Moyamoya Disease and Syndrome

Robert J. Singer, M.D.
Department of Neurosurgery
Neurovascular Therapeutics (Adult and Pediatric)
Vanderbilt University Medical Center
Nashville, TN
robert.singer@vanderbilt.edu
MOYAMOYA DISEASE AND MOYAMOYA SYNDROME

R. Michael Scott, M.D., and Edward R. Smith, M.D.
Discussion

• Epidemiology
• Presentation
• Pathophysiological features
• Natural history and prognosis
• Diagnosis
• Screening
• Treatment
Definitions

• Moyamoya Syndrome
  – “something hazy”
  – Predisposition to stroke
  – Usually progressive stenosis of the intracranial internal carotids and their proximal branches (posterior circulation involvement rare)
  – Compensatory neovascularization involving surrounding circulation (external carotids, dural branches, cortical branches...
# Moyamoya Syndrome

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less common (moyamoya syndrome)</td>
<td>10–20</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
</tr>
<tr>
<td>Neurofibromatosis type 1</td>
<td></td>
</tr>
<tr>
<td>Cranial therapeutic irradiation</td>
<td></td>
</tr>
<tr>
<td>Down’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Rare (moyamoya syndrome)</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Congenital cardiac anomaly</td>
<td></td>
</tr>
<tr>
<td>Renal-artery stenosis</td>
<td></td>
</tr>
<tr>
<td>Giant cervicofacial hemangiomas</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td></td>
</tr>
</tbody>
</table>

Moyamoya Disease

• Patients with no known associated risk factors...
• 40% with unilateral disease on initial presentation develop contralateral findings
Moyamoya “pattern”
Epidemiology

- Most common pediatric cerebrovascular disease in Japan (3 per 100,000)
- Reported worldwide
- Peak incidence: 5 and 40
- Female: male... 2:1

Epidemiology (U.S.)

- 0.086 per 100,000
  - 4.6 for Asian Americans
  - 2.2 for African Americans
  - 0.5 for Hispanics

Ucnino K et al. Neurology 2005;65:956-8
### Symptoms at presentation

<table>
<thead>
<tr>
<th>Common</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>50–75</td>
</tr>
<tr>
<td>Transient ischemic attack (including drop attacks)</td>
<td>50–75</td>
</tr>
<tr>
<td>Hemorrhage (in adults)</td>
<td>10–40</td>
</tr>
<tr>
<td>20.0% v. 2.8% in children</td>
<td></td>
</tr>
<tr>
<td>Less common</td>
<td></td>
</tr>
<tr>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td>Rare</td>
<td></td>
</tr>
<tr>
<td>Choreiform movements</td>
<td></td>
</tr>
<tr>
<td>Cognitive or psychiatric changes</td>
<td>Japan 42%</td>
</tr>
</tbody>
</table>

Symptoms at Presentation

• Ischemic
  – Hemiparesis, dysarthria, aphasia, cognitive impairment
  – Seizures, visual deficits, syncope, personality changes
  – May be transient or fixed
    • Provocation by hyperventilation, exertion or dehydration

Tagawa T et al. Stroke 1987;18:906-10
Presentation (Hemorrhagic)

• Location: intraventricular, intraparenchymal (basal ganglia common), or subarachnoid

Courtesy: Michael Ayad, MD, PhD
Presentation

• Headache
  – Meningeal/leptomeningeal dilatation
    • May stimulate dural nociceptors
    • Persists in 63% (despite therapy)
    • Can regress post op...

Presentation

• Choreiform movements
  – Dilatation of collateral vessels in the basal ganglia
  – 8/10 showed symptomatic improvement after revascularization...

Presentation

• Morning glory disk abnormality (MGDA)
  – Enlargement and funneling of the optic disk with retinovascular anomalies (neovascularization)
Pathophysiological features

• Research targets:
  – Pathological analysis of affected tissue
  – Genetic linkage studies
  – Role of angiogenesis and extracellular matrix-related peptides in disease development and progression
Vasculogenesis/Angiogenesis...

Neurolation around 18-24 days

metabolic needs met by diffusion of amniotic fluid
(ends around day 26 when neural tube closes)

neural tube surrounded by meninx primitiva (dural progenitor) which has a vascular plexus
Vasculogenesis/Angiogenesis...

meninx primitiva contains hemangioblastic cells (splanchnopleuric mesoderm)

hemangioblastic cells condense (vasculogenesis) into blood islands and differentiate into stem cells and angioblasts...

congenital vascular malformations develop in this period of differentiation and coalescence...
(no later than the 8th week of development)
Growth factors in vasculo/angiogenesis

VEGF  Angiopoietin  Ephrins

(meditated by endothelial cell tyrosine kinases)

Table 1. Knockout animals from the VEGFR/VEGF, Tie2/Ang, and Eph/ephrin families have exhibited a variety of embryonic defects in vascular development

<table>
<thead>
<tr>
<th>Gene knockout</th>
<th>Time of death</th>
<th>Stage of vessel development</th>
<th>Causes of lethality</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGF-A [+/-]</td>
<td>E11.5</td>
<td>vasculogenesis/ (angiogenesis)</td>
<td>reduced red blood cells, defective heart and aorta formation, defective vessel connectivity, defective sprouting</td>
</tr>
<tr>
<td>VEGF-A [-/-]</td>
<td>E10.5</td>
<td>vasculogenesis</td>
<td>absent dorsal aorta, defective endothelial cell development</td>
</tr>
<tr>
<td>VEGFR-1</td>
<td>E8.5-E9.5</td>
<td>vasculogenesis</td>
<td>failure of endothelial cell formation</td>
</tr>
<tr>
<td>VEGFR-2</td>
<td>E8.5-E9.5</td>
<td>vasculogenesis</td>
<td>excess endothelial cells form abnormal vessel structures entering vessel lumens</td>
</tr>
<tr>
<td>VEGFR-3</td>
<td>E10.5-E12</td>
<td>vasculogenesis</td>
<td>defective vessel remodeling and organization, irregular large vessels with defective lumens</td>
</tr>
<tr>
<td>Ang1</td>
<td>E10.5</td>
<td>angiogenesis</td>
<td>defective vessel remodeling, organization, and sprouting, heart trabeculation defects</td>
</tr>
<tr>
<td>Ang2</td>
<td>E12.5-P1</td>
<td>maturity</td>
<td>poor vessel integrity, edema, and hemorrhage</td>
</tr>
<tr>
<td>Tie1</td>
<td>E13.5-P1</td>
<td>maturity</td>
<td>poor vessel integrity, edema, and hemorrhage</td>
</tr>
<tr>
<td>Tie2</td>
<td>E10.5</td>
<td>angiogenesis</td>
<td>defective vessel remodeling, organization, and sprouting, heart trabeculation defects</td>
</tr>
<tr>
<td>ephrin-B2</td>
<td>E10.5</td>
<td>(vasculogenesis)/angiogenesis</td>
<td>some defective vessel primordia, defective vessel remodeling, organization, and sprouting, heart trabeculation defects</td>
</tr>
<tr>
<td>EphB2/EphB3</td>
<td>E10.5 (~30%)</td>
<td>(vasculogenesis)/angiogenesis</td>
<td>some defective vessel primordia, defective vessel remodeling, organization, and sprouting, heart trabeculation defects</td>
</tr>
<tr>
<td>EphB4</td>
<td>E10.5</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>EphA2</td>
<td>viable</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>
Pathophysiologica\textbackslash{}l features

- Smooth muscle cell hyperplasia and luminal thrombosis
- Attenuation of the media with irregular elastic lamina
- Caspase-dependent apoptosis implicated as a contributory mechanism in arterial wall degredation
- Collaterals demonstrate fragmented elastic lamina, thinned media and microaneurysms (likely cause of hemorrhage) $2^\circ$ hemodynamic shear stress

Pathophysiological features

• Genetics (polygenic or AD with incomplete penetrance)
  – 6-10% proportion of first degree relatives with moyamoya
  – Associated loci on chromosomes 3, 6, 8 and 17(q25) mutation affecting TIMP-2 (tissue inhibitor of matrix metalloproteinase type 2)
  – HLA haplotypes have been described

Mineharu Y. Neurology 2008;70:2357-63
Pathophysiologica l features

• Angiogenesis and extracellular matrix related peptides
  – Increased BFGF, TGFβ-1, HGF, VEGF, HIF1-a, MMP, and intracellular adhesion molecules
  – Mechanisms of interaction are not well described

Natural History and Prognosis

• Rate of progression is high
• 2/3 have symptomatic progression over a 5 year period
• Outcome poor without treatment
• Rate of progression after surgery: 2.6%
• Neurologic status at the time of treatment predicts long-term outcome (early diagnosis is important…)

Diagnosis

- Pursue in the setting of unexplained symptoms referable to cerebral ischemia (particularly in children)
- Several imaging modalities are used...
Diagnosis (CT)

Ischemic

Hemorrhagic
“ivy” sign on FLAIR images suggests poor cortical flow

Diagnosis (Angiography)

Grade 1

Grade 4

Table 2. Suzuki Grading System.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Narrowing of ICA apex</td>
</tr>
<tr>
<td>II</td>
<td>Initiation of moyamoya collaterals</td>
</tr>
<tr>
<td>III</td>
<td>Progressive ICA stenosis with intensification of moyamoya-associated collaterals</td>
</tr>
<tr>
<td>IV</td>
<td>Development of ECA collaterals</td>
</tr>
<tr>
<td>V</td>
<td>Intensification of ECA collaterals and reduction of moyamoya-associated vessels</td>
</tr>
<tr>
<td>VI</td>
<td>Total occlusion of ICA and disappearance of moyamoya-associated collaterals</td>
</tr>
</tbody>
</table>

*Data are from Suzuki and Takaku. ECA denotes external carotid artery, and ICA internal carotid artery.


Diagnosis

- EEG- “rebuild-up” phenomenon, occurs after hyperventilation (monophasic slow waves), indicates diminished cerebral perfusion
- Transcranial Doppler (TCD)
- Perfusion studies to assess flow...
  - CTP, Xenon CT, Acetazolamide SPECT
Diagnosis (Diamox SPECT)
Treatment

- Does not reverse primary disease process
- Protects against further strokes by improving hemispheric blood flow
- Medical therapy
  - Antiplatelet agents for microthrombi
  - Calcium channel blockers for headache
Treatment

• Surgery
  – External carotid is spared by the disease and used for revascularization
    • Direct and Indirect approaches
      – direct: superficial temporal artery (STA) to middle cerebral artery (MCA)
        » can be difficult in children due to small caliber of vessels
        » benefit over indirect methods is debated
Treatment

• STA-MCA bypass (direct)

Courtesy; Gary Steinberg, Stanford University Medical Center
Treatment

- STA-MCA bypass (direct)

-Antiplatelet agents post-op

Courtesy; Gary Steinberg, Stanford University Medical Center
Treatment

• Indirect techniques
  – Omental transplant (1978)
    • STA-gastroepiploic arteries
  – Multiple burr holes
    • +/- dural opening
  – Encephaloduroarteriosynangiosis
    • STA-dura mater
  – Encephalomyoarteriosynangiosis
    • STA/temporalis muscle to pial surface
  – Pialsynangiosis
    • STA-pial surface

Reis CV et al. Neurosurgical Focus 2006
Treatment

- Indirect
  - Pialsynangiosis
PialSynangiosis
Treatment

• Indirect

Burr hole revascularization

Treatment

• **Perioperative/Intraoperative**
  – Additional risk of CVA/ischemia
    • Crying, hyperventilation can potentiate hypocarbia
    • Pain control is essential
    • Normotension/normothermia/hypervolemia
    • Supplemental $O_2$

• **Postop**
  – Volume maintainence (1.25-1.50 times normal maintenance for 48-72h)
  – Aspirin (325 mg for adults, 81mg for preteen)

Nomura S et al. Childs NervSyst 2001;17:270-4
Treatment

• Results:
  – Stroke reduction is significant postop... roughly 70% will have CVA prior to treatment
  – Postoperative stroke risk drops to around 4%...
  – 87% derived symptomatic benefit with direct/indirect and combined techniques showing equal effectiveness

Future...

- Preconditioning
- Angiogenic triggers
- Treatment for chronic ischemia

- Thanks!
Giant PICA aneurysm with bypass