Update on Aneurysm and Subarachnoid Hemorrhage

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September 6, 2014

Nothing to disclose

Objectives

- To understand evidence-based recommendations for intracerebral aneurysm (IA) detection and screening.
- To understand the evidence-based treatment algorithms for aneurysmal subarachnoid hemorrhage (SAH).

Epidemiology

- Prevalence of cerebral aneurysms is 3.6-6% (12 million in US)
- Majority are sporadically acquired lesions
- An estimated 50-80% are small and unruptured
- 20% of patients may have multiple aneurysms

Aneurysm Detection

- Most detected incidentally by imaging
- Majority are asymptomatic, unruptured
- Only 6% per year with symptoms
  - Headache (focal or generalized)
  - Cranial nerves (dilated pupil, diplopia, vision loss, dysarthria)
  - Brain stem (weakness, numbness, dizziness)
- Aneurysm rupture may be first symptom
Aneurysm Screening

- General screening not recommended or cost-effective, but remains controversial
- Exceptions in high risk genetic or rare familial conditions
  - Polycystic kidney disease, Ehlers-Danlos Type 4
  - Family history of two first-degree relatives
- Cerebral angiogram gold standard
- Newer imaging modalities commonly used: CTA, MRA

Aneurysm Risk Factors

- Older age
- More common in women
- Regional and ethnic differences
  - Highest prevalence in Japan, Finland
  - Blacks greater than whites
- Modifiable risk factors: HTN, tobacco, stimulants immunodeficiency, excessive ETOH
- Associated with trauma (dissecting), infection (mycotic), atherosclerosis, other vascular malformations (AVM)

Lifetime Rupture Risk

Genetics and Aneurysms

- Familial studies have identified several loci
- Candidate genes found potentially functionally active genes
- GWAS further identified candidate genes, but difficult to replicate

Brown RD and Broderick J. Lancet Neurol 2014; 13: 393-404

Genome-wide microarray-based mRNA and microRNA expression

• Provide unbiased information about molecular mechanisms and the foundation for functional studies.
• Identified 430 upregulated and 617 downregulated genes
• Can be good candidates for molecular markers of rupture-prone IAs and therapeutic targets


Gene expression studies

Genetics Syndromes

• Polycystic kidney disease
• Ehlers-Danlos Type 4
• Neurofibromatosis Type I
• Marfan’s Syndrome
• Pseudoxanthoma elasticum
• Fibromuscular dysplasia

Ehlers-Danlos Type 4

• Occurs in 1:50,000-500,000 persons
• Results in joint hypermobility, fragile skin, easy bruising, and scarring
• Of the five types, type IV is the most common and lethal from deficiency in type III collagen
• Aneurysms associated with this condition tend to form on medium to large arteries.

Neurofibromatosis Type I

• Occurs in 1:3,000-5,000 persons
• Begins at birth and gets progressively worse
• Results in vessel stenosis, vessel rupture, neurofibromas and the abnormal development of the muscles, bones and internal organs
• Aneurysms tend to form in medium to large-sized arteries.
**Marfan’s Syndrome**

- Occurs in 1:10,000 to 20,000 persons
- Aneurysms tend to be saccular, fusiform, or dissecting in the proximal intracranial carotid artery
- Results in elongation of the bones and abnormalities in the cardiovascular system (the heart and blood vessels) and the eyes.

**Polycystic kidney disease**

- PKD1>PKD2
  - 10% risk of cerebral aneurysms
  - Risk of SAH < 1%, cause of death in 20% of patients
  - 18% will have a positive family history of aneurysm
- Common autosomal dominant heritable disorder (1 in 400-1,000 persons)
- Cysts in the kidneys, liver, pancreas, and spleen, and hernias in the groin.
- Hypertension is common (found in 75%), contributing to aneurysm formation and rupture

**Acute evaluation**

- Life-threatening illness that warrants a high index of suspicion
- Misdiagnosis of SAH occurred in as many as 64% of cases prior to 1985, and remains approximately 12% currently
- Misdiagnosis is associated with a 4-fold higher likelihood of 1-year death or disability.

AHA recommendations for evaluation

- CT scanning for suspected SAH, and lumbar puncture for analysis of CSF is strongly recommended when the CT scan is negative.
- Selective cerebral angiography to document the presence and anatomic features of aneurysms is strongly recommended in patients with documented SAH.
- MRA or CTA can serve as useful alternative (Class II).

Class I, Level of evidence B.

High volume centers

- Treatment volume is an important determinant of outcome for intracranial aneurysms – higher volume (>60 cases per year) equals lower mortality and better long-term outcomes.
- High volume centers should have appropriate specialty neurointensive care units, neurointensivists, vascular neurosurgeons and interventional neuroradiologists to provide the essential elements of care.

Why does it matter?

- Transfer from low volume centers is only 15%
- High-volume centers are under utilized <4.5%
- Transfer of patients may be cost-effective
- Lack of awareness of these benefits

Figure 1: Outcomes after SAH

Figure 2: Neurologic Complications after SAH

Objectives

• Rebleeding
• Delayed cerebral ischemia
• Hyponatremia and volume management
• ICU care: Glucose, anemia, temperature control and DVT prophylaxis

Medical Management

Rebleeding

• Up to 14% of SAH patients may experience re-bleeding within 2 hours of the initial hemorrhage
• Re-bleeding was more common in those with a systolic blood pressure >160mm Hg
• Anti-fibrinolytic therapy may reduce re-bleeding

Antifibrinolytic therapy

• Avoid delayed or prolonged antifibrinolytic therapy
• Antifibrinolytic therapy is relatively contraindicated in patients with risk factors for thromboembolism
• Patients treated with antifibrinolytic therapy should have close screening for deep venous thrombosis
• Consider an early, short course of antifibrinolytic therapy
• Antifibrinolytic therapy should be discontinued 2 hours before planned endovascular aneurysm ablation

Rebleeding

• Increased time to treatment is associated with increased rates of preoperative re-bleeding
  – 0 to 3 days, 5.7%
  – 4 to 6 days, 9.4%
  – 7 to 10 days, 12.7%
  – 11 to 14 days, 13.9%
  – 15 to 32 days, 21.5%
• Post-op re-bleeding did not differ among time intervals (1.6% overall)

Preventing Rebleeding

• Early aneurysm repair.
• Surgical clipping or endovascular coiling is strongly recommended to reduce the rate of rebleeding.
• Blood pressure should be monitored and controlled to balance the risk of strokes, hypertension-related re-bleeding, and maintenance of cerebral perfusion pressure
• Treat extreme hypertension (MAP >110 mmHg) with an unsecured, recently ruptured aneurysm

Delayed Cerebral Ischemia (DCI)

**Nimodipine**
- Oral nimodipine (60 mg every 4 h) should be administered after SAH for a period of 21 days
- The value of other calcium antagonists, whether administered orally or intravenously, remains uncertain
- With hypotension, dosing intervals should be changed, or may be discontinued.

**Pressors**
- Patients clinically suspected of DCI should undergo a trial of induced hypertension
- Choice of vasopressor should be based on the other pharmacologic properties of the agents
- Blood pressure augmentation should progress in a stepwise fashion with assessment of neurologic function

**Volume**
- The goal should be maintaining euvolemia, rather than attempting to induce hypervolemia
- Consider a saline bolus to increase CBF in areas of ischemia as a prelude to other interventions
- Hemodilution in an attempt to improve rheology should not be undertaken except in cases of erythrocythemia.

**Endovascular**
- The use of routine prophylactic angioplasty is not recommended
- Endovascular treatment using intra-arterial vasodilators and/or angioplasty may be considered for vasospasm related DCI
- Rescue therapy for ischemic symptoms that remain refractory to medical treatment

DCI Novel Treatment

- Drugs such as statins, sodium nitrite, dantrolene, cilostazol, eicosapentaenoic acid
- Intracranial delivery of nimodipine or magnesium
- Volume strategies with albumin, and target-directed volume goals

Statins

- Patients on statins prior to presentation with aneurysmal SAH should have their medication continued in the acute phase
- Acute statin therapy in statin-naive patients remains controversial for reducing DCI and poor outcomes after SAH
- STASH trial did not detect any benefit in the use of simvastatin 40 mg for long-term or short-term outcome in patients

Hyponatremia

- Na <135 mEq/l occurs in 30-50% of patients
- Associated with hypovolemia in cerebral salt wasting
- Euvolemia or hypervolemia in SIADH/SIAD
- Complex interplay of both with neurohormonal effects:
  - hyperreninemic hypoaldosterone syndrome

Sodium Management

- Do not treat with fluid restriction
- Use extreme caution to avoid hypovolemia if vasopressin-receptor antagonists are used
- Mild hypertonic saline solutions can be used to treat hyponatremia
- Limit free water intake via intravenous and enteral routes
- Hydrocortisone or fludrocortisone may be used to limit natriuresis and hyponatremia
- High dose corticosteroids are not recommended
- Hormonal replacement with stress-dose corticosteroids may be considered

Medical complications

- Fever, hyperglycemia and anemia requiring transfusion were most associated poor neurological outcomes (mRS>2)
- Deep venous thrombosis (DVT) is an important quality outcome with wide practice variability.

- Cardiac and pulmonary complications are common.
- Troponin leak and cardiac dysfunction have been associated with worse outcome.
- Target euvelema in cases of pulmonary edema or acute lung injury
- Standard management of heart failure

Cardiac complications

- Sympathetic stimulation induces catecholamine release in the myocardium
- Leads to impaired systolic and diastolic function, repolarization abnormalities, and myocardial damage
- Definite causal relationship with worse vasospasm and neurological outcome remains unclear

Fever Management

- Growing evidence that fever is associated with poor neurological outcomes
- 25% from non-infectious etiologies
- Small studies of safety of aggressive fever control
- Significant practice variability
- Use of IV paracetamol and acetaminophen in recent studies

Glucose control

- Hyperglycemia is associated with worse outcomes
- Aggressive treatment of hypoglycemia after SAH generally beneficial in subgroup analyses
- Limited safety data on insulin infusion in SAH
  - Microdialysis studies showing cerebral hypoglycemia with low normal serum glucose
  - Target serum glucose <200 mg/dl?

Optimal Hgb/Hct?

- Anemia (Hgb <11 g/dl) occurs in over 80% SAH patients
- Anemia requiring transfusion associated with worse outcome
- Optimal Hgb target is unknown
- Hemodilution advocated for vasospasm
  - Target Hct 30% to optimize O2 delivery and blood viscosity
  - New measures of PbtO2 and microdialysis suggest cerebral hypoxia at these levels
- Transfusion associated with 55% increase risk of thrombotic event per unit transfused

DVT prophylaxis

- Incidence of DVT 1.5-18%, worse in poor grade patients
- Sequential compression devices should be routinely used in all patients
- Unfractionated heparin for prophylaxis could be started 24 h after undergoing surgery
- Unfractionated heparin and low molecular weighted heparin should be withheld 24 h before and after intracranial procedures

Conclusions

• General screening for aneurysms is not recommended, but consideration for familial and genetic risk
• With SAH, emergency management and triage critical
• Neurological and medical complications are common, and have a significant burden on outcomes after SAH
• Future challenge is to incorporate emerging evidence and new technologies to improve our understanding and refine current management strategies
• New evidence-based guidelines can improve our practice variability and target areas for future studies