UNIT NO. 4

CLINICAL SEQUELAE OF ATHEROTHROMBOSIS : STROKE

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ABSTRACT

Stroke is a major cause of death and disability. It occurs due to brain damage from lack of blood flow. Management includes making an accurate diagnosis, ruling out important differential diagnoses, determining the mechanism of the stroke, instituting appropriate secondary prevention measures, starting early rehabilitation, and taking steps to prevent complications. Stroke patients are best managed by a multi-disciplinary team in the setting of a geographically-well placed acute stroke unit.

INTRODUCTION

Atherothrombosis is a global disease. One of its most devastating and disabling manifestations is stroke. As our population ages, family physicians will see a continuing rise in the number of stroke patients in the years to come, many of whom will be disabled and will need holistic care.

STROKE MECHANISMS

Stroke occurs when a part of the brain is damaged due to lack of blood flow. By definition, a stroke is said to have occurred if the neurological symptoms or signs are due to a vascular cause and last at least 24 hours; if they last less than 24 hours, a transient ischaemic attack (TIA) is said to have occurred. The approach to stroke and TIAs is similar; TIAs are harbingers of a stroke to come.

There are a number of mechanisms for stroke, broadly divided into 'haemorrhage' and 'ischaemia'. Local data shows the following pattern:

Hemorrhagic stroke

- Primary cerebral haemorrhage, usually from hypertension – 24%
- Arteriovenous malformation (AVM) bleeding – 1%
- Subarachnoid haemorrhage (SAH) from aneurysmal rupture – 1%
- Rare causes of haemorrhagic stroke include the use of anticoagulants, antiplatelets or thrombolysis, and moya-moya disease.

Ischaemic stroke

- Large artery occlusion from cardioembolism, usually atrial fibrillation (AF) – 10%
- Occlusion of small intracranial arteries, leading to "lacunar syndromes" – 40%.
- Atherothrombotic stenosis/occlusion of the extracranial carotid arteries leading to intracranial embolism or hypoperfusion – 10%
- Intracranial large artery occlusion from atherothrombosis – 15%
- Rare causes of ischaemic stroke include procoagulant states and arterial dissection, particularly in the young.

Thus, atherothrombosis accounts for up to two thirds of all strokes in Singapore.

Atherothrombosis refers to thrombus developing over a ruptured atherothrombotic plaque, or haemorrhage into an atheromatous plaque. Both processes lead to occlusion of the artery and consequent distal cerebral ischaemia. Embolism of plaque material further downstream may also occur, referred to as atheroembolism. These concepts underlie the use of antithrombotics and agents that may affect the processes leading to atherosclerosis and vascular occlusion.

Interruption of blood flow results in a core area of brain tissue suffering severe ischaemia and cell death, surrounded by a penumbra of relative ischaemia that is potentially salvageable. Over the hours that follow, with the failure of compensatory mechanisms, tissue in the penumbra will succumb and die. This has lead to emergent therapies targeted at saving the penumbra, to be given within the first few hours after stroke.

CLINICAL SYNDROMES

The signs and symptoms that a patient develops depend on the site and size of the stroke. A medium-sized stroke in the frontal lobe may cause relatively mild symptoms, while a small stroke in the brainstem can be devastating.

The commonly occurring syndromes, and common location of lesions, are:

- Hemiparesis – Motor pathway in contralateral frontal cortex, deep white matter, brainstem
- Hemianaesthesia – Sensory pathway, usually contralateral thalamus
- Dysarthria – Motor control of bulbar muscles
- Dysphasia – Language centre in dominant frontal, temporal lobe
- Hemianopia – Visual pathways in contralateral occipital, less commonly temporal, parietal lobes
- Diplopia – Brainstem
- Incoordination – Ipsilateral cerebellum or cerebellar pathways, contralateral cerebellar pathways
- Giddiness – Brainstem
- Severe headache and vomiting – Large stroke
- Loss of consciousness – Brainstem stroke, large stroke.

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ASSESSMENT OF PATIENTS

The clinical approach to a patient with suspected stroke involves the following steps, with information from a good history and physical examination, followed by relevant investigations:

1. *Is it a stroke?* – To rule out differential diagnoses such as mass lesions (e.g., tumour, subdural haemorrhage), infections (e.g., abcess, encephalitis), metabolic derangements (e.g., hypo- or hyperglycaemia, hypo- or hypernatraemia), immune diseases (e.g., multiple sclerosis) or, other neurological diseases (e.g., complicated migraine, post-seizure Todd's paralysis).
2. *Where in the brain the stroke is located?*
3. *What type of stroke is it?* – Haemorrhagic or ischaemic.
4. *What is the mechanism for the stroke?* – Primary haemorrhage from hypertension, aneurysmal subarachnoid haemorrhage, cardioembolism, atherothrombosis, etc.
5. *Are there complications?* – These would include respiratory compromise, "malignant" edema of the stroke, recurrent stroke, hydrocephalus, etc.

The ABC (airway, breathing, circulation) status should always be assessed prior to more-detailed evaluations.

INVESTIGATIONS FOR A STROKE

In investigating a stroke, the physician aims to the following questions: "What, where and how" did the stroke occur?

What and Where is the Stroke?

Computed Tomography of the Head

Ischemic strokes are four times more common than haemorrhagic strokes, and the differentiation is rapidly and reliably made with a Computed Tomography (CT) head. Occasionally, the diagnosis of small subarachnoid haemorrhages may be difficult, because of difficulty visualising small amounts of blood in the sulci spaces.

CT scans are widely available, and also relatively inexpensive, compared with some of the newer imaging modalities available. However, identifying an acute infarct reliably on CT scan is not easy, especially if the infarcts are small. It is possible to identify large ischemic infarcts early on CT scans, due to the combination of vasogenic and interstitial edema. These include:

- loss of the grey-white differentiation
- sulcal effacement, where the sulci spaces are "compressed" or lost
- asymmetrial compression of the ventricles
- "insular ribbon sign" where there is diminished attentuation of the grey matter in the insular cortex and claustrum
- blurring of the definition between the lentiform nucleus and internal capsule.

These changes are more apparent when comparison is made with the uninvolved contra-lateral brain.

Old infarcts usually show up as clearly defined dark/ hypodense spaces. Besides being insensitive to early small ischemic infarcts, CT head scans are also prone to artifacts if imaging is adjacent to bony structures (such as the in the posterior fossa, or spinal cord).

Magnetic Resonance Imaging

Magnetic Resonance Imaging (MRI) works on the principle that body nuclei will react to radio frequency pulses in the presence of a powerful magnetic field. Hydrogen nuclei are most frequently used because of its abundance in the body. MR spectroscopy studies other nuclei, such as carbon and phosphorus. Manipulation of various MR parameters allows images to be obtained with differing qualities.

Diffusion weighted imaging (DWI) allows ischemic strokes to be identified within minutes of onset.

T1 weighted (T1W) and T2-weighted (T2W) imaging also allow identification of acute ischemic strokes, though not as early as DWI. They have the added advantages providing better anatomic definitions, and identifying subacute and chronic infarcts. Perfusion imaging (PWI), as the name suggests, quantifies blood flow and may identify ischemic tissue at risk of further infarction.

MRI is more sensitive than CT, in particular with small and early ischemic strokes. However it does not define haemorrhage as well, though there are sequences (e.g. fluid attenuated inversion recovery or FLAIR) that are sensitive to the presence of blood.

CT head and especially MRI will usually resolve the "What and Where" question:

1. Non-stroke conditions such as brain tumour and encephalitis are excluded.
2. Differentiation between ischemic and haemorrhagic stroke is accurate.
3. There is also localisation and quantification of the size of the stroke. These scans also give an idea on the age of the stroke.
4. Old strokes maybe identified as well.

How did it occur?

In stroke medicine, the "how" question is important in assessing the risk of future recurrent strokes, and instituting appropriate treatments to minimise that risk. These investigations generally evaluate

- the cardiac and cerebral vascular tree
- laboratory tests to identify diseases associated with an increased risk of stroke or that promote a pro-thrombotic state.

The cardiac and cerebral vascular tree is studied with Doppler machines, CT and MR machines and/ or contrast angiography.

Cardiac sources of stroke can arise from structural cardiac lesions in the atria/ ventricles, walls or valves. Examples of specific cardiac etiologies include intra-cardiac clots, ventricular aneurysms or large akinetic segments, right to left

shunts and bacterial endocarditis. These are usually identified using transthoracic or transesophageal echocardiogram (TTE or TEE), MR imaging and contrast angiography. The use of cardiac contrast or agitated saline during echocardiogram allows, in addition, the identification of right to left shunts in the heart. Rhythm abnormalities such as paroxysmal atrial fibrillation require rhythm monitoring. Aortic arch disease is another source of stroke that can be studied using TEE

Neurovascular imaging allows the identification of occlusive lesions in the vascular tree that may account for an ischemic stroke. Most ischemic strokes are due to diseases in the cerebral vascular tree – ranging from the tiny penetrating vessels frequently implicated in lacunar strokes to the large extracranial internal carotid arteries implicated in cortical strokes. The diseases vary from atherosclerotic plaques to dissection, fibromuscular dysplasias and inflammatory stenosis.

Ultrasound Imaging and Doppler Sonography

Modern day ultrasound machines provide duplex (structural imaging) and Doppler (flow imaging) functions. They are widely available, relatively inexpensive and non-invasive, making it ideal in acute stroke imaging. Accurate imaging requires a well-trained physician or sonographer. Intracranial vessels can be assessed using the Transcranial Doppler (TCD) machines – the main limitation to its application is the availability of temporal windows. Because ultrasound is a sound wave, it needs to penetrate the temporal bone and be reflected back to the transducer of the machine in order for blood flow to be studied. Thick temporal bones will impede these, mainly through absorption of sound energy. This problem is more prevalent in Asian population, especially the elderly females. In a local Singaporean study, up to 50% of elderly stroke women had no temporal windows.[1]

Duplex and Doppler scans are especially useful in studying the extracranial Internal Cerebral Artery (ICA). Previous studies have shown that patients with non-disabling strokes due to severe extracranial ICA disease (70%-99% stenosis) have a 30% risk of recurrent stroke in 2 years that is significantly reduced by carotid endarterectomy.[2] There is some variation in the measurement of ICA stenosis depending on modality used to identify stenosis and the method of measurements used. Duplex and Doppler ultrasound allow rapid & non-invasive means of identifying severe stenosis. Duplex scanning visualises stenotic lesions (unless there is heavy calcifications, causing artifacts) while Doppler scans measure the turbulent flow at the site of these lesions. The combination of a tight Duplex stenotic lesion with high systolic and diastolic velocities on Doppler accurately identifies a severe symptomatic stenosis. Such disease is rare in the Asian population; local Singaporean data have shown that 70-100% disease is found in less than 7% of patients.[3]

Computed Tomographic Angiography (CTA) & Magnetic Resonance Angiography (MRA) are not limited by absence of temporal windows. However, caution is need with CTA if patients suffer from renal impairment. They have the added advantage of not being dependent on trained sonographers.

With the above investigations, there is a limit to the spatial resolution of smaller vessels, which is best studied on cerebral angiography, the "gold standard" for diagnostic imaging of the cerebral vasculature. However, it is invasive and associated with a less than 1% risk of major stroke or death especially with advanced age, elevated serum creatinine, hypertension, and a lengthy angiographic time.

Other Imaging modalities such as Single–photon emission computed tomography (SPECT) and Positron Emission Tomography (PET) are not widely used clinically, and are more investigational. SPECT provide information about perfusion and can demonstrate local hypoperfusion in acute stroke.

The patient's presentation and physician's clinical suspicions should dictate laboratory investigations. In a typical elderly stroke patient, a screen for diabetes and hyperlipidaemia is warranted. Lifestyle factors should be analysed, as the coexistence of many contributory diseases increases the risk of stroke and its recurrence.

Young patients with stroke should be aggressively investigated for treatable conditions. These include screening for hematologic diseases that promote thrombosis, such as protein C or S deficiency, and autoimmune diseases like the antiphospholipid syndrome or systemic lupus erythematosis. The list of diseases that cause young/unusual stroke is long, and a detailed clinical history may clue in to the course of investigation. For instance in a drug offender, cocaine abuse should be sought for while in a young woman, oral contraception increases risk of stroke.

With the combination of vascular and laboratory studies, the physician can usually arrive at a conclusion to the type of stroke suffered, anticipate the neurological prognosis for recovery and determine the cause of the stroke. With this, he can also better plan at secondary preventive measures, including the use of anti-thrombotics (anti-platelets or anticoagulants) and other specific medications or surgeries aim at reducing the risk of recurrent strokes.

MEDICAL MANAGEMENT

Acute stroke is an unstable situation. About 20% will deteriorate within the first week. Therefore, all patients with acute stroke are best managed in a hospital in a Stroke Unit (SU).[4] An SU typically refers to a geographical location where stroke patients are cohorted and managed by a multidisciplinary team of healthcare professionals trained in the care of stroke patients. An SU can also be a mobile team of healthcare professionals moving around the hospital, caring for stroke patients wherever they may be. A geographical location is preferred over a mobile team. SUs reduce mortality, morbidity and institutionalisation post-discharge; in addition, patients receive earlier therapy and length of stay (and thus costs) may be reduced. Care

may be better coordinated by using stroke care paths.

Thrombolysis is efficacious if administered very soon after the onset of ischaemic stroke, increasing the chance of full recovery by 30%.[5] Treatment within 3 hours reduces poor outcomes by 42% (95% CI – 26% to 54%). However, it is currently impossible to predict reliably who will develop fatal intracranial haemorrhage post-thrombolysis. Thrombolysis is best performed in specialist centres with expertise in its administration and in the management of its complications. The use of other agents that affect coagulation in ischaemic stroke is being investigated, and a trial of an agent that reduces continued bleeding in cerebral haemorrhage is in progress.

The search continues for neuroprotectants that are safe and effective in protecting the ischaemic penumbra from further damage.[6] Only nimodipine has been found to be effective in protecting the brain from the ischaemic effects of vasospasm from SAH.

The following medical and nursing measures should be instituted early:

1. Close observation – For neurological deterioration. While the Glasgow Coma Score (GCS) is widely used, a more appropriate method may be a stroke-specific scale, such as the National Institutes of Health (NIH) Stroke Scale or the Orgogozo scale.
2. Correct hypoxia – Supplemental oxygen needs to be given if there is evidence of hypoxia (e.g., low oxygen saturation).
3. Avoidance of aggressive reduction of elevated blood pressure (BP) – BP is often elevated post-stroke, due to stress, fear, pain or loss of cerebral autoregulation. It usually comes down spontaneously over the following hours without any specific interventions. BP can usually be left untreated as long as it is below 200 to 220 mmHg, unless there is a pressing indication to lower it, such as acute myocardial infarction, cardiac failure, aortic dissection or cerebral haemorrhage.
4. Maintenance of normoglycaemia – Hyperglycaemia in the setting of acute stroke is associated with a poor outcome. Insulin may be needed to lower elevated blood sugar. Dextrose-containing solutions are best avoided.
5. Control hypothermia – Hypothermia is associated with a poor prognosis. Antipyretics are used; antibiotics may be needed if a bacterial infection is the cause.
6. Adequate nutrition – Patients should receive adequate food and water, appropriate to their needs. This may need to be modified in the setting of hypertension, diabetes mellitus, hyperlipidemia, obesity, etc.
7. Prevent complications – The risk of aspiration is reduced by a careful dysphagia screen followed by appropriate feeding regimens. Urinary infection risk is lowered by the avoidance of in-dwelling catheters and good perineal hygiene. Risk of constipation and urinary retention can be reduced by laxatives and stool softeners, and the chance of developing decubitus ulcers can be lowered by regular turning and care of pressure points. Finally, the risk of deep venous thrombosis is decreased by the use of graduated stockings and subcutaneous heparin.

SURGICAL MANAGEMENT

There is only a limited role for surgery in acute stroke.[7] Decompression of large cerebral infarcts by a wide craniectomy reduces mortality from 90% to 50%, with some reduction in mortality; it is best reserved for young patients with a large non-dominant hemisphere infarct.[8] Cerebellar decompression is usually performed for life-threatening large cerebellar infarcts and haemorrhages. Extraventricular drainage is performed for acute hydrocephalus. The routine removal of intraparenchymal haematomas does not confer benefit.

SECONDARY PREVENTION

The risk of a recurrent stroke ranges from 5% to 15% per year. Appropriate secondary prevention measures depend on the underlying mechanism of the stroke:

1. Atherothrombosis – Antiplatelets reduce the risk of recurrent vascular events by up to 22%.[9] Regimens include aspirin (50 to 325 mg/day), clopidogrel (75 mg/day), ticlopidine (250 mg bid) and low-dose aspirin (25 mg bid) plus slow-release dipyridamole (200 mg bid). Treatment is life-long. The early initiation of aspirin within 48 hours after an ischaemic stroke confers additional recurrence reduction in as little as 2 weeks.
2. Atheroembolism from moderate or severe carotid stenosis – Carotid endarterectomy (CEA) by an experienced surgeon, plus aspirin, can reduce recurrent stroke by up to 65%.[10] Angioplasty and stenting are still investigational, and are best reserved for patients unable to undergo CEA.
3. Cardioembolism – Anticoagulation with warfarin, with a target international normalised ratio (INR) of 2 to 3, reduces recurrent embolism by 66%.[11]
4. Ruptured aneurysms - Good grade patients can be clipped surgically. The insertion of Guglielmi coils also reduces recurrent rupture.
5. Ruptured AVM – These can be excised surgically, embolised using special “glue”, or obliterated by gamma knife surgery. Combination treatment may be needed.
6. Blood pressure lowering – After the acute phase of stroke is over, blood pressure lowering using angiotension converting enzyme inhibitor (ACE-I)-based regimens further reduces the risk of stroke.[12] This applies to ischaemic and haemorrhagic stroke, and hypertensive and non-hypertensive patients.
7. Lipid lowering – Lowering of lipids using statins also reduces the risk of stroke recurrence by 25%.[13]
8. Diabetes mellitus needs to be controlled, smoking must stop and hormone replacement therapy should be discontinued.

REHABILITATION

About 10% to 30% of stroke victims recover fully, 30% recover partly and 30% do not recover at all. About 10%

die in hospital. Rehabilitation is the cornerstone of stroke management. It aims to train the stroke survivor to be independent, as well as to reduce complications. It should be started as soon as possible post-stroke. Rehabilitation includes passive ranging, active movements and intensive regimens. Training may be needed to regain competence in the activities of daily living. Dysphasia and dysphagia may also need to be addressed. The multidisciplinary team led by an experienced physician will also need to work with the family, and educate the patient and family on the disease.

A caregiver may need to be identified and trained to provide good after-care following hospital discharge. After a period of intensive therapy, the patients may benefit from continued rehabilitation in a step-down facility before going home.

Careful attention will need to be given to the hemiplegic arm. Painful shoulder subluxation is not uncommon, and contractures may develop in poorly exercised limbs. Caregivers need to look out for the complications often suffered by patients who are bed-ridden or severely disabled, such as pneumonia, urinary infection and decubitus ulcers.

Depression is often overlooked, and may impair return to optimal function. Early treatment is helpful. Recurrent stroke or a particularly located stroke may cause vascular dementia.

CONCLUSION

Stroke is a devastating manifestation of atherothrombosis. Efforts should be made to prevent stroke by blood pressure control, cessation of smoking, treatment of atrial fibrillation, lipoid lowering in those with coronary artery disease, treatment of TIAs and a healthy lifestyle. The treatments for acute and completed stroke are efficacious when applied appropriately, but none are able to repair fully the damaged brain. Prevention remains the key.

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LEARNING POINTS

1. **Stroke occurs when a part of the brain is damaged due to lack of blood flow, either from occlusion or rupture of brain arteries.**
2. **The common clinical features of stroke include hemiparesis, hemianasthesia, dsyarthria, dysphagia dysphasia, hemianopia, diplopia, incoordination, giddiness, severe headache and loss of consciousness.**
3. **Important differential diagnoses of stroke include intracranial mass lesions(e.g. tumour, subdural haemorrhage) and infections(e.g. abcess, encephalitis), metabolic derangements(especially hypoglycemia), immune diseases(e.g. multiple sclerosis) and uncommon complications of other neurological illnesses(e.g. complicated migraine, post-seizure Todd's paralysis).**
4. **Computed Tomography of the head and magnetic resonance imaging will resolve "what and where" is the stroke.**
5. **Treatments aim to reduce recurrence, prevent and detect complications, and early rehabilitation, all in the setting of a geographically-placed acute stroke unit.**