Rare Causes of Stroke

Jay Hinkle MD
Vascular Neurologist
Washington Regional Medical Center, Fayetteville, Arkansas
Cerebral Venous Sinus Thrombosis

- More common in pediatric population
- In adults more common in younger patients
- Women > Men
- Rarely manifests as a stroke syndrome with sudden neurologic deficits
Venous System

Major cerebral veins and sinuses

- Superior sagittal sinus
- Inferior sagittal sinus
- Superior cerebral veins
- Great cerebral vein (of Galen)
- Straight sinus
- Transverse sinus
- Occipital sinus
- Sigmoid sinus
- Cavernous sinus
- Internal jugular vein
Cerebral Venous Sinus Thrombosis - Causes

- Hypercoagulable States
  - Cancer, pregnancy, genetic, contraceptives

- Infections

- Dehydration

- Trauma

- Dural AV Fistulas
Mechanism for Stroke

Mechanisms of cerebral venous thrombosis

- Obstruction of dural sinuses
- Increased venous pressure
- Venous and capillary pressure
- Capillary perfusion
- Cerebral perfusion
- Cerebral blood flow
- Failure of energetic metabolism
- Cytotoxic edema
- Parenchymal hemorrhage
- Vasogenic edema
- Impairment of CSF absorption
- Impaired intracranial pressure
- CSF: cerebrospinal fluid
CVST - Symptoms

- Increased ICP – Headache, nausea, emesis, visual changes, papilledema
- Encephalopathy, Coma
- Seizures
- Focal neurologic signs
- Can present with ischemic and hemorrhagic stroke
Imaging in CVST
Treatment of CVST

• Anticoagulation
  • Typically 3-6 months if provoked then repeat imaging to assess for recanalization
  • Unprovoked: 6-12 months
  • Recurrence or underlying hypercoagulable state: Indefinite treatment

• Treatment of coexisting infection

• Lumbar puncture, lumbar drain, Acetazolamide for increased ICP

• Antiepileptic medications

• Endovascular thrombectomy
  • For patients who continue to decline despite anticoagulation
  • Involvement of deep venous system
  • Coma
MELAS

- Mitochondrial inheritance

- Point mutations in DNA affecting proteins involved in intracellular energy production

- Increased anaerobic metabolism and elevated lactic acid

- Myopathy, seizures, stroke, encephalopathy/dementia, short stature, diabetes, cardiomyopathy, hearing loss, psychiatric disorders
• “Stroke-like” episodes: cortical blindness, hemianopsia, hemiparesis

• Neuronal hyperexcitability, edema, breakdown of blood-brain barrier

• Vascular endothelial dysfunction, impaired vasodilation

• MR-Spectroscopy, CSF and serum lactate, EMG, Muscle biopsy

• Evidence for treatment is lacking
  • Arginine, Citrulline, CoQ10, Vit K1, K3, C, Riboflavin, Dicholoroacetate, Creatine
Moya-Moya

- Non-atherosclerotic, non-inflammatory narrowing/occlusion of larger arteries, typically distal internal carotid arteries inside the skull
- Japanese term for “puffy”, “obscure”, “hazy” used to describe angiographic appearance of collateral circulation which develops
- Chronic and progressive disorder
- Unknown etiology but thought to be genetic
• Can present during childhood and adulthood
• Ischemic strokes more common in children
• Hemorrhagic strokes more common in adults
• Primary Moya-Moya Disease

• Secondary Moya-Moya Syndrome
  • Atherosclerosis
  • Down Syndrome
  • Neurofibromatosis
  • Cranial radiation
  • Meningitis
  • Autoimmune disorders such as Lupus
  • RBC disorders: polycythemia, Sickle Cell, Thalassemias
Moya-Moya Pathology

- Involves stenosis and/or occlusions of the distal internal carotid arteries bilaterally

- Proximal middle cerebral and anterior cerebral arteries also involved

- Pathology:
  - Thickening of the intima
  - Tortuosity or duplication of elastic tissue layers of arteries
  - Decreased muscular layer of arteries
Moya-Moya Treatment

- Aspirin favored over anticoagulation given risk of hemorrhage
- Calcium channel blockers, dipyridamole for vasodilatory effect
- IV-tPA has not been tested. Use caution given risk of hemorrhage
- Monitor for coexisting CV risk factors, Radiation history
- Rule out infectious/inflammatory vasculitis conditions
- Surgery: Aim to improve blood flow to ischemic areas and reduce stress on small collateral vessels which can result in hemorrhage
Surgical Options for Moya-Moya

Associated with better collateralization and clinical improvement, more difficult to perform, immediate.

Direct STA – MCA Bypass

Indirect Bypass – Encephaloduroarteriosynangiosis (EDAS)

May be safer, preferred in pediatric patients and older patients with medical comorbidities

More hemorrhagic complications –
Cervical Artery Dissection

- Overall not common but in young patients accounts for 20% of strokes

- Tear in the wall of the artery

- Traumatic and nontraumatic

- They typically occur in the extracranial segments of arteries where it is more mobile in the neck
Conditions Associated with Dissection

- Fibromuscular dysplasia
- Ehlers-Danlos Syndrome
- Marfan Syndrome
- Osteogenesis Imperfecta
- Cystic medial necrosis
- Reticular fiber deficiency
- Homocystinuria
- AD polycystic kidney disease
- Alpha-1 antitrypsin deficiency
- Cervical artery tortuosity
Cervical Artery Dissection
Carotid Dissection with development of pseudoaneurysms

Neurology 2010; 64:8.
Symptoms

- Pain ipsilateral to dissection
- Ipsilateral monocular vision loss
- Contralateral neurologic symptoms
- Most symptoms occur early within days to 1 week after onset of pain
- Occlusion or severe stenosis most likely associated with stroke rather than dissection without hemodynamic compromise
- Dissections often asymptomatic and found incidentally
Treatment of Dissection

- Not an exclusion for IV-tPA
- Typically IV Heparin bridging to Warfarin until INR 2-3
- DOACs such as Apixaban, Rivaroxaban, Dabigatran
- Aspirin + Plavix
  - Used for intracranial dissection given risk of SAH with anticoagulants
  - Subacute or chronic discovery of dissection, asymptomatic individuals
- No clear evidence favoring anticoagulation over antiplatelets
  - CADISS Trial
- Anticoagulation for at least 3 months
  - Repeat CT angiogram
  - If continued occlusion/stenosis then continue for another 3 months
  - Recanalization unlikely if occlusion/stenosis still present after 6 months
  - Convert to aspirin at this point
Prognosis of Dissection

- Most strokes occur in the first 1-2 weeks
- Vessel healing occurs in 50-60% after 6 months
- Recurrent Dissection 1-2% per year
- Recurrent ischemic stroke 1-2% per year
- Stroke from development of pseudoaneurysm: 2% in the first 12 months
CADASIL

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

- Mutation in NOTCH3 gene on chromosome 19
  - Transmembrane protein important in vascular smooth muscle development
  - Accumulation of abnormal protein in vessel walls
  - Increased thickness of small arteries and reduction in diameter

- Presents in 30-50 year old age group

- Disorder of small vessels resulting in lacunar strokes
CADASIL - Presentation

• Ischemic events
  • Lacunar strokes

• Cognitive impairment
  • Subcortical, vascular dementia, gait disorder

• Migraine with aura

• Psychiatric symptoms
  • Depression, apathy most common
MRI Brain in CADASIL

Diagnosis of CADASIL

- Genetic testing demonstrating NOTCH3 mutation
- Granular osmiophilic material on skin biopsy

Tikka et. al., CADASIL and CARASIL. Brain Pathology 24, 525 – 544, 2014
CADASIL – Treatment and Prognosis

- No specific treatment
- Screen for typical cardiovascular risk factors
- Aspirin
- Donepezil may help with executive dysfunction
- Early onset does not predict rapid progression
- Age of death 65-70

Sickle Cell Disease

- Autosomal recessive inheritance
- Point mutation in beta chain of hemoglobin which results in polymer formation of hemoglobin inside RBCs
- Decreases elasticity of RBCs, abnormal red blood cell membrane
- Increased adherence to vascular endothelium
- Vaso-occlusions
Cerebrovascular complications with their locations in sickle cell disease

Management of Stroke in SCD

- Thrombolytic therapy: Data is limited, ICH risk is higher
- Aspirin is generally prescribed
- Simple blood transfusion
- Exchange Transfusion
  - Goal HbS < 30% of total hemoglobin concentration
Systemic Vasculitides

- Polyarteritis Nodosa
- Wegener’s Granulomatosis
- Rheumatoid Arthritis
- Cryoglobulinemia
- Takayasu’s Arteritis
- Hepatitis B and C
Primary Angitis of the CNS (CNS Vasculitis)

- Unknown etiology
- Inflammation of cerebral blood vessels
  - Small vessels and leptomeningeal vessels
- Segmental process
- Stroke in less than 20% of cases
- Inflammatory markers not usually elevated
- Not a systemic vasculitis
PACNS - Presentation

- Subacute, step-wise progression
- Headache, nausea, emesis
- Encephalopathy
  - Amnestic states, disorientation, somnolence, coma
- Seizures
- Focal neurologic symptoms develop later
- Systemic signs such as fever and weight loss are uncommon
CNS Vasculitis Work Up

- Cerebrospinal fluid: Modest elevation in protein and WBCs with lymphocytic predominance
- Inflammation segmental with skip lesions
- Cerebral angiography: “beaded” appearance of smaller, distal artery segments
  - Angiography can be normal in up to 40% of cases due to small vessel involvement which may not be visible
- Biopsy can be negative given segmental nature of lesions
Antiphospholipid Antibody Syndrome

- Autoimmune production of antibodies against cell lipids/proteins which alter coagulation pathways

- Binding to glycoproteins which attach to endothelial cells and initiate inflammation and coagulation cascade

- Primary APLS or secondary APLS (Associated with Lupus, infection, drugs such as Procainamide, Hydralazine, Quinidine, Phenothiazones)

- Venous or arterial thrombosis

- Considered in younger patients who develop embolic appearing stroke with no CV risk factors
APLS Clinical Presentation

• Venous Thrombosis: DVT most common

• Arterial Thrombosis: Stroke most common, both large and small vessels

• Miscarriages

• Thrombocytopenia, anemia, Skin changes, renal failure
APLS: Laboratory Testing

- **Lupus Anticoagulant – Most Specific**
  - Functional Assay, diluted Russell viper venom
  - Elevated PTT despite mixing patient’s plasma with normal plasma
  - Correction of prolonged clotting with addition of phospholipids
  - False positive if on heparin

- **Anti-Beta2 Glycoprotein Antibodies – Most Specific**

- **Anti-Cardiolipin antibodies**
APLS - Diagnosis

• Clinical Criteria – 1 or more of the following
  • One or more venous, arterial, or small vessel thrombosis in any tissue or organ, with unequivocal imaging or histologic evidence of thrombosis
  • One or more unexplained deaths of a morphologically normal fetus at ≥10 weeks gestation, or one or more premature births of a morphologically normal neonate before 34 weeks gestation because of eclampsia, preeclampsia, or placental insufficiency, or three or more consecutive spontaneous pregnancy losses at <10 weeks gestation

• Laboratory Criteria - 1 or more of the following, 2 positive results 12 weeks apart
  • IgG and/or IgM cardiolipin antibodies > 40 units
  • IgG and/or IgM anti-beta2 glycoprotein antibodies > 40 units
  • Detection of Lupus Anticoagulant
APLS - Treatment

- Patients with abnormal labs but no history of thrombosis are not prophylactically started on anticoagulation

- Main treatment after diagnosed thrombosis is Warfarin, Goal INR 2-3, Lifelong therapy

- Bridging for surgical procedures necessary with Heparin

- Recurrent thrombosis despite Warfarin
  - Increase INR Goal 2.5-3.5
  - Switch to Enoxaparin

- DOACs such as Rivaroxaban, Apixaban, Dabigatran not tested

- Aspirin typically added for arterial thrombosis such as stroke

- Immunosuppression used with secondary APLS such as Lupus
Various Infections Associated with Stroke and can result in Vascular Appearance

- **S. Pneumonia, N. meningitis**: focal areas of pus, pial/meningeal arteries, tend to result in small cortical infarcts
- **Listeria Monocytogenes**: brainstem arteritis
- **Bartonella Henselae**, “cat-scratch disease”, intracranial artery stenosis
- **Meningovascular Syphilis**: intracranial stenosis, can involve spinal cord
- **Tuberculosis**: Brainstem often involved, arteries of circle of willis and posterior circulation become stenosed
- **Mucormycosis**: Spread of fungal infection through sinuses into brain (frontal lobes) and arteries resulting in stroke
- **Cryptococcus, Coccidiomycosis, Histoplasmosis, Aspergillus**: Basilar meningitis similar to Tuberculosis, involves arteries around brainstem
- **Varicella-Zoster Virus**: Direct invasion of larger arteries resulting in stenosis and stroke. Thought to spread via trigeminal nerves, more common with herpes-zoster ophthalmicus, spreads to ICA, MCA, ACA
- **HIV/AIDS**: Multiple mechanisms: opportunistic infections, medications, typical CV risk factors, drug use, hypercoaguability, malignancy
- **Taenia Solium**: Cysticercosis, pork tapeworm, direct invasion of MCAs, PCAs, ACAs, resulting in arteritis
Conclusion

• Get a good history including family history of disorders that may suggest rare etiology of stroke
• 'Common disorders are common'
• Rare disorders will often have atypical presentation or recurrent events
• Up to Date type resources are helpful