STROKES: CLASSIFICATION, INTERVENTION, & PREVENTION

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Introduction

Cerebrovascular disease is the fifth leading cause of death in the United States, preceded by heart disease, cancer, chronic lower respiratory disease, and unintentional injuries, respectively (1). Cerebrovascular disease can be divided into ischemic stroke and hemorrhagic stroke. Ischemic stroke accounts for 87% of all strokes (2). Ischemic stroke can be caused by large vessel disease, small vessel disease, cardiogenic embolism, stroke of other determined etiology, and cryptogenic stroke (3). Hemorrhagic stroke can be divided into intracerebral hemorrhage (10%), subarachnoid hemorrhage (3%). The annual incidence of stroke is 795,000 and about 24% are recurrent stroke (2). Stroke is the leading cause of disability in the adult population (4). Ischemic stroke will be emphasized in this presentation.

Classification

Using the TOAST criteria, ischemic stroke etiologies include large vessel disease, small vessel disease, cardiogenic embolism, other determined etiology, and cryptogenic (3). Etiology is important to identify as the treatment may be different.

Large vessel disease involves atherosclerotic disease of the major cerebral or precerebral arteries. Carotid endarterectomy or carotid artery stenting should be considered if there is evidence of symptomatic 70-99% stenosis. Benefit is not as clear in patients with 50-69% stenosis. Intervention should be considered within two weeks if the stroke burden is small. The SAMMPRIS trial supports medical management for treatment of symptomatic intracranial with use of dual antiplatelet therapy for 90 days followed by aspirin monotherapy and intense risk factor control (9).

Small vessel disease is also known as lacunar strokes. Lacunar strokes are commonly associated with diabetes and hypertension. The location involves brainstem or subcortical regions and are <1.5cm in diameter.

Cardiogenic embolism should be considered when an arterial occlusion is thought to be related to embolism originating from the heart. Etiologies include atrial fibrillation, left atrial or ventricle thrombus, mechanical prosthetic valve, infective endocarditis, myocardial infarction, cardiomyopathy. If atrial fibrillation is identified, anticoagulation with warfarin or novel anticoagulant drugs (apixaban, dabigatran, or rivaroxaban) should be considered. The CHADS2 VASC score can be used to predict stroke risk. Infective endocarditis should be considered if there is concomitant fever and treated with targeted antibiotics rather than antiplatelet or anticoagulation therapies.

Other determined etiologies include rare causes including migraine, dissection, hypercoagulable states, hematologic disorders, and vasculitis. Cryptogenic causes account for about 25% of ischemic strokes. Considerations for evaluation outside of standard workup could include prolonged cardiac monitoring, transesophageal echocardiogram, hypercoagulable labs, catheter angiography, and rarely testing for occult malignancy, genetic syndromes (MELAS, CADASIL, etc), lumbar puncture with CSF for primary cerebral vasculitis.

Evaluation should include neuroimaging. Non-contrast CT Head is most sensitive for hemorrhagic stroke. Hemorrhagic strokes will be hyperintense on CT whereas ischemic stroke will be hypodense on CT. A negative CT head does not rule out acute ischemia. MRI brain is more sensitive for acute stroke and should be obtained if it is not contraindicated in the patient. Gadolinium is not required for evaluation of acute ischemic stroke. Acute stroke appears hyperintense on diffusion weighted images (DWI) and hyopintense on apparent diffusion coefficient (ADC) sequences. Cerebrovascular imaging should include a CT angiogram of the head and neck or MR angiogram of the head and neck. If there are contraindications to CTA/MRA then Carotid Doppler could be considered. Transcranial Doppler imaging may be beneficial in select cases. Catheter angiography is the gold standard, is most sensitive and specific of all cerebrovascular imaging, and is utilized in select cases.

Cardiac evaluation should include ECG, telemetry, and transthoracic echocardiogram. Transesophageal echocardiogram should be considered in stroke when there is suspicion for infective endocarditis and cryptogenic stroke.

Laboratory studies should include metabolic panel, complete blood count, fasting lipid panel, hemoglobin A1C. Hypercoagulable studies should be considered in select cases.

Physical, occupational, and speech therapy should be considered along with inpatient rehabilitation evaluation.

Intervention of Ischemic Stroke
Intravenous (IV) tissue plasminogen activator (tPA) is recommended for patients within three hours of stroke symptom onset and can be considered from 3-4.5 hours (5). In 1995, the three-hour window was supported by the NINDS stroke trial which demonstrated the following major points: at least 30% of the treatment group had minimal to no disability at three months, no increase in mortality despite a 6% incidence of symptomatic intracranial hemorrhage. Selection criteria in this trial is in the list below.

Selection Criteria NINDS		
Time of onset (last known well) <3 hours	A deficit measurable on NIHSS	No evidence of ICH on CT
Exclusion Criteria NINDS		
Prior stroke or serious head trauma within 3 months	Suspicion of SAH	Current anticoagulant use with PT > 15seconds or INR> 1.7
Major surgery within 14 days	GI or GU hemorrhage within 21 days	Heparin use within 48 hours with elevated PTT
History of ICH	Arterial puncture at non-compressible site within 7 days	PLT <100,000
SBP >185 or DBP >110	Seizure at onset of stroke	Blood glucose <50 or > 400
Rapidly improving or minor symptoms		

In 2008, the ECASS 3 trial was published demonstrating support the extended time window 3-4.5 hours (6). Additional exclusion criteria included age >80, NIHSS $\geq$25, a past history of prior stroke and diabetes, and use of anticoagulants regardless of INR.

In 2015, the American Heart Association/American Stroke Association published new guidelines regarding endovascular treatment (8). Endovascular intervention includes administration of intra-arterial (IA) tPA directly at the site of occlusion and/or mechanical embolectomy. Endovascular intervention should be considered when the patient has an associated arterial occlusion. In previous studies, data did not show significant benefit using first generation mechanical embolectomy devices and/or IA tPA. Newer devices, classified as stent retrievers, now show benefit in reducing disability. The use of other classes of devices may be reasonable in some cases.

In order to qualify for endovascular intervention, you must have a related occlusion, NIHSS score of $\geq$6, age $\geq$18, and recommend treatment be initiated within six hours of symptom onset. While it is unclear if there is benefit after six hours, the sooner treatment is initiated the more likely you are to see benefit. Endovascular treatment should not preclude IV tPA. *How do I know if there is an associated occlusion*? A plain CT head without contrast helps tell you if there is any blood or if there is evidence of early or late ischemia. The CT can sometimes show a hyperdense sign suggestive of an arterial clot. A negative CT head does not rule out acute ischemic stroke. MRI is more sensitive in demonstrating acute ischemia. CT Angiogram or MR Angiogram of the head and neck will show you if there is a large artery occlusion.

If a patient presents outside of the acute interventional time window for tPA or embolectomy then antiplatelet therapy should be considered.

In the acute setting, penumbra protection should include permissive hypertension for the first 24 hours. If not treated with thrombolytic therapy blood pressure should be treated if >220/120. If treated with thrombolytic therapy, the blood pressure should be treated if >180/105. Other considerations include maintaining normothermia and euglycemia.

Cerebral blood flow is maximized in the supine position and should be considered in the first 24 hours if tolerated and the patient is not at risk of elevated intracranial pressure, aspiration, and cardiopulmonary decompensation.

Intravenous isotonic fluids should be utilized in the acute setting in most cases. Treatment should be individualized depending on cardiac and metabolic status. Fluids containing glucose and hypotonic solutions should be avoided as it may exacerbate cerebral edema and hyperglycemia.

Prevention
Many strokes can be prevented by optimal risk factor management including hypertension, diabetes, hyperlipidemia, obesity, and tobacco and alcohol use.

Antiplatelet therapy should be utilized for secondary stroke prevention. The MATCH trial has shown that dual anti-platelet therapy increases the risk of hemorrhage and does not provide improved stroke prevention in most cases; exceptions include SAMMPRIS trial as referenced above.

Hypertension is the most common risk factor for stroke. Aggressive blood pressure management should include a goal of <140/90. Initiation of anti-hypertensives in the acute settings depends on the size of the stroke and often started within 24-48 hours.

Glycemic control is important and all stroke patients should be screened for diabetes with use of hemoglobin A1C with a goal of <7.0.

Statins should be considered in patients with ischemic stroke. In the SPARCL trial, Atorvastatin 80mg/day showed benefit for secondary prevention (10). Patients intolerant of high-intensity statins should be placed on moderate intensity statins if tolerated. Target LDL should be <70 however statins can be considered for cholesterol levels that are at goal if etiology is thought to be atherosclerotic.

Moderate intensity exercise is recommended at a minimum of 3 x a week for a duration of ≥40 minutes. Instruct patients that moderate intensity exercise should cause the patient to break a sweat and increase heart rate. A BMI target of <25. A Mediterranean diet should be advocated. Screening for sleep related breathing disorders like obstructive sleep apnea should be considered as well.

Smoking cessation should be addressed at every visit. Alcohol cessation should be eliminated or limited to <1-2 units/day.

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