Arterial Ischemic Stroke in Children

C.H.Topel
Vascular Neurology Fellow
Department of Neurology

SCHOOL OF MEDICINE
UT HEALTH SCIENCE CENTER®
SAN ANTONIO

Disclosures

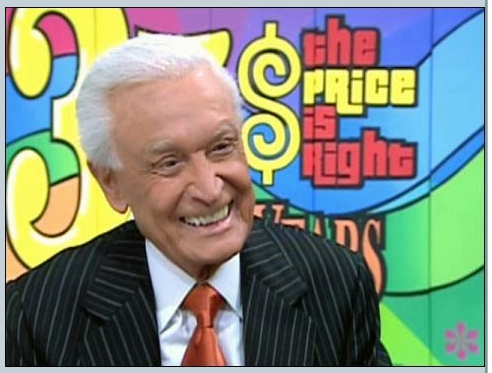
- Trained in Austin?

Objectives

- Discuss Epidemiology and demographics of pediatric ischemic stroke
- Identify common presentations
- Identify common causes and risk factors
- Establish junior neuroradiologist status!
- Discuss available treatments

Ischemic Stroke Epidemiology

- **Overall….**
- **795,000 strokes in the USA.**
- **5th leading cause of death**
- **Leading cause of morbidity**
- **Increasing age leading risk factor (sorry!)**
  - **¾ of all strokes occur age > 65**



Pediatric Epidemiology

- **Kids have stroke?!?**
- **1.2 to 8 cases in 100,000 per year**
  - Annual incidence (1 to 18 years): ~ 3/100,000 per year
  - Likely underestimated
  - Estimations are quite variable depending on the specific community studied
- **Unfortunately, rate continues to increase**
  - **Awareness! (thanks for attending!)**
  - Advances in neuro-imaging
  - Survival of children with previously considered "lethal" congenital heart conditions and leukemia

EPIDEMIOLOGY

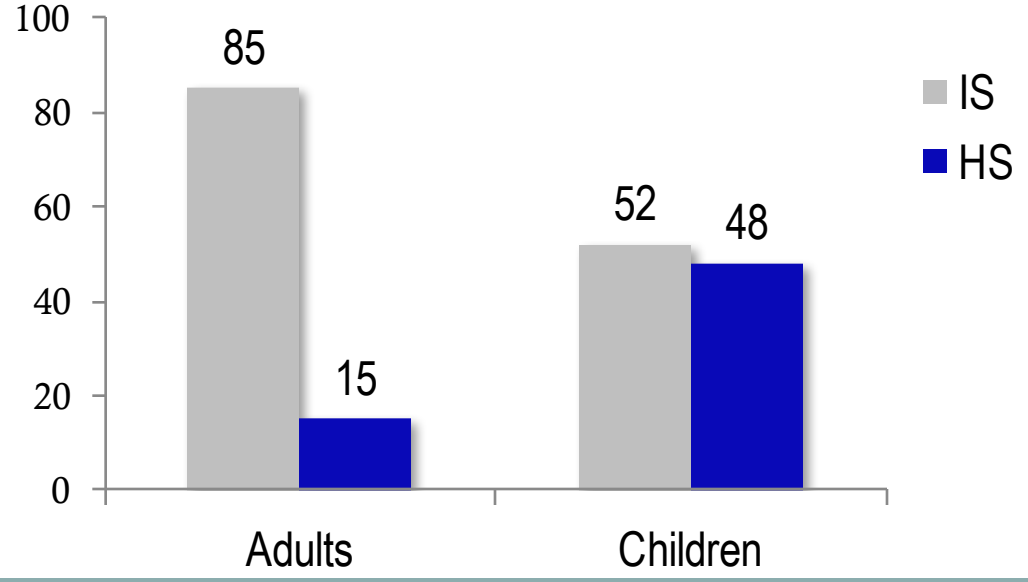
IS and HS occur at approximately the same rate

Boys are at a higher risk (60%)

Pediatric registry with 1187 arterial ischemic and CVT

Black children are at a higher risk

Not fully explained by the prevalence of SCD in this population



EPIDEMIOLOGY

10 Leading Causes of Death by Age Group, United States – 2008

	Age Groups										
Rank	<1	1-4	5-9	10-14	15-24	25-34	35-44	45-54	55-64	65+	Total
1	Congenital Anomalies 5,638	**Unintentional Injury 1,469**	**Unintentional Injury 835**	**Unintentional Injury 1,024**	**Unintentional Injury 14,089**	**Unintentional Injury 14,588**	**Unintentional Injury 16,065**	Malignant Neoplasms 50,403	Malignant Neoplasms 104,091	Heart Disease 495,730	Heart Disease 616,828
2	Short Gestation 4,754	Congenital Anomalies 521	Malignant Neoplasms 457	Malignant Neoplasms 433	**Homicide 5,275**	**Suicide 5,300**	Malignant Neoplasms 12,699	Heart Disease 37,892	Heart Disease 66,711	Malignant Neoplasms 391,729	Malignant Neoplasms 565,469
3	SIDS 2,353	**Homicide 421**	Congenital Anomalies 170	**Suicide 215**	**Suicide 4,298**	**Homicide 4,610**	Heart Disease 11,336	**Unintentional Injury 20,354**	Chronic Low. Respiratory Disease 14,042	Chronic Low. Respiratory Disease 121,223	Chronic Low. Respiratory Disease 141,090
4	Maternal Pregnancy Comp. 1,765	Malignant Neoplasms 394	**Homicide 113**	**Homicide 207**	Malignant Neoplasms 1,663	Malignant Neoplasms	**Suicide 6,703**	**Suicide 8,287**	**Unintentional Injury**	Cerebro-vascular 114,508	Cerebro-vascular 134,148
5	**Unintentional Injury 1,315**	Heart Disease 186	Heart Disease 97	Congenital Anomalies 161	Heart Disease					Alzheimer's Disease 81,573	**Unintentional Injury 121,902**
6	Placenta Cord Membranes 1,080	Influenza & Pneumonia 142	Benign Neoplasms 59	Heart Disease 132	Congenita Anomalie 467					Diabetes Mellitus 50,883	Alzheimer's Disease 82,435
7	Bacterial Sepsis 700	Septicemia 93	Chronic Low. Respiratory Disease 55	Chronic Lo Respirato Disease 64	Influenza Pneumoni 206					Influenza & Pneumonia 48,382	Diabetes Mellitus 70,553
8	Respiratory Distress 630	**Cerebro-vascular 63**	**Cerebro-vascular 41**	**Cerebro-vascular 56**	Diabetes Mellitus 204	vascular 539	vascular 2,035	Respiratory Disease 4,392	**Suicide 5,465**	Nephritis 39,921	Influenza & Pneumonia 56,284
9	Circulatory System Disease 594	Chronic Low. Respiratory Disease 54	Influenza & Pneumonia 40	Influenza & Pneumonia 49	Cerebro-vascular 189	Liver Disease 423	Diabetes Mellitus 1,854	HIV 3,730	Nephritis 4,803	**Unintentional Injury 39,359**	Nephritis 48,237
10	Neonatal Hemorrhage 556	Perinatal Period 51	Septicemia 25	Septicemia 36	Complicated Pregnancy 169	Congenital Anomalies 379	Septicemia 892	Viral Hepatitis 2,732	Septicemia 4,552	Septicemia 27,028	**Suicide 36,035**

Ranked Number 8 Among the top 10 causes of death in children

Centers for Disease Control and Prevention
National Center for Injury Prevention and Control

Source: National Vital Statistics System, National Center for Health Statistics, CDC.
Produced by: Office of Statistics and Programming, National Center for Injury Prevention and Control, CDC.

CS227502

HSC

Clinical presentation?

ORIGINAL ARTICLE

Arterial Ischemic Stroke Risk Factors: The International Pediatric Stroke Study

Mark T. Mackay, MBBS,[1] Max Wiznitzer, MD,[2] Susan L. Benedict, MD,[3]
Katherine J. Lee, MSc, PhD,[4] Gabrielle A. deVeber, MSc, MD,[5]
and Vijeya Ganesan, MD,[6] on behalf of the International Pediatric Stroke Study Group

Objective: To describe presumptive risk factors (RFs) for childhood arterial ischemic stroke (AIS) and explore their relationship with presentation, age, geography, and infarct characteristics.
Methods: Children (29 days–18 years) were prospectively enrolled in the International Pediatric Stroke Study. Risk factors, defined conditions thought to be associated with childhood AIS, were divided into 10 categories. Chi-square tests were used to compare RFs prevalence across regions and age; logistic regression was used to determine whether RFs were associated with particular features at presentation or infarct characteristics.
Results: A total of 676 children were included. No identifiable RFs was present in 54 (9%). RFs in others included

2011

676 children prospectively enrolled

Arterial ischemic stroke

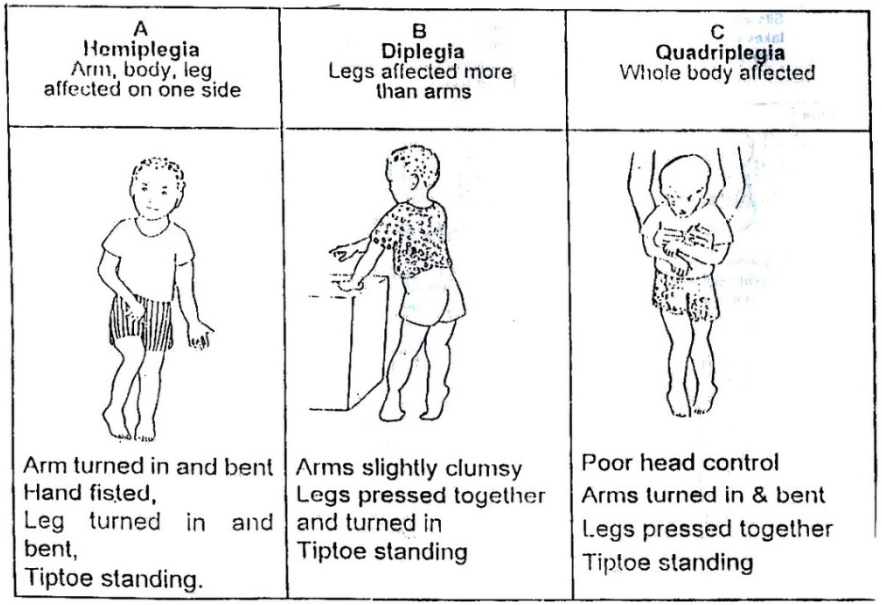
age 29 days-18 years

UTHSC

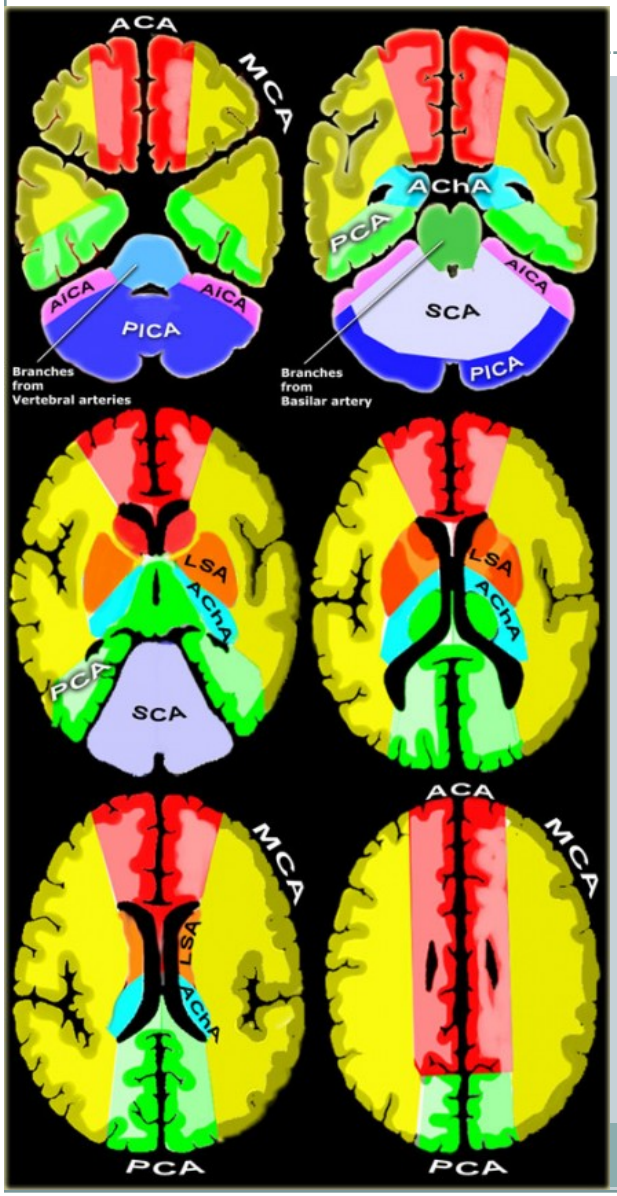
Clinical presentation?

So what does a strokes look like in a child?

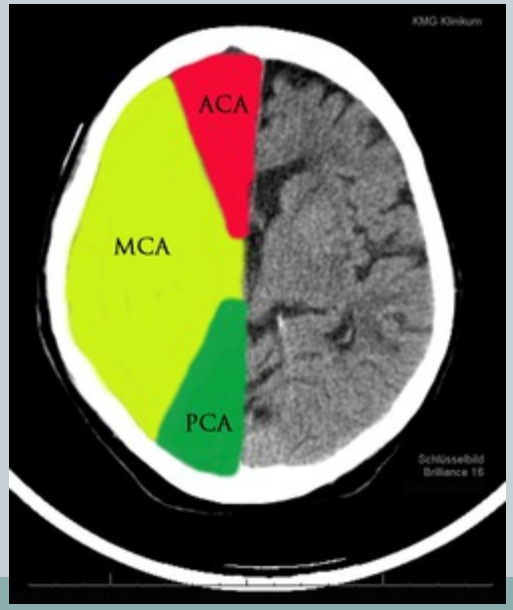
- Presenting Symptoms
  - 82% focal neurological signs
    - More common in older children
    - Of those, 86% had hemiparesis
    - 45% had speech disturbance
    - 13% visual disturbance
  - 64% had diffuse signs
    - More common in neonate/younger
    - Most common was a reduced level of consciousness,
    - Second is headache
  - 31% had seizures at presentation.



Where do they have strokes?

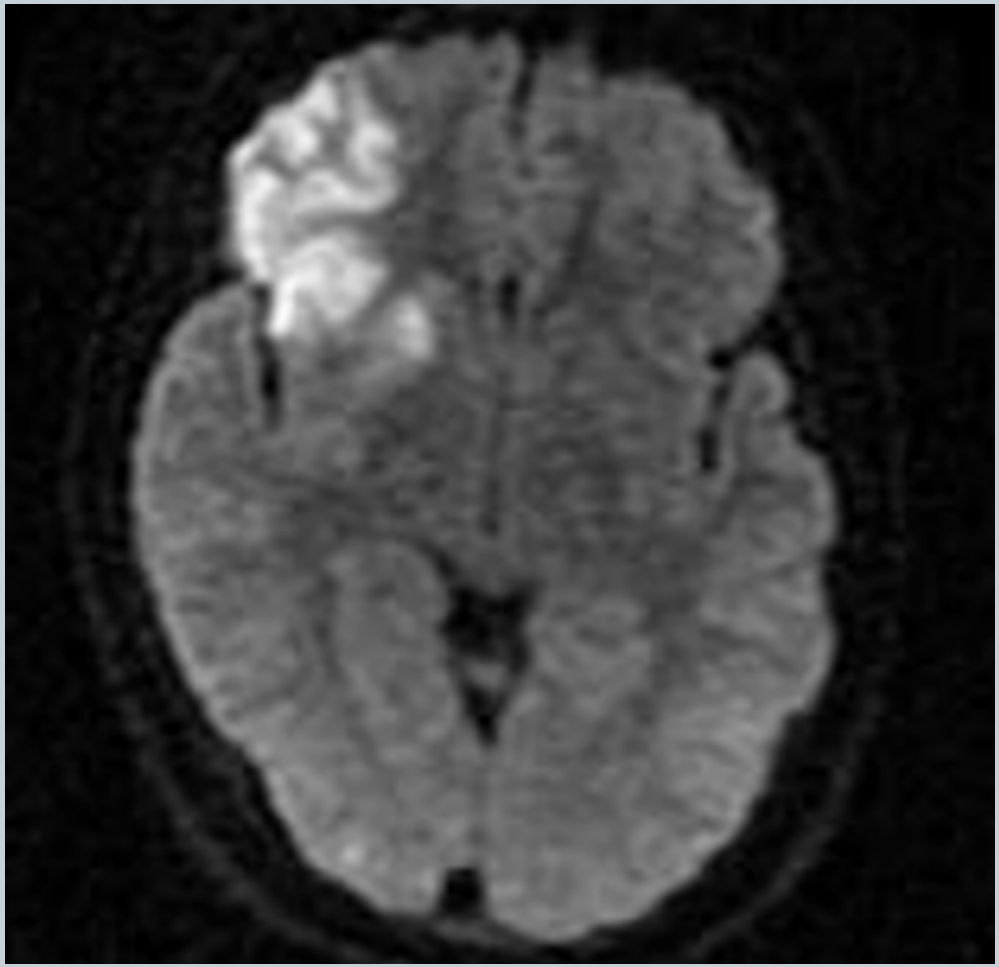


Lesion distribution, n=660[b]	
Anterior	445 (67%)
Posterior	143 (22%)
Both	72 (11%)
Number of infarcts, n=618[b]	
Single	356 (58%)
Multiple	262 (42%)
Laterality, n=641[b]	
Unilateral	477 (74%)
Bilateral	164 (26%)



What do they look like on CT?

What do they look like on MRI?



Which children get stroke?

- **Common risk factors / etiologies**

  Cerebral arteriopathy (53%)

  Congenital Heart disease (31%)

  Chronic systemic conditions (19%)

  SCD #1

  Prothrombotic states (13%)

And the not so common….metabolic causes

ETIOLOGY & RISK FACTORS

TABLE 1: Prevalence of Risk Factors and Details of Condition

ANN NEUROL 2011;69:130–140

Risk Factor Category[a]	Diagnoses Included	Frequency, No. (%)
Arteriopathy	Total	277/525 (53%)[b]
	Focal cerebral arteriopathy	69
	Moyamoya	61
	Arterial dissection	56
	Vasculitis	33
	Sickle cell arteriopathy	21
	Post varicella arteriopathy	19
	Other	10
	Unspecified arteriopathy	9

Risk Factor Category[a]	Diagnoses Included	Frequency, No. (%)
Cardiac disorders	Total	204/667 (31%)[b]
	Congenital heart disease	121
	Acquired heart disease	40
	Isolated PFO	31
	<72 hours after cardiac surgery	32
	Previous cardiac surgery	33
	Cardiac catheterization	17
	ECMO	11
	Left ventricular assist device	2
	Arrhythmia	2
	Other cardiac	3

ETIOLOGY & RISK FACTORS

TABLE 1: Prevalence of Risk Factors and Details of Condition

ANN NEUROL 2011;69:130–140

Risk Factor Category[a]	Diagnoses Included	Frequency, No. (%)
Chronic systemic conditions	Total	126/674 (19%)[b]
	Sickle cell disease	39
	Indwelling catheter	23
	Trisomy 21	17
	Other genetic disorders	17
	Hematological malignancy	16
	Iron deficiency	11
	Oral contraceptive pill	5
	Connective tissue disease	4
	Solid extracranial tumors	3
	L-asparaginase	1

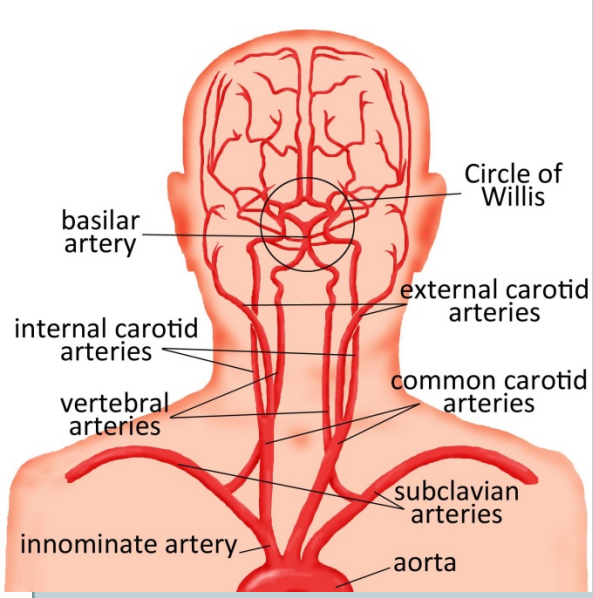
Risk Factor Category[a]	Diagnoses Included	Frequency, No. (%)
Prothrombotic states	Total	87/674 (13%)[b]
	Single	67
	Multiple	20
	MTHFR	24
	Elevated Lp (a) Acquired thrombophilia	21 20
	FVL	7
	Other genetic thrombophilia	7
	Protein S deficiency	5
	PT20210A	4
	Protein C deficiency	4
	Antithrombin III deficiency	3
	Hyperhomocysteinemia	1
	Not specified	4

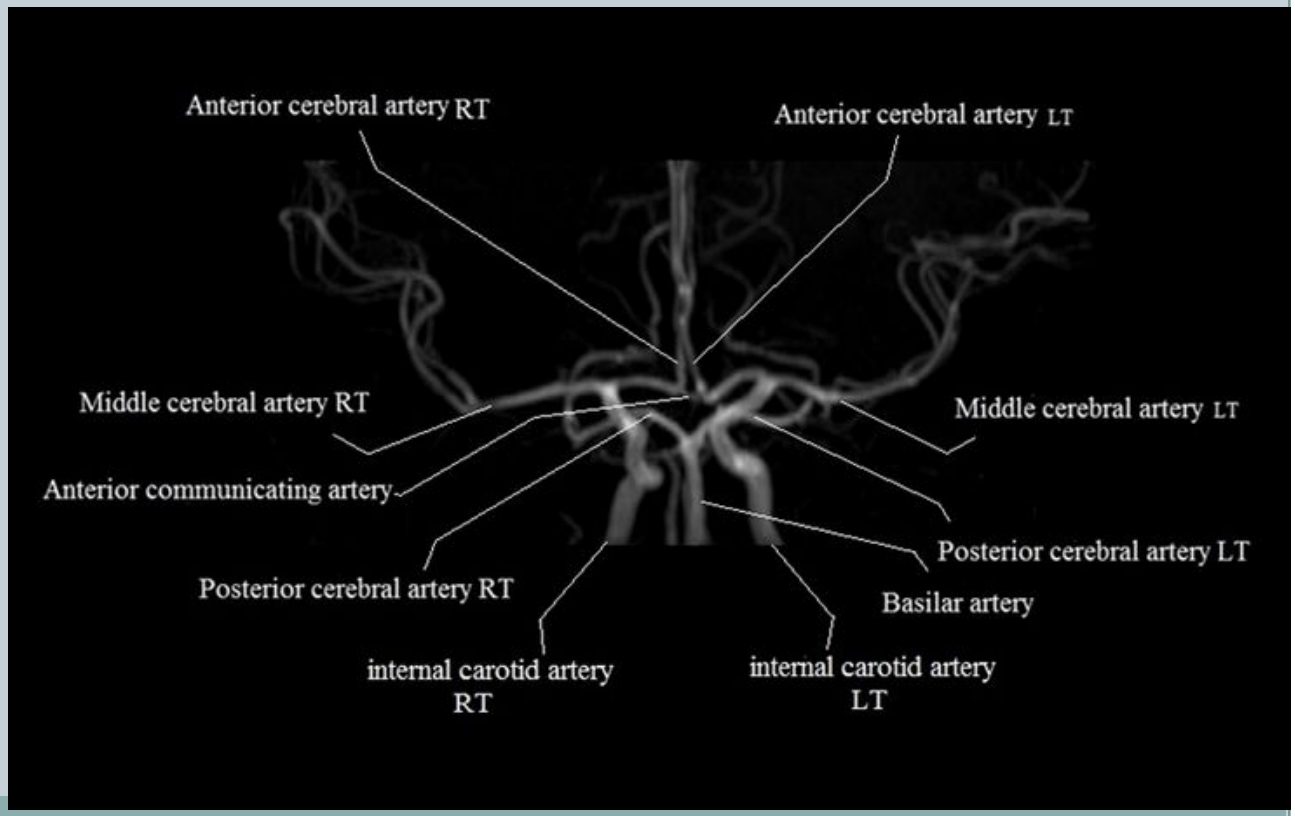
Arteriopathy

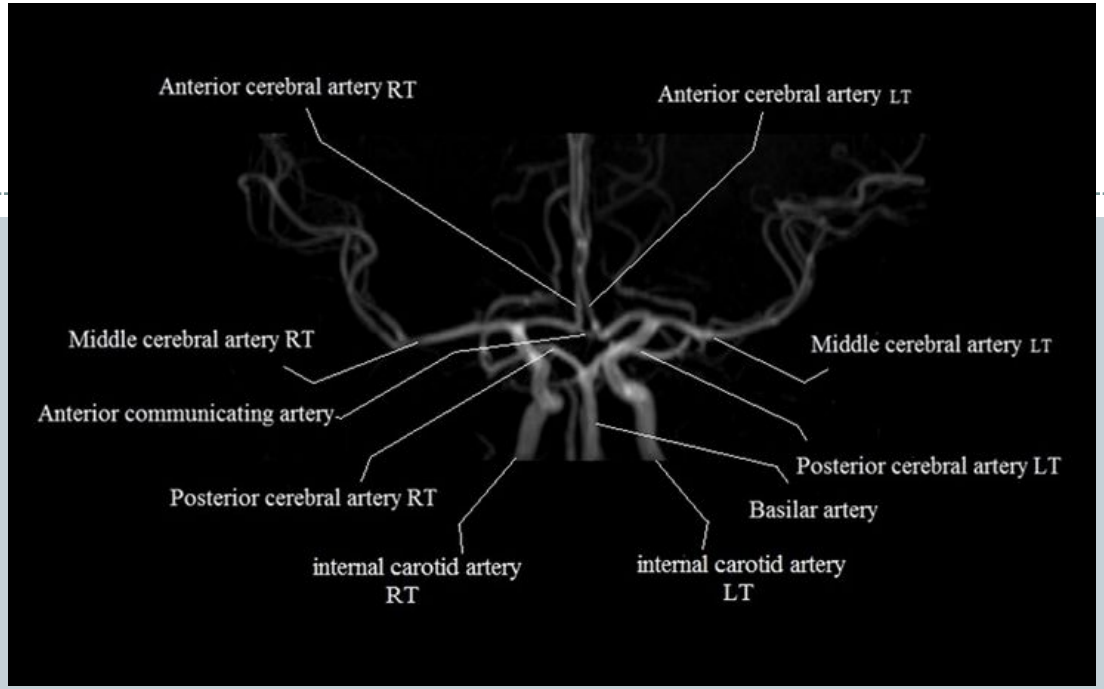
- Arteriopathy 53%
  - Focal Cerebral Arteriopathy
  - Moyamoya
  - Dissection
  - Vasculitis

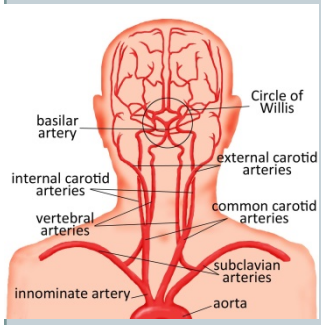
Focal Cerebral Arteriopathy

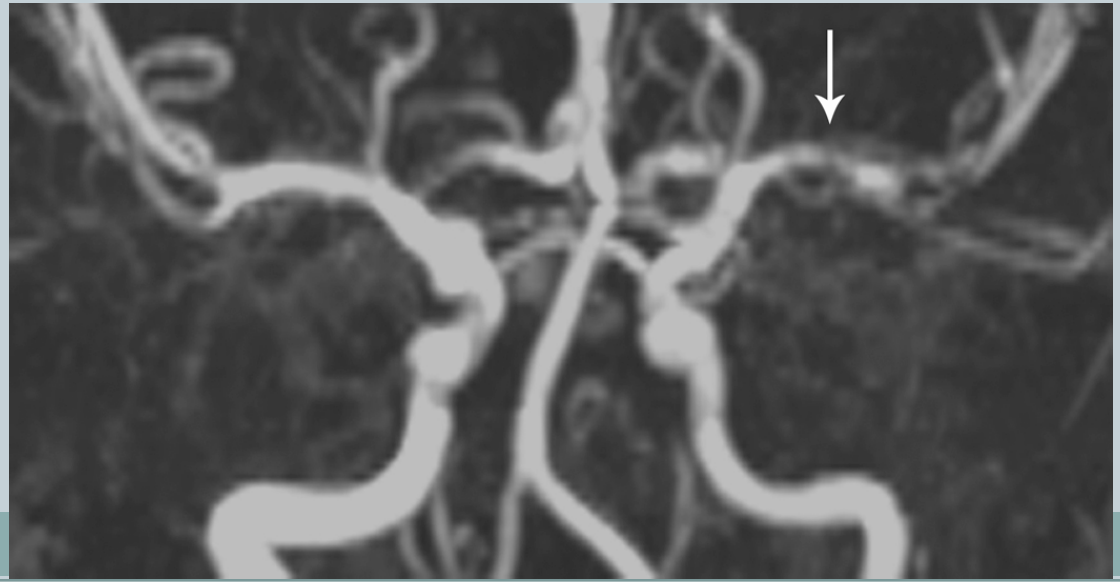
- What is it?
  - Focal stenosis of distal carotids or proximal Circle of Willis.






Anterior cerebral artery RT
Anterior cerebral artery LT
Middle cerebral artery RT
Middle cerebral artery LT
Anterior communicating artery
Posterior cerebral artery LT
Posterior cerebral artery RT
Basilar artery
internal carotid artery RT
internal carotid artery LT


Circle of Willis
basilar artery
external carotid arteries
internal carotid arteries
common carotid arteries
vertebral arteries
subclavian arteries
innominate artery
aorta



Focal Cerebral Arteriopathy

- Associated with recent Upper respiratory tract Infx
- Etiology not well understood
  - Multifactorial?
    - Inflammation (Secondary Vasculitis)?
    - Spasm?
    - Thromboembolic?

Arteriopathy

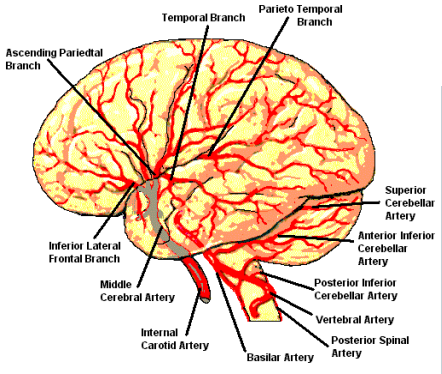
- Moyamoya
  - Hyperplasia (slow process, non-inflammatory) of intracerebral vessels causes narrowing.
  - 0.35 per 100,000
  - Collateralization
    - Sx appear when stenosis progresses and inadequate collateral supply

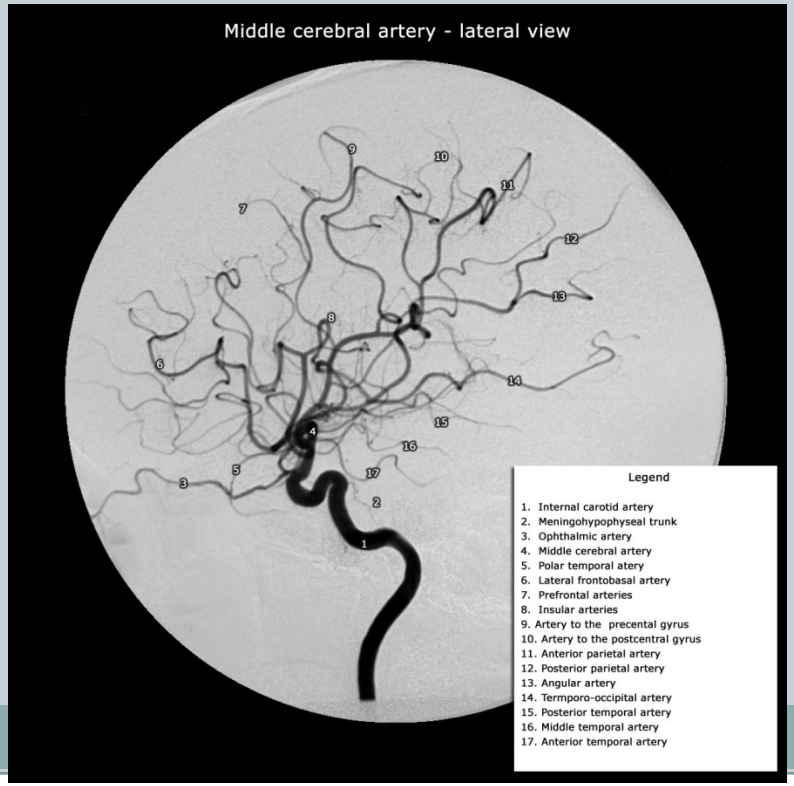
Arteriopathy

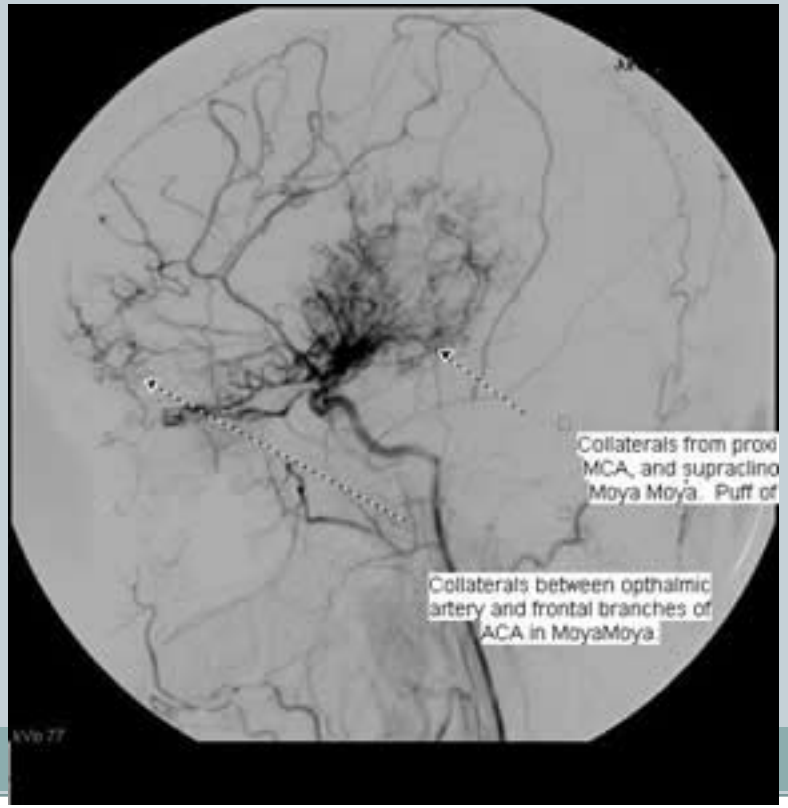
- Moyamoya
  - Differences in race and age
    - Japanese
      - **Bimodal distribution**
      - **First decade of life (AIS)**
      - **30 – 40 years (ICH)**
    - **North American**
      - **More common 3rd or 4th decade**
      - **TIA/ischemic**

Arteriopathy

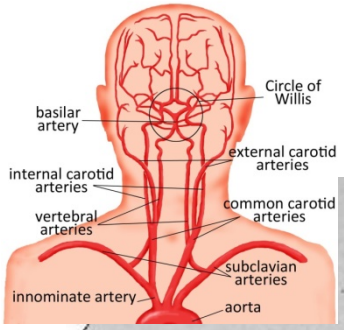
- Moyamoya
  - Puff of smoke

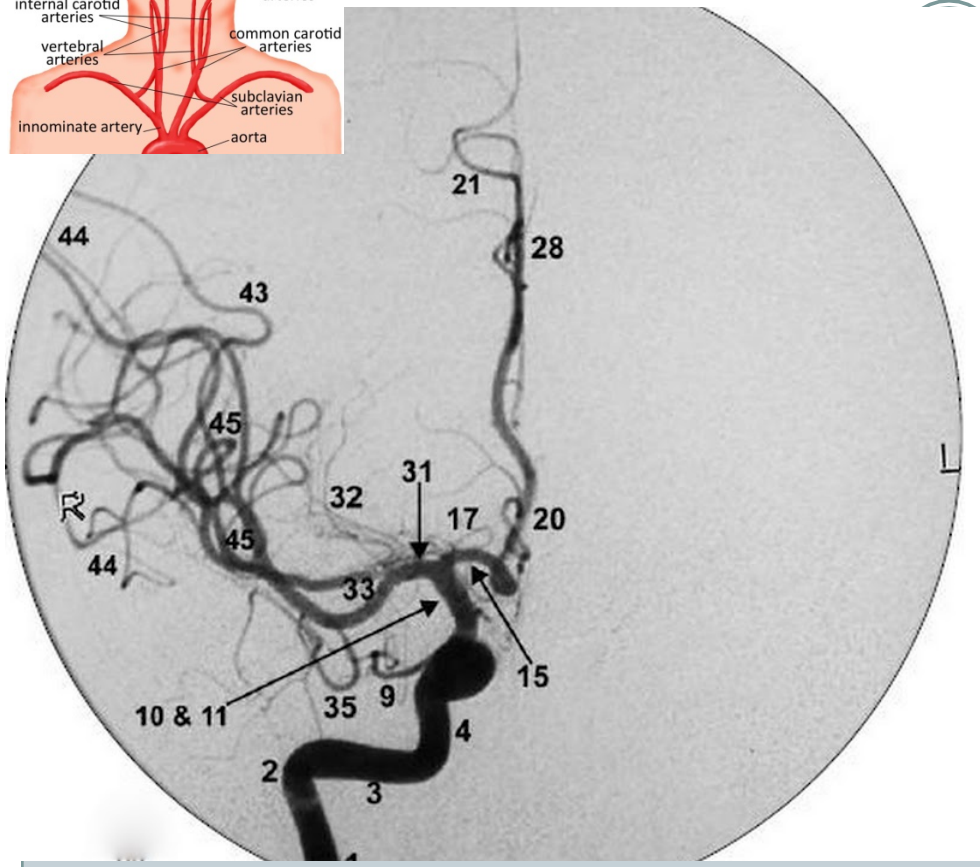






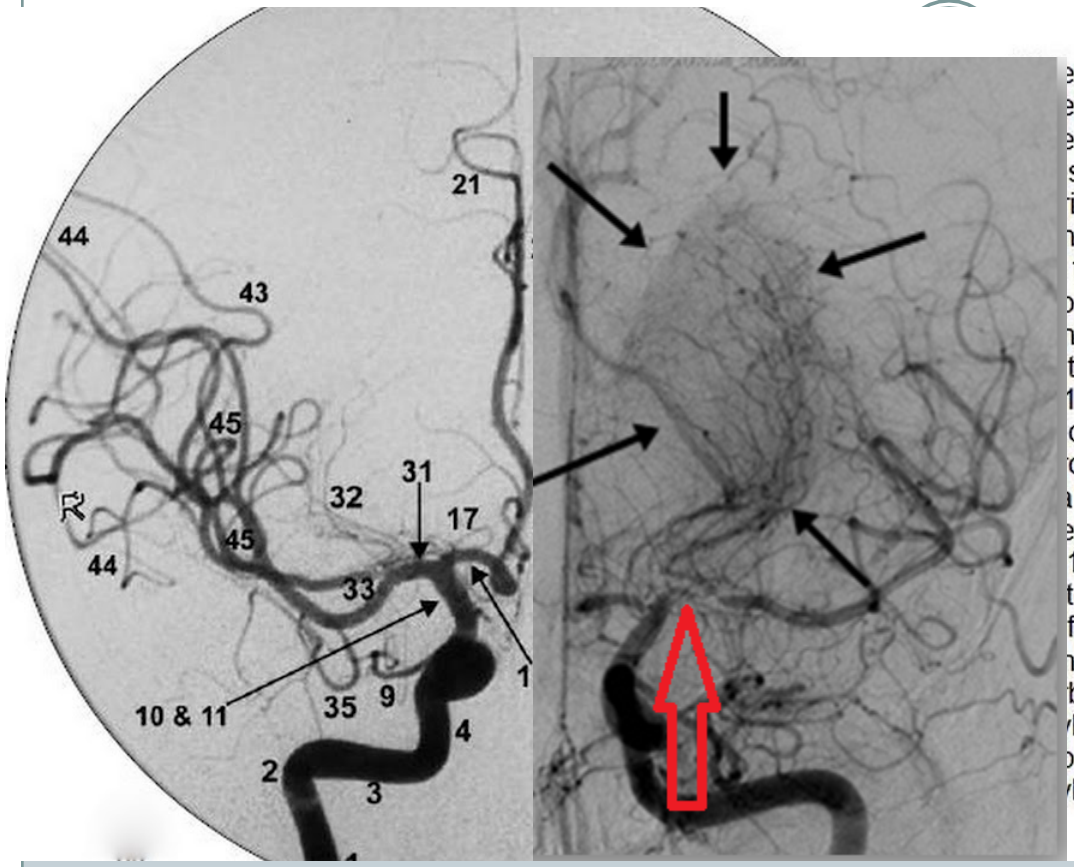
Arteriopathy





1 internal carotid artery – cervical segment
2 internal carotid artery – vertical petrous segment
3 internal carotid artery – horizontal petrous segment
4 presellar (Fischer C5) segment internal carotid artery
6 horizontal (Fischer C4) intracavernous internal carotid artery
9 ophthalmic artery
10 & 11 proximal and distal supraclinoid segment internal carotid artery
12 posterior communicating artery
13 anterior choroidal arteries
14 internal carotid artery bifurcation
15 A1 segment of anterior cerebral artery
17 recurrent artery of Heubner
20 proximal A2 segment anterior cerebral artery
21 callosomarginal branch of anterior cerebral artery
28 pericallosal branch of anterior cerebral artery
31 M1 segment of middle cerebral artery
32 lateral lenticulostriate arteries
33 bifurcation/trifurcation of middle cerebral artery
34 anterior temporal lobe branches of middle cerebral artery
35 orbitofrontal branch of middle cerebral artery
43 sylvian point
44 opercular branches of middle cerebral artery
45 sylvian (insular) branches of middle cerebral artery

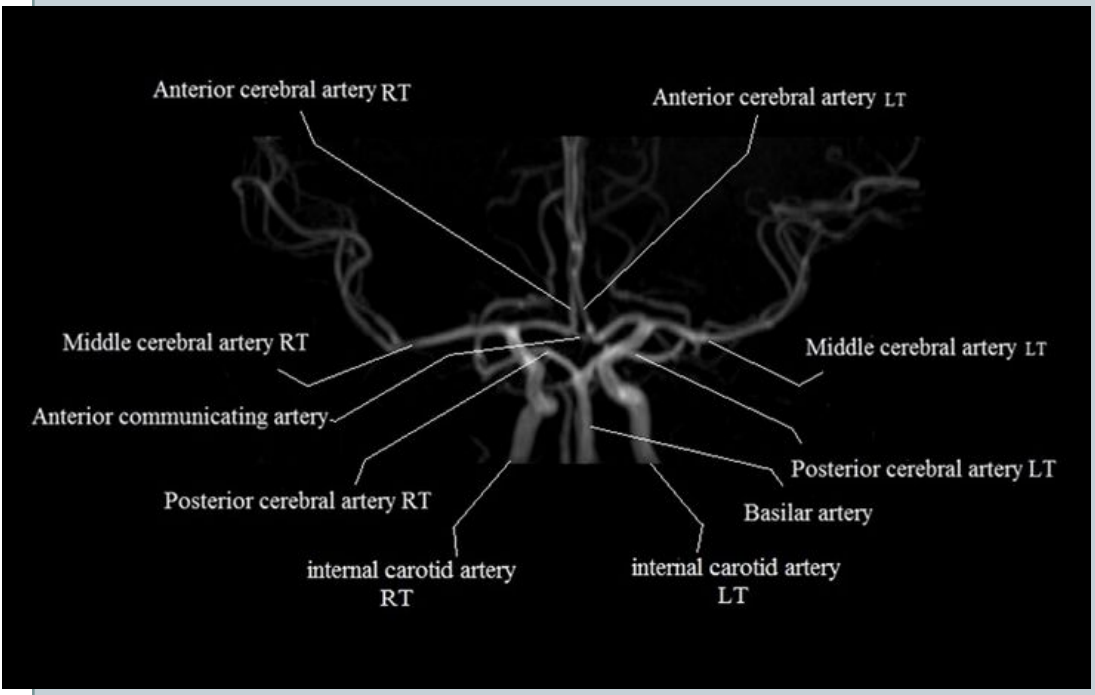
Arteriopathy

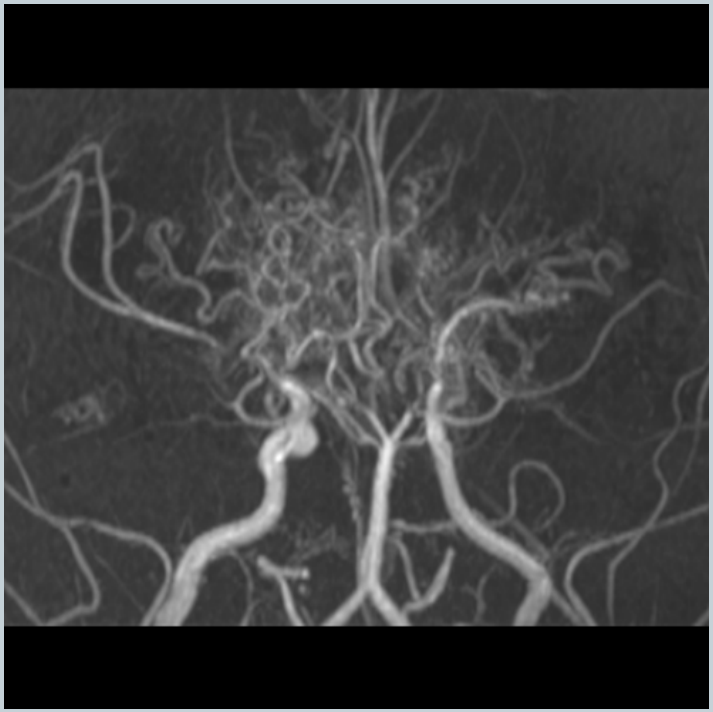


ernal carotid artery – cervical segment
ernal carotid artery – vertical petrous segment
ernal carotid artery – horizontal petrous segment
sellar (Fischer C5) segment internal carotid artery
izontal (Fischer C4) intracavernous internal carotid artery
nthalmic artery
11 proximal and distal supraclinoid segment internal carotid artery
osterior communicating artery
nterior choroidal arteries
ternal carotid artery bifurcation
1 segment of anterior cerebral artery
current artery of Heubner
oximal A2 segment anterior cerebral artery
llosomarginal branch of anterior cerebral artery
ericallosal branch of anterior cerebral artery
1 segment of middle cerebral artery
teral lenticulostriate arteries
furcation/trifurcation of middle cerebral artery
nterior temporal lobe branches of middle cerebral artery
bitofrontal branch of middle cerebral artery
lvian point
ercular branches of middle cerebral artery
lvian (insular) branches of middle cerebral artery

Arteriopathy

- Moyamoya
  - Non-invasive imaging

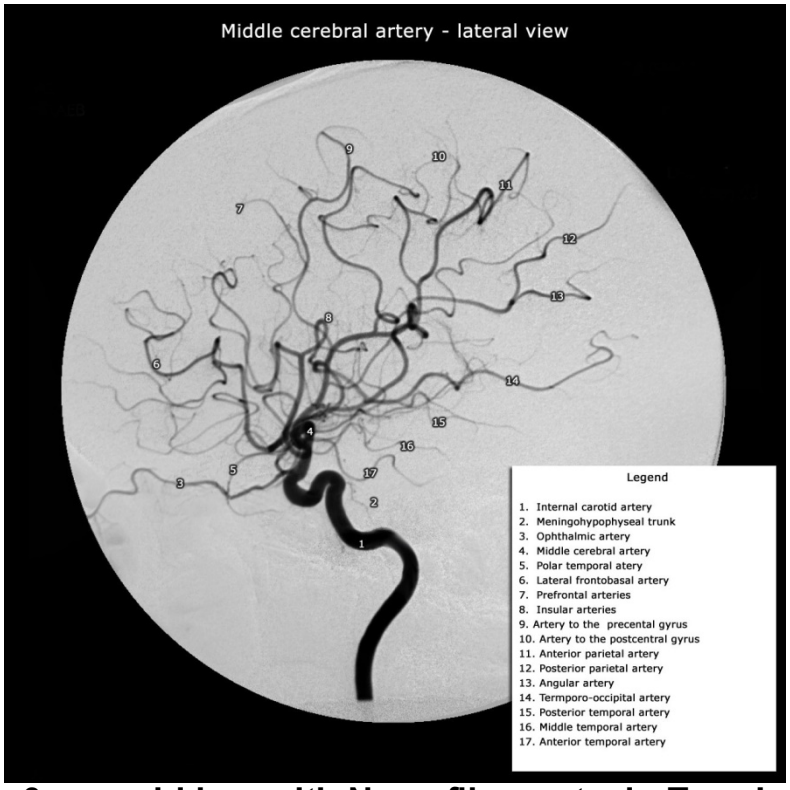




Arteriopathy

- Moyamoya
  - Genetic
    - RNF213 gene 17q25.
    - ACTA2 gene 10q23.3
    - GUCY1A3 gene 4q32.
    - Down Syndrome
    - NF1

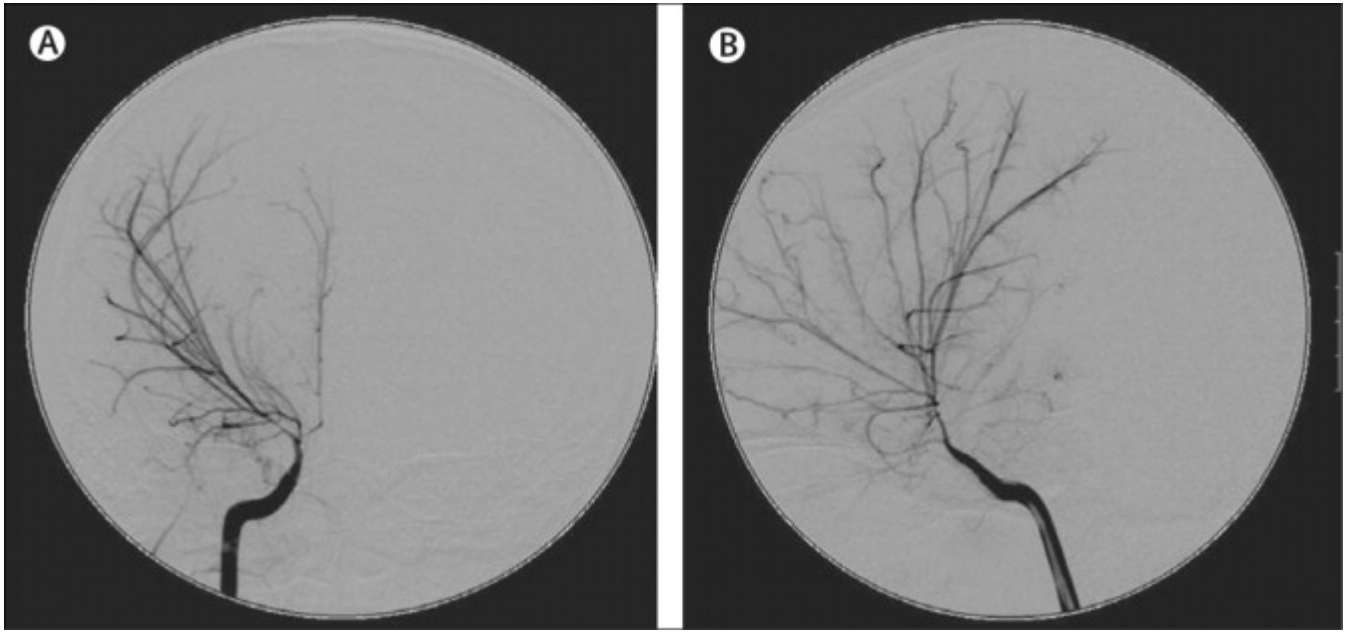
Moyamoya



8 year-old boy with Neurofibromatosis Type I

Lancet Neurol 2011; 10: 264–74

Myomoya

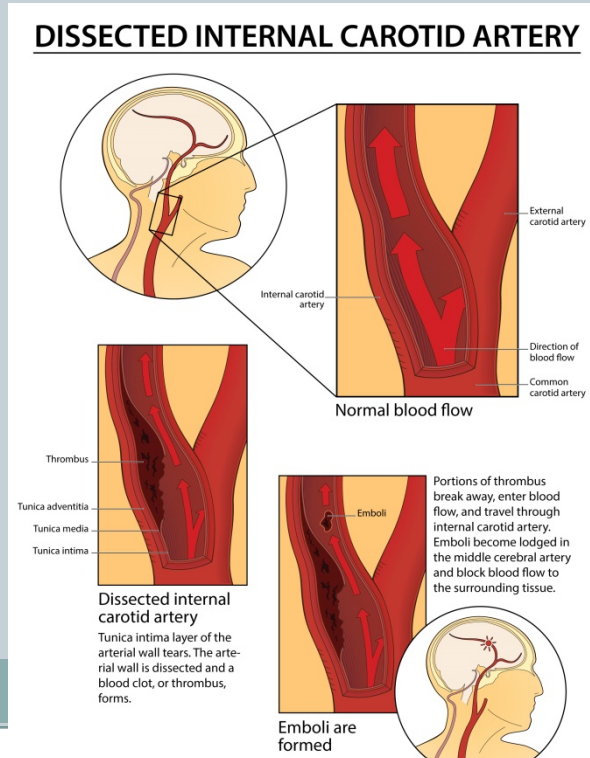


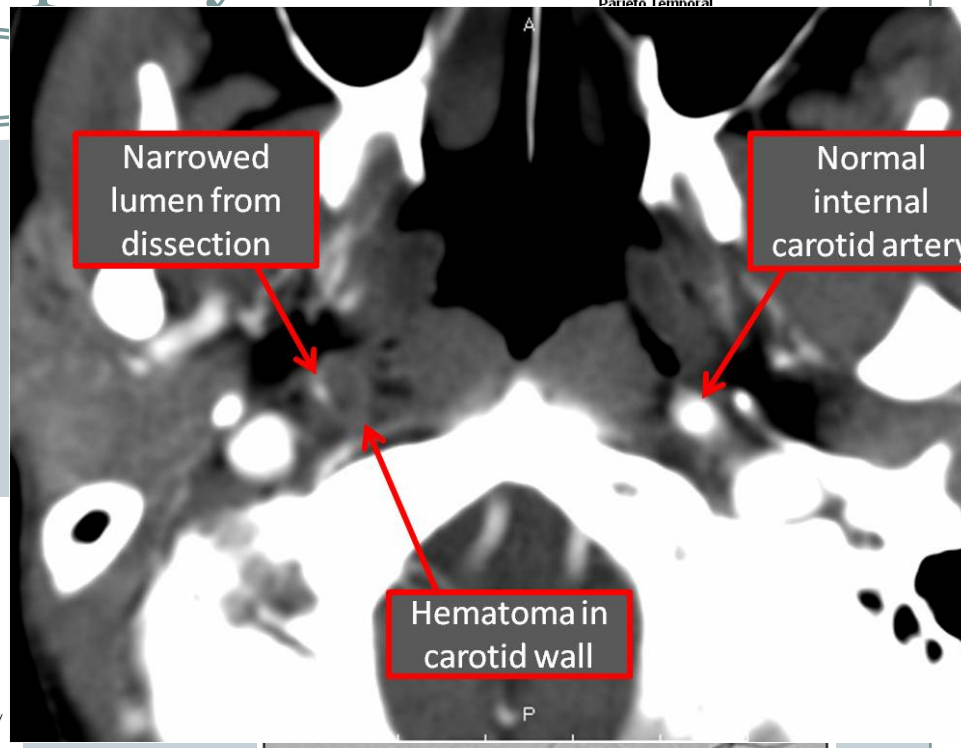
RICA of a 2.5 year old child with left hemiparesis and an R179H mutation in *ACTA2*(A)

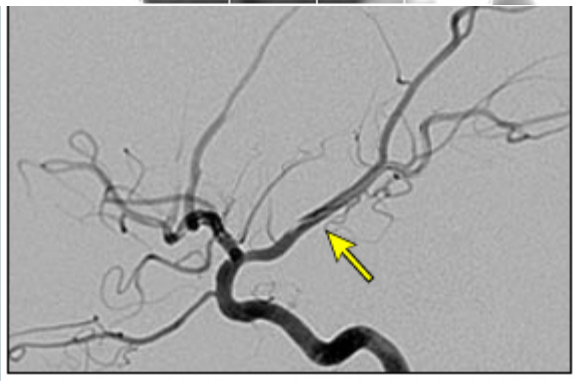
Lancet Neurol 2011; 10: 264–74

Arteriopathy

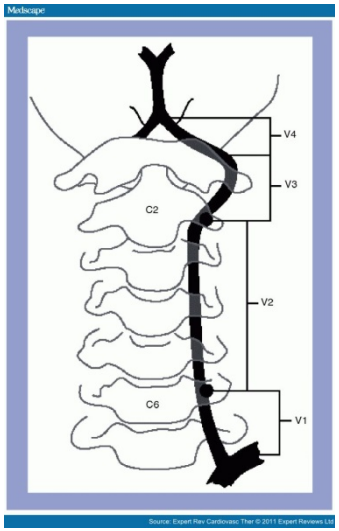
- Dissection
  - Extracranial/traumatic
  - Intracranial/spontaneous
    - Ehlers Danlos, Marfan's

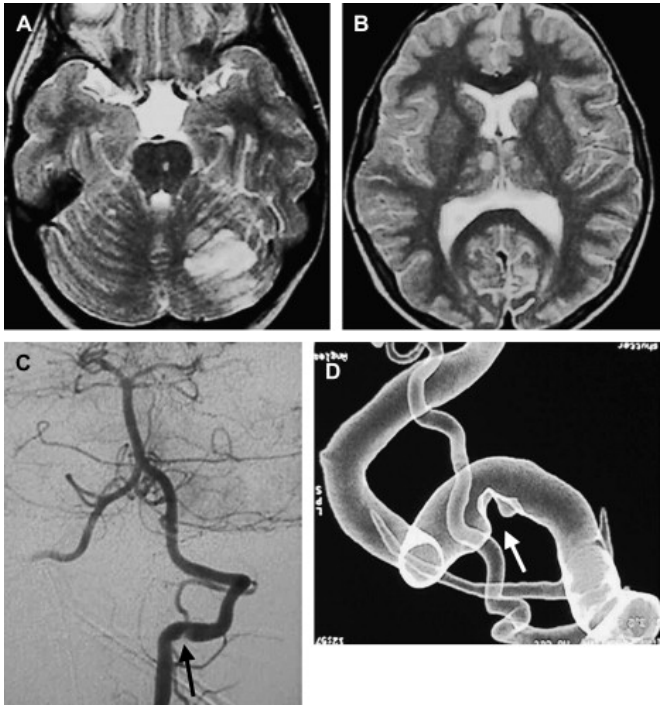






Remember the importance to confirm history, trauma, or pre-existing connective tissue disorder.





Vertebral dissection with underlying connective tissue disorder.

Six-year-old boy presenting with headaches and vertigo with repeated episodes of vertigo 1 month later

Arteriopathy

- Vasculitis (primary vs. secondary)
  - Inflammation of the cerebral vessels

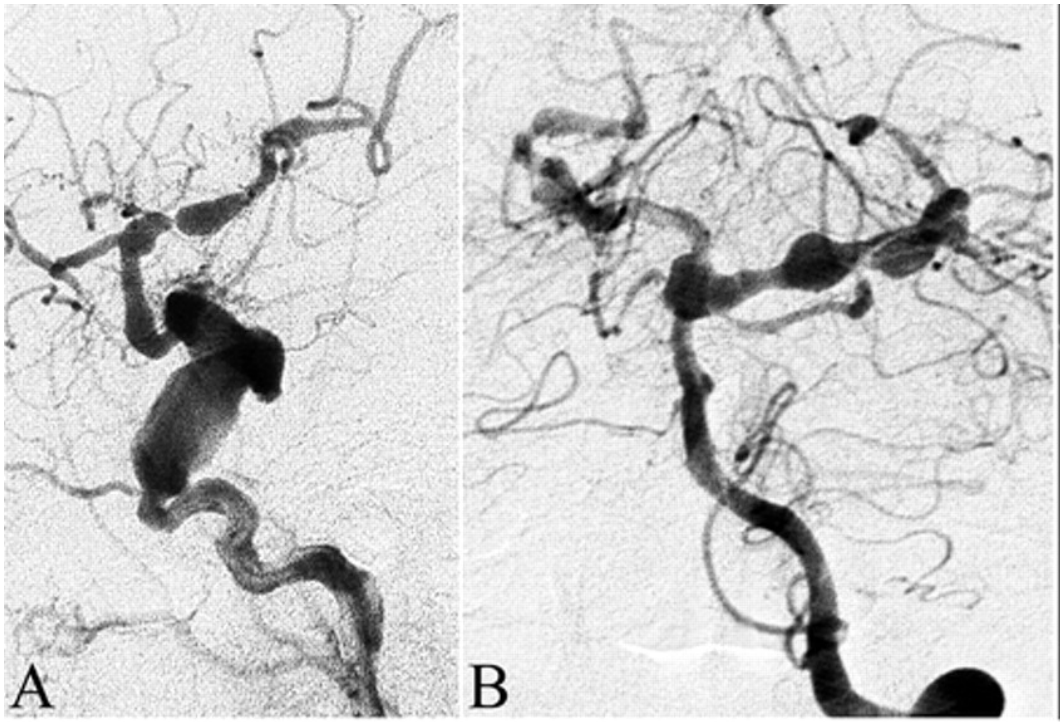
    Primary
    - Takayasu arteritis
      - Inflammatory phase, systemic illness, malaise, fever, fatigue
      - Typically female
      - Unknown cause
      - Often anemia and elevated labs ESR, CRP
    - Kawasaki Disease
      - Age < 5
      - High fever x 5 days
      - Erythema of the lips or oral cavity
      - rash on the trunk
      - swelling or erythema of the hands or feet
      - swollen lymph node in the neck of at least 15 mm
  - In adults, Polyarteritis nodosa, Wegener's granulomatosis

Child with Kawasaki disease
(red eyes, dry cracked lips, red tongue)

Arteriopathy

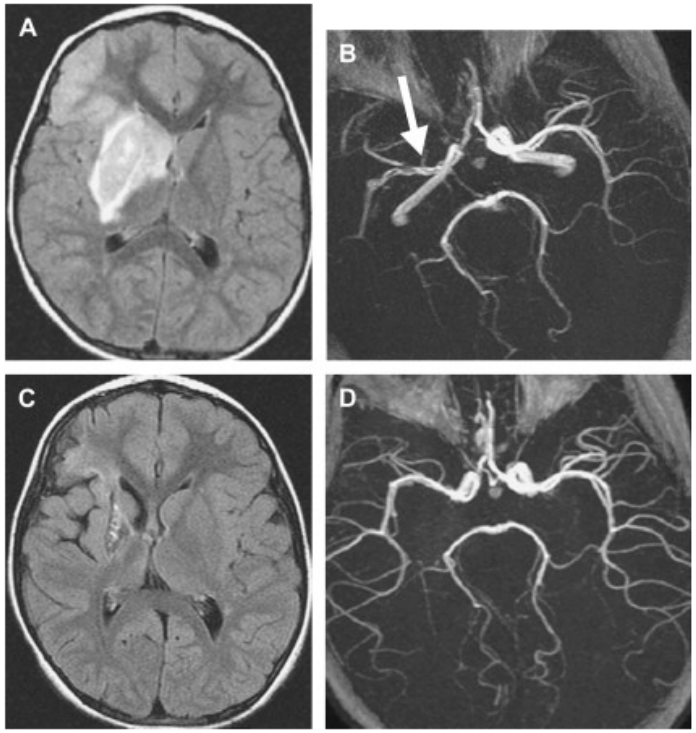
- Vasculitis
  - Secondary
    - Collagen vascular disorders leading to immune complex deposition
      - SLE
    - Infectious
      - Bacterial meningitis, CNS TB
      - HIV
      - Post Varicella
        - characteristic findings include basal ganglia infarction
        - Transient cerebral angiopathy: unilateral focal or segmental stenosis
        - Average age of onset is 5 years
        - 3 – 4 months after chicken pox

HIV angiopathy



16-old boy with HIV presenting with sudden onset right-sided hemiplegia

Varicella angiopathy



7 year-old girl, 3 months post varicella infection presenting with left hemiparesis.

Neuroimag Clin N Am 17 (2007) 175–187

MCA most commonly affected

Prognosis good

UTHSC

Cardiac Disorders

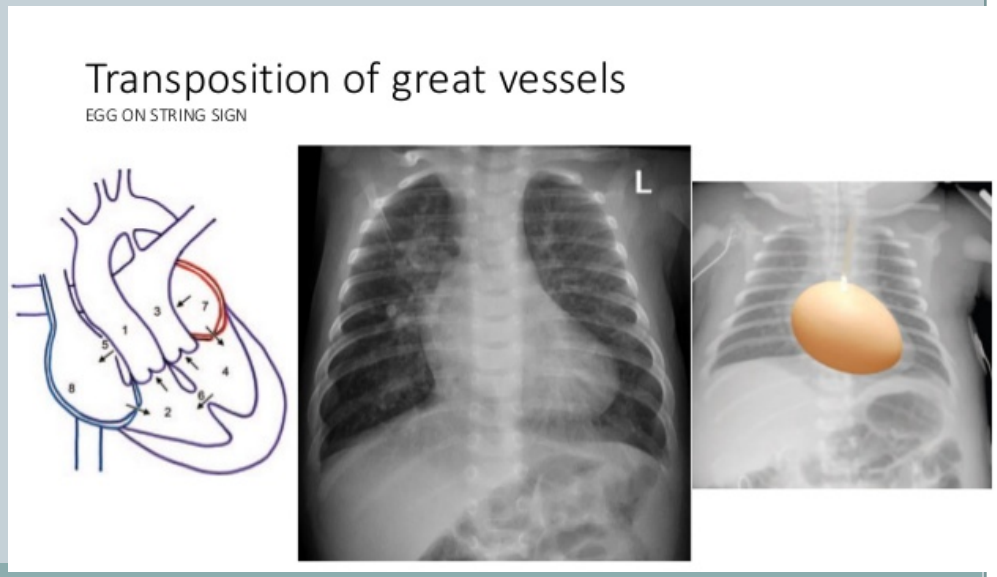
- **Cardiac disorders 31%**
  - Occurs in *uncorrected* congenital heart disease
- **Complex right-to-left shunting**
- **Systolic ejection murmur**
  - ASD, VSD
  - Patent foramen ovale (up to 35% between ages 1 to 29)
  - Transposition of great vessels

    Neonates with hypoxia

    20 : 100,000

    Needs an ASD!

    Blue Crying
    egg on a string



Cardiac Disorders

Cerebral Infarction in Duchenne Muscular Dystrophy

Nina Tsakadze, MD, PhD,* Lara W. Katzin, MD,* Sendhil Krishnan, MD,† and Réza Behrouz, DO*†‡

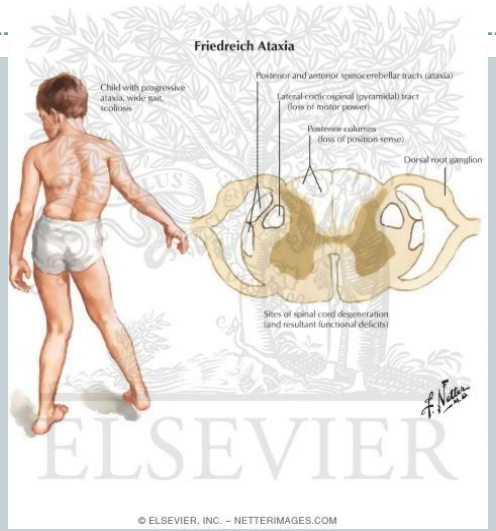
Journal of Stroke and Cerebrovascular Diseases, Vol. 20, No. 3 (May-June), 2011: pp 264-265

Cardiomyopathy with reduced LVEF

Muscular dystrophy

- **Duchenne's, X-linked, 1 : 3,600 boys**
- Cardiomyopathy common
  - 328 pts 1976 – 1987
  - Pre-clinical cardiac involvement 25% of patients under 6 years old
  - 59% between the ages of 6 and 10 years
  - Clinically evident after 10 years of age

Risk Factors



Cardiomyopathy with reduced LVEF

Friedreich's ataxia

- reduced mito expression frataxin
- neurodegeneration in spinal cord,
- 1:50,000
- staggering, stumbling
- also at risk for afib

- **Chagas' disease (Southwestern US!)**

Risk Factors

- These conditions are difficult to dx in an emergent setting.
- Remember, asking family/caretakers of past medical history is crucial!

Hematologic

- Blood disorders
  - Sickle Cell
  - Prothrombotic disorders
    - Hypercoagulable disorders to OCP use

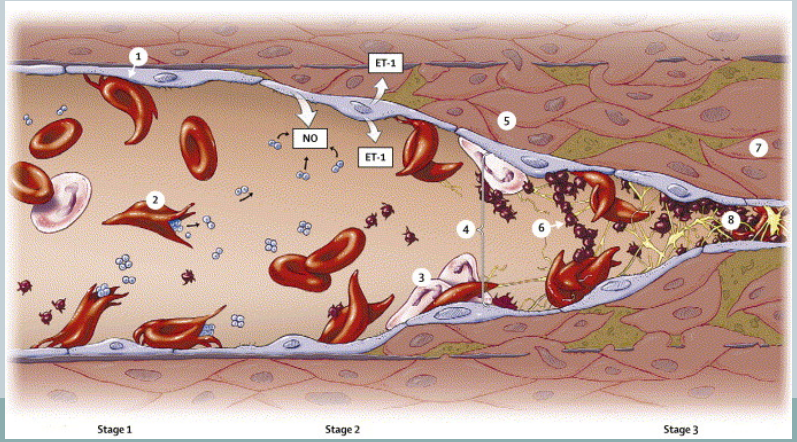
Hematologic

- Sickle Cell Disease
  - Ischemic (54%) and hemorrhagic strokes
    - Age 2-9
  - **Incidence of stroke without intervention 11% by age 20,**
  - **Increased with dehydration, high velocities on TCD, low Hb**
  - **10% will have stroke**
  - **20% silent strokes**
  - **Steno-occlusive arteriopathy**
    - **Intimal progressive stenosis**
    - **Abnormal interactions between WBC's, RBC's, platelets, and vascular endothelium**

Hematologic

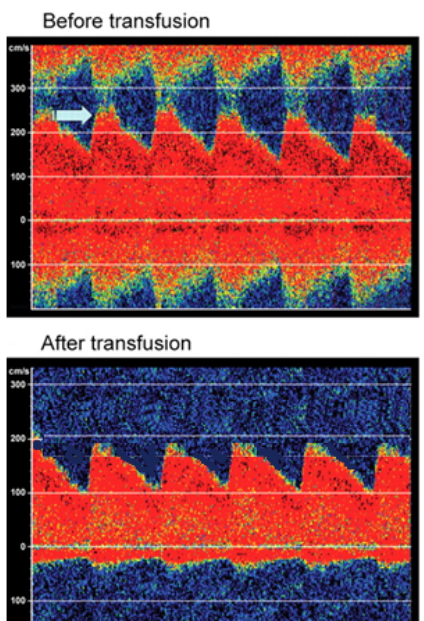
- Sickle Cell Disease
  - TCD screening test for stroke risk in children with SCD

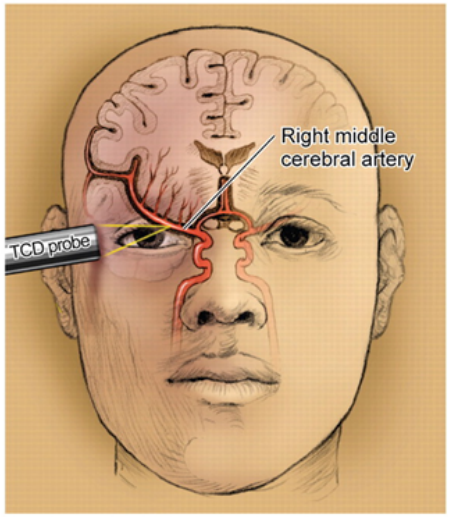
Result of TCD	CBFV (cm/sec)	Frequency of Exam
Normal	< 170	Repeat Annually
Low Conditional	170 - 184	Repeat q 3 months
High Conditional	185 – 199	Repeat q 1 month
Abnormal	> 200	Repeat q month



Hematologic

- Sickle Cell Disease
  - Stroke prevention in Sickle Cell Anemia (STOP) trials
    - Ages 2-16
    - **Exchange transfusion: Keep HbS < 30% reduced stroke 90%**
    - **Termination of transfusion in high-risk patients is associated with return of high velocity parameters and stroke risk (STOP II Trial)**



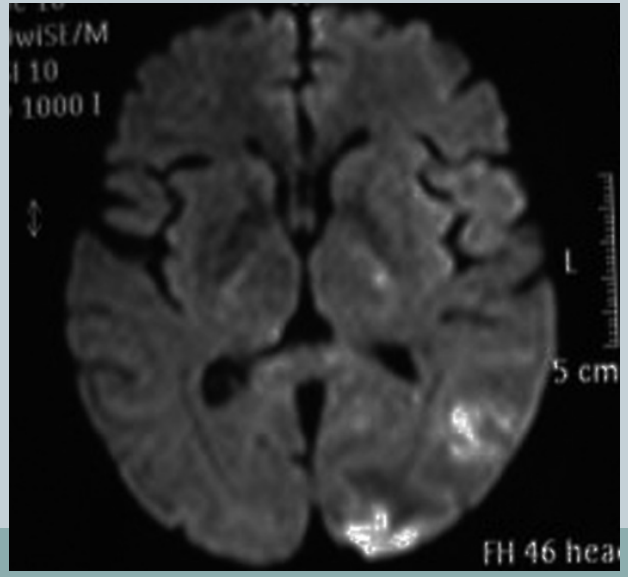


Risk Factors

- Prothrombotic states
  - Meta analysis 22 observational studies
  - Ischemic stroke associated with:
    - Protein C deficiency
    - APS
    - Factor V Leiden
    - Elevated homocysteine with MTHFR mutation
    - Oral Contraceptive with high estrogen content

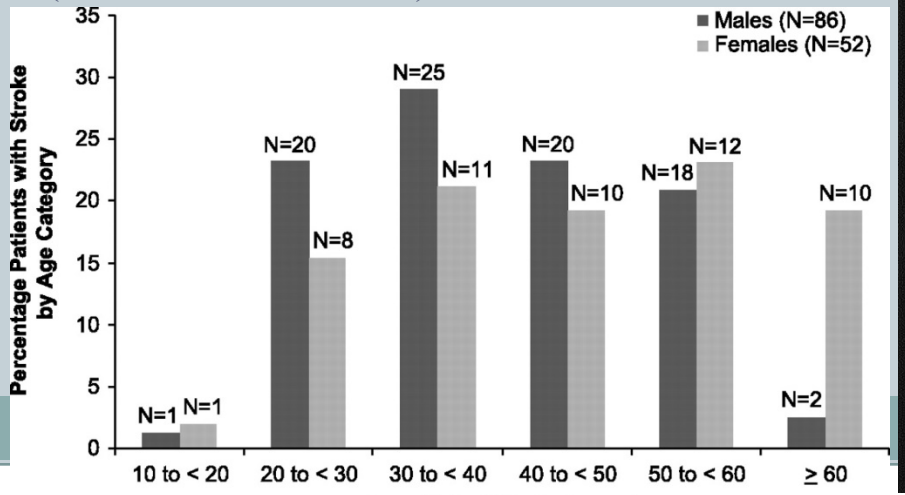
Risk Factors

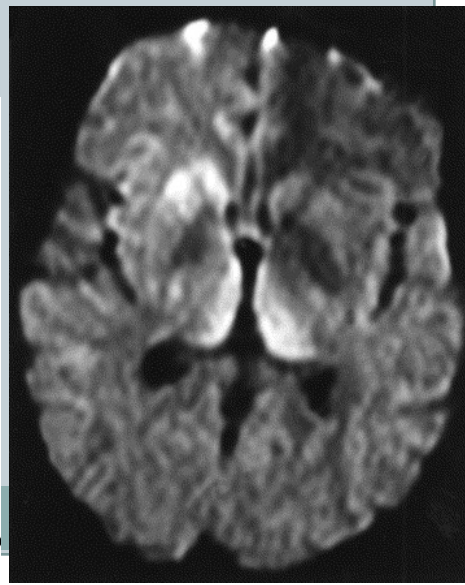
- Metabolic causes
  - MELAS
    - Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes
    - Mutations in mitochondrial DNA
    - RECURRENT metabolic failure stroke, not arterial ischemic
    - Sx appear in childhood (age 2-15)
      - Myalgias, fatigue, seizures
      - Vision loss, hemiparesis, hemisensory loss
      - Progressive, sx additive, cognitive decline



Risk Factors

- Metabolic causes
  - Fabry's Disease
    - Very rare cause of stroke in children
    - X-Linked
    - Deficiency of alpha-galactosidase A cause glycolipid accumulation within blood vessels
    - Ischemic strokes mainly in the posterior circulation
      - Pulvinar sign (also seen in CJD)



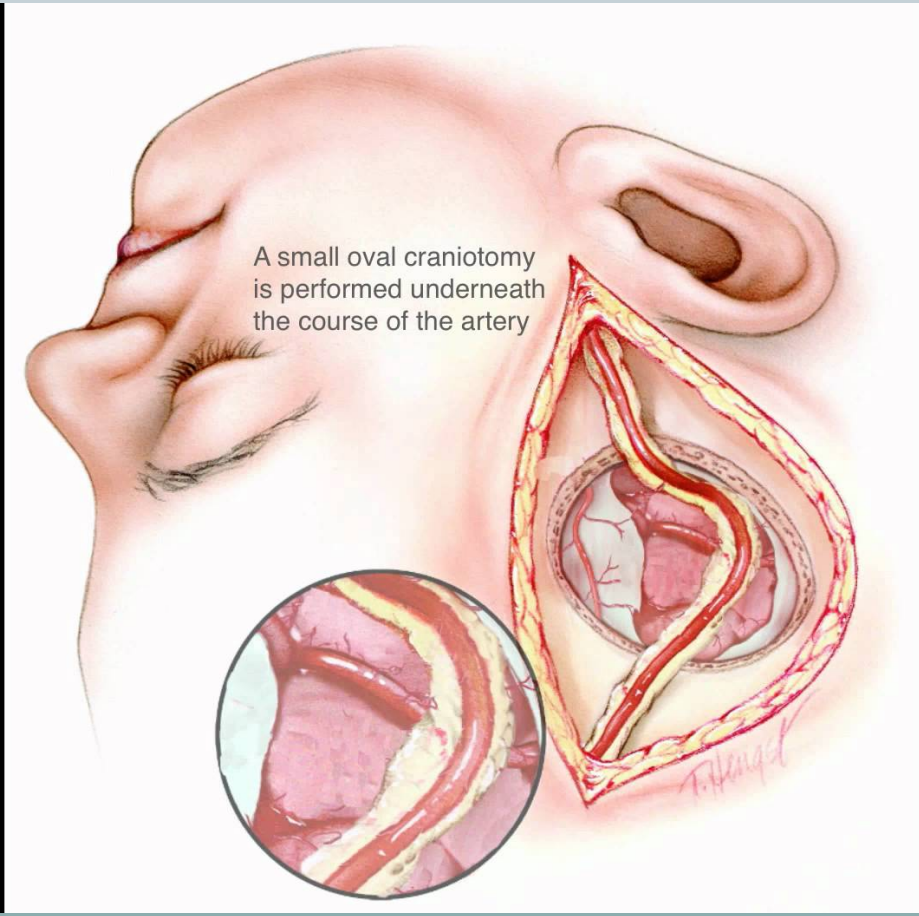


Specific Treatment therapies

- Sickle Cell
  - optimal hydration, correction of hypoxemia, and correction of systemic hypotension
  - Periodic transfusions to reduce the percentage of sickle hemoglobinin children 2 to 16 years of age with an abnormal TCD.
- Moyamoya with progressive ischemic sx
  - revascularization
  - Meta analysis 1156 pediatric pts treated direct/indirect, 86% had symptomatic benefit

Revascularization

- EDAS



Specific therapies

- **Cardiac Disorders**
  - **Correction of congenital anomaly**
  - **PFO closure may be more beneficial in children with stroke than adults**
  - **Children with cardiomyopathy and decreased LVEF may benefit from long therm anticoagulation**
- **Dissection**
  - **2008 pediatric guidelines rec 3-6 months anticoagulation**
- **Primary CNS vasculitis**
  - IV Methyl-prednisone 1g daily for 3 days followed by oral prednisolone 60 mg/day, decreasing by 10 mg at weekly intervals to 10 mg/day if possible.
- **Fabry's**
  - **Alpha galactocidase replacement**
- **Hypercoagulable states**
  - **Check homocysteine levels**
    - **If high, give Folic Acid, Pyridoxine, Vitamin B12**
  - **Anticoagulation**

So, what can we do?

- Prompt recognition and diagnosis are essential
  - ABC's
  - PMHx history/risk factors
    - PLEASE get contact info from family members/caretakers
    - Trauma?
      - Intracranial hemorrhage or ischemia from dissection?
      - Seizure?
        - Todd's paralysis?
    - Congenital risk factors?
  - Vital signs, EKG, identify obvious other causes for neuro changes
    - O2 sats (hypoxia, shunt, transposition)

So, what can we do?

- Imaging
  - MRI w/o with DWI preferred
    - Differential is often large, helps identify stroke and mimics
  - CT head to evaluate for hemorrhage if STAT MRI unavailable
  - CTA/MRA head and neck is helpful to evaluate for dissection, embolism, or arteriopathy (moyamoya)
    - Gad+? TOF?
    - Focal occlusion 2/2 embolism from vert dissection vs gradual stenosis from moyamoya.
  - CXR can help look for cardiomyopathy

So, what can we do?

- Labs
  - Glucose!
  - CBC, CMP
  - aPTT, PT, INR
  - Toxicology
  - Blood EtOH level
- If suspicious for vasculitis:
  - Conventional Angio
  - ESR, CRP, ANA, Varicella titires, HIV

So, what can we do?

- Supportive measures
  - HOB flat
  - Normoglycemia and normothermia
  - IV NS at maintenance rate
  - Permissive modest HTN
  - Supplemental O2 goal sats > 95%
  - Continuous cardiac monitoring

Can we use tPA?

- Not FDA approved <18.
- No prospective data available
  - TIPS closed to slow enrollment
- Very few observational reports

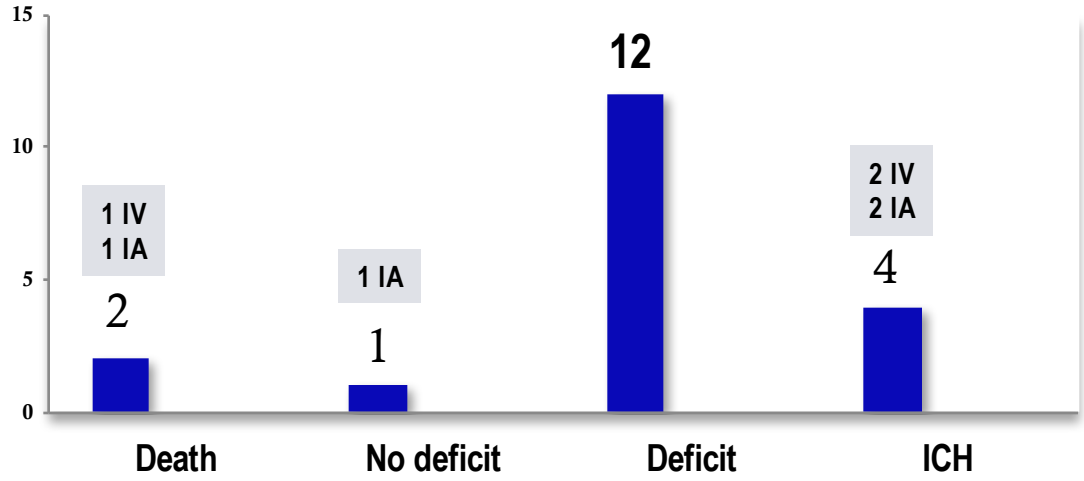
ACUTE REPERFUSION THERAPY

Use of alteplase in childhood arterial ischaemic stroke: a multicentre, observational, cohort study

The International Pediatric Stroke Study

Lancet Neurol 2009; 8: 530–36

687 children from around the world
Only 15 (2%) receive rt-PA: 9 IV and 6 IA
The median time to treatment 3·3 h (range 2·0–52·0 h) IV rt-PA
4·5 h (3·8–24·0 h) for IA rt-PA



The 9 patients in the IPSS cohort who received IV rt-PA were mostly younger, waited longer for treatment, and had worse outcomes

ACUTE REPERFUSION THERAPY

IV rt-PA – Why can't we just give it?

Between 2000 and 2003, 1.6 percent of children presenting with AIS received thrombolytic therapy *(Janujua et al, 2007)*

A significant pre-hospital and in-hospital delay exists in diagnosis of AIS in children, sometimes up to 12 hours *(Leaker et al, 1996)*

Uncertainty in diagnosis: "stroke mimicker," such as (among others) Todd's paralysis or acute demyelinating encephalomyelitis (ADEM) are more common in children.

Presentation of stroke is different in children than adults

Children seek attention much later than adults

ACUTE REPERFUSION THERAPY

IV rt-PA – Why it doesn't work as well?

Arterial AIS is much less common in children than in adults

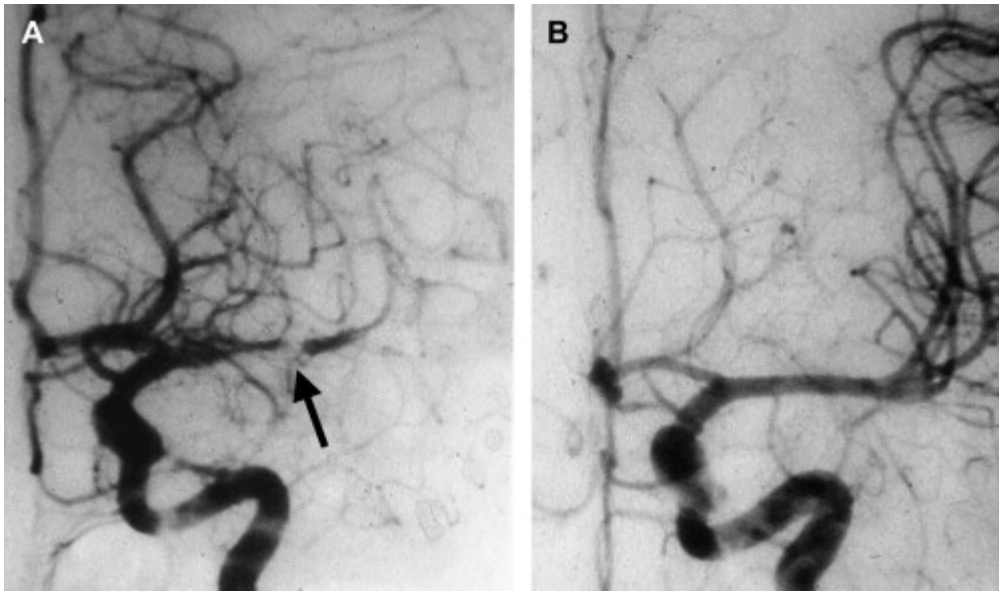
Etiologies and patho-physiological mechanisms of AIS in children are quite diverse and do not necessarily parallel those of adults.
(HTN, DM, tobacco, afib, carotid stenosis)

If the decision to administer IV rt-PA in a child with AIS is finalized, there exists no standard protocol for an appropriate dose or duration of infusion

UTHSC

ACUTE REPERFUSION THERAPY

Mechanical embolectomy



Fourteen-year-old girl with sudden onset of right hemiplegia and aphasia.

UTHSC

OUTCOMES

Mortality

3-11%

Persistent neurological deficit

Up to 66%

Recurrent event (long term)

10-20%

60% in SCD

Summary

- Childhood AIS is under-recognized.
- Risk factors are etiologies are different than those of adults
- Mimics are common (21%)
  Seizure, headache, PRES, infection, metabolic
- Remember to get contact info for family member
- Workup for acute intervention requires multiple imaging modalities.
- Treatments are more geared toward individual risk factors.
- Prospective trials?
- Guideline update?

"No one is useless in this world who lightens the burdens of another.“
Charles Dickens

References

- Sebire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: A case-control study. Ann Neurol. 1999;45:679–680.
- Scott RM, Smith JL, Robertson RL, Madsen JR, Soriano SG, Rockoff MA. Long-term outcome in children with moyamoya syndrome after cranial revascularization by pial synangiosis. J Neurosurg. 2004;100(2 suppl Pediatrics):142–149.
- Fung LW, Thompson D, Ganesan V. Revascularisation surgery for paediatric moyamoya: a review of the literature. Childs Nerv Syst. 2005;21:358 –364
- National Heart, Lung, and Blood Institute, National Institutes of Health. Clinical alert from the National Heart, Lung, and Blood Institute [press release]. December 5, 2004. June 15, 2008
- Eng CM, Guffon N, Wilcox WR, Germain DP, Lee P, Waldek S, Caplan L, Linthorst GE, Desnick RJ; International Collaborative Fabry Disease Study Group. Safety and efficacy of recombinant human alphagalactosidase A–replacement therapy in Fabry's disease. N Engl J Med. 2001;345:9–16
- Benseler SM, Silverman E, Aviv RI, Schneider R, Armstrong D, Tyrrell PN, deVeber G. Primary central nervous system vasculitis in children. Arthritis Rheum. 2006;54:1291–1297
- Sébire G, Meyer L, Chabrier S. Varicella as a risk factor for cerebral infarction in childhood: a case-control study. Ann Neurol. 1999;45: 679–680.
- Touzé E, Gauvrit JY, Moulin T, Meder JF, Bracard S, Mas JL; Multicenter Survey on Natural History of Cervical Artery Dissection. Risk of stroke and recurrent dissection after a cervical artery dissection: a multicenter study. Neurology. 2003;61:1347–135

Thank you!


Head
Jack U off
Pocket full of horses...
Darling Nikki
Dirty Mind
"Dirty Mind"