Cerebrovascular Disease

I. INTRODUCTION

Cerebrovascular disease (CVD) includes all disorders in which an area of the brain is transiently or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process.

CVD is the third leading cause of death after heart disease and malignancy and it is estimated that an average of 500,000 new strokes will occur each year in the USA. CVD is the most disabling of all neurologic diseases. Approximately 50% of survivors have a residual neurologic deficit and greater than 25% require chronic care.

Stroke incidence and mortality are declining primarily due to the successful treatment of HTN and control of risk factors.

II. CLASSIFICATION OF CEREBROVASCULAR DISEASE

- Atherothrombotic
  - Hemodynamic/occlusive
  - Artery-to-artery emboli
  - Small-artery lipohyalinosis
  - Lacunes
  - Other mechanisms
- Atrial fibrillation
- Ischemic heart disease
- Valvular heart disease
- Prosthetic cardiac valves
- Infective endocarditis
- Other, less common
- Dissections
- Hypercoagulable states
- Vasculitis
- Systemic hypotension

Acute stroke

Hemorrhage
- Intracerebral
- Subarachnoid

85% Infarction

80% Cerebrovascular disease

15% Cardiogenic embolism

5% Other, unusual
III. ISCHEMIC/EMBOLIC STROKE

A. ANATOMY

1. Carotid Artery distribution—carotid arteries perfuse the majority of the cerebrum

   Common Carotid Artery-->splits into the Internal Carotid Artery and the External Carotid Artery, then the Internal Carotid Artery-->divides into the Anterior Cerebral Artery (ACA) and the Middle Cerebral Artery (MCA); both a left and right side are present

   a. ACA-supplies the medial surface of the frontal lobe, parietal lobe and occipital lobe

   b. MCA—the largest branch of the internal carotid artery

2. Vertebrobasilar Artery distribution—perfuses base of cerebrum and majority of cerebellum

   2 Vertebral Arteries-->join to form the Basilar Artery-->branching from the Basilar Artery are the 2 Posterior Cerebral Arteries (PCA)

   a. Basilar Artery and PCA-supply the occipital lobe, brain stem and cerebellum
Imaging Acute Stroke
Conventional Imaging

- Abnormal vascular density / signal
- Vascular enhancement
- Loss of gray / white contrast
- Cortical swelling
- Suleal effacement
- Ventricular compression
B. CLASSIFICATION OF ISCHEMIC EVENTS

(These are based on the temporal course and eventual outcome.)

1. Transient Ischemic Attacks (TIAs)

   a. episodes of a temporary reduction in perfusion to a focal region of the brain causing a short-lived disturbance of function

   b. the patient experiences a temporary focal neurological deficit such as slurred speech, aphasia, amaurosis fugax (monocular blindness), or weakness or paralysis of a limb

   c. onset is rapid; usually onset is less than 5 minutes

   d. duration usually 2-15 minutes; can last up to 24 hours

   e. symptoms (vary depending on the CNS anatomy involved)

      1. sensation of swelling or numbness of the hand, arm, or one side of the face or tongue
      2. loss of strength in an arm, hand or leg
      3. difficulties in speaking or reading
f. no neurological deficit remains after the attack  
g. one episode in a lifetime to > 20 in one day  
h. may be the only warning of an impending stroke

2. Reversible Ischemic Neurological Deficit (RIND)  
   a. focal brain ischemia in which the deficit improves over a maximum of 72 hours  
   b. deficits may not completely resolve in all cases

3. Cerebral Infarction  
   a. permanent neurological disorder; the patient presents with fixed deficits  
   b. can present in 3 forms:  
      1. stable-the neurological deficit is permanent and will not improve or deteriorate  
      2. improving-return of previously lost neurological function over several days to weeks  
      3. progressing-the neurological status continues to deteriorate following the initial onset of focal deficits; may see a stabilization period, followed by further progression

C. PATHOPHYSIOLOGY

1. Atherosclerosis and subsequent plaque formation results in arterial narrowing or occlusion and is the most common cause of arterial stenosis.

2. Thrombus formation is most likely to occur in areas where atherosclerosis and plaque deposition have caused the greatest narrowing of vessels.

3. Platelet Aggregation  
   a. exposed subendothelium after injury to vessel
b. vessel collagen is exposed to blood triggering "activation" of platelets

c. release of ADP from activated platelets causes platelet aggregation

d. consolidation of platelet-plug by RBCs, coagulation factors, and formation of fibrin network

e. Thromboxane A2 (TX A2) is produced by platelets and endothelium promoting platelet aggregation and vasoconstriction

4. Coagulation Cascade

a. a series of enzyme complexes located on the surface of platelets and endothelium which lead to thrombin production

b. Thrombin (IIa) then converts Fibrinogen to Fibrin

D. CLINICAL PRESENTATION

Clinically, symptoms depend on the area of cerebral circulation affected and on the extent to which it is affected.

1. Internal Carotid Artery occlusion:

a. no characteristic clinical picture

b. may range from a TIA to infarction of a major portion of the ipsilateral (on the same side) hemisphere

c. if adequate intracranial collateral circulation is present, may see no signs or symptoms

d. Neurological symptoms:

   1. monoparesis to hemiparesis with or without a defect in vision
   2. impairment of speech or language
   3. transient monocular blindness

2. Middle Cerebral Artery occlusion:
a. most occlusions in the first portion of this artery are due to emboli and typically produce a neurological deficit

b. opportunity for collateral circulation is restricted to anastomotic blood flow from the anterior and posterior cerebral arteries on the surface of the brain

c. Neurological symptoms:

1. hemiplegia (paralysis of one side of the body)
2. hemisensory deficit
3. hemianopsia (blindness in 1/2 of the visual field)
4. aphasia (if infarct is in the dominant hemisphere)

3. Anterior Cerebral Artery occlusion:

a. Neurological symptoms:

1. weakness of the opposite leg with or without sensory involvement
2. apraxia (particularly of gait)
3. possible cognitive impairment

4. Vertebrobasilar system:

a. Neurological symptoms:

1. severe vertigo, nausea, vomiting, dysphagia, ipsilateral cerebellar ataxia
2. decreased pain and temperature discrimination
3. diplopia, visual field loss, gaze palsies

E. RISK FACTORS

1. Hypertension-most important risk factor for all stroke types; no defined BP indicating increased stroke risk, but risk increases proportionately as BP increases.

2. Heart Disease

   a. CHF
   b. CAD
c. AFib  
d. Rheumatic Heart Disease  
e. LVH  

3. TIAs, prior stroke, carotid bruits  

4. Increased hematocrit, increased fibrinogen  

5. Sickle Cell Disease  

6. Lifestyle Factors  
   a. Age (older)  
   b. Alcohol abuse  
   c. Cigarette smoking  
   d. Drug abuse  
   e. Genetic factors  
   f. Males  

7. Diabetes Mellitus  

8. Migraine HA’s  

9. Retinal emboli  

IV. TREATMENT OF CEREBROVASCULAR DISEASE  

A. GOALS OF THERAPY  
   2. Prevention of initial or recurrent stroke by modifying the underlying pathologic process.  
   3. Reduction of secondary brain damage by maintaining adequate perfusion to marginally ischemic areas and decreasing edema.  

B. TREATMENT OF TRANSIENT ISCHEMIC ATTACKS  
   1. Eliminate or control risk factors.
2. Education of patient regarding risk-factor reduction and signs and symptoms of TIAs and mild stroke.

3. Surgical Interventions
   
   a. **Carotid Endarterectomy (CEA)**
      
      1. surgical removal of the atheromatous plaque
      2. reserved for patients with an ulcerated lesion or clot that occludes \( \geq 70\% \) of blood flow in the carotid artery
      3. may decrease risk of stroke by 60% over the two years following the procedure
      4. vertebral endarterectomy no longer used

4. Endovascular procedures
   
   a. **Balloon Angioplasty**
      
      1. consists of placing a small deflated balloon in the stenosed vessel
      2. the balloon is then inflated pressing the atheromatous plaque against the wall
      3. has a risk of dislodging emboli that can be carried to the brain or retina

   b. **Stent Placement**
      
      1. experimental procedure
      2. consists of placing a stainless steel coil into the vessel which then sticks to wall of artery

5. Antiplatelet Agents
   
   a. **Aspirin**
      
      1. Mechanism of Action
         
         a. inhibition of platelet aggregation
         b. decreases release of vasoactive substances from platelets
         c. **irreversible** inactivation of platelet cyclooxygenase; effect lasts for the life of the platelet (5-7 days)
2. Efficacy

a. ASA has shown clinically significant reductions (22-24\%) in stroke risk and death in randomized trials in patients who have experienced a previous TIA or stroke (secondary prevention)
b. doses have ranged from 50 to 1500 mg/day
c. more recent trials have evaluated lower doses (30 to 325 mg/day); results indicate that lower doses may be as beneficial with less adverse effects
d. some studies suggest that ASA is more effective in men than in women (due to small number of women in studies??)
e. role in primary prevention unclear

b. **Dipyridamole (PERSANTINE)**

1. Mechanism of Action

   a. weak inhibitor of platelet aggregation
   b. inhibits platelet phosphodiesterase

2. Efficacy

   a. clinical trials have not supported the use of dipyridamole in cerebral ischemia
   b. no additive effect found with aspirin

c. **Sulfinpyrazone (ANTURANE)**

1. Mechanism of Action

   a. reversible inhibition of cyclooxygenase

2. Efficacy

   a. clinical trials have not supported use
d. **Ticlopidine (TICLID)**
1. Mechanism of Action

   a. inhibits ADP-induced platelet aggregation
   b. inhibits platelet aggregation induced by collagen, PAF, epinephrine and thrombin
   c. bleeding time prolonged
   d. minimal effect on cyclooxygenase

2. Efficacy

   a. has been shown to reduce the incidence of stroke by approximately 22% in patients who have experienced previous TIAs or stroke
   b. may be more effective than aspirin with less GI effects
   c. no gender difference seen with ticlopidine as with ASA
   d. dosed at 500 mg/day divided into 2 doses (250 mg PO BID)
   e. adverse effects:

       1. diarrhea
       2. rash
       3. increased total serum cholesterol (ratio of HDL:TChol unchanged)
       4. neutropenia occurred in 1-2% of patients; must monitor CBC every 2 weeks for the first 3 months of therapy

   [Clopidogrel : more effective (8.7% relative risk reduction) than Aspirin.]

RECOMMENDATIONS

   A. ASA has been proven to be beneficial in the secondary prevention of TIAs and in decreasing major cerebrovascular events and death; however, the correct dosage is still unknown.
B. The currently recommended dose of aspirin is 325-975 mg/day.
C. The role of aspirin in the primary prevention of TIAIs and stroke is still unclear.
D. Ticlopidine has been proven to be effective in the secondary prevention of TIAIs and stroke. Due to side effects and cost, it should be reserved for those patients who fail or cannot tolerate ASA.

6. Anticoagulation

   a. Warfarin
      
      1. no studies that prove the superiority of anticoagulants over antiplatelet agents
      
      2. may reduce the risk of stroke in patients with a prior MI
      
      3. may be useful in those patients who continue to be symptomatic despite antiplatelet therapy
      
      4. the major exception is in patients with cerebral embolism of cardiac origin
         
         a. chronic anticoagulation with warfarin has been shown to prevent cerebrovascular events in patients with NVAF
         
         b. INR adjusted to between 2.0-3.0

C. Treatment of Acute Cerebral Infarction/Ischemic Stroke

1. Accurate diagnosis is key! A CT Scan must be done to rule out a hemorrhagic stroke before initiation of any treatment.

   a. most patients do not have impaired consciousness in the first 24 hours
   b. if consciousness is impaired, suspect a stroke-related seizure, hemorrhage, hypoxia or increased intracranial pressure

2. Supportive care

   a. Maintain adequate tissue oxygenation: May require airway support and ventilatory assistance. Check for possible aspiration pneumonia.
   b. BP: In most cases, BP should not be lowered. If severe HTN, lower BP cautiously as neurological status may worsen when BP is lowered.
c. Volume status: Correct for hypovolemia and keep electrolytes in the normal range.
d. Fever: treat and look for source of fever.
e. Hypoglycemia/hyperglycemia: Keep under control. Hyperglycemia may worsen the ischemic injury.
f. DVT Prophylaxis: This is a must as stroke patients have a high risk for DVT! It is important to use either sc heparin 5,000 IU q. 8 or 12 hrs. or sc enoxaparin 30 mg q. 12 hrs. plus early ambulation!

3. Pharmacologic Therapy

[Antihypertensive treatemtn in patients with acute stroke:
SBP>230 or DBP>120-140 : Labetalol 10 mg iv(> 1 min), repeated double dose after 10 min, max 160mg.
DBP > 140 : Nitroprusside 1-3ug/kg/min iv infusion.]

a. Recombinant Tissure Plasminogen Activator (r-tPA) Protocol—(For Select Patients Only!!)

1. efficacy is influenced by the length of time between the onset of the stroke and the initiation of treatment

2. rapid diagnosis and immediate administration of tPA increases its efficacy and may limit the potential for hemorrhagic conversion of ischemic stroke

3. Inclusion Criteria:
   a. ischemic stroke within 3 hours
   b. SBP < 185; DBP < 110

4. Exclusion Criteria:
   a. isolated neurological deficit
   b. another stroke or serious head injury within the previous 3 months
   c. INR > 1.7
   d. use of heparin in the prior 48 hours
   e. major surgery in the prior 14 days
f. platelet count < 100,000/mm³

5. tPA dose:

a. 0.9 mg/kg body weight; max. dose 90 mg
b. give 10% of the dose as a bolus over 1-2 minutes and the rest as a continuous infusion over 1 hour
c. No antiplatelets or anticoagulants within 24 hours!!

6. Results:

a. improved outcome with regard to disability and death that persists 3 months after therapy
b. there is a higher incidence of intracerebral hemorrhage (6.4% vs. 0.6%)

b. Intra-arterial Thrombolysis

1. early clot lysis and recanalization in about 50% of the patients with intra-arterial streptokinase and urokinase

2. intra-arterial r-pro UK 6 mg given within 6 hours of the stroke resulted in a 58% recanalization rate vs. 14% with placebo

3. main concern is hemorrhagic transformation of the ischemic lesion

4. risk of bleeding may increase with concomitant heparin

5. should still be considered investigational until further data collected

c. Heparin

1. useful for progressing stroke; questionable role in stable or improving stroke

2. dosing: 50-70 U/kg as a loading dose, followed by 10-25 U/kg/hour; goal PTT 1.5-2.0X control

3. may opt to not use a loading dose in these patients

4. major concerns are conversion of an ischemic stroke into a hemorrhagic stroke secondary to heparin, bleeding and thrombocytopenia
5. careful selection of patients is important
d. **Low-Molecular Weight Heparin (LMWH)**
   1. Org 10172 has been studied in acute stroke patients
   2. synthetic low-molecular-weight fraction of heparin
   3. undergoing investigation in several clinical trials
   4. less risk of hemorrhage(?) and thrombocytopenia(?)
   5. cannot be recommended for treatment until the results of an ongoing multicenter study are reported