UNIT 1 CEREBRO VASCULAR DISEASES

Structure

1.0 Objectives

1.1 Introduction

1.2 Epidemiology

1.3 Normal Anatomy and Physiology

1.4 Classification

1.5 Ischaemic Cerebro Vascular Diseases

1.6 Aetiopathogenesis and Pathophysiology

1.7 Clinical Features

1.8 Laboratory Evaluation and Other Investigations

1.9 Differential Diagnosis

1.10 Prevention of Stroke

1.11 Treatment of Acute Stroke

1.12 Course and Prognosis

1.13 Let Us Sum Up

1.14 Key Words

1.15 Answers to Check Your Progress

1.16 Further Readings

1.0 OBJECTIVES

After reading this unit, you will be able to:

- define, classify and identify clinical manifestations of stroke;
- evaluate investigations, and risk factors;
- plan prevention and strategies to manage etiology and risk factors; and
- discuss prognosis.

1.1 INTRODUCTION

After reading the previous block, we will now discuss cerebro vascular lesions. Understanding of basic pathophysiology of cerebro vascular lesions have enabled neurologist to approach the problem and treat it more effectively at the molecular level. Imaging modalities like CT, MRI, angiography and 3D CT angiography have been found to be useful in making an early accurate diagnosis. Medical interventions like thrombolysis and cytoprotective measures and surgical interventions such as carotid end arterectomy and other revascularization procedures have helped in prevention of neurological deficit and future recurrences. An attempt has been made to provide information for you to be able to manage stroke and reduce its mortality and morbidity.

1.2 EPIDEMIOLOGY

Stroke is a major cause of morbidity and mortality through out the world with some hard facts about it. It is perhaps the second leading cause of death and third in the United States of America. In the US, an estimated 750,000 stroke cases occur annually. According to the American Heart Association, there are an estimated 4 million stroke survivors and that there is an incidence of one stroke every 53 seconds and one stroke death every 3.3 minutes in the US.

There is lack of reliable information on stroke epidemiology for the Indian subcontinent and its national morbidity or mortality patterns. After an acute attack as many as 30% die in first few days and amongst the survivors, 25% are rendered disabled.

Definitions

The World Health Organization (WHO) defines stroke as *"rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death with no apparent cause other than of vascular origin".*

The definition includes subarachnoid haemorrhage (SAH) but excludes transient ischaemic attacks (TIA), subdural haematomas, or haemorrhage or infarction caused by infection or tumor.

Usually, 'stroke' is defined as a rapid onset of focal neurological deficit over minutes to hours (stroke-in evolution), resulting from diseases of cerebral vasculature and its contents. **TIA implies complete recovery of such a deficit within 24 hours.** The cerebral vessels (extra/intracranial arteries, capillaries, veins and venous sinuses) may show abnormality of their lumen (e.g. narrowing by atheroma etc.) or may be occluded by thrombo-embolism. Among other factors, alterations in viscosity and morphology of blood constituents (red cells, leucocytes, platelets) also contribute to impaired blood flow. Cerebral or subarachnoid haemorrhage is consequent to rupture through some inherent weakness of the vessel wall (e.g. aneurysms, angiomatous malformations) (Table 1.1).

Table 1.1: Various Manifestations of Stroke

1)	Stroke with recovery
	• TIA
2)	Stroke with permanent deficit
	• Ischaemic
	• Haemorrhagic
	• Intracranial
	• Subarachnoid
	• Embolic

1.3 NORMAL ANATOMY AND PHYSIOLOGY

The cerebral circulation is divided into an anterior and posterior circulation (Table 1.2).

Table 1.2: Anterior and Posterior Circulation

• Anterior circulation
– Internal carotid artery and its branches
• MCA : Middle cerebral artery
• ACA : Anterior cerebral artery
• Anterior choroidal artery
• Posterior circulation
– Vertebral artery
– Basilar and Posterior cerebral artery.

The main cerebral circulation is sustained by circle of Willis formed by

- Anterior cerebral arteries and anterior communicating arteries.
- Posterior cerebral arteries and posterior communicating arteries.

The anterior circulation basically supplies majority of cerebral parenchyma except small part of occipital lobe while posterior circulation supplies cerebellum and brain stem.

Collateral arteries play an important role in cerebral circulation. The main ones are as follows: (1) the anastomoses around the orbit, of the branches of the external carotid artery with those of ophthalmic artery; (2) Circle of Willis formed by anterior communicating arteries which

connect the two anterior cerebral arteries and posterior communicating arteries which connect two posterior cerebral arteries; (3) corticopial network.

Physiology of Cerebral Circulation and Cerebral Metabolism

The brain depends on minute to minute supply of oxygenated blood. The normal functions are solely dependent upon a relatively constant supply of oxygen and glucose, as well as other nutrients derived from the blood perfusing it (55 to 70 ml of blood per 100 gm of brain per min). The principal source of energy is almost exclusively derived from oxidation of glucose and it has been estimated that 1500 gm of brain would require uninterrupted supply of 150 gm of glucose and 72 litres of oxygen per 24 hours. Constancy of cerebral circulation is maintained by a series of baroreceptors and vasomotor reflexes under the control of lower brain stem. Cerebral blood flow (CBF) is directly proportional to the arteriovenous pressure gradient, which reflects general hemodynamic parameters (heart rate, blood volume etc.); and is inversely proportional to the resistance to blood flow. If for any reason, the CBF is critically reduced below the threshold of 23 ml/100 gm/min (e.g. systemic hypotension, occlusion of major artery, etc.), and if after a short period of time, is restored to level above 23 ml, the impairment of functions are restored. *A fall of CBF below 8.0 to 9.0 ml/min results in ischaemia or infarction regardless of duration*. The state of hypo perfusion of the brain (*CBF between 8 to 23 ml/100 gm/min*) is called the **'ischaemic penumbra'**.

The mean arterial blood pressure, cerebrovascular and tissue resistance, local metabolic products (pH, PaO_2, $PaCO_2$ tension etc.) together with several known and unknown factors, help to maintain the critical threshold of blood flow for energy and metabolism. Furthermore, cortical blood flow varies in different areas of the brain and a self regulatory mechanism ('auto regulation') determines the regional flow to meet local metabolic needs. For example, with an increase in partial pressure of CO2, the arterioles dilate to increase blood flow and vice versa. The precise role of vasoconstrictor (sympathetic) and vasodilator nerve impulse in the regulation of vascular tone and local blood flow is much debated, but circulating neurochemical transmitters (serotonin, catecholamines, etc.) do modify the local needs.

Conversely, in the region of cerebral ischaemia, there is **'paralysis of auto regulation'** and the microvasculature is non-reactive to pressure change, to vasoactive agents and to other forms of stimuli. The cerebral vasculature in this ischaemic zone becomes permeable to protein and fluid leaks in the vicinity (extra-cellular cerebral edema). Such events also lead to local hemoconcentration and vascular stasis. Thus, cerebral infarction is not the mere result of ischaemia from occluded blood vessels (e.g. cerebral thrombosis or embolism), but an end result of a series of highly complex ischaemia modifying events.

To protect the brain from such haemodynamic ischaemic insult, nature has provided additional collateral pathways. Collateral circulation, described earlier, provides blood supply of good caliber with low resistance. In addition, extra cranial anastomoses between the cervical branches of the ipsilateral external carotid, subclavian and vertebral arteries have also been identified. Such **pre-Willisian arterial anastomoses** help to maintain cerebral blood supply in individuals even with occlusion of a major artery in the neck. Likewise, large precapillary anastomoses exist between the anterior, middle and posterior cerebral arteries and various cerebellar arteries. Such **post-Willisian anastomoses** further protect cerebral tissue from the effects of occlusion of single cortical branches. **Thus, in an individual with symmetrical circle of Willis, despite major extra cranial arterial occlusions, sufficient blood may still reach the territory through the collateral to prevent on-coming cerebral ischaemic insult.** On the other hand, in presence of generalized arterial disease (atherosclerosis), congenital variations and multiple skipped stenotic lesions, these collateral pathways prove inadequate in maintaining normal blood flow and predispose to cerebral ischaemia or infarction.

Some infarcts are devoid of blood and, therefore, pallid (pale infarct) whereas other show mild congestion, especially at their margins; and still others show an extensive extravasation of blood from many small vessels in the infarcted tissue (red or haemorrhagic infarct). In haemorrhage, blood leaks from the vessel directly into the brain, ventricles or subarachnoid space. Once this is arrested, blood slowly disintegrates and is absorbed over weeks and months. Mass of blood clot can cause physical disruption of tissue and pressure on the surrounding structures.

Risk Factors

Table 1.3: Risk Factors

- Modifiable
  1) Hypertension
  2) Diabetes mellitus
  3) Smoking
  4) Obesity
- Non-modifiable
  1) Age
  2) Sex

Most important risk factors (RF) (Table 1.3) are hypertension and diabetes mellitus, which are held responsible for hastening the atherosclerotic process in both the large and small arteries. Furthermore, hypertension is the most important risk factor in the genesis of primary intracerebral haemorrhage; and numerous studies indicate that long-term control of hypertension decreases the incidence of atherothrombotic cerebral infarction and intracerebral haemorrhage. Heart diseases especially heart failure, myocardial infarction/coronary artery disease play a major role. Tobacco smoking, obesity, hyperlipidaemia, altered blood viscosity etc. are also considered to be important risk factors for strokes. Cerebral embolism is usually secondary to structural cardiac disease and arrhythmias.

1.4 CLASSIFICATION

After going through the physiology of cerebral circulation, the strokes are classified as follows (Table 1.4) :

Table 1.4: Classification of Strokes

I) **Ischaemic Strokes**

With Cerebral Infarction

1) Cerebral thrombosis with or without atherosclerosis
2) Cerebral embolism (congenital and acquired valvular disease, cardiomyopathy, myocardial infarction, endocarditis, prolapsed mitral valve etc.
3) Lacunar strokes (deep, small cerebral infarcts)
4) Cerebral venous thrombosis and cortical thrombophlebitis
5) Artheritis (syphilitic, tubercular, rheumatic, Takayasu's disease, collagen diseases etc.)
6) Blood disease (polycythemia, sickle cell anaemia, thrombotic states, hyperproteinemia etc).
7) Arterial hypotension and anoxic encephalopathy
8) Dissecting aneurysms of brachio-cephalic vessels
9) Angiographic complications
10) Infarction of undermined cause

With Cerebral Ischaemia

1) Transient ischaemic attacks (platelet-fibrin micro emboli associated with atheroma etc.)
2) Arterial hypotension or haemodynamic crisis (e.g. massive gastro-intestinal bleeding).
3) Cardiac arrhythmias (atrial fibrillation, complete heart block or sick-sinus syndrome etc.)
4) Migraine
5) Local embolism from atherosclerotic plaque and paradoxical embolism
6) Miscellaneous (e.g. drugs and oral contraceptives, disseminated intravascular coagulopathy, cerebral malaria, Behcet's syndrome, congophilic angiopathy, homocystinuria, hyperviscosity syndrome, paraproteinemia, etc.)

II) **Haemorrhagic Strokes**

1) Hypertensive cerebral haemorrhage
2) Ruptured aneurysm (saccular, mycotic etc.)

3) Ruptured angioma (arterial, venous or mixed)

4) Trauma

5) Blood dyscrasias (leukaemia, purpura, hyperviscosity syndrome and other bleeding diasthesis)

6) Complication of anticoagulant therapy

7) Bleeding in brain tumours

8) Miscellaneous causes (arteritis, bleeding in haemorrhagic infarct, etc.)

9) Undetermined source (normal blood pressure without aneurysm or arteriovenous malformation)

10) Rare types (after vasopressor therapy, on exertion, arteriography)

III) **Strokes of Undetermined Origin**

1) Moyamoya disease

2) Fibromuscular dysplasia

3) Binswanger's subcortical arteriosclerotic encephalopathy

4) Leukoariosis

5) Buerger's disease (Thrombo-angitis obliterans—cerebral form)

6) Aortic arch syndrome (non-inflammatory)

Check Your Progress 1

1) Define Transient Ischaemic Attack (TIA).

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2) Enumerate type of stroke with permanent deficit.

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3) What are the important risk factors responsible for atherosclerosis and stroke?

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1.5 ISCHAEMIC CEREBROVASCULAR DISEASES

If for any reason, such as cardiac arrest or prolonged hypotension (below 70 mm Hg), the brain tissue is significantly deprived of its nutrition for more than three minutes, death of brain parenchyma (cerebral infarction) ensues. The sylvian region is commonly involved in middle cerebral artery occlusion ***(mid-field infarct)***, whereas with the internal carotid artery lesion, the cerebral infarction is mostly located in distal or watershed territory ***(end field infarction).*** A 'mid-field' infarct produced by occlusion of a small penetrating vessel with poor collateral circulation in the neighbourhood pathways, may prove catastrophic, whereas an 'end-field' infarct resulting from occlusion of a major vessel in the neck (e.g. carotid artery block), with good collateral circulation, may be asymptomatic. Obstruction to venous return can also result in infarction (e.g. cerebral venous thrombosis). Acutely infarcted brain tissue is soft and swollen, frequently herniates downwards and may compress the vital centres within the brain stem, ending in a fatal outcome. Like infarction elsewhere in the body, cerebral infarcts heal by gliosis (fibrosis). It is frequently replaced by a firm scar or a cystic cavity. It must, however, be appreciated that transient cerebral ischaemia may not leave any trace of identifiable cerebral damage by conventional tests.

1.6 AETIOPATHOGENESIS AND PATHOPHYSIOLOGY

Cerebral infarction is usually attributed to partial/total occlusion of its regional microvasculature by thromboembolism. Cerebral atheroma is by far the most common underlying intimal vascular pathology.

Recent studies on molecular and metabolic events leading to infarction have shown that there is a dense central core surrounded by a less dense zone of ischaemia ('penumbra'), and neuronal death occurs in this central focus unless perfusion is quickly restored. On the other hand, cells in the zone of penumbra remain viable for at least three hours ('therapeutic window') and can be salvaged by reperfusion, neuroprotective agents, etc. to prevent further damage. Major factors, which enhance nerve cell injury are intracellular failure of ionic pump functions or 'leaks', changes in Na/K gradients, acidosis, the release of free radicals and other unknown factors, which in turn disrupt blood brain barrier (BBB) and the microvascular function. Here, energy depletion from brain hypoxia is one of the key events that fails to maintain normal concentrations of cellular adenosine triphosphate (ATP), leading to delay in re-synthesis of macromolecular proteins essential for cell structure. Such energy failures also induce proteolysis and lipolysis, in addition to production of arachidonic acid and platelet activating factors, free radicals etc. resulting in further neuronal damage **(ischaemic cascade hypothesis)**. Thus, the severity of cerebral infarct is not the mere result of ischaemia from occluded vessels but the end result of several highly complex **'ischaemia-modifying factors'**. The precise role of leukocyte-endothelial interactions, receptor activation, post-ischaemic hypo/hyper perfusion injuries, nitric oxide, nerve growth factors and gene expression are under study.

1.7 CLINICAL FEATURES

Obesity, feeble to absent or unequal peripheral arterial pulsations, vascular bruits, raised blood pressure, postural hypotension and retinopathy may be detected on a general physical examination.

Before a thrombotic lesion becomes manifest, in about 60 per cent of the subjects, prodromal warning symptoms may precede an oncoming insult. These episodes of TIA are usually brief (lasting for a few minutes to less than an hour) and may come on singly or in successive spells over a number of hours, days or months but usually leave no significant residual signs. These TIAs, which may come at any time to the day or night and which do not appear to be related to posture or the level of blood pressure, may resolve altogether. In some cases, an evolving or a full blown stroke follows the last ischaemic spell. Haemodynamic crisis, disturbances in haemostasis, failure of collateral circulation and other 'ischaemia modifying factors' have been considered as alternative possibilities for stroke where no source of embolisation (heart, atheromatous plaques in aorta or its branches) has been found after complete investigations.

When the stroke evolves in a stepwise manner (thrombus in evolution) the symptoms may appear in each limb in succession or simultaneously. This stuttering, intermittent progression, rather than a slow gradual onset, is very typical of cerebral thrombosis. Not infrequently, the stroke may announce itself abruptly as a single major catastrophic event (accomplished infarction or completed stroke). The other clinical manifestations depend on the site of the arterial occlusion. The specific neurovascular syndromes which may result, are described below:

Internal Carotid Syndrome

The cervical portion of the internal carotid artery, near the carotid sinus is a common site for both severe atheroma and thrombotic occlusion. About 30 per cent of all occlusive lesions are located in this segment. Many of these lesions may be silent or asymptomatic and sufficient blood reaches the occluded territory through the external 'carotid-ophthalmic' anastomosis or from superficial and deep cervical anastomoses or from the opposite carotid artery through the anterior segment of the circle of Willis.

In symptomatic carotid thrombosis, *'warning symptoms' precede a major insult in 50 per cent of the subjects*. These symptoms include brief episodes of confusion, difficulty with speech (aphasia, dysarthria, dyslexia) and paraesthesia, with or without motor weakness of the opposite side. Ipsilateral 'amaurosis fugax' (transient monocular blindness) fleeting or semi-permanent hemiplegia or hemisensory deficit is pathognomonic of a carotid artery syndrome. However, it is noted in only 15 to 20 per cent of the subjects.

The carotid occlusions are almost indistinguishable from those of a middle cerebral syndrome. Feeble internal carotid or superficial temporal artery pulsations, dilated pupil, poorly pulsating retinal vessels (with or without optic atrophy) on the side of suspected carotid lesion and ocular or cervical bruits on the ipsilateral side may suggest the correct diagnosis. Carotid Doppler sonography or angiography are of great help for an accurate diagnosis; and also to ascertain the degree of stenosis and the collateral flow.

In subjects with an old or silent occlusive carotid axis lesion on one side, a 'new' lesion on the other side may prove catastrophic. Here, the physical findings of a bilateral hemiplegia (quadriplegia) with coma can be easily mistaken for a basilar artery syndrome.

Anterior Cerebral Syndrome

The cortical branches mainly supply the medial and superior surface of the frontal lobe and the parietal lobe up to the paracentral lobule. The penetrating branches supply the anterior limb of the internal capsule and part of the head of the caudate nucleus.

An anterior cerebral occlusion proximal to the anterior communicating artery, in subjects with a symmetrical circle of Willis, is frequently asymptomatic. An occlusion, distal to the anterior communicating artery, manifests itself by a sensory-motor paralysis of the opposite lower extremity, with mild weakness of the opposite shoulder. Mental changes, rectal and urinary incontinence, gait disturbances, apraxia, grasp and sucking reflexes may accompany the above findings.

Occlusion of an unpaired anterior cerebral artery (supplying both the hemispheres) results in a *cortical type of paraplegia*, with sphincter incontinence and a mental state in which the patient is alert but mute (akinetic mutism). Aphasia and hemianopia are never seen.

Occlusion of the penetrating branches of the so called Heubner's artery is frequently blamed for ataxic tremor of the contralateral limbs. Frontal ataxia, apraxia (ideomotor dyspraxia) of the limbs and gait may also be present.

Middle Cerebral Syndrome

The cortical branches supply most of the lateral surface of the cerebral hemisphere, except for the regions supplied by the anterior and posterior cerebral arteries. The areas include sensory-motor cortex, motor and sensory speech centres, auditory area and visual radiation. The penetrating branches (lenticulostriate arteries) supply the putamen, globus pallidus, genu and posterior limb of the internal capsule.

The clinical picture of middle cerebral artery occlusion is variable. Contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia and aphasia (dominant and non-dominant) is the common outcome. However, occlusion of upper division results in contralateral hemiparesis with sensory deficit and expressive aphasia (Broca's aphasia) whereas Wernicke's aphasia is commonly seen with occlusion of the lower division on dominant side. Even monoplegic symptoms can occur with occlusive lesions of single cortical branches.

Occlusion of penetrating branches (lenticulostriate arteries) have been repeatedly blamed for a dense sensorimotor hemiplegic syndrome ("capsular hemiplegia") but with such an occlusion, significant sensory loss seldom occurs, whereas 'pure motor hemiplegia' is not uncommon.

Posterior Cerebral Syndrome

This artery supplies the medial and inferior portions of the occipital and temporal lobes. Its branches also supply the mid-brain, cerebral peduncle and most of the thalamic and sub thalamic regions.

Thrombotic occlusions of the posterior cerebral arteries are relatively rare. A contralateral homonymous hemianopia is the most significant finding and this results from infarction of the primary visual area (calcarine cortex); the central vision is frequently spared, even in cases with bilateral disease **(gun-barrel vision).** Other manifestations of visual dysfunction include illusory or distorted vision, visual-object agnosia and various forms of dyslexia with dysgraphia. The pupillary reflexes are preserved. A contralateral hemiplegia from lesion of the cerebral peduncle (peduncular hemiplegia) and thalamic syndrome (Dejerine and Roussy syndrome) may also be present. In the thalamic syndrome, there is varying degree of sensory loss to all modalities and spontaneous burning or agonizing pains are frequent (analgia dolorosa). Memory loss (amnesia) denotes a lesion of the medial temporal cortex. Contralateral involuntary choreoathetosis or ataxic tremors are rarely observed.

Vertebro-basilar Syndrome

Both vertebral arteries, after traversing through the bony vertebral canal, unite intracranially to form the basilar trunk. Their short para median and long circumferential branches supply the entire brain stem, cerebellum and the vestibular apparatus. Ischaemic disorders, therefore, manifest by episodes of vertigo, dizziness, diplopia, dysarthria, dysphasia, incoordination of the gait and limbs and bilateral signs of sensori-motor deficits. Occipital headaches may be present.

Ipsilateral 3rd nerve palsy (dilated pupil, ptosis and external strabismus) with contralateral hemiplegia (Weber's syndrome) or with crossed cerebellar ataxia (Claude's syndrome) is diagnostic of mid-brain localisation. Homolateral paralysis of the 6th (abducens) and 7th (facial) nerves (internal squint and facial palsy) with contralateral hemiplegia and hemianaesthesia (Millard-Gubler syndrome) is suggestive of a pontine lesion. Palatal paralysis and ataxia of limbs, with impairment of posterior column sensations on one side of the body, together with diminution of pain and thermal sense on the opposite limbs (Wallenburg's syndrome) indicates a lateral medullary infarction.

Not infrequently, quadriplegia with a bilateral conjugate, lateral gaze and de-efferented and mute state have been described (locked-in syndrome), suggestive of infarction of basal points (sparing tegmentum) from mid basilar occlusion.

Occlusion of isolated cerebellar branches may produce dizziness, nausea, vomiting, nystagmus, appendicular or truncal ataxia without sensory-motor deficit in any limb. Such a syndrome should be differentiated from cerebellar haemorrhage where emergency surgical decompression proves life saving.

1.8 LABORATORY EVALUATION AND OTHER INVESTIGATIONS

After detailed history and meticulous neuromedical examination including palpation and auscultation of brachiocephalic and peripheral pulses, the relevance and priority of any laboratory test in acute stroke should be the clinicians' judgement. The value of careful ophthalmoscopic examination of retina and its vasculature for disease and embolic fragments needs greater emphasis. Often, stroke subjects are rushed for treatment with CT scan in absence of valuable clinical data.

According to American Heart Association (AHA) guidelines, all patients with stroke should have following investigations:

Routine haematological tests

Complete Blood cell count

Platelets count

Prothrombin time

Partial Thromboplastin time

Serum Electrolytes and Glucose

Renal panel

Hepatic panel

Routine diagnostic tests

Electrocardiogram

Chest radiograph

In addition EEG may be required if seizure is suspected to be the cause of altered consciousness.

Special tests for detection of sickle cells, LE cells, RA test or protein electrophoretic pattern are performed when indicated. 2-D Echo or holter monitoring should be done only when required. Examination of cerebrospinal fluid (CSF), within 7 days of ictus, is very helpful in diagnosis of 80 per cent of haemorrhagic strokes and nearly 90 per cent of subarachnoid haemorrhage (SAH) cases.

Computerized tomography (CT) is a single most important non-invasive investigation to distinguish an infarction from cerebral hematoma. This modality is almost 100% sensitive for diagnosis of intracranial haemorrhage.

The precise role of newer neuroimaging tests like magnetic resonance imaging (MRI) and positron emission tomography (PET) are also helpful in visualizing hypoxic lesions producing TIA/RIND which are often missed by CT scan. Peri-infarct parenchyma which appears normal on CT scan often shows abnormality on MRI; and ischaemic/demyelinating lesions or ischaemic penumbra surrounding the lesions can be differentiated. MRI has structural advantage over CT, the most important being clear identification of structures in the posterior fossa, brain stem infarction, especially lacunes. Angiography remains the gold standard for assessment of CBF. Digital subtraction angiography (DSA), by intravenous route, not only outlines the entire brachio-cephalic circulation but is considered relatively safe and non-invasive procedure. Unfortunately, it has failed to give clear-cut definitions of abnormalities

as visualized (e.g. atheromatous plaques), and many centers have now reverted to intra-arterial DSA, by selective catheterization, to study the areas of interest, mainly for symptomatic carotid artery stenosis. Duplex carotid scanning and MR angiography are other valuable scanning procedures.

1.9 DIFFERENTIAL DIAGNOSIS

Prodromal warning symptoms, abrupt onset of a focal neurological deficit, stuttering or intermittent progression, a constellation of symptoms and signs diagnostic of a well defined neurovascular syndrome, clear CSF, some degree of recovery and evidence of vascular disease elsewhere in the body (absent carotid pulsations or bruits over the major vessels, history of angina pectoris, myocardial ischaemia or a previous stroke, arrhythmia, intermittent claudication in the legs with feeble pulses is highly suggestive of stroke.

Bogousslavsky *et al* reported 1000 consecutive patients with cerebral infarction or haemorrhage. Headache was a presenting complaint in 51% of non-comatose patients with haemorrhage but also occurred in 16% of those with infarction. Pure motor hemiparesis was present in 49% of patients with infarction compared with 17% of the patients with haemorrhage. Pure sensory symptoms were rare. Language disturbances occurred in both group of patients but isolated Wernicke's aphasia or Wernicke's aphasia with hemianopia was rare in those with haemorrhage. Progressive neurological deficit and decreased consciousness were most common in patients with haemorrhage (52% and 50%, respectively) but also occurred in patients with cerebral infarction (26% and 11%, respectively). This suggests that although the history and physical examination often suggests the correct diagnosis, enough overlap exists so that diagnostic imaging should be performed in all cases of suspected stroke.

In distinguishing cerebral haemorrhage from cerebral infarction the following collective criteria, though not always diagnostic, may prove helpful in suspecting an intracerebral bleed. These are: (i) moderately severe to intense headache (throbbing, pulsating or pounding) in a known hypertensive subject, accompanied by nausea and vomiting; (ii) altered state of consciousness (drowsiness progressing to deepening coma) with irregular respiration; (iii) neck stiffness accompanied by dissociated eye movements, or forced gaze deviation; (iv) blurred disc margins or pre-retinal haemorrhage, with changes suggestive of hypertensive retinopathy; (v) hemiparesis on one side with shivering movements or even frank convulsions on the non-paralysed side, or quadriparesis with an extensor plantar response on both sides, etc. The blood in CSF will help to settle the diagnosis.

However, haemorrhagic cerebral infarction in a hypertensive subject and occult intracerebral bleed (hematoma or slit haemorrhage) may even show a clear CSF at onset, and here the value of urgent CT scanning to arrive at a diagnosis cannot be ignored. It should be noted that immediate mortality from massive cerebral infarction is in the range of 30 per cent, and nearly 30 per cent survive from small intracerebral bleed. Therefore, another CSF examination on the third or fourth day may reveal slight xanthochromia. On the other hand, embolic haemorrhagic cerebral infarction and a leaking intracerebral bleed may show blood-stained CSF and an angiographic examination as well as a CT scan may prove very useful in arriving at a diagnosis. Other investigations are of little diagnostic help.

Subdural hematoma and other mass lesions (e.g. intracerebral hematoma, brain tumor, brain abscess, etc.) may mimic a stroke. Here, a clinical history of headaches or seizures, papilloedema, raised spinal fluid pressure and xanthochromia with elevated protein, midline shift or a calcified pineal gland (when present) on skull X-rays, high voltage slow waves on EEG and abnormally high local concentration of radio-isotope in brain scan, all point to the true nature of the lesion. Cerebral angiography helps to settle the diagnosis, whereas isodense subdural hematomas may be misdiagnosed as infarct on CT scan. A history of head injury, careful cranial examination for marks of injury, a blood stained CSF and characteristic X-ray findings (e.g. fracture) easily differentiate post traumatic conditions from strokes. When depressed consciousness occurs without an adequate history, the differential diagnosis may also include metabolic abnormalities (hypoglycemia, electrolyte imbalance, thiamine deficiency), toxic ingestion, endocrinopathy, seizure or psychiatric disorder.

Post-epileptic hemiplegia (Todd's paralysis) with complete recovery may simulate transient cerebral ischaemia. Clinical history suggestive of seizure disorders with EEG abnormalities in a young subject proves helpful in arriving at a correct diagnosis. Posterior fossa tumors, the administration of sedatives or tranquillizers, multiple sclerosis, vestibular disorders and hysteria may simulate vertebro-basilar artery disease, but seldom present diagnostic problems. Here,

meticulous history with serial clinical observations proves more helpful rather than fancy tests including a CT scan.

Check Your Progress 2

1) Describe clinical features of middle cerebral syndrome.

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2) Which is gold standard assessment for cerebral blood flow (CBF)?

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1.10 PREVENTION OF STROKE

During the past five years, important results in an unprecedented number of clinical trials have refined the approach to stroke prevention. Stroke prevention is cost-effective and often cost-saving. Most strokes can now be prevented using proven interventions, but the challenge remains to apply these treatments effectively in clinical practice.

The primary aim of prevention is to identify and modify treatable risk factors like diabetes, hypertension, heart disease and smoking. Patient should be advised to take a low animal fat diet, reduction in dietary salt, avoid alcohol consumption and moderate exercise.

Etiology and Risk Factor Management

Stroke is a heterogeneous syndrome in which multiple disorders can lead to occlusion or rupture of blood vessels supplying the brain. Optimal prevention depends on identifying the specific cause of threatened stroke. Severe cervical carotid artery stenosis is present in about 15 per cent of patients with brain ischaemia.

Isolated Systolic Hypertension: Treatment of isolated systolic hypertension in the elderly reduces the risk of stroke and is generally well tolerated if carefully administered. A recent large, randomized trial showed that the benefits of treatment can be achieved with dihydropyridine calcium channel blockers and angiotensin-converting enzyme inhibitors. Treatment also reduces the incidence of congestive heart failure and other cardiovascular events.

Cholesterol Reduction with Statin Drugs: At present, the value of cholesterol reduction with statins to prevent stroke has not been established specifically by clinical trials for patients with threatened stroke. Nonetheless, the use of statins in patients with cerebral ischemia to prevent myocardial infarction and vascular death is often clinically indicated. There is growing consensus for the use of statins in the primary prevention of stroke but final recommendations are yet to come.

Homocysteine: Elevations of serum total homocysteine levels have been correlated with risk for myocardial infarction and ischemic stroke, especially in middle-aged persons. Because small doses of folate correct the abnormality, there is considerable interest in this easily treatable potential risk factor for stroke.

Antiplatelet Therapies

In the medical therapy for secondary prevention, antiplatelet agents have important role. Aspirin and ticlopidine are widely recognized as being effective for prevention of recurrent stroke in patients with TIA or ischemic stroke. Two additional antiplatelet therapies for stroke prevention have recently emerged: clopidogrel and high-dose dipyridamole. **Other new antiplatelet agents**, such as the oral glycoprotein-IIb/IIIa inhibitors triflusal and indobufen, have not yet been adequately tested in patients with threatened stroke because of cerebrovascular disease.

Aspirin: Most clinicians prescribe 325 mg per day. The U.S. Food and Drug Administration recently recommended that aspirin dosages between 50 and 325 mg per day be used for stroke prevention.

Ticlopidine: Ticlopidine is given in a dose of 250 mg twice a day.

Monitoring of the white blood cell count is required every two weeks during the first three months of therapy with ticlopidine to detect leukopenia, which occurs in 1 to 2 per cent of recipients; skin rash and diarrhoea preclude continued use of ticlopidine in about 15 per cent of patients. Because of these potential side effects, most clinicians reserve ticlopidine for use

in patients who experience cerebral ischemia while they are taking aspirin or for aspirin-intolerant patients.

Clopidogrel: Clopidogrel, a congener of ticlopidine is given in dosage of 75 mg per day The toxicity of clopidogrel in a dosage of 75 mg per day was comparable to that of aspirin in a dosage of 325 mg per day, with no increase in leukopenia. Clopidogrel is considered to be second line treatment in patients intolerant for aspirin and first line treatment for patients with stroke and peripheral arterial disease. The main hinderance to its use is its cost.

Dipyridamole: Dipyridamole combined with aspirin was widely used in the early 1980s for stroke prevention, until critical analysis cast doubt on its efficacy. A recent large European randomized trial found high-dose dipyridamole (200 mg twice daily, in a sustained-release preparation) plus aspirin (25 mg twice daily) to be superior to aspirin alone, with a 21 per cent risk reduction relative to aspirin (P=0.006). Efficacy of four antiplatelet agents are given in Table 1.5. Aspirin is recommended as first-line antiplatelet therapy, reserving clopidogrel for "aspirin failures" or aspirin-intolerant patients.

Table 1.5: Antiplatelet Therapies for Stroke Prevention: Estimates of Comparative Efficacy

Agents	Dosage	Stroke	
		Relative risk reduction versus placebo (%)	NNT versus aspirin*
Aspirin	75-1300 mg/day	25	
Ticlopidine	250 mg twice daily	25-40	~80
Clopidogrel	75 mg/day	30	~250
Dipyridamole: With Aspirin	200 mg twice daily	35-40	~80

* NNT versus aspirin — the number needed to treat with the agent instead of aspirin for one year to prevent one stroke. A stroke rate of 8 per cent per year was used for these calculations

Role of Anticoagulation

Warfarin: Available antiplatelet agents offer only partial protection against strokes (i.e., 25 to 40 per cent risk reduction), and more efficacious antithrombotic agents would be useful. However, anticoagulation with warfarin has not been established as beneficial for patients with TIA or ischemic stroke caused by common cerebrovascular diseases. In contrast, warfarin is highly efficacious for prevention of stroke in patients with cardioembolic causes of brain ischaemia. Some clinicians advocate the use of warfarin for patients with inoperable symptomatic carotid stenosis, intracranial atherosclerotic stenosis or "antiplatelet failures".

Clinical trials continue to demonstrate important benefits of warfarin (target INR: 2 to 3) for primary and secondary stroke prevention in high-risk patients with nonvalvular AF. Adjusted dose warfarin therapy reduces the risk of stroke in patients with AF by about two thirds. Aspirin therapy for preventing stroke in AF patients reduces strokes by about 20 per cent.

There are various surgical measures besides medical therapy, these include carotid end-arterectomy and intracranial-extracranial anastomosis to prevent stroke.

1.11 TREATMENT OF ACUTE STROKE

The treatment of stroke has been revolutionised in the last two decades, comprising various newer investigative and therapeutic modalities have made it possible to treat actively and reduce the mortality and sequaelae associated with stroke. Medical treatment includes the treatment for hypertension, the treatment of acute neurological complication and specific medical therapy.

Supportive care

The initial evaluation of the patient with ischaemic stroke should identify any critical areas that need to be immediately addressed. The ABC – airway, breathing and circulation – are functions that may require immediate attention and support. There is a general agreement in the AHA guidelines to recommend airway support and ventilatory assistance in patients with a depressed level of consciousness; and supplemental oxygen to hypoxic patients.

Elevated Blood Pressure: Unless systolic blood pressure exceeds 220 mm Hg or diastolic

pressure exceeds 120 mm Hg (sustained on repeated measurement), elevated blood pressure should not be treated within the first days after ischemic stroke. The ischemic penumbra loses autoregulation, and perfusion is directly linked to mean arterial pressure. Acute elevations in blood pressure are often transient, and spontaneous declines are common. Overzealous treatment of hypertension following acute ischemic stroke can convert the ischemic penumbra into an infarct. The two exceptions to this general recommendation are as follows: (1) after use of tissue plasminogen activator (t-PA), blood pressure should be maintained below 185/110 mm Hg, and (2) in the presence of myocardial infarction, heart failure or aortic dissection, elevated blood pressure should be treated aggressively. If antihypertensive therapy is necessary, agents that have a rapid onset and predictable response should be used.

Fever: In patients with acute stroke, fever is not uncommon. Whatever the cause, fever should be suppressed in these patients. In experimental models of brain ischaemia as well as in clinical studies, even mild elevations in body temperature consistently worsen the neurologic outcome from ischaemic insults.

Hyperglycemia: In the setting of acute stroke, hyperglycemia may be deleterious to the ischemic penumbra by permitting anaerobic metabolism with the creation of local lactic acidosis. It has not been shown that control of glucose improves stroke outcome in humans; however, based on observational and experimental studies, the general consensus is that glucose levels should be kept below 150 mg per dL (8.3 mmol per L).

In the treatment of acute neurological complications measures are taken to control the brain oedema, maintain adequate cerebral perfusion and to prevent brain herniation. The initial treatment for brain oedema includes fluid restriction, treatment of hypoxia and head end elevation by 20×30° later on if there is deterioration in the condition then patient may be treated by osmotic diruretics (Mannitol, Glycerol) and by ventilatory support. Corticosteroids do not have role in the management of cerebral oedema. Convulsions are usually treated with parenteral anticonvulsant drugs like Epsolin and calmpose.

Patients are usually observed for haemorrhagic transformation of infarcts and CT head can give reliable information.

Pharmacologic Interventions

Improved outcome with the use of intravenous thrombolysis is perhaps the most important advance that has been made in the care of patients with ischemic stroke. More than two dozen agents and interventions are currently undergoing clinical testing for use in the treatment of acute ischemic stroke. The only specific intervention validated by adequate clinical trials and labeled for this use by the U.S. Food and Drug Administration (FDA) is t-PA (given within three hours of stroke onset). However, the results of ongoing clinical trials may soon expand available therapeutic options.

Thrombolytics

Thrombolytic therapy had been a subject of controvery because of high incidence of intracerebral haemorrhage. The current American recommendations are to treat selected patients with t-PA (tissue plaminogen activator). It has been shown that its use within three hours of ischaemic stroke onset, there was substantial improved long-term functional outcome in these cases if given within three hours of ischaemic stroke onset. Intra-arterial delivery of thrombolytic agents has been tried in the carotid and the vertebrobasillar circulation but no good results. Over all benefits by streptokinase, Aspirin and Heparin in treatment of acute ischaemic strokes did not show promising result.

Cytoprotective Agents: These agents increase the tolerance of neurons to ischemia and have shown promising results in experimental models. None, however, has been shown to be beneficial in adequate clinical trials to date. Various potentially neuroprotectants are:

Sodium /Calcium Channel modulators: Fos-phenytoin, Nimodipine, 8W6 19C 89, Lifarzine.

NMDA antagonists: Competetive–Selfotel, Eliprodil and Noncompetitve–Cerestat, Remacemide desglycine.

Energy restorers: Piracetam

GABA Agonists: Clomethiazole

Miscellaneous actions: Lubeluzole

Large trials testing citicoline and clomethiazole should be completed soon. These agents appear to be safer than fibrinolytic therapies and may have a longer time window for efficacy.

Among all the neuroprotective agents, calcium channel antagonists have shown promising beneficial agents. Nimodipine is the widest compound used, produces less symptoms of hypotension, fewer cardiac inotropic and chronotropic effects and has better penetration into the brain and brain vessels. The dosage ranged from 60-240 mg/day. The greatest benefit was seen in patients within 12 hours of onset of stroke in patients within 12 hrs of the onset of stroke.

There are certain complications related to stroke. These include pneumonia because of aspiration, urinary tract infection due to catheter, venous thrombo embolisium and pressure sores, these should be adequately treated.

Check Your Progress 3

1) Enumerate Antiplatelet drugs.

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2) What are the surgical measures used in stroke?

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3) Enumerate agents used as cytoprotective agents.

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4) Name one thrombolytic agent used in acute stroke.

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1.12 PROGNOSIS

In subjects who survive, some degree of recovery is the rule. Chances of significant recovery are remote when no improvement is noted within the first 6 to 8 weeks. About 20 to 25 per cent of the subjects with massive cerebral infarction and brain swelling die during acute phase. Here, old age, presence of severe neurological deficit with coma and pyrexia, intercurrent infections, and basilar artery thrombosis are of grave prognostic significance. Recurrent episodes are frequent, but there is no way to predict the same in a given subject. However, *control of 'risk factors' is beneficial.*

Management of Haemorrhagic Stroke

No specific strategies have been found useful in improving the prognosis except treatment of bleeding disorder. 70% die of hypertensive intracerebral haemorrhage. The size and location of the haematoma determine the prognosis. General management is basically the same as in ischaemic stroke.

1.13 LET US SUM UP

Stroke is one of the leading cause of death and disability and community surveys from different regions of India reveals incidence from 44-842,000 per 100,000 persons. After an acute attack as many as 30% die in first few days and 25% are rendered disabled amongst the survivors. Various risk factors like Hypertension, Diabetes mellitus, smoking and obesity have been implicated in causation of stroke. Diagnosis is based on good clinical history, precise neurological examination with laboratory evaluation including CT Scan, MRI and angiography (both Magnetic resonance and catheter angiography). Management of acute strokes has improved because of early reporting of cases, more availability of acute care, trial of thrombolytic therapies during and after lapse of therapeutic windows, better management of cerebral oedema and therapies by newer neuroprotective agents. Neuroimaging has helped to

predict the future outcome, and cerebral oedema and preventive therapy in need based cases. The role of surgery for ischaemic lesions as well as for vasoocclusive disease is now well established which includes end-arterectomies, various by-pass surgeries, thromoboctomies and revascularisation procedures.

1.14 KEY WORDS

Internal carotid syndrome : Atheroma and thrombotic occlusion of cervical portion of the internal carotid artery leading to symptoms of difficulty with speech and paraesthesia, with or without motor weakness of the opposite side.

Middle cerebral syndrome : Contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia and aphasia contribute part of syndrome.

Mid-field infarct : Occulation of middle cerebral artery in sylvian region.

Transient Ischaemic Attack (TIA) : Sudden onset of focal neurological deficit over minutes to hours and complete recovery within 24 hrs.

Vertebrobasilar syndrome : Manifestation by episodes of vertigo, dizziness, diplopia, dysarthria, dysphagia, in co-ordination of the gait and limbs and bilateral signs of sensori-motor deficits.

1.15 ANSWERS TO CHECK YOUR PROGRESS

Check Your Progress 1

1) TIA is usually defined as rapid onset of focal neurological deficit over minutes to hours. Recovery is complete within 24 hours.

2) This includes ischaemic, haemorrhagic and embolic type.

3) Most common risk factors are hypertension, diabetes, smoking and obesity.

Check Your Progress 2

1) Middle cerebral syndrome is characterised by contralateral hemiplegia, hemianaesthesia with or without homonymous hemianopia and aphasia.

2) Angiography (both DSA and MRI) remains the gold standard for assessment of CBF.

Check Your Progress 3

1) Antiplatelet drugs are a) Aspirin b) Ticopidine and c) Clopidrogel

2) Various surgical measures used are Endarterectomis, thrombectmies and revascularisation procedure.

3) Cytoprotective agents available are calcium channel modulators, piracetam, Glomethiazole. Amongst all, the nimodipine is the widest compound used.

4) Tissue Plaminogen activator (t-PA) is commonly used within 3 hours of ischaemic stroke onset.

1.16 FURTHER READINGS

Easton, J.D., Hauser, S.L., Martin, J.B. (1998), "Cerebrovascular Diseases" in Fauci, A.S. *et al*., *Harrison's Principles of Internal Medicine,* 14th edn., McGraw Hill, Inc. NY pp 2323-2348.

Taylor, C.L., Selman, W.R. (2000), "Emergensy Management of Ischemic Stroke", *Neurosurgery Clinics of North America*, 11(2) 365-375.

Wolf, P.A., D'Agostino, R.B. (1998), "Epidemiology of Stroke", in Barnet, H.J.M., Mohr, J.P., Stein, B.M., Yatsu, F.M. (eds), *Stroke Pathophysiology, Diagnosis and Management*, 3rd edn., Churchill Livingstone Philadelphia PA, 3-28.