STROKE REVIEW AND NEW FRONTIERS IN MANAGEMENT

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INTRODUCTION

Stroke is a sudden focal or global neurological dysfunction of vascular origin with disability lasting more than 24 hours or resulting in death. When disability lasts for less than 24 hours, it is termed transient ischaemic attack (TIA). It is the third most common cause of death in most western population after coronary artery disease and cancer[1]. It is thus the commonest life-threatening neurological disorder in terms of both morbidity and mortality and the resulting disability is the most important single cause of severe disability among western people living in their own homes[2].

Stroke, the major consequence of cerebrovascular disease afflicts all ages but certainly is more usual in the sixth to eighth decades of life. As public health, medical, and social advances continue to extend life expectancy, we can expect an increase in the size of the world community at risk of stroke, in the new millenium.

EPIDEMIOLOGY

The age-adjusted annual death rate from stroke is 116 per 100,000 population in the USA and some 200 per 100,000 in the UK. It is higher in Afro-Caribbean populations than Caucasian. In Africa, it accounts for 0.9-4.0% of hospital admissions, and 2.8-4.5% of total death[3]. Case fatality rate averages about 35%[4], but could be as low as 14.9% or as high as 77% when due to cerebral hemorrhage[5].

RISK FACTORS

Identification of stroke risk factors and implementation of activities to eliminate or diminish their impact are essential to reduction of stroke morbidity and mortality. For an individual, the presence of any single or combined risk factors in itself/themselves does/do not predict that a stroke will occur; conversely, the absence of any known stroke risk factors does not ensure that a stroke will not occur. However, it can be confidently asserted that the probability of a stroke occurring is clearly influenced by the presence of these risk factors.

Some stroke risk factors are genetic and are difficult or impossible to influence (e.g. age, sex), some are environmental and are more easily preventable (e.g. infections), some are a function of personal lifestyles and are controllable (e.g. cigarette smoking, alcohol), and some are a combination of familial and environmental factors and are often manageable (e.g. hypertension). The risk factors are

a. Arterial Hypertension: There is substantial evidence that systolic hypertension, diastolic hypertension and combined systolic and diastolic hypertension are important independent risk factors for stroke.
b. Age: stroke is commonest in the sixth to eighth decades of life.
c. Diabetes mellitus.
d. Heart Disease e.g. rheumatic heart disease, coronary artery disease with myocardial infarction, cardiac arrhythmia, cardiomyopathies, atrail myxomas, congestive heart failure.
e. Transient ishaemic attack and Completed Stroke: TIA is an urgent medical matter demanding early evaluation and appropriate intervention to prevent stroke occurrence. The more frequent the TIAs, the higher the probability of stroke. Previous stroke is a greater risk factor for subsequent stroke than is TIA alone.
f. Obesity: It is a risk factor for heart disease and thus may be a secondary risk factor (via heart disease) for stroke.
g. Platelet Hyperaggregability.
h. Alcoholism: Acute alcoholic episode or chronic alcoholism.
i. Smoking: Cigarette smoking is an important risk factor.
j. Hyperlipidaemia: Hypercholesterolemia and increased concentrations of low density lipoprotein (LDL) are important as risk factors for atherosclerosis per se, and correction for the effect on atherosclerosis has been shown to reduce significantly the risk for stroke.
k. Infections: A wide variety of infection with cerebral infestation have been demonstrated as risk factors stroke. These cerebral infections include malaria, tuberculosis, helminthic infestation, syphilis and leptospirosis, HIV.
l. Genetic or familial factors: These as independent variables in stroke are yet inconclusive. These factors appear to be important when linked to other variables such as hypertension.
m. Other factors
   - male sex
   - cold temperature
   - high oestrogen contraceptive in females
   - low socio-economic status
   - increase hematocrit in males
   - decreased hematocrit in females
   - high dietary intake of sodium
   - low dietary intake of potassium
   - Hyperuricaemia

Strokes can be divided into two broad categories based on the nature of the cerebral lesion: infarcts and hemorrhages. A cerebral infarct is the result of temporary or permanent occlusion of a feeding artery, extracranially or intracranially, or (more rarely) of venous thrombosis. A spontaneous cerebral hemorrhage is due to the rupture of an abnormal artery (aneurysm or arterio-venous malformation) or arteriole in the brain parenchyma.

TYPES OF STROKE

Stroke could be due to:

a. Occlusion of vessels (Ischaemic stroke) either by
   (i) thrombus
   (ii) embolus
b. Rupture of a vessel (Hemorrhagic stroke):
   (i) Intracerebral hemorrhage (ICH) bleeding into brain substance
   (ii) Subrachnoid hemorrhage (SAH) bleeding into the subarachnoid space and ventricles (SAH).

CLINICAL FEATURES

These depend on type of stroke, the blood vessel affected and site in the brain.

(i) The vessel involved

A. Thromboembolic infarction:

a. Anterior Cerebral Artery Territory
   - contralateral motor weakness worse in lower limbs
   - loss of sphincteric action e.g. urinary incontinence
   - presence of grasp reflex (involuntary grasping reactions of affected hand).

b. Middle Cerebral Artery Territory
   - Contralateral motor weakness worse in arm and face
   - Contralateral sensory deficit
   - Aphasia (if dominant cerebral hemisphere is affected).
   - Visual impairment (loss of vision in one half of visual field or unilateral visual neglect).

c. Vertebrobasilar System
   - Complete loss of vision on one side of visual field or in only the upper half.
   - Widespread hemisensory abnormalities: - Dysesthesias (troublesome pain), spontaneous pain, loss of several sensory modalities.
   - Visual perception difficulties not explained by visual field defects – loss of ability to recognize visually objects, pictures, colors or graphic symbols.

d. Cerebellar infarction: hemiataxia, hypotonia, loss of balance and inability to stand, intense nystagmus, vertigo, vomiting.

e. Brain stem infarction: Diplopia, deafness, dysequilibrium, dysphagia, dysphonia, vertigo, ataxia.

Type of Stroke

A. Thromboembolic: occurs on awakening or associated with heart rhythm irregularity.

B. Intracerebral Hemorrhage
   - Headache (severe)
   - Nausea and vomiting
   - Persistent alteration of consciousness
   - Seizures
   - Onset with activity

C. Subarachnoid Hemorrhage
   - Sudden severe headache usually occipital
   - Vomiting
   - Loss of consciousness
   - Neck stiffness

D. Others: Amnesia, agnosia, apraxia, delirium, dementia, brisk jerk reflex, babinski sign, nystagmus, tinnitus.

Differentiating Between Difference Causes of Stroke

Feature	Cerebral (Thrombotic) Infarction	Cerebral Embolism	Intracerebral Hemorrhage	Subarachnoid Hemorrhage (SAH)
1. Mode of Onset	During sleep or waking	At rest/ activity	Activity, news, coitus	Activity, coitus
2. Initial symptoms	Weakness	Palpitation, dyspnoea	Severe headache, vomiting, loss of consciousness	Very severe headache (Thunderclap) Neck pain Neck stiffness Vomiting Seizure Alteration in level of consciousness Focal/Global deficit

Differential Diagnosis

1. Cerebral abscess.
2. Meningitis.
3. Epilepsy.
4. Subdural hematomas
5. Brain tumor
6. Migraine headache
7. Hysteria.

PATHOPHYSIOLOGY OF ACUTE STROKE

The various molecular changes that occur in acute stroke have dual mechanisms especially when of the ischaemic variety. These vascular and ischaemic mechanisms though occurring concurrently usually start with the vascular component.

The vascular event commonly starts as a cerebrovascular occlusion whose resulting damage usually depends on the degree and duration of this flow impairment. Based on these few variables, the vulnerable neurons such as the pyramidal neurons in the CA1 and CA4 zones of the hippocampus are affected sparing other neurons and glial cells[6], although the duration could be brief with maximum damage occuring within this period. The occlusion could reduce or even abolish the delivery of oxygen and glucose to affected vascular territories with severity bearing an indirect relationship to the distance from the occlusion. A persistent loss of electrical potentials (persistent anoxic depolarisation) lasting between five and sixty minutes kills some or all of the selectively vulnerable neurons within the affected vascular bed but when it lasts more than 1 hour, infarction begins in the central zone of lowest cerebral blood flow enlarging progressively in a circumferential fashion towards the periphery[7]. In severely ischaemic brain, persistent shortage of high energy phosphates is an overwhelming determinant of injury and unless there is restoration of energy exchange (ATP) with cerebral blood flow, necrosis is inevitable. Though this energy value is not the immediate cause of all death because all brain tissues tolerate loss of ATP for several minutes and the great majority recover fully when blood flow is restored even after an hour of complete ischaemia[7]. After ischaemia onset, the energy demands of the

brain could exceed the brain's capacity to synthesize ATP anaerobically from its meagre stores of glucose and glycogen and leads to depletion of high energy phosphates and fuels need for their synthesis.

Hyperglycaemia or an increase in brain carbohydrates usually accelerates or worsens infarction in animals and this is due to accumulation of lactate and unbuffered hydrogen in proportion to the existing carbohydrate stores at the onset of ischaemia. Potassium ions leave the cell while Na, Cl and Ca ions enter and many neurotransmitters, including excitatory amino acids (glutamate, aspartate) are released in potentially toxic concentrations. In moderate ischaemia however, compensatory mechanisms act to maintain near normal ATP concentrations and membrane ion gradients and so preserve cell viability. However if this moderate ischaemia goes on for several hours, cell death occurs.

A similarity however in both cell deaths due to moderate and severe ischaemia is that dysregulation of calcium ion homoestasis features prominently. The haemorrhagic variety bears a similar mechanism with the ischaemic variety because of its vascular aetiology too. Though a common pathogenesis can be described for both types, the haemorrhagic type has the peculiarity of a relationship with high blood pressure in the patients and berry vascular malformations. An upsurge in this blood pressure above the cerebrally adjusted high systolic and diastolic values leads to bleeding into various blood spaces. A reduction or obstruction in the needed supply to the area supplied by the affected vessel leads to ischaemia thus linking the final common pathway.

Ischaemic varieties could also eventually bleed i.e. have a haemorrhagic conversion hence the need for early diagnosis and a thorough understanding of the pathological mechanisms of both varieties. This is because bleeding occurs when the embolus fragments with reperfusion via distal vessels that have previously been rendered ischaemic or cortical collateral channels. Risk factors for haemorrhagic conversion include large infarct volume, midline shift, increasing age but unlike bleeding in the initial haemorrhagic variety, hypertension or anticoagulation therapy play no roles.

MANAGEMENT OF STROKE

Management of stroke is carried out at 3 levels

1. Prevention of stroke.
2. Management of acute stroke and complications which may develop in the immediate or sub acute post stroke period. (2^{nd}-4^{th} week post stroke)
3. Post stroke rehabilitation.

1. Prevention

Stroke prevention itself is sub-classified into primary and secondary prevention.

a. Primary Prevention: This includes measures taken to prevent or treat correctable risk factors including those earlier mentioned. The general goal is to prevent artheroma development. Primary prevention will therefore include regulation of blood pressure, dietary modification to exclude saturated fat, cessation of cigarette smoking, weight reduction. It therefore involves lifestyle adjustment on a wide front. Primary prevention may also involve commencement of antiplatelet agents, including aspirin, fish oil supplements are also said to be high in poly unsaturated fat and may thus be protective against atheroma development.

b. Secondary Prevention: In secondary prevention, the aim of treatment is different in that patient considered as a candidate for secondary prevention already shows clinical features of threatened stroke, such as onset of cerebral or retinal ischaemic events, which signal the failure of primary preventive strategies. Presence of target organ symptoms frequently indicates superimposition of thromboembolism on the primary disease process. Secondary prevention therefore involves aggressive treatment of existing risk factors. In summary it translates into the following steps

(i) Reduction of BP: by judicious use of antihypertensive agents, weight reduction, exercise, reduction of sodium and increase in potassium intake.

(ii) Cessation of tobacco use: Tobacco has been found to increase platelet aggregability and increase fibrinogen concentration. Cessation of smoking will produce a reduction in risk of thromboembolic events secondary to increased coagulability of blood.

(iii) Dietary adjustments: as earlier discussed

(iv) Cessation of alcohol use: Excessive alcohol use may increase BP, triglyceride levels, paroxysmal atrial fibrillation, and cardiomyopathy with ventricular thrombi.

(v) Adjustment of associated conditions and risk factors –

1. tight control of blood sugar in diabetics to slow down the rate of development of diabetic angiopathy which is a known risk factor for both arterial and venous infarcts
2. prompt diagnosis and early treatment of heart conditions such as arrhythmias especially atrial fibrillation and the sick sinus syndrome, valvular lesions, infective conditions, and myocardial damage.
3. Exercise: Commencement of exercise has been shown to reduce BP, increase HDL levels, and control obesity.
4. Prompt recognition and early treatment of haematological conditions such as polycythaemia.
5. Cessation of high oestrogen oral contraceptive use.
6. Prompt institution of therapy for conditions which may produce coagulopathy (either hyper or hypo) e.g. cancer, pregnancy, post operative or post partum states.
7. Sickle cell disease: prevention of sickling episodes
8. Vasculitis: use of steroids and antibiotics to reduce inflammation.
9. Intravenous drug abuse: associated with formation of septic vegetations on the valves that may embolise.

(vi) Long term use of antiplatelet agents: Antiplatelets therapy should be promptly instituted following thromboembolic phenomena or on recognition of disease states predisposing to thromboembolism especially cardiac diseases like recent myocardial infarct, arrhythmias, prosthetic heart valve insertion.

MANAGEMENT OF ACUTE STROKE

Management of acute stroke can be broadly categorized into:

1. Acute/Emergency care which includes both medical and surgical management modalities in the immediate post-stroke period up to the end of the first week.
2. Subacute care: which involves prevention and treatment of the complications of stroke usually 2nd to 4th week post stroke.
3. Long term care/rehabilitation

1. Acute/Emergency Care

Emergency care of acute stroke must begin with a rapid assessment of the patient in order to obtain baseline information from history, examination and investigations that will confirm the diagnosis of stroke, assess subtype and severity of stroke, assess risk factors, and inform management protocol. Initial assessment must include the following:

(i) Assessment of cardiopulmonary status
(ii) Assessment of neurologic status, site, type, severity of stroke and associated neurologic deficits.

History must seek to elicit information as to onset and rate of progression of symptoms. History of preceding headache, vomiting, neck stiffness, seizures and coma must be confirmed or excluded. History of previous metabolic disease such as DM, preceding known hypertension, symptoms suggestive of transient ischaemic attacks must be elicited. Previous cardiac conditions such as recent myocardial infarction, arrhythmias, congestive heart failure, rheumatic fever must be sought. History of intravenous drug use; is also important. History of severe headache with focal signs indicates a lobar haemorrhage[8]. History of pain in the neck, side of face, teeth, jaw or retro-orbital area may indicate vertebral or carotid artery dissection.

Physical examination should seek to exclude or confirm type of stroke and severity. After exclusion of overt signs of head and neck injury, specific signs that will estimate size and location of infarct must be sought. Level of consciousness must be ascertained. Hemiparesis, forced gaze deviation, will suggest a large hemispheric or critical brainstem lesion; especially if accompanied by decreased level of consciousness. Hemiparesis involving face, arm, leg in an alert patient suggests a small, deep lesion involving a confluence of motor fibres. Behavioural abnormalities such as aphasia, hemineglect, without gaze preference suggests smaller hemispheric lesions. Ocular fundus examination should be done in all stroke patients. Examination should also take note of signs of other risk factors such as obesity, signs of diabetes mellitus like dehydration, septic spots. A thorough cardiovascular examination must be carried out as it may reveal features of cardivascular disease like arrhythmias, valvular disease, carotid bruit, congestive heart disease. Examination should also seek to exclude other causes of coma (in a comatose stroke patient) such as hepatic or renal encephalopathy.

INVESTIGATIONS

Patients with acute stroke must be comprehensively investigated from the onset, and should include serum biochemistry for sugar, electrolytes, urea, liver enzymes. Haematological parameters such as white cell count, haematocrit, clotting profile must be done to rule out abnormalities. Haemoglobin genotype is mandatory in a young person with stroke, especially in this environment.

Cardiovascular Investigations

Cardiovascular investigations such as Holter monitoring must also be done to rule out intermittent atrial fibrillation (sick sinus syndrome) which may result in sudden death. Contrast transesophageal or standard transthoracic echocarchographs may reveal the presence of septal defect*. Standard angrography may reliably demonstrates large vessel stenosis, duplex Doppler usually readily delineates the severity of internal carotid artery stenosis. Transcranial doppler may also infer a right to left event (such as a patent foramen ovale) when it shows microbubbles in the intracranial vessels after injection of 10cc of agitated normal saline into the antecubital veins.

Neuroimaging

Neuroimaging by use of Computerized axial Tomography and Magnetic Resonance Imaging are the investigations of choice in acute stroke; especially before instituting anticoagulant, antiplatelet and surgical therapy in these patients. MRI has the advantage of being able to detect infarction as early as 45 minutes after stroke[9]. However CT scan demonstrates infarctive lesions best between 7-10 days after the event. MRI will identify all but the smallest lesions and is superior to CT in identifying brainstem lacunar infarcts lesion and posterior fossa lesions. However, recent findings show that CT may be considered equal to MRI for documenting infarcts in the first few hours[10]. CT is superior for detecting haemorrhage or bony abnormalities. Newer neuroimaging techniques now exist; and include fluid alternating inversion recovery imaging; diffusion, perfusion, functional magnetic resonance imaging, and magnetic resonance. Spectroscopy Vascular lesions can also be defined using spiral computed tomographic angiography, magnetic resonance angiography and extracranial and transcranial ultrasonography. Cerebral blood flow measurements with xenon CT, SPECT and RCBF techniques are also being used to evaluate regional hypoperfusion.

TREATMENT OF ACUTE STROKE

Acute phase of stroke is generally accepted to be the period of the first 7 days. Both medical and surgical modalities exist for managing stroke.

A. MEDICAL MANAGEMENT

In the acute period following stroke, attention must be paid to the following

1. Maintenance of fluid and electrolyte balance. As many of these patients are admitted in a fluid depleted state, institution of early fluid and electrolyte therapy must be carried out. Care must be taken to avoid administration of hypoosmolar solutions (such as 5% dextrose) which will worsen the cerebral oedema[11], and inappropriate ADH secretion has been found to occur in 10% of all stroke

patients[12]. Haemodilution with plasma expanders has been shown to increase cerebral blood flow on cardiac output.

2. Cardiopulmonary function maintenance: Airway maintenance is critical to ensuring good oxygenation and avoidance of CO_2 retention, as these will lead to worsening of cerebral oedema. Oxygen therapy may be necessary in the presence of compromised respiratory function. Arterial blood gases concentration must be monitored.
3. Blood pressure: maintenance of appropriate blood pressure is essential to management of stroke. Hypotension is rare in ischaemic CVD but may follow after cardiovascular events such as myocardial infarction. The tendency is for blood pressure to rise following an acute stroke and spontaneously decline thereafter. Hypotension may be treated by infusion of volume expanders such as plasma or low molecular weight. Aggressive treatment of blood pressure may produce hypotension and repeat infarction. However, severely elevated blood pressure with evidence of end organ damage such as aortic dissection may necessitate use of antihypertensives, in which case calcium channel blockers (which have a dual role in stroke) may be employed.
4. Nutrition: passage of a nasogastric tube for drug administration and nutrition is recommended, especially in unconscious patients or those with dysphagia or deglutiton problems from cranial nerve palsies.
5. Anticonvulsant therapy: oral anticonvulsant mono therapy such as use of phenytoin sodium may become necessary in patients with focal seizures following haemorrhagic stroke with a clot.
6. Oral and perineal toileting.
7. Institution of early physiotherapy within the first 24 hours post stroke to prevent development of contractures, is recommended[13].

SPECIFIC NEUROLOGICAL INTERVENTIONS

1. Cerebral Infarction: in recent years, much work has been done on the use of thrombolytic agents for rapid recanalisation of thrombosed vessels. In order to be successful, reperfusion must be accomplished quickly within a few hours of occlusion. This can be accomplished surgically or medically; surgical techniques for achieving recanalisation include direct surgery and angioplasty.

Surgical

Carotid endarterectomy has been confirmed as being effective in preventing further brain ischaemia in patients with symptomatic severe carotid artery stenosis. Angioplasty is a new and important treatment modality[14] and is carried out by intervention radiologists and other, physicians trained in endovascular therapeutics, who dilate the extracranial carotid and vertebral arteries percuteonously. Stents are often placed during angioplasty to maintain patency. This method has been found equally useful in patients with subarachnoid haemorrhage, stenotic intracranial vertebral, internal carotid and middle cerebral artery lesions[15]. Feared complications include arterial wall dissection , vasospasm and occlusion of penetrating arterial branches.

Medical

Use of thrombolytic agents for rapid recanalisation is now a reality, and may be administered intravenously or intrarterially. However the complication of haemorrhage is a very real possibility. Trials on administration of recombinant tissue type plasminogen activator (rTPA) have shown that this treatment can reduce stroke morbidity in these patients[16,17]. However this can only be done after CT scanning has excluded haemorrhagic lesions. Criteria to be met before a patient is considered eligible for rTPA administration include[18]

(i) commencement must be within 3 hours of the stroke.
(ii) Prior CT scan must have ruled out haemorrhagic stroke.
(iii) Patient must not have had significant head trauma within the 3 months preceeding the stroke.
(iv) Patient must not have been on anticoagulant therapy within 2 weeks preceding stroke.
(v) Patient must not have any history of cerebral, upper GI or urinary tract bleeds.

Intra-arterial administration is recommended in patients with occlusion of the internal carotid, mainstem middle cerebral and basilar arteries. Intravenous rTPA is best given to those with intravenous circumferential artery occlusions.

ROLE OF ANTICOAGULANTS AND ANTIPLATELET AGENTS

Prophylaxis against thrombosis and subsequent embolism has long since been considered a standard part of stroke management. Recent research has uncovered new knowledge in this area.

Prophylaxis depends on the source and nature of thrombo embolic fragments. Antibiotics are most effective against bacterial endocarditic emboli. Drugs that alter platelet function (aggregability, adhesiveness and secretions) are most effective against white platelet fibrin thromboemboli that form an irregular surfaces in fast moving arterial streams. Aspirin, ticlopidine, clopidogrel, NSAIDS, abciximab and CO_3 fatty acids all alter platelet function. Heparin , heparinoids low molecular weight heparin and warfarin type anticoagulants are most effective against the formation and propagation of erythrocyte-fibrin red clots such as form in areas of reduced blood flow like dilated cardiac atria, ventricular aneurysms, distended leg veins and tight stenotic arteries.

Antiplatelet Agents

Aspirin was first shown to reduce death from antiplatelet agents: non fatal stroke. Studies have shown a 22% risk reduction for vascular end points (stroke, myocardial infarction and vascular death from aspirin). However no consensus on optimal dose has been reached. Ticlopidine hydrochloride was later developed and was shown to be more effective in preventing recurrent ischaemic events but also had more side effects including neutropenia[20]. Clopidogrel, a new thiopyridine derivative similar to tichopidine but with superior activity to ASA in reducing combined end point of ischaemic stroke myocardial infarction and vascular death. Frequency of neutropenia was less than

with tidopidine. More recently drugs have been discovered that inhibit platelet glycoprotein Iib/IIIa complex and its binding to fibrinogen. These include Abciximab which consists of monoclonal antibodies to the complex.

Anticoagulants

Standard anticoagulants such as warfarin and heparin have long been in use. Warfarin has been conclusively shown to be effective in preventing strokes in patients with CVD in the acute phase, anticoagulant therapy is used to prevent further development of the thrombus, though not without risk of haemorrhage. Recently, fractionated heparins especially low molecular weight heparins are being used as they have less tendency to cause thrombocytopenia and may be given safely subcutenoulsy at home without the need to monitor plasma thromboplastin times. Low molecular weight heparin are also more effective in preventing phlebothrombosis in lower extremities and pulmonary embolism. Administration must be preceded by CT scan to exclude haemorrhagic CVD. Lumbar puncture is contraindicated in these patients because of possibility of epidural haematonia. A plasma thromboplastin time of x 1n5-2 of normal is aimed for.

NEUROPROTECTIVE AGENTS[15]:

Drugs have been developed that ameliorate damage due to cellular metabolic consequencies of ischaemic injury. In ischaemic brain tissue, calcium moves into the cells via calcium conducting channels and excitotoxic amino acids, free oxygen radicals and leucocytes are attracted to the ischaemic zone, promoting cytotoxic injury to neurones. Changes in growth factors and gene expression also contribute to cell death. Knowledge of mechanisms or cell death have led to the development of many neuroprotective agents with diverse sites of action as listed below.

Table 1

Neuroprotective Agents

Voltage-sensitive calcium-channel antagonists (e.g. nimodipine, amlodipine and flunarazine hydrochloride).
Noncompetitive N-methyl-D-aspartate receptor antagonists (e.g. dextromethorphan, eliprodil, aptiganel hydrochloride, and remacemide hydrochloride).
Competitive N-methyl-D-aspartate antagonists (e.g. selfotel)
Calcium-channel modulators (eg. Eliprodil and ACEA-1021)
Antioxidants (e.g. tirilazad mesylate [a 21-aminosteroid, superoxide dysmutase])
Alpha-amino-3-hydroxy-5-methyl-4-sixazole propionic acid and kainate receptor antagonists (eg NBQX and YM90K)
Presynaptic y-aminobutyric acid inhibitors (e.g. fosphenytoin sodium)
y-Aminobutyric receptor agonists (eg clomethiazole)
Presynaptic modulation of glutamate release (eg riluzole)
Adenosine analogs (eg prophentofylline)
Calpain antagonists (eg AK275)
Polypeptide growth factors (eg basic fibroblast growth factor)
Antiadhesion molecules (eg antibodies against intercellular adhesion molecule 1 and CD11b/18)
Lecithin synthesis (eg citicoline)
Apoptosis inhibitors (eg cycloheximide)

Clinicians are hopeful that these agents can mitigate ischemic damage and delay neuronal death long enough to allow reperfusion.

NEUROTRANSMITTER REPLACEMENT/ENHANCEMENT

Agents which enhance recovery and improve normal function of damaged brain tissue and neurotransmission after stroke include single dose dextroamphetamine which combined with physical therapy has been shown to accelerate motor recovery in patients with acute hemplegia caused by ischaemic stroke[21]. Treatment with bromocruptive and carbidopa with levedopia has been used in an attempt to improve aphasia caused by stroke.

MANAGEMENT OF CEREBRAL OEDEMA AND RAISED INTRACRANIAL PRESSURE

Cerebral oedema and raisid intracranial pressure (ICP) are both potentially fatal complications of both ischaemic and haemorrhagic CVD and cause many of the deaths in the first week post ictus. Decreasing level of consciousness and worsening neurological deficit are indications of development of significant cerebral oedema. Modes of therapy include elevation of the head by 75-30°, use of osmotic diuretic agents such as glycerol and mannetol, hyperventilation and surgically by drainage of CSF via ventriculostomy.

Mechanical hyperventilation produces hypocapnia and reduces cerebral volume. IV mannitol 0.25-0.5 g/kg infused rapidly over 15-30 mihutes rapidly lower ICP. Intravenous glycerol is also useful but may produce subclinical haemolysis[22]. Steroids have been found not to be useful in the management of oedema in stroke as the oedema is and not vasogenic[11]. IV Furosemide is also useful in reducing cerebral oedema and lowering ICP.

Activities that are known to increase ICP such as coughing, straining at urine or faeces must also be avoided. Paralysis with metocurine (rather than pancuronium which increases bp at 0.3mg/kg body weight, with mechanical ventilation has been suggested. Adequate bp control will also assist in lowering ICP. It is important to note that use of glypotonic solutions must be strictly avoided when cerebral oedema is suspected, and hyponatremia must be promptly treated.

MANAGEMENT OF INTRACRANIAL HAEMORRHAGE (INCLUDING SUBARACHNOID HAEMORRHAGE)

Hypertension is the commonest cause of intracranial haemorrhage (ICH) both in Africa and world wide[23,24], and commonest site of bleed is into the basal ganglia[25]. Spontaneous intracranial haemorrhage generally manifests as either of 2 clinical syndromes, the first being a sudden onset of elevated ICP produced by the mass effect of the blood clot, with associated midline shift, ventricular compression or transfentonial hemiation and the second being focal signs appropriate to the site of clot Epilepsy may complicate ICH and is more common with lobar haemorrhage than with deep seated or basal ganglia haemorrhage.

Subarachoid haemorrhage (SAH) may be due to rupture of either an anemysm or an arteriovenous malformation (AVM). They are responsible for between 5-10% of strokes[26]. In the middle decades, aremysms are the most common cause of stroke. In the 5th decades, frequency of anemysms is x2 of other causes and 25 times that of AVM though frequency of AVM and aremysm is about even in the second decade.

Features of patients with ICH varies widely and it is not possible to generalize about management which may be surgical or medical. Evacuation of clot may be done as early as 12 hours after the bleed without risk of significant rebleed. However, this would no doubt be considered more logical in a young patient with subcortical haematoma, rather than in an elderly patient with a large dominant hemisphere haematunia whose pupils have been dilated and fixed from the outset. Studies[27] have however shown no significant difference between patients managed surgically and those managed medically, since mortality from craniotomy may be as high as 60%[28]. Therefore, medical management involving bed rest, avoidance of activities increasing ICP, maintenance of fluid and electrolyte balance, avoidance of dehydration (which increased the risk of ischaemia, prompt recognition and treatment of syndrome of inappropriate ADH secretion (SIADH), use of calcium channel blockers for gentle control of blood pressure should be considered. Newer surgical techniques now exist, such as CT guided stereotaxic aspiration and use of urokinase to dissolve the clot before aspiration.

SUBACUTE MANAGEMENT OF STROKE

Management of stroke in the subacute phase (ie after the first week) is aimed at preventing complications.

COMPLICATIONS OF STROKE

Though varied and numerous, complications of stroke are somewhat preventable if early treatment is instituted and rigorous attention paid to medical factors that contribute to this. Recovery could be nearly complete and sometimes immediate.

The complications can be divided into

A. Cerebral
B. Systemic
C. Secondary to treatment

A. Cerebral Complications

1. Cerebral herniation: This is transtentorial herniation and is the commonest cause of death incidence of which peaks within 24 hours for cerebral.
2. Cerebral oedema: This directly results in raised intracranial pressure.
3. Haemorrhagic transformation: This occurs in 74% of all strokes within 4 days[29]. Haemorrhagic strokes are how ever often cardioembolic in origin.
4. Acute hydreophilis: due to compressor of the aqueduct by blood on edema leading to deterioration or death.
5. Seizure: these are usually single and local and complication 11% of infarcts or haemorrhages. The presence usually indicates cortical involvement. However this activity does not influence normality or morbidity significantly and is usually controlled with monotherapy[30,31].
6. Depression: This occurs in about 50% of acute stroke patients[6] with this correlating with proximity of the lesion to the anterior left hemisphere in the acute phase but not in the subacute phase[33].

B. Systemic Complications

1. Hypertenison: though this is a risk factor for stroke. Stroke can also worsen a pre-existing hypertensive state or even initiate hypertension. This has been associated with tran sient increases of plasma catecholamines[34] although it is not known if this correlates with ischaemia of autonomic control areas of the brain (e.g. insular contex or hypothalamis).
2. Fever: This correlates with stroke severity in most cases being due to infection mostly (urinary or pulmonary) or deep venous thrombosis but occasionally is the direct result of stroke especially when large or associated with intraventricular or hypothalamic haemorrhage[35]. It accompanies about 44% of acute stroke. Slight increases in fever could even have severe outcomes and the longer the fever persists, the poorer the prognosis. Studies in animal models have suggested changes in blood brain barrier permeability, intracerebral acidosis and impaired phosphate metabolism and enhanced release of excitatory aminoacids all of which were reversed by cooling.
3. Endocrine Abnormalities: There have been reports of blood sugar increase without a previous history of dia betes in as many as 28% of acute stroke patient. This may be related to increased concentrations of plasma catecholamines and cortisol[37] which then interfere with peripheral glucose metabolism. This hyperglycaemia whether chronic or transitory is associated with reduced cerebral blood flow, increased cerebral oedema and larger infarcts[38]. Inappropriate antidiuretic hormone secretion occurs in 10% of cerebral infections and 14% of cerebral haemorrhages and could initiate or exacerbate cerebral oedema[39] and this could manifest as clinical deterioration, seizures, plasma sodium concentration and stroke score decline reaching up to 7-9 days. In most cases however, hyponatremia is an incidental finding and is unassociated with symptoms.
4. Cardiac Complications: Though stroke and coronaryh e a r t disease often coexist, stroke could affect the heart independent of ischaemia. Stimulation of the insular cortex area can induce cardiac arrhythmias[40] and thus a stroke in this area can induce uncontrolled hypotension from cardiac dysfunction[39] and this require close monitoring being especially vulnerable to stroke extension.
5. Pulmonary Embolism: In a study 9% of the patients had a pulmonary embolism and 53% of the patients deep vein thrombosis[41] and these had no correlation with age, obesity, days in bed or severity of motor impairment. It could affect the patient's outcome via fever or hypoxia.
6. Infection: This mostly is not a direct consequence of stroke but of poor management. Thus pulmonary and urinary infection must be guarded against and promptly treated as they influence mortality and morbidity.
7. Pressure sores: Occasionally encountered especially in elderly patients with infarction; though it more frequently occur due to poor management and skin infection. It can cause fever leading to clinical deterioration.
8. Aspiration: This and dysphagia are common in patients with stroke and is commoner in those with brainstem involvement. It could then progress to pneumonia and secondary deterioration from hypocia and pyrexia[39].
9. Contractures and joint stiffness.

C. Complications of Treatment

These include

1. Fever with adverse drug reactions.
2. Inappropriate antiduretic hormone secretion due to carbmazepine or chlorpropamide.
3. Sedation and depression induced by tranquilizers.
4. Impairment of cerebral autoregulation by stroke with worsening by hypotensive agents.
5. Haemorrhage from anticoagulants.
6. Bedsores – due to inadequate turning.
7. Myocardial infarction – due to ischaemia from hypoten -sive agents.

Treatment of Complications

Since the treatment of these complications betters the outcome of the patient with stroke, care his to be taken to manage them effectively especially those due to the poor management.

In patients showing clinical deterioration due to fluid accumulation (edema), mannitol may be temporarily effective unlike steroids that have shown no improvement of haemorrhage or infarct edema[42,43]. Due to the high risk of re-embolisation, antecoagulation is often considered for pateints with cardioembolic strokes. These should however not be prescribed for large infarcts or those with mass effect and not until that 4 days after a stroke onset since by seizure activity can be controlled with mild antiepileptics in 9 monotherapy and reduces with adequate management of the predisposing haemorrhage and/ or edema. Antidepressant therapy can bring about a improvement especially if the depression goes on for a long time[44].

The treatment of post stroke hypertension is controversial because lowering of system pressure leads to impairment of cerebral autoregulation and could jeopardize cerebral blood flow. However severe increases >200mmHg systolic and >120mmHg diastolic should be traced with short acting agents such as sodium nitroprusside or intravenous labetalol so that the BP can be reversed quickly if need be. These should also be frequent monitory of neurological states and blood pressure[39]

A reduction of fever usually reduces the severity of ischaemic damage but studies are underway to ascertain if cerebral cooling is beneficial in human stroke as in animal models[39].

Fluid restriction helps in the management of patients with inappropriate antidiuretic hormone secretion and being an incidental finding most times, hypanetrenia needs no therapy. Patients with blood glucose in the frankly diabetic range should be treated with insulin by infusion and subsequently investigated for latent diabetes[39] and in those with borderline diabetic glucose concentrations, glucose deficient diet can be given. Patients with cardiac complications must be properly investigated and specific appropriate treatment given with close monitoring.

Prophylaxis with antithromboembolism agents and low dose subcutaneous heparin 5000 units twice daily is useful in acute stroke patients although it is better to with hold heparin if intracerebral haemorrhage is suspected. Infections should be treated with appropriate antibiotics to reduce it's influence on mortality, pressure sores are better prevented by turning patients regularly and use of a ripple mattress. Treatment of the sores could be with dressing (e.g. with honey). Patients with stroke should be fed in an upright position with food in appropriate consistency and small boluses. They also should be encouraged to cough gently after each swallow and to smaller several times after each bolus[39]. Early mobilization and physical rehabilitation aids in preventing contractures and joint stiffness.

The complications of treatment can be managed by a reconsideration of the therapy and dosages and if indicated a stoppage of the therapy so as to minimize or completely eradicate the complications due to these therapies.

Rehabilitation

A. Psychological

The stroke patient goes through five psychological stages[45]. These are

(i) Crisis: this is at the sudden onset of incapacitating neu rological deficit.
(ii) therapy – when the patient is hopeful of full recovery.
(iii) realization – when the patient realizes that some of the defect may be permanent.
(iv) adjustment – when the patient adjusts to life with residual handicap.

Since depression occurs in up to 50% of patients[6], there is need for psychological rehabilitation for the stroke patient. This could involve psychologists, psychotherapists and the family members especially during the realisation and adjustment phases.

B. Physical: This is important for restoration of function to weak limbs. Physiotherapy should be intensive in the acute and subacute phases and this has been known to improve functional outcome[13]. This rehabilitation involves physiotherapists, family members and the stroke patient himself.

C. Family: Because of the need to be fully accepted into the family, he having been away from family for so long, the social workers might need to pay visits to the family of the patient to encourage them to give psychological support to the patient.

D. Social: to gain acceptance back into the community especially to make facilities available for his use and to provide necessary facilities to accommodate the residual handicaps at the patient.

E. **Occupational:** The occupational therapist will help the patient to readjust back to his work environment. He also helps in soliciting cooperation from fellow workers and putting needed facilities at his disposal especially to cater for the handicaps.

F. Language Therapy: this is necessary on patients with dysphasia and will require rehabilitation by speech and language[45].

PREVENTION OF RECURRENCE

Prevention of stroke recurrence essentially involves taking the same steps as for secondary stroke prevention as earlier discussed, after identification of those risk factors specific to that patient.

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