Pediatric Neuroangiography: A Case-Based Approach

Time for Stroke Conference

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Disclosures

- Chief Medical Officer: ChemoFilter
- Scientific advisory: Medina
- Consulting: Stryker, Silk Road
- Data Safety and Monitoring Committee: DAWN trial (Stryker)
- Core Imaging Lab: MAPS trial (Stryker), FRED trial (Microvention)
- Grant support: NIH-NIBIB, ASNR Foundation
- I will discuss off-label uses of drugs (tPA) and devices (stents, balloons, calcium channel blockers)
- Videos from vendors will be shown
- I have borrowed liberally from my colleagues and acknowledge their kind help: Christopher Dowd, MD, Joey English, MD, PhD, Daniel Cooke, MD, Peter Jun, MD, Van Halbach, MD, Randall Higashida, MD, Charles Stout, MD, PhD

Outline

- Techniques and special concerns
- Age specific pathology
- Illustrative cases

Techniques and Special Concerns

- Physically small
  - 4 Fr sheath, 4 Fr dx catheter
- Low blood volumes
  - Slow heparinized saline arterial drips
- Highly reactive arteries
  - Ultrasound guided puncture, nitropaste
- Inability to remain still
  - Anesthesia support

Age Specific Pathology

- Genetic syndromes
- Congenital AV fistulas
- Vascular dysplasias
- Traumatic injuries
- CNS neoplasms

Case 1

Pediatric Stroke

- Annual incidence: 2.3 to 13/100,000 children
- Neonatal incidence: 1/5000 live births
- Dx often delayed
- Over 50% cause long term sequelae
- 6-19% recurrence in first few years

Amlie-Lefond et al., Lancet Neurology 7:425-35, 2008

Pediatric Stroke

- Etiologies
  - Arteriopathy (up to 80%)
    - Trauma, NF1, Moyamoya, trisomy 21
  - Infection (meningitis, endocarditis)
  - Congenital heart disease
  - Hypercoagulability, sickle cell disease
- Lack of adult risk factors (until what age?)
  - Smoking
  - Sympathomimetic drug abuse

Case 2

Pediatric vs Adult Aneurysms

Pediatric	Adult
2-5%	95-97%
1-3M:1F	3F:1M
ICA bifurcation	AComA
Giant 20-40%	Giant uncommon
Rarely mult (except HIV)	15% mult
Post circ 20-40%	5.5%

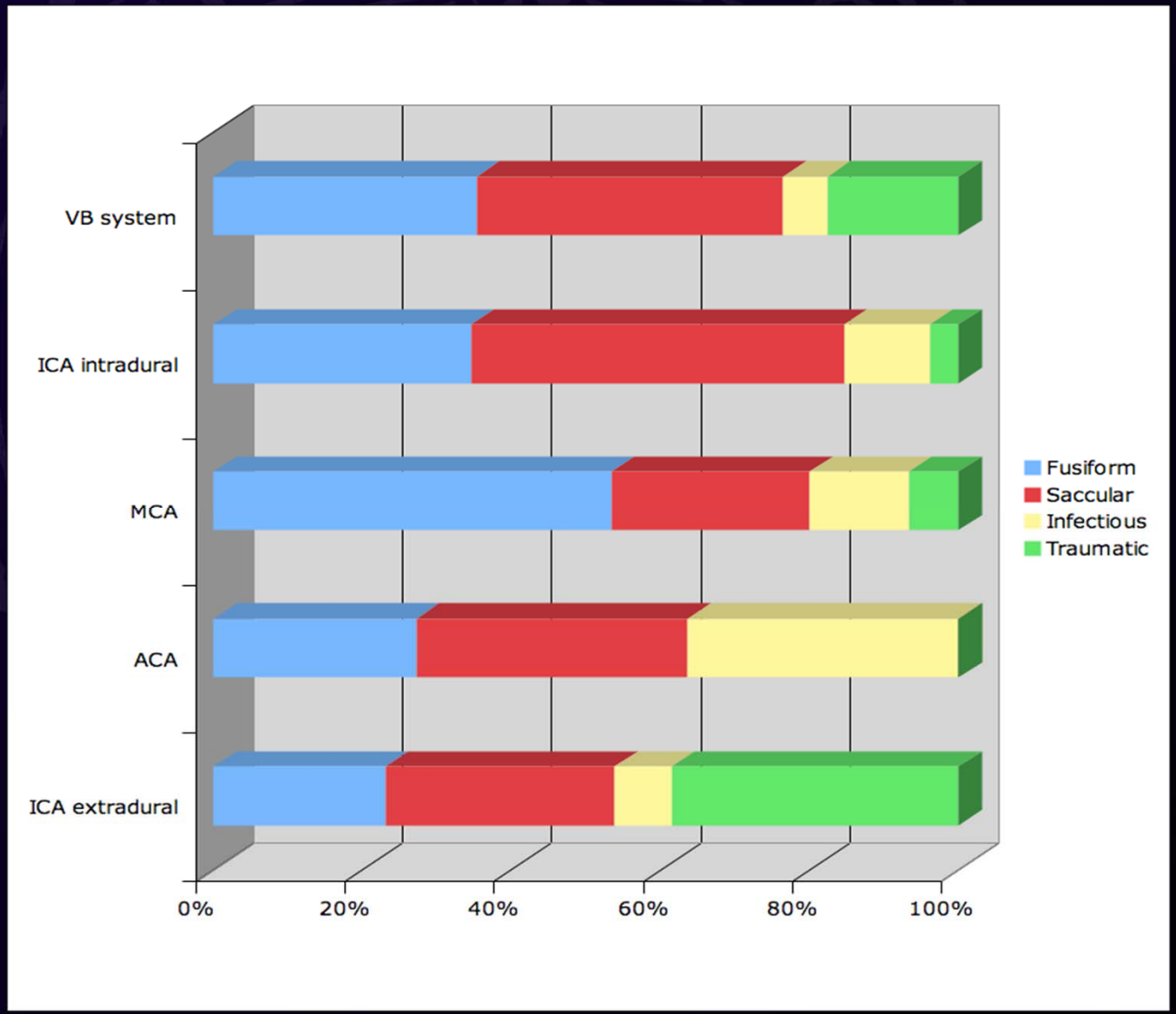
Pediatric Aneurysm Presentation

Headache	45%
Stroke	18%
Cranial Neuropathy	16%
Nausea/Vomiting	15%
Vision Changes	13%
Trauma	12%
Asymptomatic	7%
Seizure	4%
Pulsatile Tinnitus	1%

28% Rupture

Hetts et al., AJNR 30:1315-24, 2009

Aneurysm Etiology and Location



Hetts et al., AJNR 30:1315-24, 2009

When Do New or Enlarging Aneurysms Arise?

Entire Cohort

- 81 patients
- Gender M39:F42
- Age Range 0.3–18 years
- Mean Age 12.2±5.1 years
- Mean Follow Up 3.8±4.4 years

New/Enlarging Subset

- 7 patients (9%)
- Gender M4:F3
- Age Range 4–17 years
- Mean Age 10.7±4.6 years
- Mean Time to New Aneurysm 3.9±3.7 years
- Range of Time to New Aneurysm 0.8-12 years

Hetts et al., AJNR 30:1315-24, 2009
Hetts et al., AJNR 32:2017-22, 2011

Comorbidites in Patients with New/Enlarging Aneurysms

- AIDS
- X-linked Severe Combined Immunodeficiency (SCID)
- Tricuspid Atresia
- Vascular Birthmark
- Microcephalic Osteodysplastic Primordial Dwarfism Type II (MOPD II)
- Hemiatrophy

Pediatric Aneurysms: Summary

- 9% of children with aneurysms develop a new or enlarging aneurysm an average of 4 years later (range: 10 mo to 12 yrs)
- Most children with new aneurysms have identifiable comorbidities
- Fusiform aneurysms are overrepresented
- New aneurysms may be in different vessel
- Close imaging and clinical follow up is warranted

Case 3

Angiographic evaluation of SAH

- What constitutes a complete angiogram?
- Internal carotid arteries (head)
- External carotid arteries (head)
- Vertebral arteries – *including cervical segments*
- Assess vessel origins with common carotid and subclavian arteriograms

Perimedullary AVF

- Type IV spinal vascular malformation
- Micro (group 1 and 2) and macro (group 3)
- Demographics (Antonietti et al., *AJNR* 2010)
  - Group 1: 54 y (40-65 y)
  - Group 2: 45 y (16-82 y)
  - Group 3: 17 y (2-40 y)
- Presentations: myelopathy, SAH
- Pathophysiology: venous hypertension, cord compression

Treatment Options

- Surgery – often best for micro AVF
- Embolization
  - Favorable for macro AVF or large varices
  - Favorable for young children
- Medical – alteration of coagulation or venous hypertension may temporize but not cure

Case 4

Look before you leap

- 3 day old girl
- Severe CHF, pulmonary HTN, “occipital infarct”
- Transferred for emergent embolization
- MRI scan obtained

Vein of Galen Malformations

- AV shunt to median vein of prosencephalon (midline Prosencephalic Vein of Markowski)
- Embryological precursor to vein of Galen
- Congenital
- Clinical
  - neonates: high output CHF
  - infants: hydrocephalus, ↑ head circumference
  - children: MR, seizure, ↑ facial/scalp vv., *hemorrhage*

VOGM Angioarchitecture

- True Vein of Galen Malformation
  - Choroidal: persistent primitive choroidal aa; numerous small shunts *(neonates; ill)*
  - Mural: direct AV fistulas to wall of median prosencephalic v.; fewer larger shunts *(infants; less ill)*

- "False" VOGM: dilated vein of Galen 2º to AVM/AVF; acquired vein of Galen ectasia drains AVM/AVF and normal brain.

VOGM Natural History

- Cardiac
  - L -> R shunt causes high output CHF, R heart failure, pulm. HTN, hepatic and renal failure, coagulopathy
- Neurological
  - "Hydrovenous disorder"
  - AV shunt + venous outflow restriction -> venous HTN -> atrophy -> DD and HCP

VOGM: Hydrocephalus

- *Rarely* 2º to aqueductal obstruction by varix
- ↑ venous pressures (often >30mm), ↓ CSF absorption, arachnoid granulation immaturity, ↑ CSF volume
- Avoid CSF shunting!
  - changes cerebrifugal medullary v. outflow to cerebripetal -> ↑ venous congestion -> sz, DD, hemorrhage
- Endovascular Rx of AVF to ↓ venous HTN

VOGM: Treatment

- No treatment
- Medical: CHF management
- Surgical: disconnection of AV shunts
- Endovascular:
  - Transarterial
  - Transtorcular
  - Transvenous
  - Transarterial → venous
  - Transvenous → arterial

➢ *Complete cure not required, staged Rx preferable*

Outcomes: Pediatric VOGM

- Features associated with poor neurological outcomes:
  - Neonatal presentation, CHF, choroidal angioarchitecture

Outcome	Fullerton et al. Neurology 2003	Lasjaunias et al. Neurosurgery 2006
Complete Occlusion	21/27 (77.8%)	118/216 (54.6%)
Death	4/27 (14.8%)	23/216 (10.6%)
No neurologic or developmental disability	14/27 (51.2%)	143/216 (66.2%)

NGAVF Early Presentation

Neonates - First month of life (8/23)

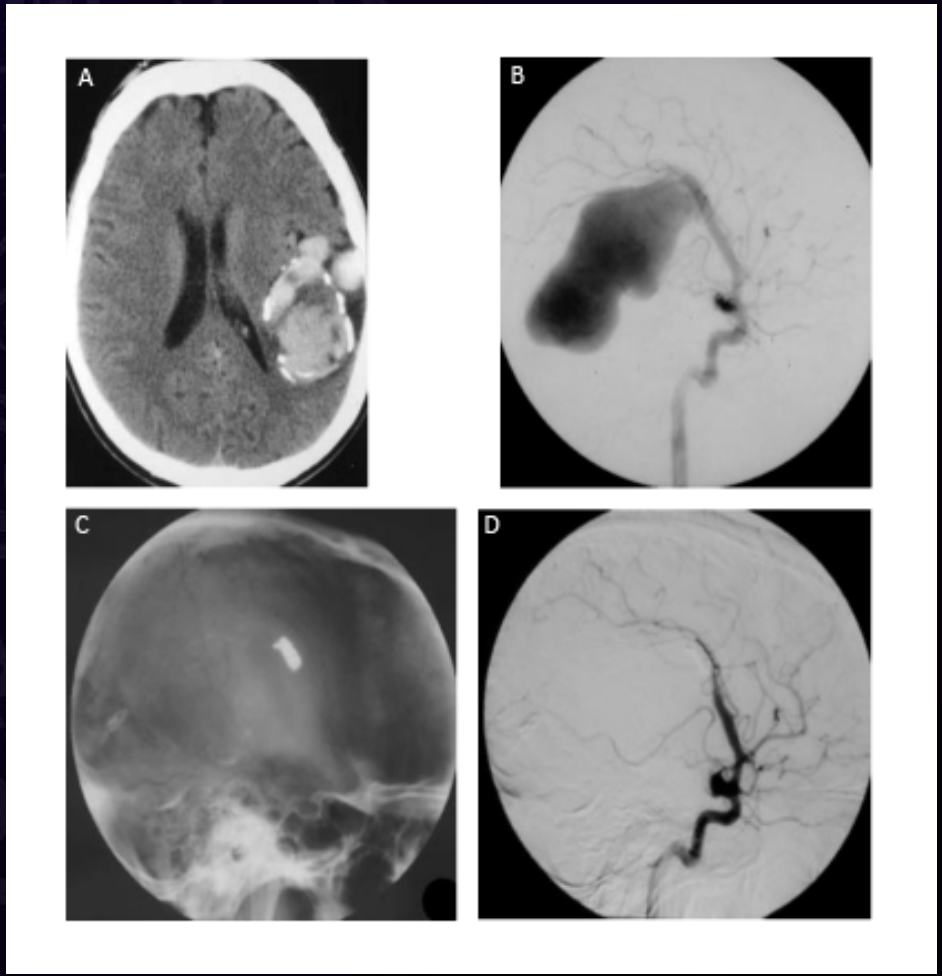
- (7/8) with CHF and large complex fistulas with multiple sites of AV shunting
- (1/8) scalp segmental cutis aplasia, enlarging scalp hemangioma, facial venous malformation, HCP, asymmetric facial weakness

NGAVF Delayed Presentation

After first month (15/23)

- Single hole fistulas predominated
- Associated symptoms
  - Seizure (8/15)
  - Headache (5/15)
  - Focal neurologic deficit (4/15)
  - Hemorrhage (3/15)

Single hole AVF with giant varix



Outcomes: Pediatric NGAVF

- NGAVFs are heterogeneous lesions with similar morbidity and mortality as VOGMs

Outcome	NGAVF - Hetts et al. 2012	VOGM - Fullerton et al. 2003	VOGM - Lasjaunias et al. 2006
Complete Occlusion	15/23 (65.2%)	21/27 (77.8%)	118/216 (54.6%)
Death	2/23 (8.7%)	4/27 (14.8%)	23/216 (10.6%)
No neurologic or developmental disability	11/23 (47.8%)	14/27 (51.2%)	143/216 (66.2%)

PEDIATRIC AVMs: SPECIAL FEATURES

- Neonates/Infants:
  - Multiple pial AV fistulas (continuum with NGAVF)
  - Present with CHF
- Children:
  - Smaller nidus c/t adults
  - Increased frequency of hemorrhage
  - Increased frequency of IV hemorrhage

Recent AVM Research at UCSF

- To determine if clinical presentation and angioarchitectural features differ between children and adults with brain AVMs

Materials and Methods

- UCSF brain AVM database queried
  - Prospectively collected since 2001
- Patients with nidal AVMs were analyzed
  - VOGM, DAVF, NGAVF excluded
- Demographics and angioarchitecture abstracted and analyzed with logistic univariate and multivariable models

Demographics and Presentation

	Children (0-18 y) (n=203)	Adults (≥19 y) (n=630)	P Value
Age at Dx (yrs)	12±5	43±15	
Female Gender	101 (50%)	321 (51%)	0.687
Ethnicity			0.014
Non-Hispanic White	*88 (43%)*	*343 (54%)*	
Black	*11 (5%)*	*42 (7%)*	
Hispanic	*71 (35%)*	*153 (24%)*	
Asian	*31 (16%)*	*82 (13%)*	
Native American	*1 (<1%)*	*8 (1%)*	
Hemorrhage	119 (59%)	256 (41%)	<0.001

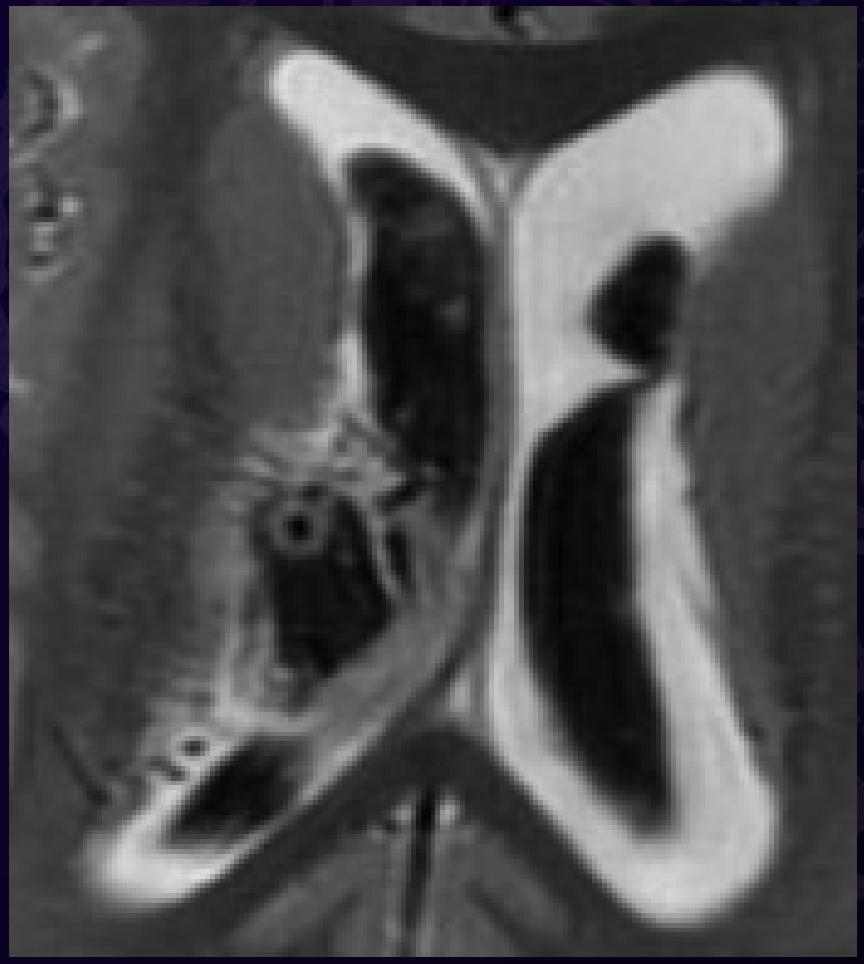
Results: Demographics

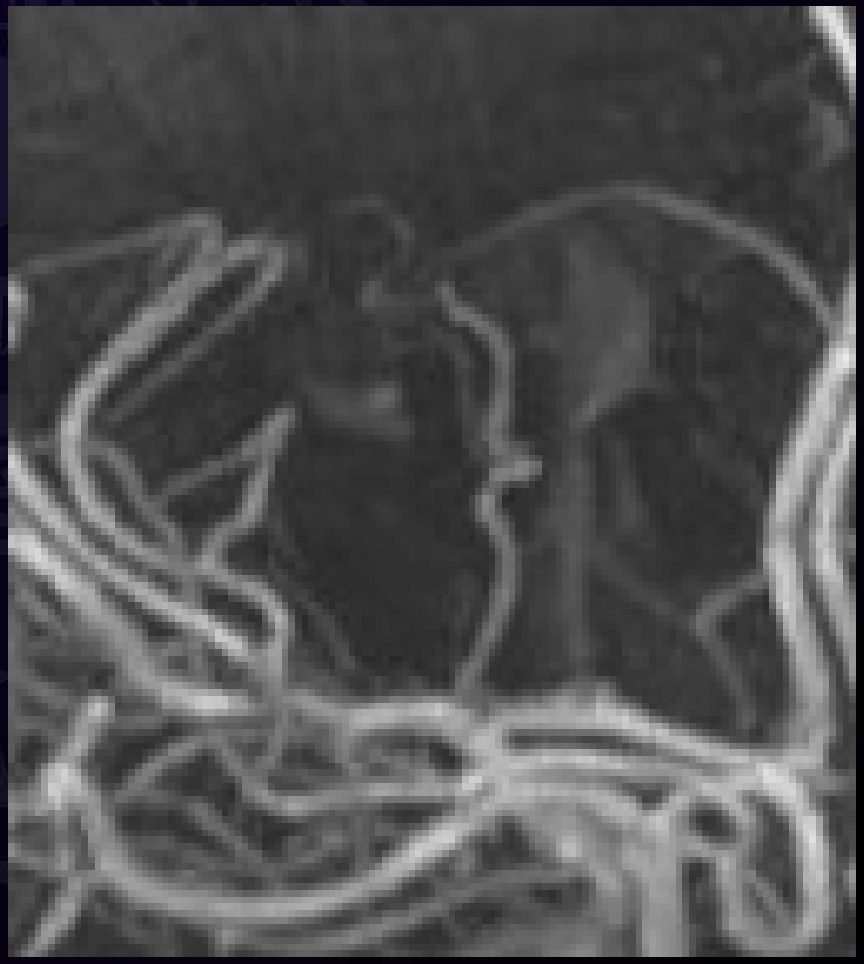
- Children more likely to present with AVM hemorrhage than adults
  - OR 2.1 (95% CI 1.45 to 2.91)
- Overrepresentation of Hispanic children as compared to adults

Angioarchitecture: Nidus and Feeding Arteries

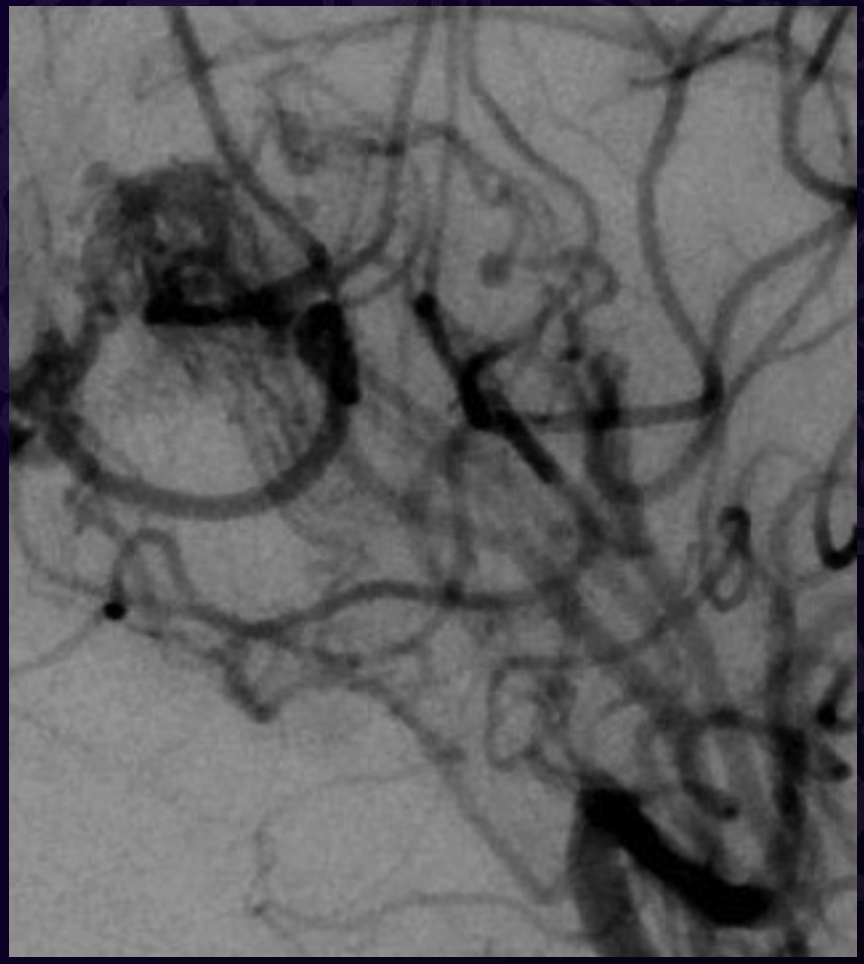
	Children (n=203)	Adults (n=630)	P Value
Nidus Size <3 cm	95 (53%)	322 (55%)	0.069
Nidus Size 3-6 cm	68 (38%)	237 (41%)	
Nidus Size >6 cm	15 (8%)	23 (4%)	
AVM Border Diffuse	38 (23%)	102 (19%)	0.218
Lobar Location	125 (71%)	430 (77%)	0.013
Central Location	78 (44%)	201 (36%)	0.075
Feeding Artery Aneurysm Related to Shunt Flow	21 (13%)	151 (29%)	<0.001

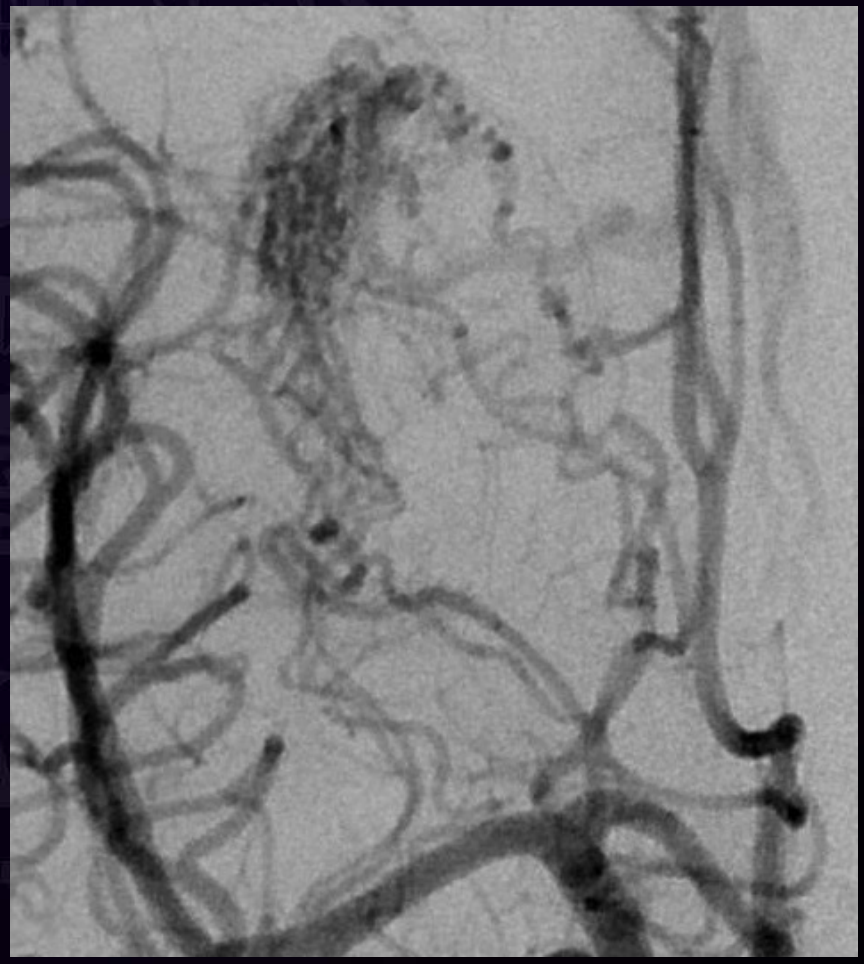
3 yo M with IVH



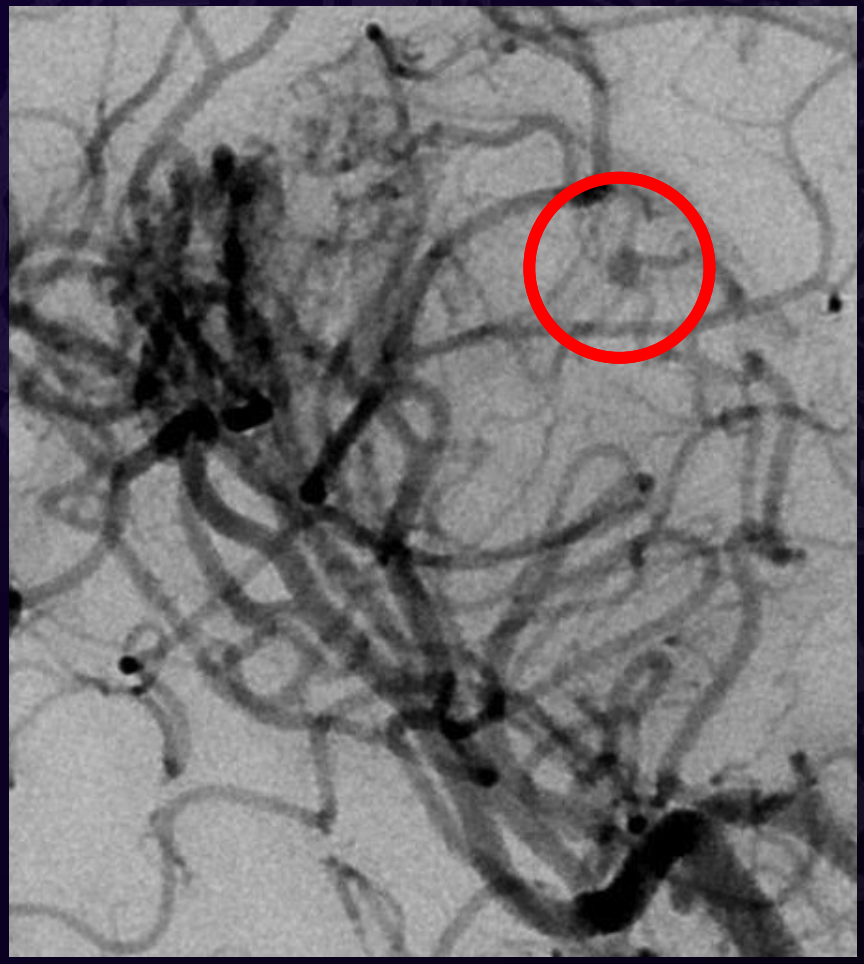


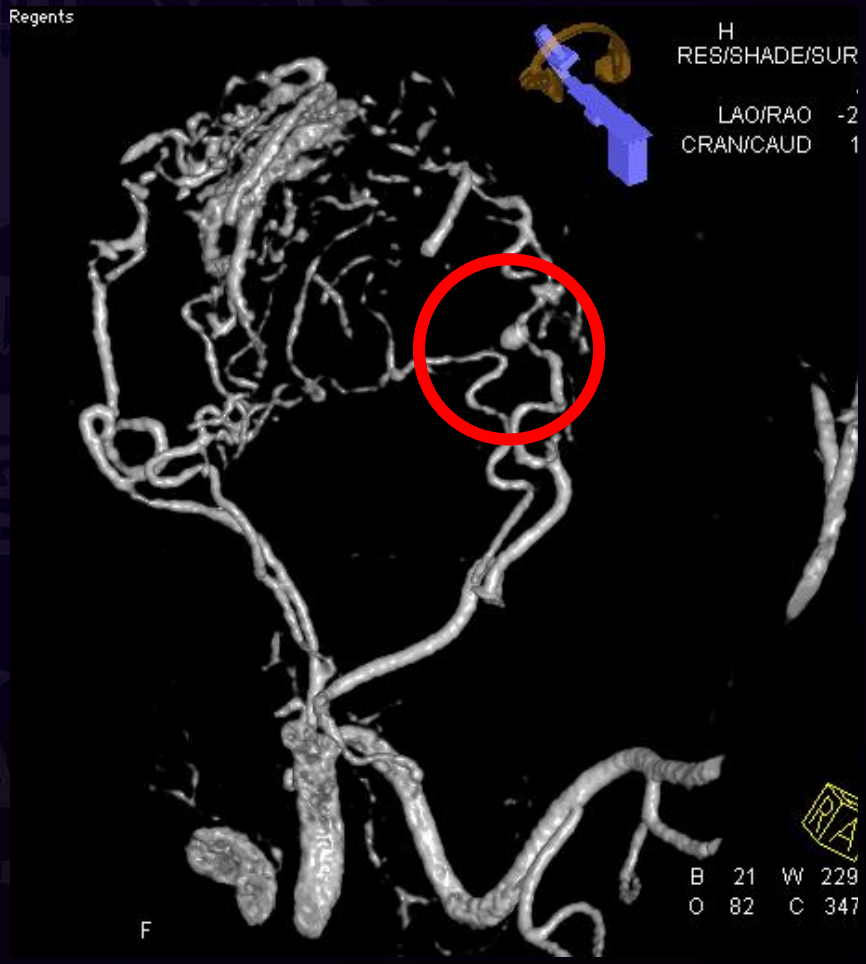
Corpus striatum AVM





Recurrent artery of Heubner feeding artery aneurysm





Angioarchitecture: Venous

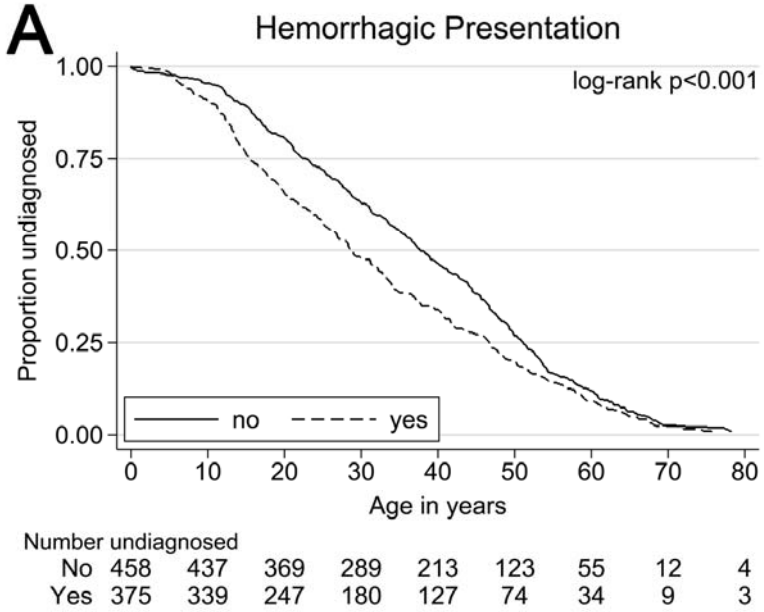
	Children (n=203)	Adults (n=630)	P Value
Venous Drainage			<0.001
Superficial	*67 (37%)*	*322 (55%)*	
Deep	*51 (28%)*	*83 (14%)*	
Superficial and Deep	*61 (34%)*	*177 (30%)*	
Venous Ectasia	45 (35%)	228 (52%)	<0.001
Venous Stenosis			0.144
0-24%	*75 (56%)*	*191 (44%)*	
25-49%	*22 (16%)*	*71 (16%)*	
50-74%	*24 (18%)*	*102 (23%)*	
75-99%	*12 (9%)*	*59 (14%)*	
100% (occlusion)	*2 (1%)*	*13 (3%)*	

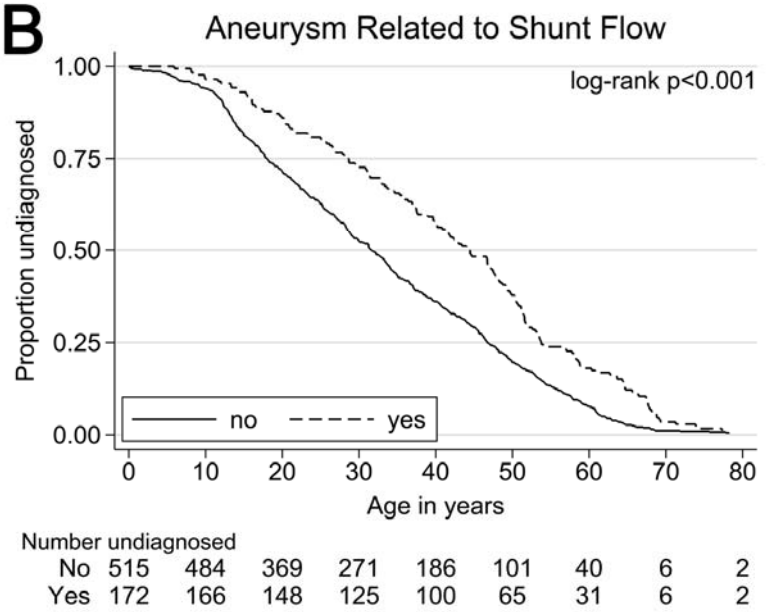
Results: Angioarchitecture

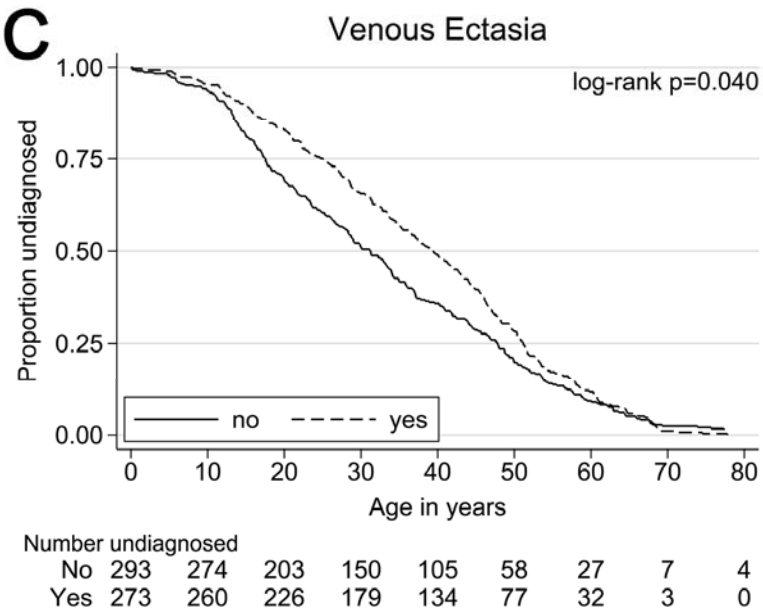
- Size and diffuseness of AVM nidus did not differ between children and adults
- Larger AVMs did present at younger ages (mean 26.8 y for >6 cm vs. 37.1 y for <3 cm)
- Location and venous drainage did differ
  - Children more likely to have exclusively deep venous drainage than adults
  - Children more often harbored deeply-located AVMs; adults more frequently had lobar AVMs

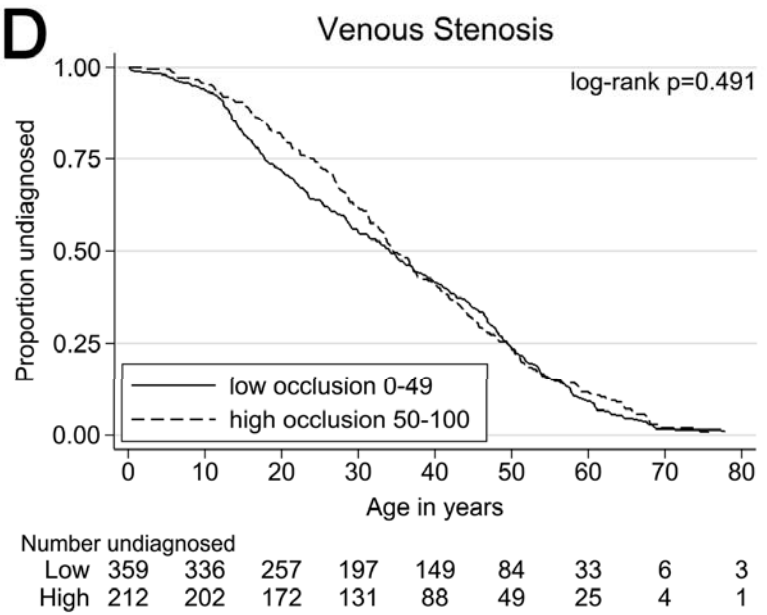
Results: Angioarchitecture

- Venous ectasia and feeding artery aneurysms were underrepresented in children
  - ? due to hemodynamic stress
  - take time to develop


A
Hemorrhagic Presentation
log-rank p<0.001
Proportion undiagnosed
1.00
0.75
0.50
0.25
0.00
no
yes
0 10 20 30 40 50 60 70 80
Age in years
Number undiagnosed
No 458 437 369 289 213 123 55 12 4
Yes 375 339 247 180 127 74 34 9 3


B
Aneurysm Related to Shunt Flow
log-rank p<0.001
Proportion undiagnosed
1.00
0.75
0.50
0.25
0.00
no
yes
0 10 20 30 40 50 60 70 80
Age in years
Number undiagnosed
No 515 484 369 271 186 101 40 6 2
Yes 172 166 148 125 100 65 31 6 2


C
Venous Ectasia
log-rank p=0.040
Proportion undiagnosed
1.00
0.75
0.50
0.25
0.00
no
yes
0 10 20 30 40 50 60 70 80
Age in years
Number undiagnosed
No 293 274 203 150 105 58 27 7 4
Yes 273 260 226 179 134 77 32 3 0


D
Venous Stenosis
log-rank p=0.491
Proportion undiagnosed
1.00
0.75
0.50
0.25
0.00
low occlusion 0-49
high occlusion 50-100
0 10 20 30 40 50 60 70 80
Age in years
Number undiagnosed
Low 359 336 257 197 149 84 33 6 3
High 212 202 172 131 88 49 25 4 1

Discussion

- AVM presentation with hemorrhage in all patients:
  - Deep venous drainage, supply by perforators, nidal aneurysms, multiple aneurysms, supply by posterior circulation, basal ganglia location[1]
  - Children more likely to present with hemorrhage than adults[2]
- AVM presentation with hemorrhage in children:
  - Smaller AVM nidus, only deep venous drainage, infratentorial nidus location[3]

[1]Turjman *Neurosurg* 1995
[2]Fullerton *Stroke* 2005
[3]Ellis *JNIS* 2012

Discussion

- Subsequent AVM hemorrhage in all patients:
  - Small number of draining veins, venous ectasias, deep nidus location[1]
  - Age (increasing), deep nidus location, only deep venous drainage[2]
  - Ethnicity: Hispanic patients more likely to have subsequent hemorrhage than white patients (OR 3.1, p = 0.013)[3]
- Subsequent AVM hemorrhage in children:
  - Children are <u>less</u> likely to have second hemorrhage during follow up than adults[4]

[1]Stefani *Stroke* 2002
[2]Stapf *Neurology* 2006
[3]Kim Stroke 2007
[4]Fullerton *Stroke* 2005

Conclusion

- AVMs and their draining veins were more likely to be located deep within the brain in children
  - Do centrally-located AVMs arise earlier in development?
  - Or, do central AVMs have intrinsic features making them more likely to come to clinical attention early in life?

Conclusion

- Although children with brain AVMs were more likely to come to clinical attention due to hemorrhage than adults, certain high risk features (venous ectasia, feeding artery aneurysms) were underrepresented in children
- Perhaps this helps explain the lower reported risk of hemorrhage during follow up in children

PEDIATRIC DAVFs: SPECIAL FEATURES

- Congenital
- CHF, macrocephaly
- Higher flow rates, larger shunts
- Higher mortality

Pediatric DAVF Outcomes

Outcome	UCSF Study	(Kincaid et al. 2001)
Complete AVF Occlusion	6/21 (28.6%)	3/7 (42.9%)
No Neurological or Developmental Delay	4/21 (19%)	2/7 (28.6%)
Death	4/21 (19%)	2/7 (28.6%)

Comparative Outcomes

Comparison to other pediatric intracranial AVFs

Outcome	UCSF DAVF 2012	UCSF NGAVF 2011	UCSF VOGM 2003	Bicetre VOGM 2006
Complete AVF Occlusion	6/21 (29%)	15/23 (65%)	21/27 (78%)	118/216 (55%)
No Neuro Deficit or Devel Delay	4/21 (19%)	11/23 (48%)	14/27 (51%)	143/216 (66%)
Death	4/21 (19%)	2/23 (9%)	4/27 (15%)	23/216 (11%)

CNS Arteriovenous Shunting Lesions

- Vascular malformations
  - AVM
  - DVA
  - Cavernous malformation
  - Capillary telangiectasia
  - Transitional vascular malformation
- Dural AV fistula
- Traumatic AVFs

- Pediatric lesions
  - AVM
  - Pial NGAVF
  - Dural AVF
  - Vein of Galen malformation
- Spinal vascular lesions
  - AVM
  - Perimedullary AVFs
  - Spinal dural AVF

Case 5

Retinoblastoma

- Loss of Rb tumor suppressor gene
- Unilateral, bilateral, or "trilateral" disease
- Traditional management of advanced dz
  - enucleation
  - combo: radiation, IV chemorx, cryo, laser
- IA chemotherapy first described 1958 (TEM)
- ICA chemotherapy (melphalan) Japan 1990s to 2000s with balloon inflated above OA

Intraarterial Chemotherapy for Ocular Retinoblastoma

- Small guide catheter (4Fr) to proximal ICA
- Small microcatheter (1.5 Fr) to OA origin
- Low dose x-ray settings, minimize angiograms
- Infuse weight based dose of melphalan over 30 minutes
- Early results: excellent regression of tumors
- Prevent enucleation or mets in 70% of eyes over 2 years of follow up (Gobin, 2011)

Conclusion

- Children are not small adults
- Age-specific diseases
- Assiduous technique
- X-ray and chemotherapy dose minimization
- Endovascular therapy for vascular and nonvascular conditions

Thank You

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