Rare Causes of Stroke (All ages)

- Cerebral venous thrombosis (CVT)
- Sporadic angiopathies
- Genetic angiopathies
- Hereditary connective tissue disorder
- Nonhereditary systemic disorders with skin involvement
- Nonhereditary systemic disorders with eye involvement
- Nonhereditary systemic disorders with eye and ear involvement
- Misc Genetic Disorders
- Substance Abuse
Stroke in Women

- Projections indicate that the prevalence and incidence of stroke will increase by 2020 in both genders, but that these figures are magnified in women.

- By 2050, mortality from stroke will be 30% higher in women than men.

- The social impact of stroke is greater in women because women have poorer functional outcome after stroke.
Stroke in Women

- Stroke is common after menopause
- Less common before menopause.
  - Migraine with aura
  - Cerebral venous thrombosis
  - Postpartum angiopathy (postpartum reversible vasoconstriction syndrome)
  - Oral contraceptives with high content of estrogen
Pediatric Stroke

- Arteriopathy
- Infection
- Cardiac
- Hematological
- Other causes

Pavlakis and Levinson. Stroke 2009;40[suppl 1]:S79-S81
Cerebral Venous Thrombosis
Epidemiology

- Rare condition, 5 people/million/year
- More commonly seen in young individuals
- 30-40% present with ICH
- Mortality and morbidity 6-10%
Treatment

- Heparin therapy, level B
- Concomitant ICH related to heparin therapy is not contraindicated
- Thrombolysis, among patients showing deterioration despite adequate anticoagulation, thrombolysis can be used, possibly in those without ICH
Treatment

- Absence of clear cut guidelines, treatment largely depends on clinical presentation.
- Anticoagulation with heparin is best studied and the only modality with reasonable evidence to support its use in CVT.
- Endovascular therapy carries higher risk of bleeding complications compared to anticoagulation, especially if pre-treatment ICH is present.
Sporadic Angiopathies
Sporadic Angiopathies

- FMD
- Endovascular lymphoma
- Vasculitis
- Call-Fleming syndrome
- Moya-Moya
Fibromuscular Dysplasia

- Noninflammatory arteriopathy
- Affects extracranial cephalic, renal, splanchnic and iliac arteries.

- Clinically
  - Hypertension
  - 1/3 may have cerebral aneurysms
  - Predisposition toward arterial dissections
- Annual risk of stroke about 1-2%
Endovascular Lymphoma

- Fever, dyspnea, cough, hypoxemia
- More frequent in the lung
- High mortality
- CXR – bilateral fine linear infiltrates

Pathology
- Neoplastic large lymphoid cells in the intravascular compartment
Reversible Cerebral Vasoconstriction (Call-Fleming Syndrome)

- **Clinical Symptoms**
  - Acute onset severe headache, nausea, vomiting (mimics SAH and/or migraine)
  - Hypertension
  - Seizures
  - Strokes
- **CSF** - normal (possibly mild pleocytosis)

- **Conditions Associated**
  - Pregnancy, eclampsia, drugs (e.g. cocaine), pheo

- **Treatment**
  - Nimodipine or verapamil
  - ?Glucocorticoids
Moya-Moya Syndrome

- Primary Moya-Moya Syndrome – due to genetic cause - ~10% cases
- Secondary Moya-Moya – due to other cause (e.g. sickle cell disease)
- Means “puff of smoke”
- Pathology – progressive narrowing of the terminal ICA and proximal M1 segments with development of small collateral vessels
Moya-Moya – Clinical Presentation

- Ischemic stroke - 63% (more common in pediatrics)
- Hemorrhagic stroke - 22% (more common in adults)
- Epilepsy - 8% (more common in pediatrics)
- Other - 7% (e.g. cognitive decline)
Associations with Moya-Moya

- Sickle cell disease
- Neurofibromatosis
- Downs syndrome
- Post-radiation
- Heavy smoking
- Estrogens
Surgical Treatments

- Encephaloduroarteriosynangiosis – artery is sutured to the surface of the brain
- Encephalomyosynangiosis – temporalis muscle is placed over the brain
- STA-MCA bypass – superficial temporal artery is connected to an MCA branch (e.g. M4)
Congenital Angiopathies
Congenital Angiopathies

- Sturge Weber
- PHACE
- Hereditary Hemorrhagic Telangiectasia (HHT)
- Cavernous Malformation
Sturge-Weber Syndrome

- 1 in 5000 to 1 in 10,000 births
- Clinical findings
  - Port wine angiomas
  - Cataract and glaucoma
- Neurological
  - AVM, angioma (leptomeningeal, intracerebral, cerebellar and spinal cord)
  - Seizure, occlusive disease, SAH, ICH (more rare)
PHACE Syndrome

- **Posterior fossa**: These are brain malformations that are usually present at birth. These brain malformations do not form after the infant is born.

- **Hemangioma**: The hemangioma usually covers a large area on the skin of the head or neck (greater than 5 cm). The term "segmental" is sometimes used to describe these hemangiomas.

- **Arterial lesions**: The abnormalities of the blood vessels in the neck or head.

- **Cardiac abnormalities/aortic coarctation**: These are abnormalities of the heart or the blood vessels that are attached to the heart.

- **Eye abnormalities**.
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu)

- Autosomal dominant
- Males or females, any ethnicity
- Telangiectasias on skin, nasal and visceral areas
- Epistaxis
- Pulmonary AVMs (predisposes to brain abscess)
- Multiple cerebral AVMs, fistula, sometimes aneurysms
Hereditary Connective Tissue Disorders
Hereditary Connective Tissue Disorders

- Ehler’s Danlos type IV
- Marfans
- Pseudoxanthoma elasticum
- Menke’s syndrome
- Homocysteinuria
Ehlers-Danlos Syndrome

- Type IV is vascular form
  - Abnormal Collagen type III
- Clinical
  - Thin translucent skin (veins easily apparent), easy bruising, hyperextensible small joints
  - Features (large eyes, thin pinched nose, thin lips, slim body)
  - Arterial, intestinal, uterine fragility
- Neurological
  - Intracranial aneurysm, dissections, fistula
- Diagnosis
  - Fibroblast culture, DNA test of COL3A1 gene, skin biopsy shows abnormal collagen
Marfan’s Syndrome

- Autosomal dominant
- Fibrillin gene mutation
- Eye
  - Detached retina, lens dislocation (occurs in 80% of patients)
- Musculoskeletal
  - Arachnodactyly (long slender fingers/toes), high arched palate, long limbs, scoliosis
- Heart
  - Aortic aneurysm, aortic dissection, valvular insufficiency (MVP and AI)
- Neuro
  - Carotid dissection, cerebral aneurysms
Pseudoxanthoma Elasticum

- Congenital or acquired
- Elastic fiber degeneration in the dermis with calcifications

Clinical features

- Sometimes small stature, mental retardation and sex developmental retardation
- Ocular
  - Choroidal lesions with macular degeneration and angioid streaks, “orange peel” retina
- Skin
  - Yellow, leathery, “chicken skin” on neck and flexures
- Neurological
  - Dissections, aneurysms, multiple small vessel infarctions
Nonhereditary systemic disorders with skin involvement
Nonhereditary systemic disorders with skin involvement

- Malignant Atrophic Papulosis (MAP)
- Sneddon’s Syndrome
- Divry-Van Bogaert Syndrome
- Epidermal Nevus Syndrome
- Eosinophil-Induced Neurotoxicity and Cerebral Infarction
- Kawasaki Syndrome
Malignant Atrophic Papulosis (MAP): Kohlmeier-Degos Disease

- Children or young adults
- Sporadic
- 1 in 5000 to 1 in 200,000 patients
- Occlusive endarteropathy/proliferative vasculopathy involving small and medium sized arteries and veins
- Neurologically
  - Multifocal infarcts or hemorrhages
MAP

- Dermatologic
  - Erythematous papules with central atrophy (2-5 mm) on trunk and limbs

- GI
  - Anorexia, diarrhea, abd pain, intestinal obstruction, hemorrhage

- Ophtho
  - Can involve nearly any eye structure (conjuctiva, sclera, retina, choroid, uvea, optic tracts, eyelid, etc)
  - Can involve other organs (multi-organ infarction)
Sneddon’s Syndrome

- Livedo racemosa (also found in other autoimmune diseases, e.g. SLE, RA)
- Ischemic strokes
- Anti-phospholipid antibody positive
- Sex ratio women to men 2:1
- Arteriolar narrowing
Sneddon’s Syndrome

- Etiology
  - Unknown
  - Some association with cigarette smoking, hypertension and oral contraceptives
  - Antiplatelets or anticoagulation
Diffuse Meningocerebral Angiomatosis and Leukoencephalopathy: Divry-Van Bogaert Syndrome

- Congenital recessive (children and adult forms)
- Death between 10-15 years from onset
- Skin
  - Diffuse symmetrical livedo reticularis
- Neurological
  - Dementia
  - Seizures
  - Motor disturbances
- Pathology
  - Brain infarcts
  - Demyelination
  - Cerebromeningeal angiomatosis
  - Fibrotic changes of vascular walls with fatty degeneration and amyloid deposition
Epidermal Nevus Syndrome

- Sporadic
- Newborns and young patients
- Two types
  - Epidermal Nevi and brain infarcts
  - Hemimegalencephaly, gyral malformation, mental retardation, seizures, facial hemihypertrophy
- Angiography
  - Vessel dysplasia - segmental beading and dilations
  - Fusiform aneurysms
Eosinophil-Induced Neurotoxicity and Cerebral Infarction

- Hypereosinophilia is usually secondary to an allergic or parasitic process
- Neurological manifestations
  - Axonal neuropathy, Dementia, Stroke
- Pathophysiology
  - Release of medial basic protein causes endothelial damage
  - Hypercoagulability
  - Eosinophil induced cardiomyopathy
- Treatment
  - Immunosuppression, treat underlying cause
Kawasaki Syndrome

- Children, rarely young adults
- Clinical manifestations
  - Fever
  - Skin - Generalized erythema and skin peeling
  - Mucous membranes
  - Conjunctivitis
  - Lymphadenopathy
  - Cardiac
- Strokes
  - Vascular occlusions
  - Aneurysms
  - Cardioembolic stroke
Nonhereditary Systemic Disorders with Eye Involvement
Nonhereditary Systemic Disorders with Eye Involvement

- Eale’s Disease
- Acute Posterior Multifocal Placoid Pigment Epitheliopathy
Eale Disease

Rare and idiopathic vasculopathy occurring in young men

More common in India and Pakistan

Optho
- Recurrent retinal and vitreous hemorrhages (poor peripheral retinal perfusion, vascular sheathing)

Neuro
- Small and medium vessels occlusive disease
- Non-inflammatory perivascular infiltrative disorder
Acute Posterior Multifocal Placoid Pigment Epitheliopathy

- Young adults
- Acute onset of bilateral blurry vision
- Multi-focal yellowish-white placoid lesions of the retinal pigmented epithelium
- A good ophthalmologist would make this diagnosis

Neuro

- Aseptic meningitis (headache and neck stiffness)
- Stroke (cerebral vasculitis), may get referred for angiogram

Cause is unknown

- Some treat with immunosuppressants, esp. if vasculitis present
Nonhereditary Systemic Disorders with Eye and Ear Involvement
Nonhereditary Systemic Disorders with Eye and Ear Involvement

- Susac’s
- Cogan’s
Retinocochleocerebral Arteriopathy (Susac’s disease)

- Clinical manifestations:
  - Diffuse encephalopathy
  - Branch retinal artery occlusions
  - Hearing loss
  - Self-limited, ?autoimmune

- MRI
  - Multifocal chronic and/or acute infarcts
  - Involve corpus callosum
  - May involve basal ganglia and thalamus
  - May enhance
Cogan’s Syndrome

- Ages 20s-30s

- Autoimmune – possibly a reaction to Chlamydia pneumonia

- Inflammation of cornea and inner ear

- Cerebral Vasculitis

- Sx – fever, fatigue, dizziness, weight loss, hearing loss

- Immunosuppressive tx
Other Genetic Disorders
Other Genetic Disorders

- Hereditary dyslipoproteinemia
- Organic acidemias
- Mitochondrial encephalomyopathies
  - MELAS, MERRF, MERRF/MELAS overlap syndrome, Kearns-Sayre syndrome
Misc genetic disorders

- Fabry disease (-galactosidase-A deficiency)
- Homocystinuria (cystathionine -synthase deficiency, or 5, 20-MTHFR)
- Subacute necrotizing encephalomyelopathy (Leigh disease)
- Sulfite oxide deficiency
- Neurofibromatosis type 1
- HERNS
Neurofibromatosis

✧ Type I – chromosome 17, lisch nodules, café au lait, axillary freckles, peripheral nerve tumors

✧ Type II – chromosome 22, acoustic neuromas, meningiomas

✧ Cerebrovascular
  ✧ Involvement of cerebral arteries is uncommon
  ✧ Occlusions of the distal ICA or proximal anterior circulation associated with Moya-moya changes
  ✧ Sometimes aneurysms

✧ Splanchnic and renal artery abnormalities
Fabry’s Disease

- Congenital X-linked disease of α-galactosidase deficiency
- Lysosomal storage disease - glycolipid accumulation in vessel walls
  - Dx by enzyme activity in peripheral leukocytes
- Clinical features
  - Neuropathy
    - Painful small fiber neuropathy in first decade (usually the first sign)
  - Skin
    - Redish purple angiokeratomas 1-2 mm on trunk, proximal limbs, in clusters
  - Eyes
    - Cataracts, abnormally tortuous retinal vessels
  - Brain
    - Vessel occlusion (small vessel) and ICH usually in 3rd or 4th decade
  - Renal failure (proteinuria) usually cause of death
Guideline

- Enzyme replacement therapy with genetically engineered galactosidase A effectively reduces both symptoms and the frequency of vascular complications.

- Individuals with Fabry disease should receive galactosidase replacement therapy (Class I, Level of Evidence B).

Stroke 2008;39;2644-2691;
Homocysteinuria

- Autosomal recessive

- Clinical features
  - Premature atherosclerosis
  - Mental retardation
  - Ectopia lentis (90% of cases)
  - About 50% of patients experience a thromboembolic event by age 30 years

- Diagnosis
  - Prenatal screening, elevated homocysteine in serum and urine

- Treatment
  - Vitamin replacement, low methionine diet, other
CADASIL

- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
- Clinical features
  - Stroke, dementia, migraine, psychiatric illness
- Diagnosis
  - Notch 3 mutation
  - Skin biopsy – electron micrograph shows granular osmiophilic material (GOM)
HERNS

- Hereditary endotheliopathy with retinopathy, nephropathy, and stroke
- Rare autosomal dominant disorder
- Neurological
  - Similar to CADASIL (but vision loss and renal involvement in HERNS)
- Renal
  - Hematuria, proteinuria
  - Similar to Fabry’s (but no neuropathy and presence of retinopathy in HERNS)
- MRI
  - Contrast enhanced subcortical lesions
MELAS

- Mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes
- Maternal inheritance
- Clinical features
  - Stroke often by age 40
  - Migraines
  - Seizures
  - Dementia
  - Lactic acidosis
- Diagnosis
  - Muscle biopsy shows ragged red fibers
  - Mutation in tRNAleu(UUR) A-to-G transition at nucleotide 3243 accounts for 80% of cases. (A good way to make the diagnosis)
Clinical Presentations

- 80% ischemic
- 20% hemorrhagic or CVST
- Stroke accounts for 10% of seizures in term neonates

Risk factors
- Cardiac disease, coagulation disorders, infection, trauma, drugs, placental disorder, asphyxia.

Recurrent stroke risk factors
- Thrombophilia, complex congenital heart disease, dehydration
Management Recommendations

Class I

- Correct markedly low platelets in ICH patients
- Replace deficient coagulation factor in ICH patients
- Vitamin K for Vit-K dependent coagulation disorders
- Ventricular drainage for hydrocephalus after ICH

Class II

- It is reasonable to treat dehydration and anemia
- It is reasonable to use rehab and PT
- It is reasonable to give folate and B vitamins to patients with MTHFR mutation to normalize homocysteine levels
- Hematoma evacuation is reasonable to reduce high ICP
- Anticoagulation may be considered in severe thrombophilia, multiple emboli or propagating CVST despite supportive therapy

Class III

- Thrombolytics are not recommended until more safety/efficacy information is known

Roach et al. Stroke 2008;39;2644-2691
Pediatric Arterial Ischemic Stroke
Pediatric Stroke

- Arteriopathy
  - ~50% of pediatric (age 1 month-18 years) strokes
  - Risk of recurrent stroke highest – 66% at 5 years
- Infection
  - ~25% of pediatric stroke
- Cardiac
  - ~10-30% of pediatric stroke
- Hematological
  - Less common than previously thought
- Other causes

Pavlakis and Levinson. Stroke 2009;40[suppl 1]:S79-S81
Management Guidelines
Acute Medical Management –
RCP Guidelines

- Oxygen: maintained WNL (Level D)
- Temperature: maintained WNL (Level D)
- Glucose: None
- BP: None

- Decompressive surgery: Early neurosurgical referral should be considered in children with stroke and depressed level of consciousness or other signs of high ICP (strong consensus)

Antithrombotic Management

- Acute Systemic Thrombolysis: No specific guideline
  - RCP - “There is currently no evidence to support use of thrombolytic agents such as tpa”
  - ACCP - “The risk benefit ratio is unknown”
- Acute intraarterial thrombolysis: None
- Acute, nonthrombolytic management of idiopathic AIS:
  - RCP - Aspirin (5 mg/kg/day) once there is radiologic confirmation of stroke, except in ICH and Sickle Cell (Strong consensus).
  - ACCP - Heparin for 5-7 days until cardioembolic stroke or dissection has been excluded.
Secondary Prevention

- **Idiopathic AIS:** Aspirin
  - RCP - 1-3 mg/kg/day (strong consensus)
  - ACCP - 2-5 mg/kg/day (Grade 2C)
- **Dissection:**
  - RCP - Anticoagulation should be considered for extracranial dissection until vessel is shown to have healed or for maximum of 6 months (strong consensus)
  - ACCP - 5-7 days of LMWH or UFH followed with VKAs or LMWH for 3-6 months (Grade 2C)
- **Cardioembolism:**
  - RCP - Anticoagulation should be considered (strong consensus)
  - ACCP - 5-7 days of LMWH or UFH followed with warfarin or LMWH for 3-6 months (Grade 2C)
- **Antiphospholipid Abs:** None
- **Inherited thrombophilia:** None