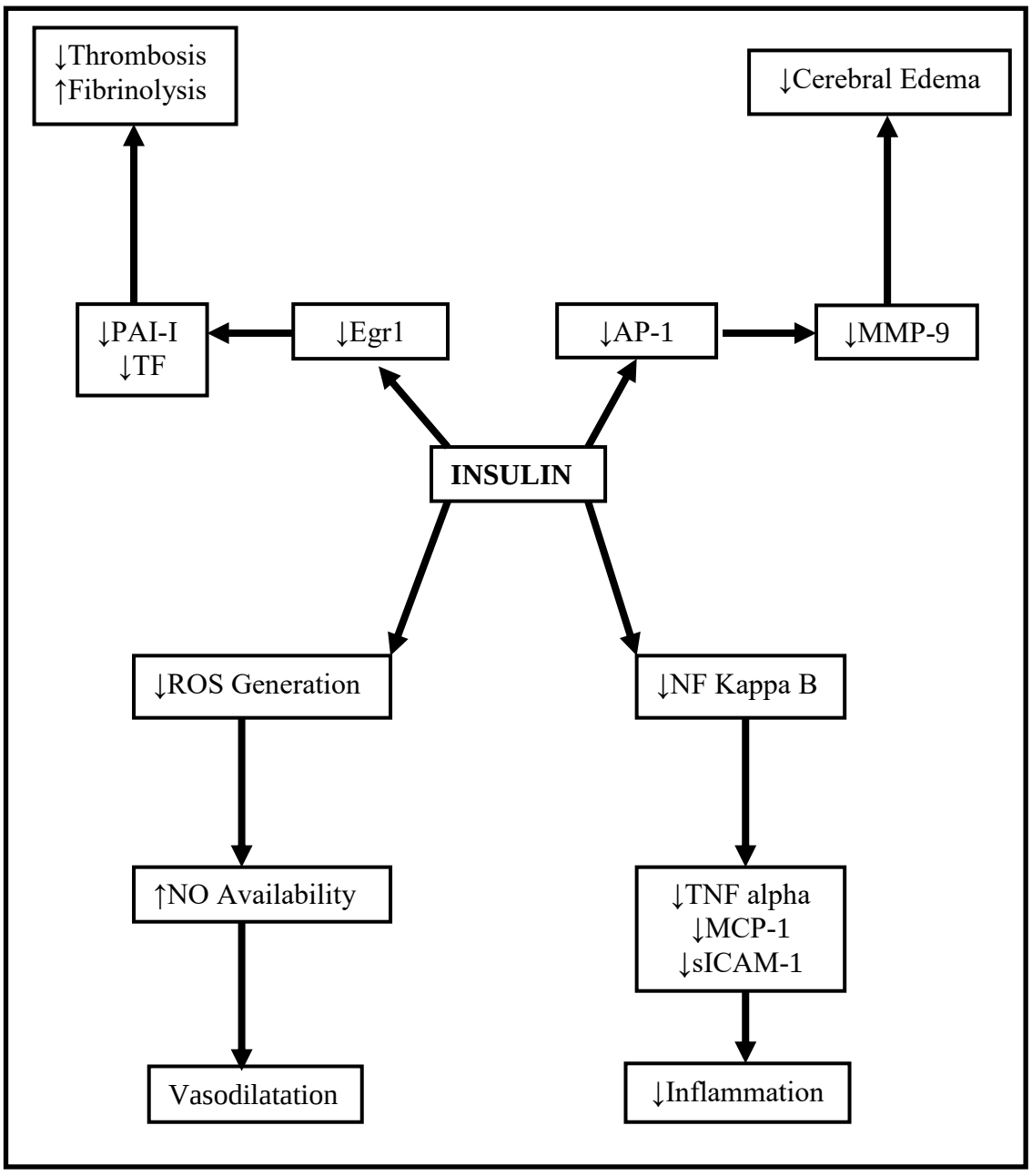
c) Insulin causes reduction in the plasma concentration of vascular endothelial growth factor (VEGF), a cytokine that induces an increase in the expression of MMP-9. [94] It has also been shown that VEGF can cause the loss of endothelial cell tight junctions. It is possible that VEGF and MMP-9 may act in a synergistic fashion to cause a disruption of the blood–brain barrier during ischemia because hypoxia is the major factor inducing an increase in the expression of VEGF. The fact that insulin suppresses MMP-9 and VEGF, both of which are mediators of ischemic damage, suggests strongly that it may have a beneficial role in the treatment of an acute stroke. Moreover, insulin-mediated suppression of TF and PAI-1 can produce an anticoagulant effect.

d) High catecholamine levels in the circulation during acute stroke can increase the production of free fatty acids. Free fatty acids decrease the generation and the stability of prostacyclin, [95] which is important for not only vasodilatation but also for preventing platelet aggregation. Insulin inhibits lipolysis, leading to a decrease in plasma-free fatty acids and thus may exert an antiplatelet and anticoagulant effect.

e) Insulin increases endothelial NO release and the expression of NO synthase (NOS) expression in the endothelial cells. [96] Generation of NO would

potentially help in vasodilatation and improved blood flow to the penumbra but also result in decreased production of ICAM-1. In addition, insulin has a direct inhibitory effect on platelet aggregation, mediated through the NO–guanylate cyclase-cGMP pathway activated by NO generated by NOS in platelets. [97] The antiplatelet effect of insulin may also potentially mediate further anti-inflammatory activity because platelet aggregation leads to the release of CD40 ligand (also called CD 154) contained in α-granules of platelets. CD40 ligand is a major mediator of inflammation.

Figure No. 10: Anti Inflammatory, Anti Coagulant and Vasodilatory Effects of Insulin



MATERIALS AND METHODS

SOURCE OF DATA

Cases of Cerebral Infarction admitted to BLDEA's Sri B. M. Patil Medical College Hospital and Research Centre, Bijapur in 1 year span of Nov 2007 – Nov 2008.

METHOD OF COLLECTION OF DATA

Sample Size: Prevalence of stroke in Indian scenario is 200 per 1,00,000 population (95% level of confidence with 10% margin of error), the worked out sample size using following statistical formula is 76. Prevalence of infarction among all cases of stroke is 80%. So the calculated sample size is 60.

Statistical formula: $n = \frac{(1.96)^2 \times p \times (1 - p)}{d^2}$ Where n= Sample size, p=Prevalence rate and d = Allowable error

Study Design: Random Blood Glucose levels were done on admission. Patients were scored based on NIH Stroke scale on day 1, at the time of discharge and then again on day 30 to assess the clinical outcome (wherever feasible).

1. Diabetic status was assigned on the basis of history of diabetes or treatment with hypoglycemic agents or elevated HbA1c or persistent/ marked hyperglycemia.
2. Stress hyperglycemia is defined as admission blood glucose > 140 mg% and normal HbA1c with no prior history of Diabetes or being on anti diabetic treatment.
3. Infarct size on CT scan brain < 3 cm^2 is small, 3-5 cm^2 is moderate and > 5 cm^2 is large infarct.
4. NIHSS score less than 5 indicates mild neurologic impairment, 5-15 indicates moderate, 15-25 indicates severe and score more than 25 indicates very severe neurologic impairment.

INCLUSION CRITERIA

All cases of cerebral infarction presenting within 24 hours of onset.

EXCLUSION CRITERIA

1. Previous history of stroke
2. Transient ischaemic attacks
3. Haemorrhagic stroke
4. Cerebellar / Brain stem infarction
5. Intracranial space occupying lesions
6. Cerebral Venous Thrombosis.

PROPOSED METHOD OF STATISTICAL ANALYSIS:

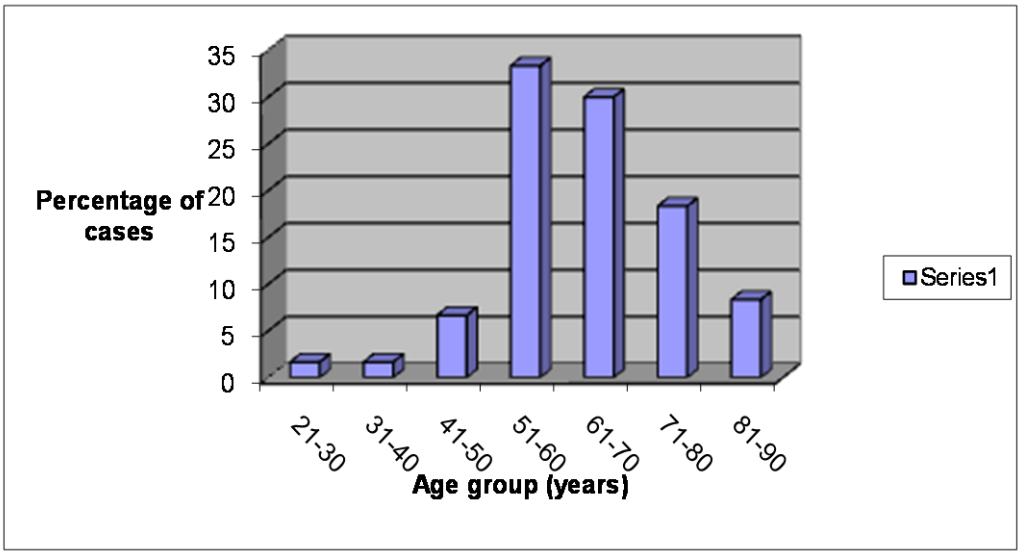
1. Diagrammatic representation
2. Mean ± Standard deviation
3. 't' test

RESULTS

TABLE No. 2 - Age Distribution of Cases (n=60)

AGE GROUP	NUMBER OF CASES	PERCENTAGE
21 – 30	1	1.66
31 – 40	1	1.66
41 – 50	4	6.66
51 – 60	20	33.33
61 – 70	18	30
71 – 80	11	18.33
81 – 90	5	8.33

GRAPH No. 1 : Age Distribution of Cases

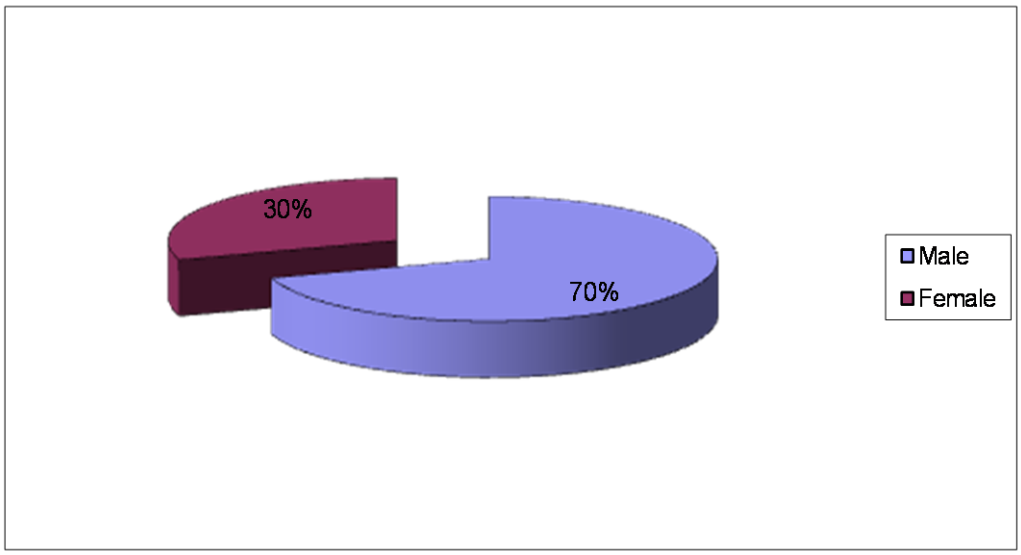


In this study, maximum number of patients were in the age group of 51 – 60 years. Next commonest age group was 61 – 70 years.

TABLE No. 3 : Sex Distribution of Cases (n = 60)

SEX	NUMBER OF CASES	PERCENTAGE
Male	42	70
Female	18	30

GRAPH No. 2 : Sex Distribution of Cases

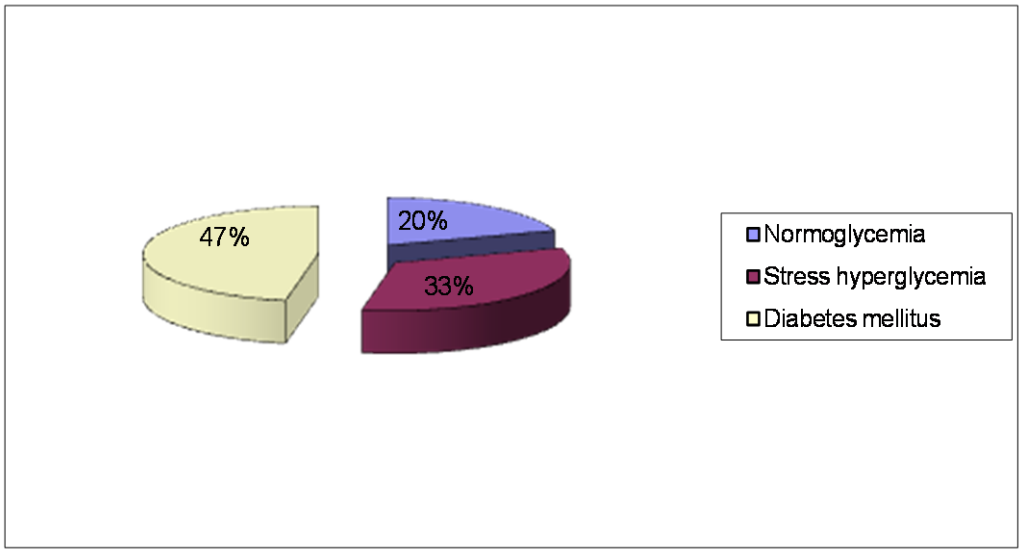


In this study, 70% of the cases were males and rest 30% were females. There was male preponderance with male : female ratio of 2.33.

TABLE No. 4 : Glycemic Status in the Study Group (n = 60)

GLYCEMIC STATUS	NUMBER OF CASES	PERCENTAGE
Normoglycemia	12	20
Stress hyperglycemia	20	33
Diabetes mellitus	28	47

GRAPH No. 3 : Glycemic Status in the Study Group

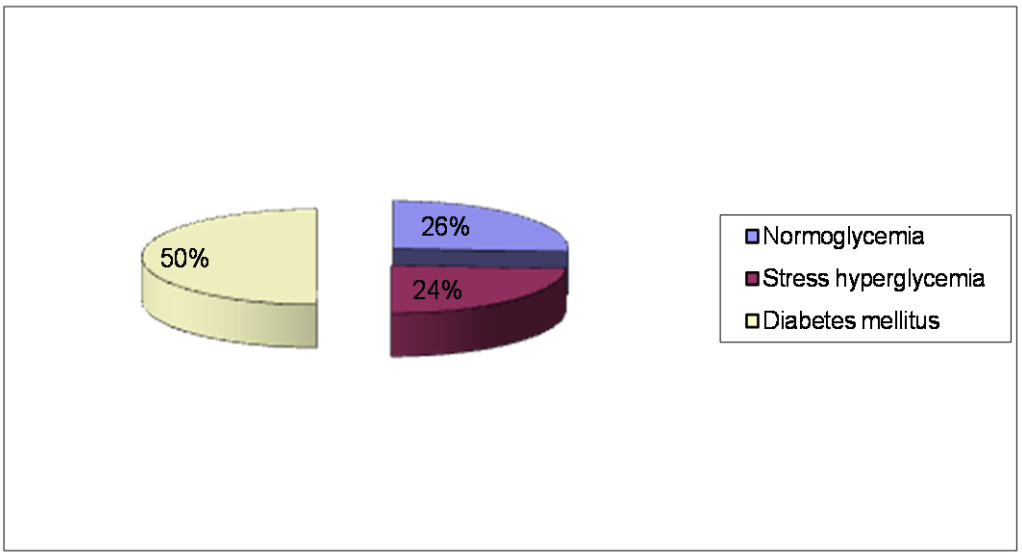


In this study, 20% cases were normoglycemic, 33% had stress hyperglycemia and 47% were diabetic.

TABLE No. 5 : Glycemic Status in the Male Group (n = 42)

GLYCEMIC STATUS	MALE	PERCENTAGE
Normoglycemia	11	26.19
Stress hyperglycemia	10	23.81
Diabetes mellitus	21	50

GRAPH No. 4 : Glycemic Status in the Male Study Group

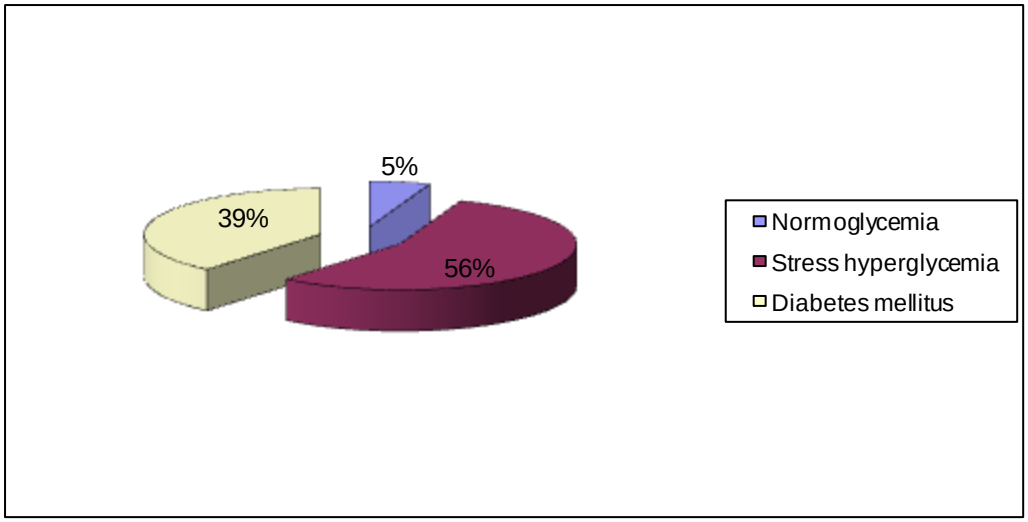


In this study, of all the male patients, 26.19% were normoglycemics, 23.81% had stress hyperglycemia and 50% were diabetic.

TABLE No. 6 : Glycemic Status in the Female Group (n = 18)

GLYCEMIC STATUS	FEMALE	PERCENTAGE
Normoglycemia	1	5.5
Stress hyperglycemia	10	55.55
Diabetes mellitus	7	38.88

GRAPH No. 5 : Glycemic Status in the Female Study Group

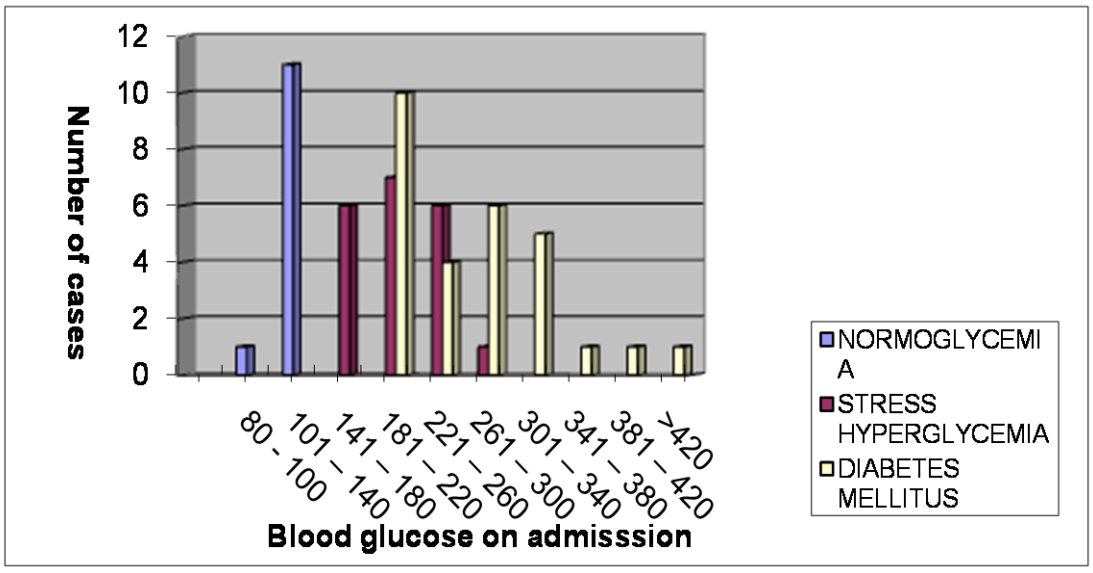


In this study, of all the female patients, 5.5% were normoglycemics, 55.55% had stress hyperglycemia and 38.88% had diabetes mellitus.

TABLE No. 7 : Blood Glucose on Admission (BGA) in Various Glycemic Groups

BGA	NORMOGLYCEMIA (n = 12)	STRESS HYPERGLYCEMIA (n = 20)	DIABETES MELLITUS (n = 28)	TOTAL (n = 60)
80 - 100	1			1
101 – 140	11			11
141 – 180		6		6
181 – 220		7	10	17
221 – 260		6	4	10
261 – 300		1	6	7
301 – 340			5	5
341 – 380			1	1
381 – 420			1	1
>420			1	1

GRAPH No. 6 : Blood Glucose on Admission in Various Study Groups

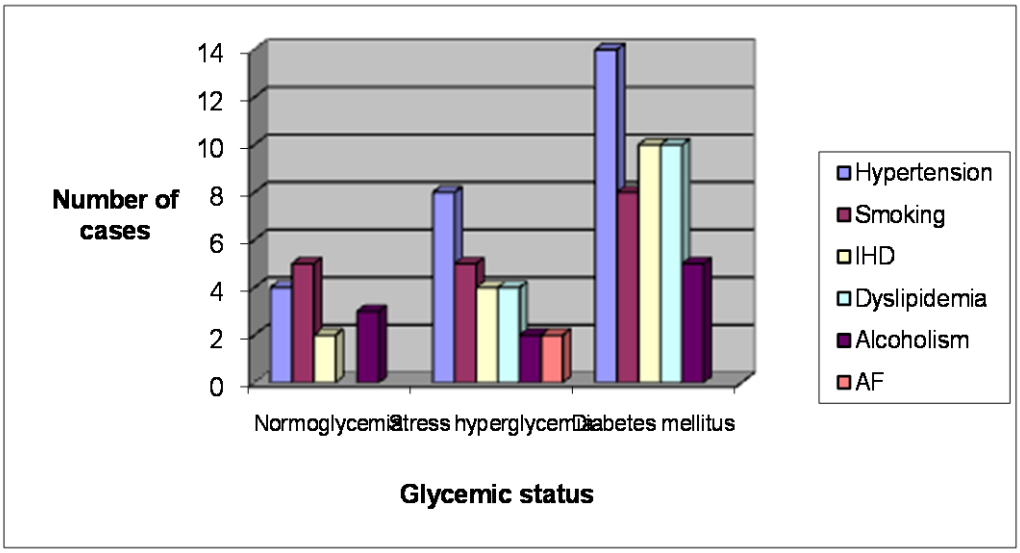


In this study, the random blood glucose on admission ranged from 101 – 450 mg/ dl. Most of the cases had blood glucose between 181 – 220 mg/ dl. Only one patient had blood glucose > 420 mg/ dl on admission. The range of blood glucose was 80 – 140 mg/ dl in the normoglycemic group, 141 – 300 mg/ dl in the stress hyperglycemia group and 181 – 450 mg/ dl in the Diabetes mellitus group. Out of the 60 patients, 48 had RBS > 140 mg/ dl.

TABLE No. 8: Risk Factors in the Study Group

GLYCEMIC STATUS	Essential Hypertension	Smoking	Ischemic Heart Disease	Dyslipidemia	Alcoholism	Atrial Fibrillation	Total
Normoglycemia	4	5	2	-	3	-	14
Stress Hyperglycemia	8	5	4	4	2	2	25
Diabetes Mellitus	14	8	10	10	5	-	47
Total	26	18	16	14	10	2	

GRAPH No. 7: Risk Factors in the Study Group

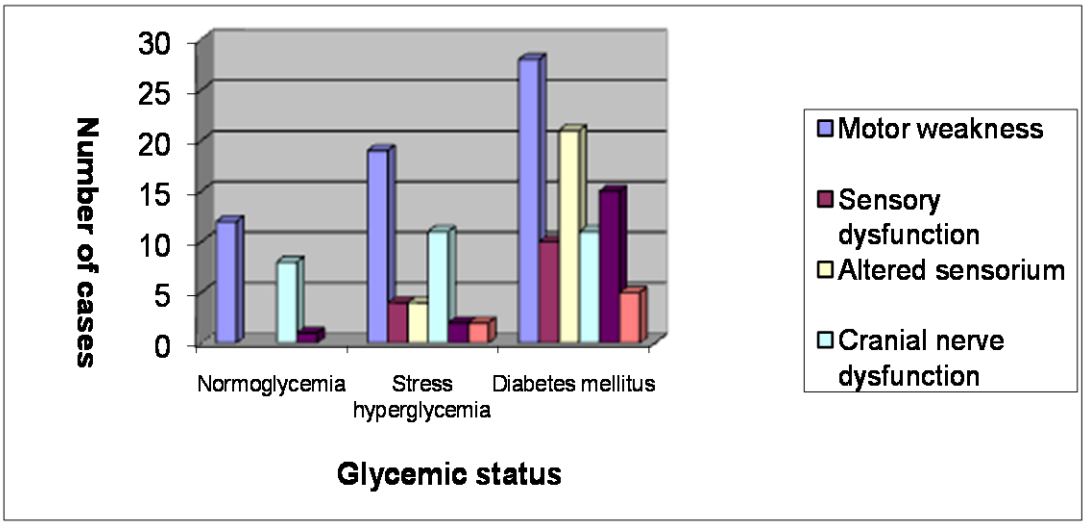


In this study, the common risk factors were Hypertension, Smoking, Ischemic heart disease, Dyslipidemia, Alcoholism and Atrial fibrillation. Hypertension and smoking were the commonest risk factors in the normoglycemia group, whereas Hypertension, Smoking, Ischemic heart disease and Dyslipidemia were the commonest risk factors in the stress hyperglycemia and Diabetes mellitus group.

TABLE No. 9: Clinical Presentations in the Study Group

Presentation	Normoglycemia (n = 12)	Stress hyperglycemia (n = 20)	Diabetes mellitus (n = 28)	Total (n = 60)
Motor Deficit	12	19	28	59
Sensory Deficit	-	4	10	14
Altered sensorium	-	4	21	25
Cranial nerve dysfunction	8	11	11	30
Language disturbances	1	2	15	18
Seizures	-	2	5	7

GROUP No. 8 : Clinical Presentations in the Study Group

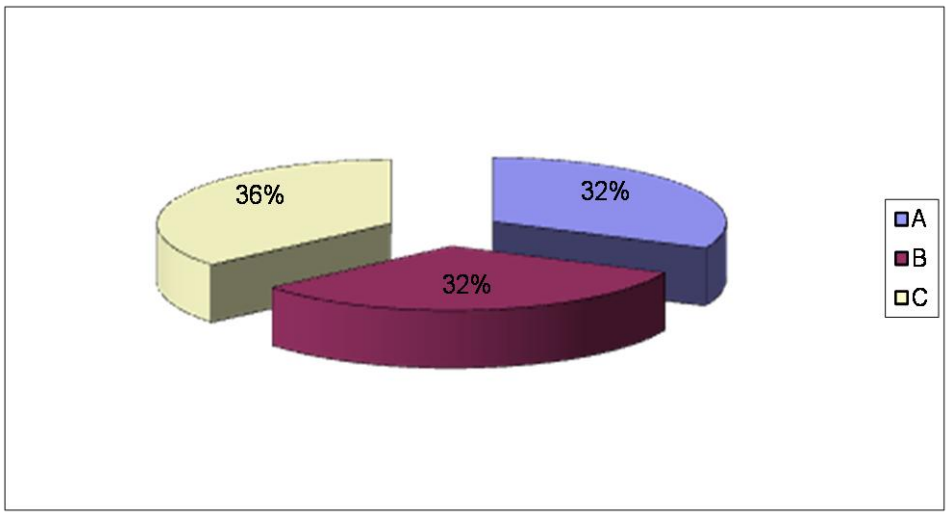


In this study, all patients except one had motor weakness. Other common presentations were cranial nerve dysfunction, altered sensorium, language disturbances, sensory impairment and seizures. The severity of the presenting complaints worsened from normoglycemia to stress hyperglycemia with maximum insult to the Diabetes mellitus group.

TABLE No. 10 : Infarct Size in the Study Group

INFARCT CLASS	SIZE	NUMBER	PERCENTAGE
A	SMALL < 3 cm^2, extending < 2 CT slices (1slice = 10mm)	19	31.66
B	MEDIUM > 3 cm^2 < 5 cm^2, > 2 CT slices	19	31.66
C	LARGE > 5 cm^2, involving large vascular territory	22	36.66

GRAPH No. 9: Infarct Size in the Study Group

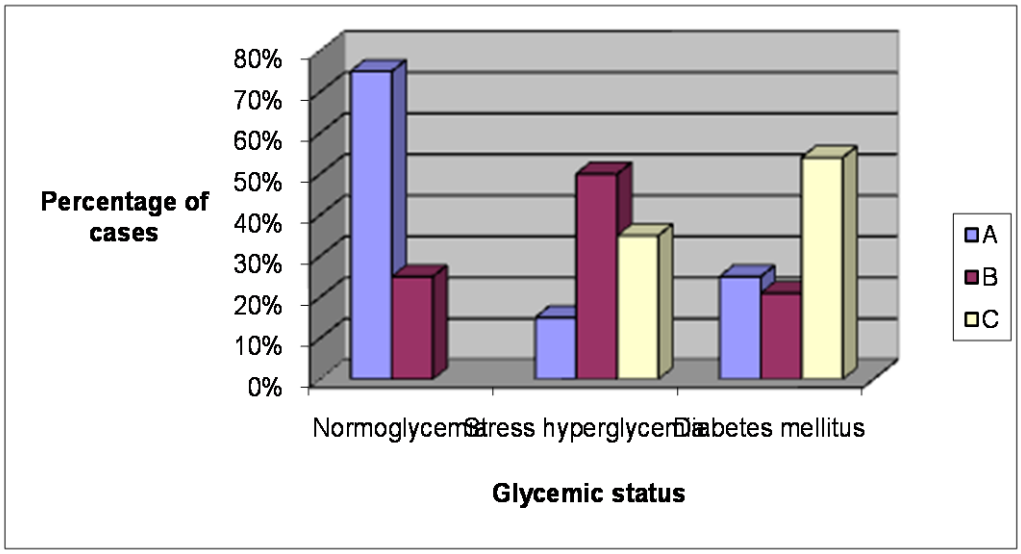


In this study group, small and medium sized infarcts accounted for 31.66% of cases each and 33.66% cases had large sized infarcts.

TABLE No. 11 : Infarct Size in each Glycemic Group (n = 60)

INFARCT SIZE	NORMOGLYCEMIA (N)	%	STRESS HYPERGLYCEMIA (SH)	%	DIABETES MELLITUS (DM)	%
A	9	75	3	15	7	25
B	3	25	10	50	6	21.4
C	-	-	7	35	15	53.6
TOTAL	12		20		28	

GRAPH No. 10 : Infarct Size in each Glycemic Group



Most of the small sized infarcts occurred in the normoglycemia group, medium sized infarcts in the stress hyperglycemia group and most of the large sized infarts occurred in the diabetes group.

In the normoglycemia group, 75% had small sized infarcts and 25% had medium sized infarcts. There were no large sized infarcts in this group.

In the stress hyperglycemia group, 15% cases had small sized infarcts, 50 % cases had medium sized infarcts and 35% had large sized infarcts.

In the Diabetes mellitus group, 25% had small sized infarcts, 21.4% had medium sized infarcts and 53.6% had large sized infarcts.

TABLE No. 12 : Test of Significance Between NIHSS Score on Admission and at Discharge by Glycemic Status and Small Sized Infarct

GS	n	Mean ± SD on admission	Mean ± SD at discharge	t value	p-value
Normoglycemia	9	13.88 ± 4.7	5.77 ± 1.85	5.59	0.000656
Stress hyperglycemia	3	14 ± 2.0	8.0 ± 1.73	3.94	0.01781
Diabetes mellitus	7	15.85 ± 3.23	10.43 ± 4.15	2.74	0.01927

In this study, it was observed that small sized infarcts were more common in the normoglycemia group. The baseline NIHSS score was lowest in the normoglycemia group and highest in the diabetes mellitus group. This indicates that diabetes mellitus group had severe stroke for even small sized infarcts as per increase in NIHSS score.

TABLE No. 13 : Test of Significance Between NIHSS Score on Admission and at Discharge by Glycemic Status and Medium Sized Infarct

GS	n	Mean ± SD on admission	Mean ± SD at discharge	t-value	p-value
Normoglycemia	3	13 ± 2.64	7 ± 1	3.70	0.0453
Stress hyperglycemia	10	15.1 ± 3.44	10 ± 2.74	3.62	0.0019
Diabetes mellitus	6	16.5 ± 3.44	11.33 ± 1.50	3.42	0.01247

In this study, it was observed that medium sized infarcts were more common in the stress hyperglycemia group. The NIHSS score correlates with the glycemic status, with increase in scores with change in the glycemic status. The baseline NIHSS scores as well as the scores at discharge were higher in the diabetes mellitus group than the stress hyperglycemia group than normoglycemia group for medium sized infarcts.

TABLE No. 14 : Test of Significance Between NIHSS Score on Admission and at Discharge by Glycemic Status and Large Sized Infarct

GS	n	Mean ± SD on admission	Mean ± SD at discharge	t-value	p-value
Stress hyperglycemia	7	22.71 ± 2.81	12.25 ± 3.59	5.02	0.00373
Diabetes mellitus	5	27.0 ± 4.67	18.72 ± 5.25	4.18	0.000486

In this study, large sized infarcts were more common in the diabetes mellitus group. There were no large sized infarcts in the normoglycemia group. The stress hyperglycemia group had higher NIHSS score on admission and at discharge compared to diabetes mellitus group.

TABLE No. 15 : Significance Between NIHSS Score on Admission and at Discharge by Glycemic Status

GS	n	Mean ± SD on admission	Mean ± SD at discharge	t-value	p-value
Normoglycemia	12	13.66 ± 4.2	6.08 ± 1.72	5.78	0.0000405
Stress hyperglycemia	20	17.6 ± 4.84	10.17 ± 3	5.71	0.0000026
Diabetes mellitus	28	21.96 ± 6.80	14.45 ± 5.76	4.31	0.000077

As per the above tables, NIHSS score on admission and at discharge increases as the glycemic spectrum changes from normoglycemia to diabetes mellitus, indicating worsening severity of score with change in the glycemic status from normoglycemia to diabetes mellitus. The diabetes mellitus group had more severe stroke as per NIHSS score for any infarct size. There was slower progression in the scores from day of admission till discharge as the glycemic spectrum changed from normoglycemia to stress hyperglycemia to diabetes mellitus.

Thus, for any infarct size NIHSS score was highest in the diabetes mellitus group and NIHSS score at discharge also increased from normoglycemia to stress

hyperglycemia to diabetes mellitus group. It was also observed that rate of recovery of stroke was slowest in diabetes mellitus group compared to stress hyperglycemia.

TABLE No. 16 : Significance Between NIHSS Score on Admission and at 30 days by Glycemic Status (n = 18)

GS	n	Mean ± SD on admission	Mean ± SD at 30 days	t-value	p-value
Normoglycemia	5	11.4 ± 3.57	2.6 ± 0.89	5.36	0.00424
Stress hyperglycemia	7	14.71 ± 2.98	6.71 ± 3.14	4.9	0.000381
Diabetes mellitus	6	21.16 ± 4.57	12 ± 4.73	3.41	0.00667

It was observed that mean NIHSS score on admission and at 30 days was more in diabetes mellitus group. There was slower progression of the scores and poorer recovery as the glycemic status changed from normoglycemia to stress hyperglycemia to diabetes mellitus group.

TABLE No. 17 : Significance Between Blood Glucose on Admission, HbA1c and Glycemic Status for each of the Infarct Sizes

Infarct size	Normoglycemia		Stress hyperglycemia		Diabetes mellitus	
	RBS	HbA1c	RBS	HbA1c	RBS	HbA1c
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Small (A)	125 ± 14.85	4.25 ± 0.7	173.66 ± 12.42	4.93 ± 0.64	219.71 ± 39.42	6.31 ± 0.318
Medium (B)	138 ± 2.081	4.33 ± 0.230	174 ± 46.3	5.01 ± 0.54	255.66 ± 93.92	7.05 ± 0.66
Large (C)			256 ± 19	5.28 ± 0.38	291.66 ± 61.007	7.36 ± 0.49

In this study, it was noted that for all infarct sizes, mean random blood glucose on admission was highest for the diabetes mellitus group. Also the mean HbA1c values increased for each infarct sizes as the glycemic status increased from normoglycemia to stress hyperglycemia to diabetes mellitus group.

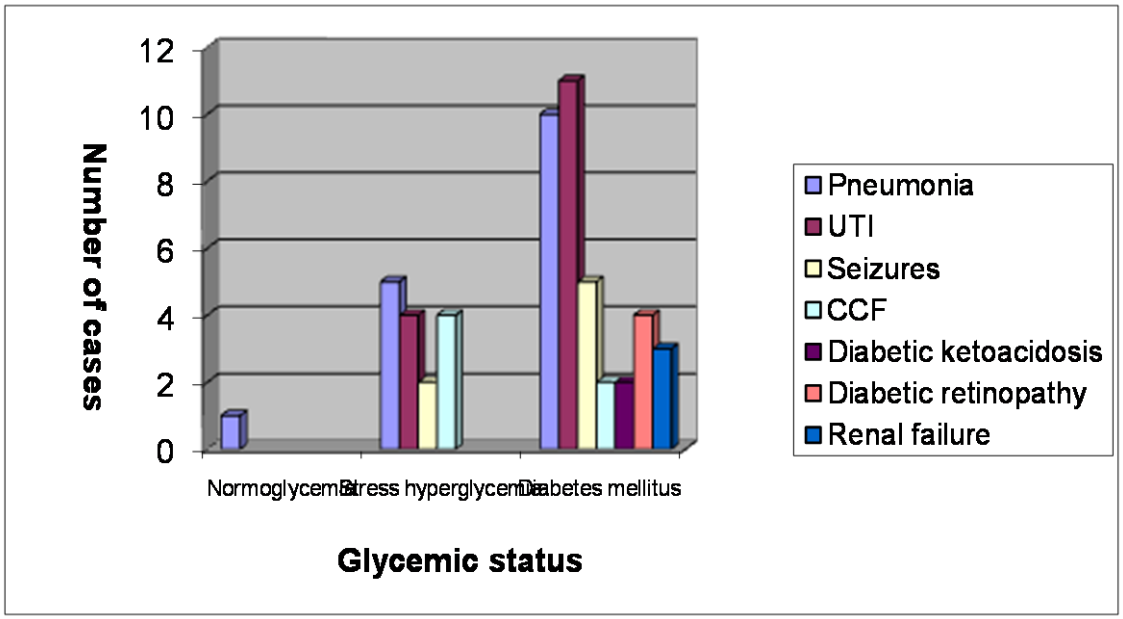
Both Random blood glucose values and HbA1c values correlated well with infarct size. HbA1c and blood glucose on admission were lowest in the

normoglycemia group, while higher blood glucose cases had larger size infarcts and thus more severe stroke.

TABLE No. 18 : Complications in the Various Glycemic Groups

COMPLICATIONS	Normoglycemia (n = 12)	Stress hyperglycemia (n = 20)	Diabetes mellitus (n = 28)	Total (n=60)
Pneumonia	1	5	10	16
Urinary tract infection	-	4	11	15
Seizures	-	2	5	7
Congestive cardiac failure	-	4	2	6
Diabetic ketoacidosis	-	-	2	2
Diabetic retinopathy	-	-	4	4
Renal failure	-	-	3	3

GRAPH No. 11 : Complications in the Study Group



In this study, the most common complications were Pneumonia (16 cases), urinary tract infection (15 cases) , Seizures (7 cases) and Congestive cardiac failure (6 cases). Other complications were Diabetic retinopathy (4 cases), Renal failure (3 cases) and Diabetic ketoacidosis (2 cases). Most of the complications occurred in the Diabetes mellitus group.

DISCUSSION

Stroke is the third leading cause of death, next only to ischemic heart disease and cancer. Hyperglycemia in both diabetic and non – diabetic (stress hyperglycemia) patients is associated with poor prognosis, both in terms of mortality and functional recovery. This study correlated the clinical profile and outcome of cerebral infarction in relation to glycemic status on presentation.

Sixty consecutive patients with cerebral infarction admitted to Sri B. M. Patil Medical College Hospital who met the inclusion criteria were included in the study. The age group of the patients ranged from 21 – 90 years with mean age of 60.85 ± 11.93 years. This finding is comparable to Bravata D. M. et al where the mean age was 73 ± 13 years. [98] The youngest patient was aged 26 years and the oldest was 82 years. Maximum number of patients were in the age group of 51 – 60 years.

There were 70% male and 30% female patients, with M:F ratio of 2.33 : 1. Kushner et al in their study reported M : F ratio was 1.7 : 1.5. [99] Hyvarinen M et al reported 55% men and 45% women in their study of 21,706 cases.[100]. The mean age of male patients was 61.16 ± 14.88 years and the mean age of female patients was 57.33 ± 12.07 years.

Out of the 60 patients, 20% were normoglycemics, 33% had stress hyperglycemia and 47% had Diabetes mellitus. Sarkar RN et al noted 38% diabetics in their study of 450 patients. [5] In this study, stress hyperglycemia was defined as admission blood glucose levels > 140 mg / dl with normal HbA1c levels. Gentile NT, Michael W, Seftchick BS, et al defined hyperglycemia as blood glucose levels >/- 130 mg/dl.[101] Capes et al noted that cutoffs to define hyperglycemia ranged from 108mg/ dl to 180 mg/ dl in various studies. [102] Diabetic status was assigned on the basis of history of Diabetes , treatment with hypoglycemic drugs or elevated HbA1c. In this study, incidence of hyperglycemia (Admission blood glucose > 140 mg/ dl) was 80%.

Among the study groups, incidence of stress hyperglycemia in males was 23.81% and in females it was 50.55%. Incidence of Diabetes mellitus was 50% in males and 38.88% in females. Thus there was higher percentage of Diabetes in males and higher percentage of Stress hyperglycemia among the females. Jhanghorbani M et al noted a stronger association between hyperglycemia and stroke in women than in men. [103]

In this study, the random blood glucose on admission ranged from 101 – 450 mg/ dl. Most of the cases had blood glucose between 181 – 220 mg/ dl. Only one patient had blood glucose > 420 mg/ dl on admission. The range of blood glucose was 80 – 140 mg/ dl in the normoglycemic group, 141 – 300 mg/ dl in the stress hyperglycemia group and 181 – 450 mg/ dl in the Diabetes mellitus group, with 80% patients having blood glucose on admission in hyperglycemia group of > 140 mg/ dl.

In this study, the common risk factors were Hypertension, Smoking, Ischemic heart disease, Dyslipidemia, Alcoholism and Atrial fibrillation. Hypertension and smoking were the commonest risk factors in the normoglycemia group, whereas Hypertension, Smoking, Ischemic heart disease and Dyslipidemia were the commonest risk factors in the stress hyperglycemia and Diabetes mellitus group. These are comparable to other studies on risk factors in stroke. [20-24]

Commonest presentation is motor weakness. Others were cranial nerve dysfunction, altered sensorium, language disturbances, sensory impairment and seizures. The severity of the presenting complaints worsened from normoglycemia to stress hyperglycemia with maximum insult to the Diabetes mellitus group.

The size of the infarcts on CT scans were classified as small (<3 mm^2), medium (>3mm^2 but < 5 mm^2) and large (>5mm^2). In this study, patients with small and medium sized infarcts were 19 (31.66%) each and 22 patients (33.66%) had large sized infarcts. Among the normoglycemics, the percentage of small and medium sized infarcts were 75% and 15%. None of them had large sized infarct. Among those with stress hyperglycemia small, medium and large sized infarcts were 15%, 50% and 35%. Among the diabetics, percentage of patients with small, medium and large sized infarcts were 25%, 21.4% and 53.6%. Thus the stress hyperglycemia group had higher percentage of medium sized infarcts and Diabetes mellitus group had higher percentage of large sized infarcts. There is increase in the infarct size with worsening of the glycemic status. Mehta S noted increased infarct size with hyperglycemia.[104]

The clinical severity of stroke was measured using the NIHSS stroke scale on admission and at discharge for all the patients and also on 30th day, wherever feasible. A decrease in the score from baseline was taken as a sign of recovery.

1. In patients with small sized infarcts, NIHSS score on admission for normoglycemia, stress hyperglycemia and diabetes group was 13.88 ± 4.7, 14 ± 2 and 15.5 ± 3.09. At discharge it was 6.22 ± 2.33, 8 ± 1.73 and 10.43 ± 4.15 respectively.

2. In patients with medium sized infarcts, the score for normoglycemia, stress hyperglycemia and diabetes mellitus was on admission was 13 ± 1.52, 15.1 ± 3.44 and 16.5 ± 3.44 and at discharge it was 6.6 ± 1.53, 10 ± 2.77 and 11.33 ± 1.5 respectively.
3. In patients with large sized infarcts, the score on admission for stress hyperglycemia and diabetes mellitus was 22.71 ± 2.81 and 27 ± 4.67 and at discharge it was 12.25 ± 3.59 and 18.72 ± 5.25 respectively.

Johnston et al noted that infarct volume significantly predicted NIHSS score on admission. [105]

Out of the 60 patients, 18 patients could be evaluated again on 30th day. For these patients, the NIHSS score on admission for normoglycemia, stress hyperglycemia and Diabetes mellitus group was 13.88 ± 5.172, 17.6 ± 4,85 and 21.535 ± 7.29 and on 30th day it was 3.8 ± 1.483, 6.71 ± 3.14 and 12 ± 4.73 respectively. Gentile NT et al noted that hyperglycemia was associated with higher admission severity score. Admission hyperglycemia was an independent predictor of of mortality even after controlling for disease severity.[101]

The NIHSS score on admission and at discharge and also by 30th day wherever feasible, was found to increase as the glycemic spectrum changes from normoglycemia to diabetes mellitus, indicating worsening severity of score with change in the glycemic status from normoglycemia to diabetes mellitus. The diabetes mellitus group had more severe stroke as per NIHSS score for any infarct size. There was slower progression in the scores from day of admission till discharge as the glycemic spectrum changed from normoglycemia to stress hyperglycemia to diabetes mellitus.

Sarkar RN et al, Bruno A et al, Weir CJ et al, Umpierrez GE et al have demonstrated that hyperglycemia predicts a poor outcome.[5, 47, 106,107]

Thus, for any infarct size NIHSS score was highest in the diabetes mellitus group and NIHSS score at discharge also increased from normoglycemia to stress hyperglycemia to diabetes mellitus group. It was also observed that rate of recovery of stroke was slowest in diabetes mellitus group compared to stress hyperglycemia compared to normoglycemia group. Gray et al observed complete functional recovery in patients with normoglycemia on admission.[110] Out of the 60 patients, 7 of them died during the hospital stay, 3 from the stress hyperglycemia group and 4 from the diabetes mellitus group. All of them had large sized infarcts. Thus higher stroke

severity and higher mortality was associated with the stress hyperglycemia and diabetes mellitus group, increasing in proportion to the worsening glycemic status. The increased mortality was related to the stroke size but not related to the stroke type or location.

Poppe AY et al found that the strongest predictor of poor outcome and death was persistent hyperglycemia at baseline and at 24 hours.[108] Yong M et al non diabetic patients with persistent hyperglycemia had the worst prognosis assessed by neurological improvement, functional outcome, mortality and haemorrhagic transformation.[109] Capes SE et al have reported a 3 – fold increased risk on mortality in poststroke hyperglycemia, summarizing 9 studies in non diabetic patients.[102] Hyvarinen M et al confirmed in their study that diabetes is a predictor of stroke mortality.[100]

Both Random blood glucose values and HbA1c values correlated well with infarct size. HbA1c and blood glucose on admission were lowest in the normoglycemia group, while higher blood glucose cases had larger size infarcts and thus more severe stroke. Cox NH et al noted that hyperglycemia in conjunction with normal HbA1c, which probably represents a 'stress' response, is associated with poor prognosis for recovery from stroke.[111]

In this study, the most common complications were Pneumonia, urinary tract infection, Seizures and Congestive cardiac failure. Other complications were Diabetic retinopathy, Renal failure and Diabetic ketoacidosis. Most of the complications occured in the Diabetes mellitus group. Dalal noted hypertension as the most important risk factor in the Indian scenario. [17] Gentile et al noted hypertension (78%), congestive cardiac failure (14%) and hemorrhagic transformation of infarct in their study.[101]

LIMITATIONS OF THE STUDY

1) Sample size is small
2) The management of hyperglycemia and stroke per sec were not standardized.
3) Extended follow – up of the patients was not possible.

Nevertheless, the strong association between admission hyperglycemia and poor prognosis after stroke suggests that glucose level is an important risk factor for morbidity and mortality after stroke. These results highlight the need for further research to determine whether glucose lowering at the time of admission can improve outcomes.

SUMMARY

1) Maximum number of patients were in the age group of 51 – 60 years, with mean age of 60.85 ± 11.93 years.
2) The male to female ratio of 2.33 : 1.
3) The incidence of hyperglycemia was 80%. There were 20% normoglycemics, 33% with stress hyperglycemia and 47% with Diabetes mellitus.
4) There was higher percentage of Diabetes in males and higher percentage of Stress hyperglycemia among the females.
5) The common risk factors were Hypertension, Smoking, Ischemic heart disease, Dyslipidemia, Alcoholism and Atrial fibrillation.
6) Commonest clinical presentation was motor weakness. Others were cranial nerve dysfunction, altered sensorium, language disturbances, sensory impairment and seizures. The severity of the presenting complaints worsened from normoglycemia to stress hyperglycemia with maximum insult to the Diabetes mellitus group.
7) The stress hyperglycemia group had higher percentage of medium sized infarcts and Diabetes mellitus group had higher percentage of large sized infarcts.
8) More the admission blood glucose levels, more severe was the clinical presentation with higher NIHSS scores.
9) Progressive increase in the NIHSS score across all groups was noted, irrespective of the infarct size as the glycemic status changed from normoglycemia to Diabetes mellitus.
10) The NIHSS score increased as the infarct size increased across all the groups.
11) The rate of recovery was good in normoglycemia group but poorer in the hyperglycemia group, being more in stress hyperglycemia than Diabetes mellits group.
12) Admission blood glucose levels and HbA1c levels correlated well with infarct size in the diabetes group. Patients with lower HbA1c levels had smaller sized infarcts, while poorly controlled Diabetics had larger sized infarcts with poorer recovery and increased mortality.
13) Commonest complications were Pneumonia, urinary tract infection, Seizures and Congestive cardiac failure. Other complications were Diabetic retinopathy, Renal failure and Diabetic ketoacidosis. Most of the complications occurred in the Diabetes mellitus group.

CONCLUSION

1) Admission blood glucose levels, HbA1c levels and NIHSS scores correlate well with infarct size.
2) Patients with hyperglycemia were found to have increased NIHSS scores on admission and poorer recovery irrespective of infarct size. However, prognosis worsened from stress hyperglycemia group to diabetes mellitus group.
3) Hyperglycemia group had increased incidence of complications and greater mortality than normoglycemia group.
4) Tight control of blood glucose levels immediately during admission and during follow - up improves outcome.

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PROFORMA

Name: IP no:

Age: Date of admission:

Sex: Date of discharge:

Occupation: Duration of hospital stay:

Marital status:

Address:

Telephone no :

Diabetic status:

PRESENTING COMPLAINTS:

Onset and progression: abrupt/over minutes/ over days evolution

Altered sensorium

Language disturbances

Behavioral disturbances

Headache and vomiting

Seizures

Preceding TIA

Cranial nerve dysfunction

Weakness of limbs Right/left

Sensory dysfunction Right/left

Gait

PAST HISTORY

TIA / stroke

Diabetes Duration
Medications
Complications

Hypertension COPD

IHD Head injury

Rheumatic heart disease Craniotomy

Congestive heart failure Malignancy

Chronic renal failure Coagulopathies

Chronic liver diseases Medications

Specify any other medical illness

PERSONAL HISTORY

Diet

Appetite

Sleep

Bowel

Bladder

Habits- Smoking
Alcohol intake

Oral contraceptive intake

Hormone Replacement Therapy

FAMILY HISTORY

Diabetes

Hypertension

Ischaemic heart diseases

Cerebrovascular accidents

Obesity

GENERAL PHYSICAL EXAMINATION

VITAL SIGNS

Pulse	Height
Peripheral pulses	Weight
Blood pressure	BMI

Respiration-rate and rhythm

Temperature

Carotids

Any other signs

SYSTEMIC EXAMINATION

CVS

RS

PA

NEUROLOGICAL EXAMINATION

Glasgow coma scale

NIH stroke scale

Higher mental functions

Mini mental state examination

Level of consciousness

Orientation

Emotional state

Language

Spontaneous speech

Comprehension

Naming

Reading

Writing

Calculation

Agnosia

Apraxia

Memory- Immediate
Recent
Remote

Agitation/ delirium

Cranial nerve examination

Olfaction

Visual acuity

Visual fields

Colour vision

Pupil light reflex, accommodation

Optic fundi

External occular movements

Size of palpebral fissures

Diplopia

Nystagmus

Facial sensation

Muscles of jaw

Facial muscles

Hearing

Palatal movements

Trapezius and sternocleidomastoid

Tongue

Motor examination

Limb

Nutrition	Right upper limb	Left upper limb
	Right lower limb	Left lower limb
Tone	Right upper limb	normal/increased/decreased
	Right lower limb	normal/increased/decreased
	Left upper limb	normal/increased/decreased
	Left lower limb	normal/increased/decreased
Power	Right upper limb	Left upper limb
	Right lower limb	Left lower limb

Reflexes

Superficial reflexes

Deep tendon reflexes

Reflexes	BJ	SJ	TJ	KJ	AJ
Right					
Left					

Release reflexes

Plantar reflexes

Right flexor/extensor/equivocal
Left flexor/extensor/equivocal

Involuntary movements

Sensations

Right upper limb	normal/increased/decreased
Right lower limb	normal/increased/decreased
Left upper limb	normal/increased/decreased
Left lower limb	normal/increased/decreased

Signs of meningeal irritation

Signs of cerebellar involvement- co-ordination, tremors, nystagmus

Gait

Skull and Spine

INVESTIGATIONS

1. Blood examination

Hb%		Gm/dl
TC		Cells/cu.mm
DC		%
Polymorphs		%
Lymphocytes		%
Eosinophils		%
ESR		mm/1 hour
Platelet count		cells/cu.mm
BT	min	sec
CT	min	sec

2. Urine examination

Albumin
Sugar
Microscopy

3. Blood sugars at admission

RBS	FBS	PPBS	HbA1c

Glycemic status:

Normoglycemic	Stress hyperglycemic	Newly diagnosed Diabetes	Known Diabetic

4. Fasting lipid profile

5. ECG

6. Fundoscopy

7. CT scan brain

Date and Number

Report
Size of the infarct on CT scan: small/medium/large

8. NIHSS Score

On admission	At discharge	On day 30

9. Other investigations

10. Complications

NATIONAL INSTITUTE OF HEALTH STROKE SCALE

Tested Item	**Title**	**Responses and Scores**
1A	Level of consciousness	0—alert
		1—drowsy
		2—obtunded
		3—coma/unresponsive
1B	Orientation questions (two)	0—answers both correctly
		1—answers one correctly
		2—answers neither correctly
1C	Response to commands (two)	0—performs both tasks correctly
		1—performs one task correctly
		2—performs neither
2	Gaze	0—normal horizontal movements
		1—partial gaze palsy
		2—complete gaze palsy

3	Visual fields	0—no visual field defect
		1—partial hemianopia
		2—complete hemianopia
		3—bilateral hemianopia
4	Facial movement	0—normal
		1—minor facial weakness
		2—partial facial weakness
		3—complete unilateral palsy
5	Motor function (arm)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 10 seconds
		3—no effort against gravity
		4—no movement
6	Motor function (leg)	0—no drift
	a. left	1—drift before 5 seconds
	b. right	2—falls before 5 seconds
		3—no effort against gravity
		4—no movement
7	Limb ataxia	0—no ataxia
		1—ataxia in one limb
		2—ataxia in two limbs
8	Sensory	0—no sensory loss
		1—mild sensory loss
		2—severe sensory loss
9	Language	0—normal
		1—mild aphasia
		2—severe aphasia
		3—mute or global aphasia
10	Articulation	0—normal
		1—mild dysarthria
		2—severe dysarthria
11	Extinction or	0—absent

	inattention	
		1—mild (loss 1 sensory modality)
		2—severe (loss 2 modalities)

BLDEA'S SHRI B.M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR-586103

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT:

CLINICAL PROFILE OF CEREBRAL INFARCTION AND ITS OUTCOME IN RELATION TO GLYCEMIC STATUS ON PRESENTATION – A PROSPECTIVE STUDY

GUIDE : DR.M.S.BIRADAR
PROFESSOR AND HOD OF MEDICINE

P.G. STUDENT : DR. NARONE.UTKARSHA C.

PURPOSE OF RESEARCH

I have been informed that this study is to find out the Clinical profile and outcome of cerebral infarction patients with hyperglycemia compared with those with euglycemic status.

PROCEDURE

I understand that I will undergo detailed history and clinical examination after which I will have to undergo few laboratory investigations including CT scan brain (plain).

RISKS AND DISCOMFORTS

I understand that there is no risk involved and I may experience mild pain during the procedures performed.

BENEFITS

I understand that my participation in this study will involve use of clinical skills and will help in a systematic approach in the management of cerebral infarction. Moreover the results will help in adequate control of hyperglycemia which is found to result in a favourable outcome.

CONFIDENTIALITY

I understand that medical information produced by this study will become a part of my hospital records and will be subject to the confidentiality and privacy regulation of the said hospital. If the data is used for publication, the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION

I understand that I may ask more information about the study at any time.

REFUSAL OR WITHDRAWAL FROM PARTICIPATION

I understand that my participation is voluntary and I may refuse to participate or may withdraw from the study at any time.

INJURY STATEMENT

I understand that in the unlikely event of injury to me during the study, I will get medical treatment but no further compensation.

(Signature of Guardian) (Signature of the Patient)

KEY TO MASTER CHART

A	-	Small sized infarct
a	-	Alcoholic
AF	-	Atrial Fibrillation
B	-	Mediun sized infarct
C	-	Large sized infarct
CCF	-	Congestive cardiac failure
DM	-	Diabetes mellitus
Dys	-	Dyslipidemia
D	-	Diabetic ketoacidosis
d	-	Diabetic retinopathy
Ex	-	Expired
F	-	Female
H	-	Essential Hypertension
HbA1c	-	Glycosylated hemoglobin
I	-	Ischemic heart disease
M	-	Male
N	-	Normoglycemia
NIHSS	-	National Institute of Health Stroke Scale
P	-	Pneumonia
R	-	Renal failure
S	-	Smoking
SH	-	Stress Hyperglycemia
Sz	-	Seizures
U	-	Urinary tract infection

MASTER CHART

Sl. No	Name	Age (Years)	Sex	Glycemic Status	Infarct size	NIHSS Score on Admission	NIHSS Score on discharge	NIHSS Score on Day 30	Risk Factors	Motor Deficits	Sensory Deficits	Altered sensorium	Cranial Nerve Involvement	Language Disturbances	Blood Glucose on admission (mg/ dl)	HbA1c (%)	Complications
1	GR	51	M	N	A	11	4	2	H	✓			✓		125	4	
2	SJ	65	M	N	A	20	6		H	✓			✓		89	4.3	
3	SB	55	M	N	A	16	8	2	S	✓			✓		140	5	
4	RT	64	M	N	A	15	6		I	✓				✓	136	5	
5	BP	80	M	N	A	19	8		S	✓			✓		126	4.2	
6	SB	42	M	N	A	10	4		S,a	✓					134	4.1	
7	MK	50	M	N	A	8	4	3	S	✓					130	5.3	
8	MD	54	M	N	A	18	8		H	✓			✓		124	4.2	
9	IK	50	F	N	A	8	4	2	I	✓					121	4.6	
10	BB	80	M	N	B	10	8		S,a	✓			✓		136	4.7	
11	NS	75	M	N	B	14	6	4	S,a	✓			✓		140	4.6	
12	NY	65	M	N	B	15	7		H	✓			✓		139	4.2	P
13	SK	62	F	SH	A	14	7	5	H,I	✓	✓				164	4.2	
14	SS	70	M	SH	A	16	10		S	✓			✓		168	5.2	

Sl. No	Name	Age (Years)	Sex	Glycemic Status	Infarct size	NIHSS Score on Admission	NIHSS Score on discharge	NIHSS Score on Day 30	Risk Factors	Motor Deficits	Sensory Deficits	Altered sensorium	Cranial Nerve Involvement	Language Disturbances	Blood Glucose on admission (mg/ dl)	HbA1c (%)	Complications
15	RH	60	F	SH	A	12	7		I		✓				189	5.4	
16	SH	64	F	SH	B	14	8	4	H	✓					177	6	U,Sz
17	MD	65	M	SH	B	19	12		H,S,a,	✓			✓		198	4.9	P
18	NS	75	M	SH	B	21	16		S,a	✓			✓		181	5	P
19	SN	65	F	SH	B	10	7	5	H,AF	✓					170	4.8	CCF
20	KS	26	F	SH	B	14	8	4		✓		✓			190	5.4	P
21	SS	65	F	SH	B	16	9		H	✓			✓		155	4.5	CCF
22	RM	55	M	SH	B	10	8		Dys	✓					194	5.4	U
23	PM	66	M	SH	B	15	9	7	Dys	✓			✓		153	4	
24	IB	58	M	SH	B	16	12		H	✓			✓		215	4.9	
25	SR	70	F	SH	B	16	11	10	I	✓	✓		✓		215	5.2	U
26	SH	46	F	SH	C	24	7		H,I	✓				✓	243	5.2	
27	SM	65	M	SH	C	23	Ex		H	✓		✓		✓	245	4.9	P,Sz
28	PP	75	M	SH	C	28	Ex		Dys	✓			✓		254	4.6	P
29	SM	50	F	SH	C	20	14	12	AF,H	✓	✓	✓			247	5.8	CCF
30	MK	70	M	SH	C	20	13		S	✓			✓		251	5.1	U

Sl. No	Name	Age (Years)	Sex	Glycemic Status	Infarct size	NIHSS Score on Admission	NIHSS Score on discharge	NIHSS Score on Day 30	Risk Factors	Motor Deficits	Sensory Deficits	Altered sensorium	Cranial Nerve Involvement	Language Disturbances	Blood Glucose on admission (mg/ dl)	HbA1c (%)	Complications
31	SP	42	F	SH	C	23	15		AF	✓		✓	✓		298	5.4	CCF
32	SB	30	M	SH	C	21	Ex		Dys,S	✓			✓		254	5.4	
33	AB	80	M	DM	A	14	12		I,S	✓			✓	✓	190	6	U
34	RD	73	F	DM	A	13	6		I	✓		✓			295	6.4	Sz,D
35	GT	82	M	DM	A	15	5	4	H	✓		✓			200	6.4	U
36	SK	50	M	DM	A	21	16		H,S,a	✓			✓	✓	252	6.4	P
37	BS	55	M	DM	A	18	12		H,I	✓			✓		192	6	CCF
38	BR	52	M	DM	A	18	14		I,S	✓			✓	✓	212	6.1	U
39	SP	75	M	DM	A	12	8		I	✓	✓				197	6.9	
40	BP	55	M	DM	B	14	10		Dys,H	✓		✓	✓	✓	205	7.1	U
41	TN	70	M	DM	B	12	10		H	✓					410	8	U
42	BB	64	M	DM	B	16	11		Dys,H	✓		✓	✓		267	7	d
43	BB	55	F	DM	B	17	11		I	✓		✓			210	7.4	CCF
44	AK	60	F	DM	B	18	12	10	I,a	✓	✓	✓		✓	210	6	Sz
45	LB	55	F	DM	B	22	14	12	Dys,H	✓			✓	✓	232	6.8	U
46	SI	75	F	DM	C	31	Ex		H	✓		✓		✓	250	7.4	P,R

Sl. No	Name	Age (Years)	Sex	Glycemic Status	Infarct size	NIHSS Score on Admission	NIHSS Score on discharge	NIHSS Score on Day 30	Risk Factors	Motor Deficits	Sensory Deficits	Altered sensorium	Cranial Nerve Involvement	Language Disturbances	Blood Glucose on admission (mg/ dl)	HbA1c (%)	Complications
47	SP	64	F	DM	C	26	18		Dys	✓	✓	✓			316	7.8	P
48	SB	74	M	DM	C	20	16	14	S	✓		✓		✓	285	6.9	U,P
49	KR	64	M	DM	C	19	10		Dys,HS	✓		✓			429	7.8	Sz
50	SP	52	M	DM	C	24	16	14	H,S	✓	✓	✓			295	8	U,D,P
51	BW	50	M	DM	C	25	18		Dys,H	✓	✓	✓			284	7.9	P,d
52	SP	64	M	DM	C	29	Ex		I,S,a	✓	✓	✓	✓	✓	192	6.8	R,d
53	SS	50	F	DM	C	28	20	18	Dys	✓	✓	✓		✓	206	7.2	U,d
54	NJ	66	M	DM	C	31	24		H,I	✓		✓		✓	312	6.6	P
55	NJ	80	M	DM	C	34	Ex		Dys	✓		✓	✓	✓	316	7.8	R
56	BY	58	M	DM	C	29	20		H	✓		✓		✓	260	7.1	U
57	SA	58	M	DM	C	29	27		S,a	✓	✓	✓	✓		343	6.8	P
58	SB	60	M	DM	C	20	12		Dys,a	✓		✓		✓	306	6.9	Sz
59	KM	45	M	DM	C	27	Ex		Dys, H,I	✓	✓	✓	✓	✓	295	8	U,P
60	CG	55	M	DM	C	33	25		H	✓	✓	✓			340	7.4	P,Sz