Childhood cerebral vasculitis

Vijeya Ganesan

Senior Lecturer in Paediatric Neurology

Neurosciences Unit, Institute of Child Health

University College London

v.ganesan@ucl.ac.uk

- Classification
- Disease phenotypes
- Role of imaging

Childhood primary angiitis of the CNS (cPACNS)

- Medium/large vessel (angiography +)
  - Non-progressive
  - Progressive
- Small vessel (angiography -)

Panel 1: Criteria for primary angiitis of the CNS (PACNS) and childhood PACNS

- The presence of an acquired otherwise unexplained neurological or psychiatric deficit
- The presence of either classic angiographic or histopathological features of angiitis within the CNS
- No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease

Patients should meet all three criteria to be diagnosed with PACNS.[2] Childhood PACNS mandates a patient age of ≤18 years at diagnosis and excludes neonates (1 month of age)

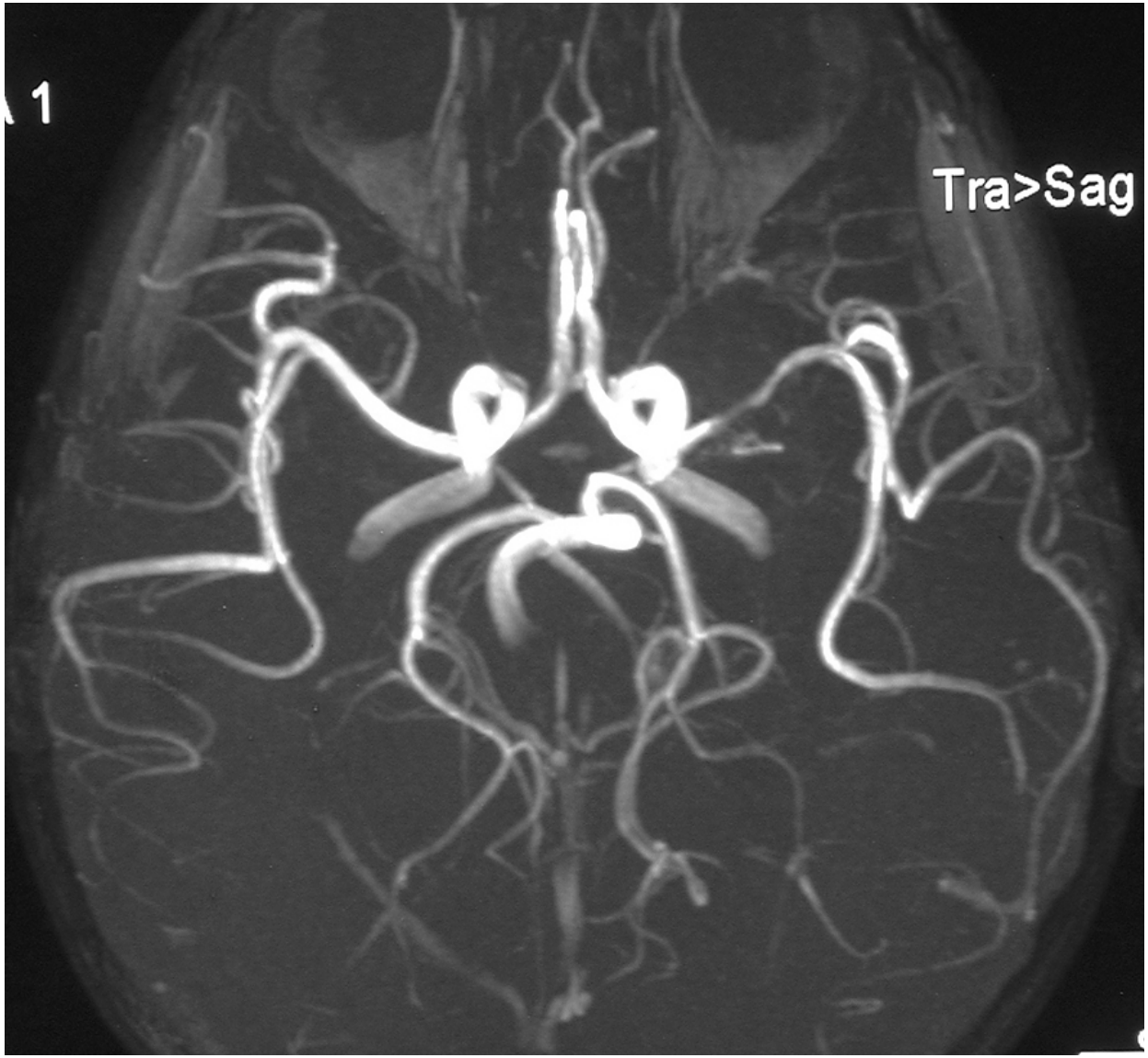
NP cPACNS

- Acute AIS; diffuse features in 10%
- Inflammatory markers normal
- Angiography +
- +/- vessel wall imaging

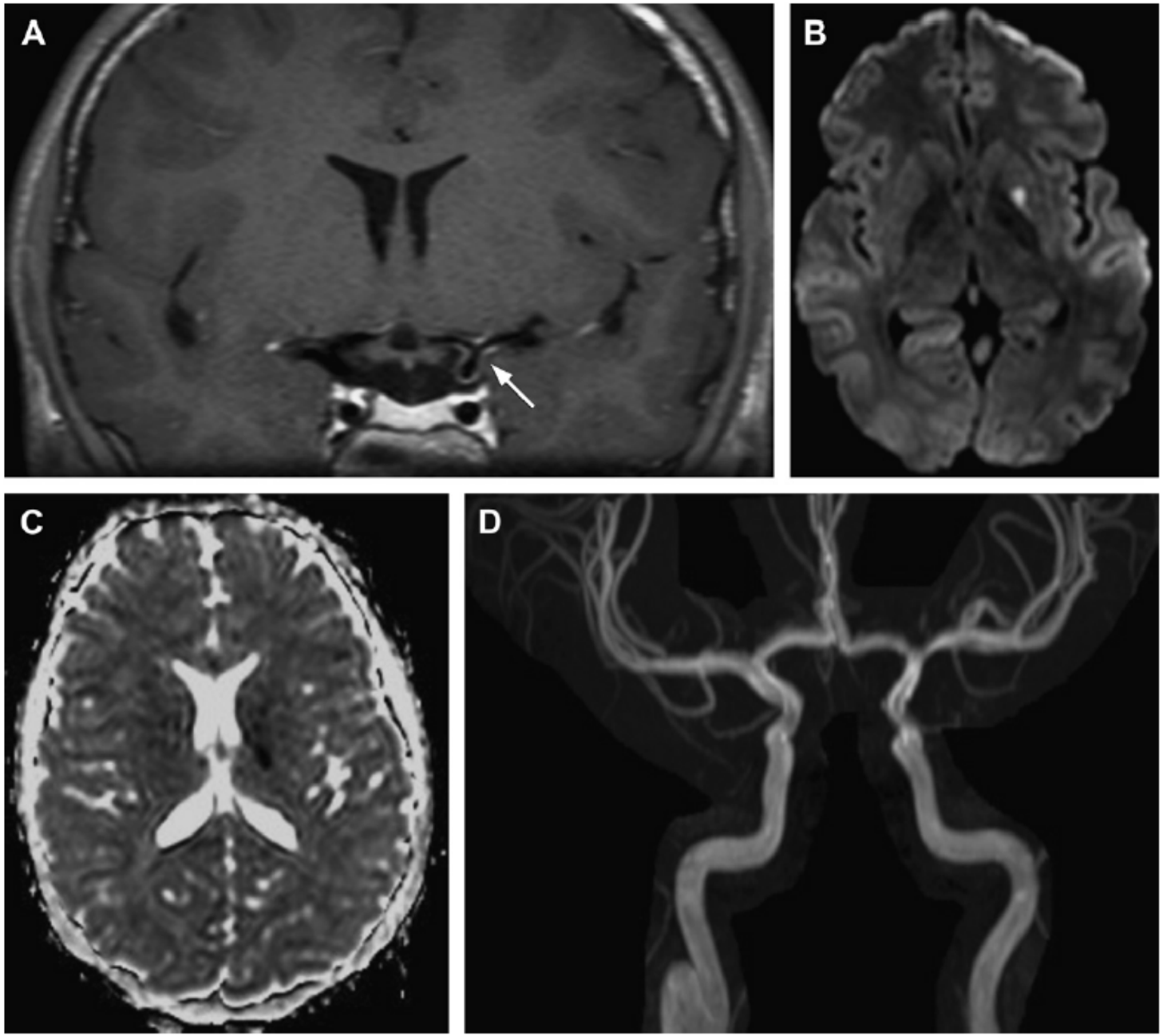
NP cPACNS vs TCA/FCA

- Likely to be the same entity
- Imaging features identical
- Monophasic

- Role of steroids/immunomodulation controversial

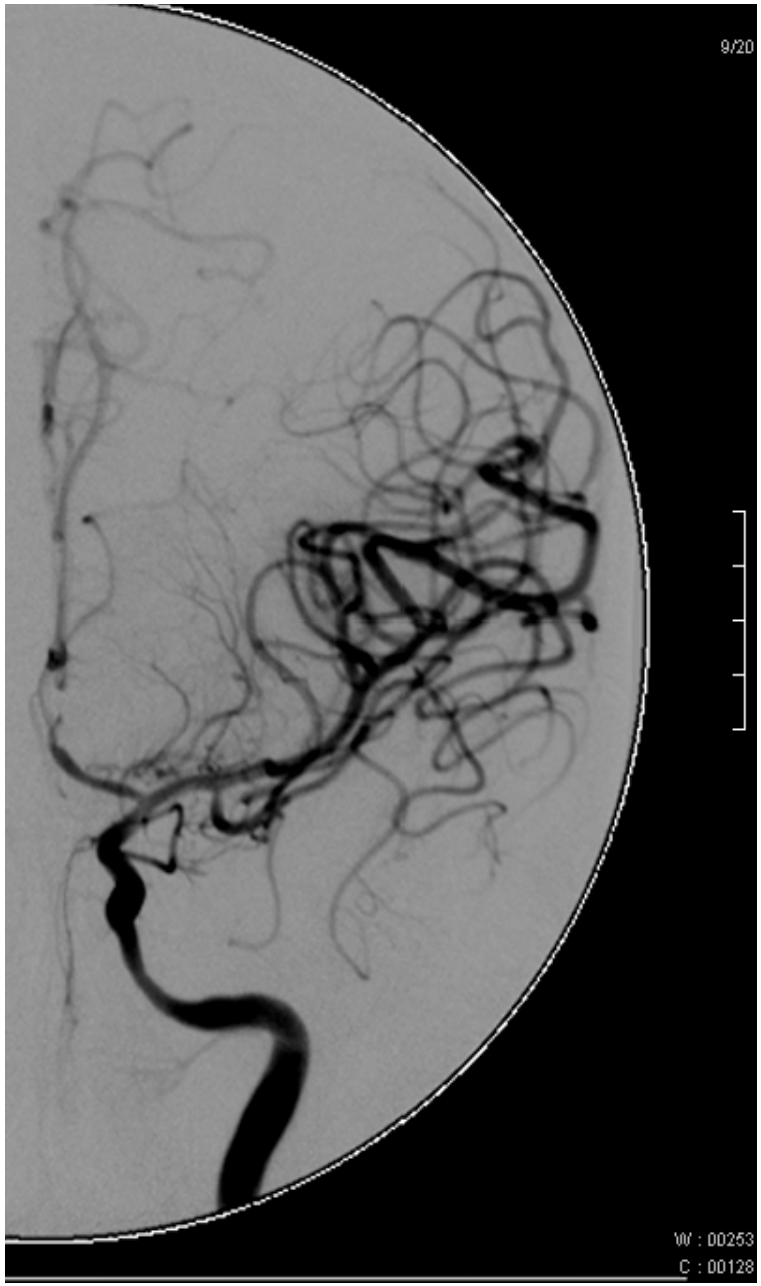


? FCA ?monophasic PACNS


A
B
C
D

P cPACNS

- Diffuse features common and often insidious
- Headache common
- Inflammatory markers and CSF studies freq. normal
- Multifocal imaging abnormalities more common in both brain and arteries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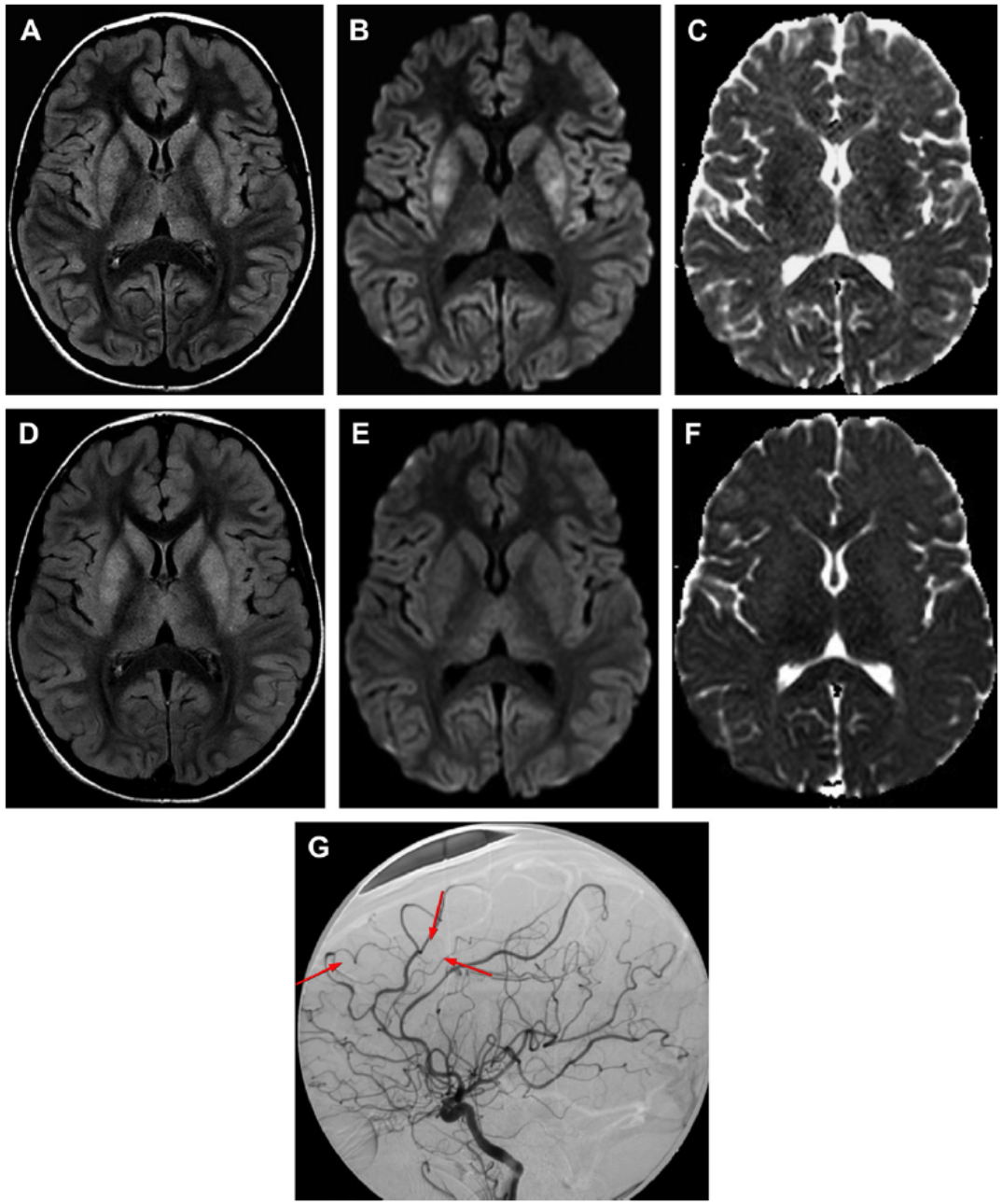

P cPACNS

8y, fever confusion, seizures.

Normal blood/CSF

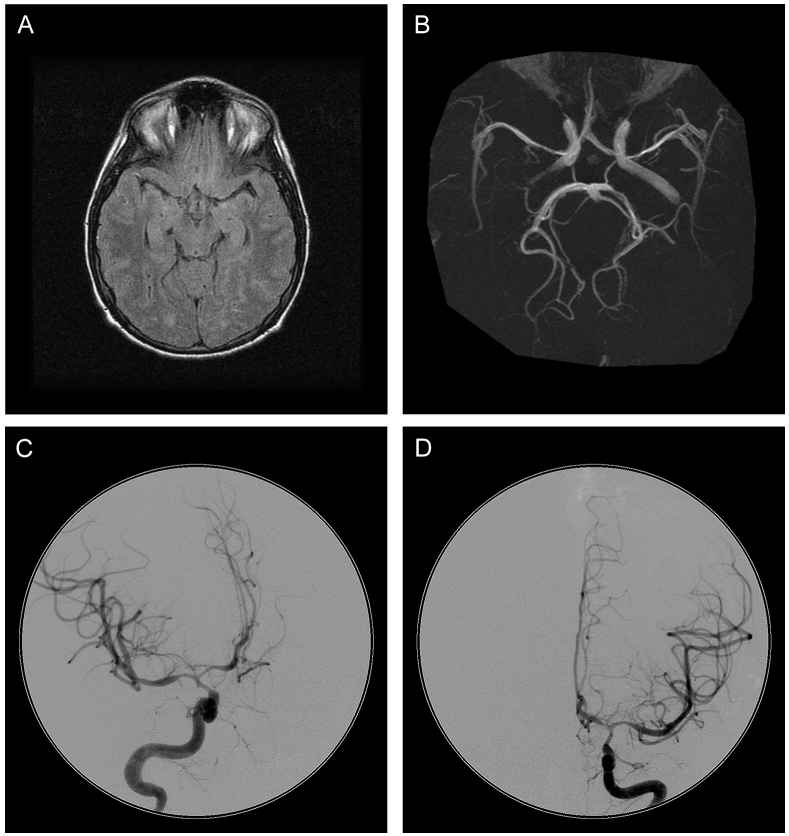

Figure 2. Neuroimaging of a 16-year-old boy with progressive large vessel primary central nervous system vasculitis presenting with severe headaches, cognitive decline and focal neurological deficits. **A**, ill-defined, multifocal lesions in multiple vascular territories on axial MRI T2/fluid-attenuated inversion recovery images. These lesions are not diffusion restricted (diffusion weighted images not shown). **B**, magnetic resonance angiography demonstrates multiple, bilateral vascular stenosis affecting both proximal and distal segments of all major cerebral vessel with evidence of irregularity and beading. **C** and **D**, conventional angiography confirms the presence of proximal and distal vascular stenoses in multiple, bilateral cerebral vessels.

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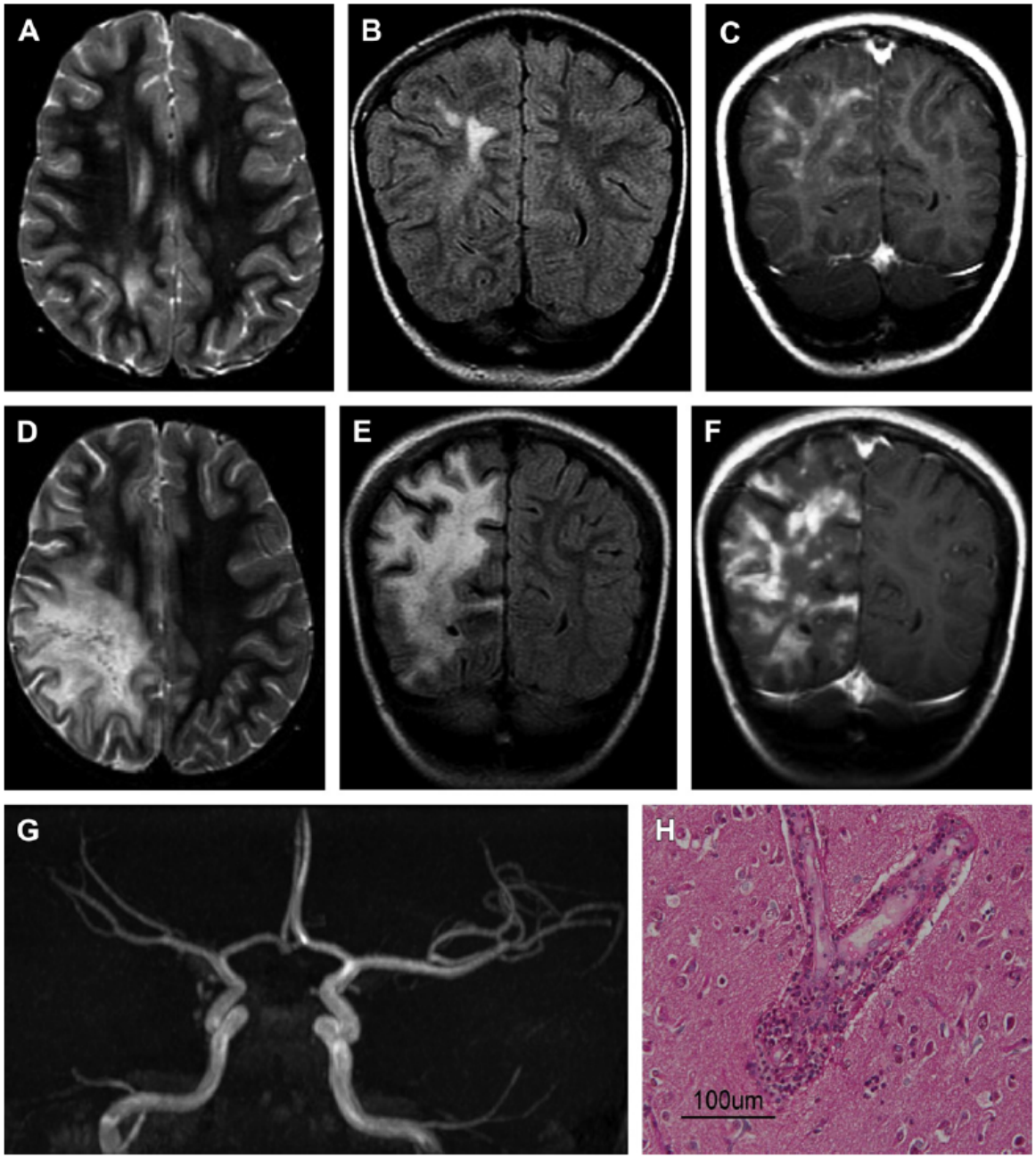
DOI: 10.1177/0883073812459352

P cPACNS

- Steroids
- Cyclophosphamide

SV cPACNS

- Encephalopathy, focal deficits, seizures
- +/- systemic features
- CSF often abnormal
- Inflammtory lesions + Gd enhancement
- Normal MRA/CA
- Biopsy



SV cPACNS

5y, seizures,
L hemiparesis,
cognitive decline

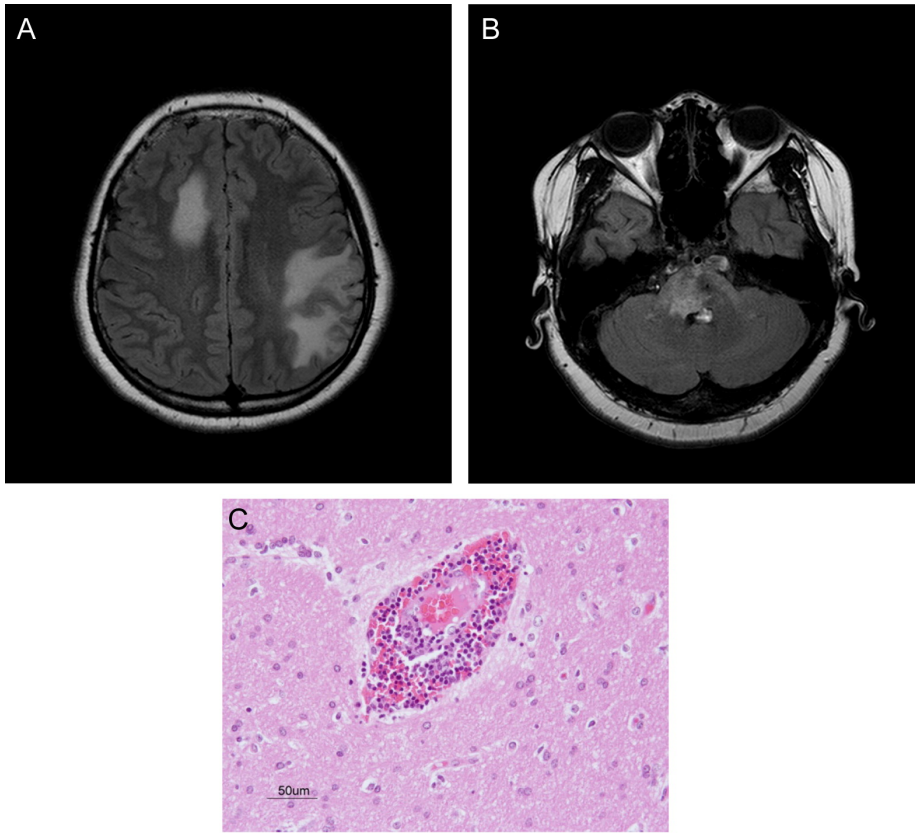


Figure 3. Neuroimaging and brain biopsy of a 12-year-old girl with small vessel childhood primary central nervous system vasculitis presenting with severe cognitive decline and seizures. **A**, bilateral inflammatory lesions affecting both gray and white matter on axial MRI T2/fluid-attenuated inversion recovery images. These lesions are not diffusion restricted (diffusion weighted images not shown). **B**, an extensive brain stem lesion in the same child. Magnetic resonance angiography and conventional angiography in the child were normal (not shown). **C**, lesional brain biopsy of a frontal inflammatory lesion identified on MRI. Hematoxyllin and eosin staining reveals a lymphocytic infiltrate targeting the vascular wall of a small muscular artery. Electron microscopy demonstrates endothelial cell activation and no evidence of viral inclusions (not shown).

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Table 2. Childhood secondary Central Nervous System vasculitis and Central Nervous System vasculitis mimics

Secondary Central Nervous System vasculitis (Figure 4)

Infections[35]

- Bacterial (*Mycobacterium tuberculosis*, *Mycoplasma pneumonia*, *Streptococcus pneumonia*)
- Viral (Epstein-Barr virus, cytomegalovirus, enterovirus, varicella-zoster virus, hepatitis C virus, parvovirus B19, West Nile virus)
- Fungal (*Candida albicans, Actinomycosis, Aspergillus*)
- Spirochete (*Borrelia burgdorferi, Treponema pallidum*)

Rheumatic and inflammatory diseases[51,52,55,57-59]

- Systemic vasculitis such as granulomatosis with polyangiitis, microscopic polyangiitis, Henoch–Schonlein purpura, Kawasaki disease, polyarteritis nodosa, Behçet's disease
- Pediatric systemic lupus erythematosus, juvenile dermatomyositis, morphea
- Inflammatory bowel disease
- Autoinflammatory syndromes
- Hemophagocytic lymphohistiocytosis

Other[33]

- Drug-induced vasculitis
- Malignancy-associated vasculitis

Nonvasculitis inflammatory brain diseases

Demyelinating disorders[67,68]

- Multiple sclerosis, acute demyelinating encephalomyelitis, optic neuritis and transverse myelitis

Antibody mediated inflammatory brain disease[71-73]

- Anti-NMDA-receptor encephalitis, neuromyelitis optica, antibody-associated limbic encephalitis (antibodies against LGI, AMP, AMP-binding protein), presumed antibody associated disease such as Hashimoto's encephalopathy, celiac disease and pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections

T cell associated inflammatory brain disease[69,74]

- Rasmussen's encephalitis

Granulomatous inflammatory brain disease[70]

- Neurosarcoidosis

Other

- Febrile infection-related epilepsy syndrome[82]

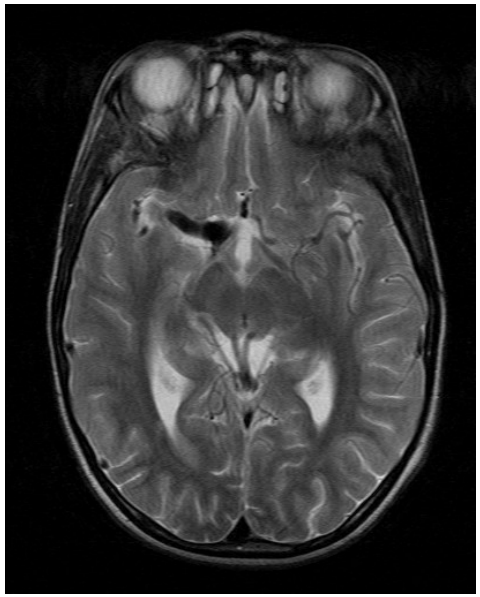
Noninflammatory vasculopathies[10,11,61-63,83]

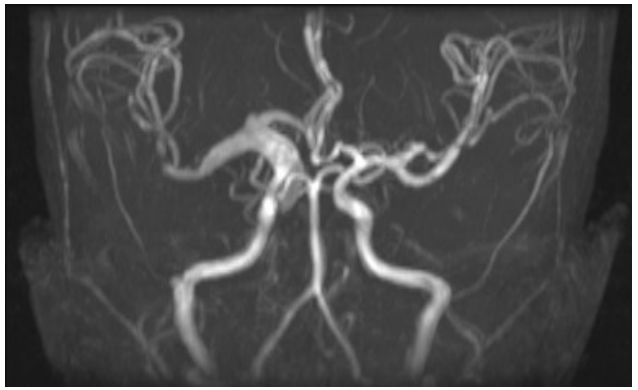
- Intracranial arterial dissection
- Moyamoya disease
- Fibromuscular dysplasia
- Hemoglobinopathies (sickle cell disease), thromboembolic disease
- Radiation vasculopathy, graft versus host disease
- Metabolic and genetic diseases such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, mitochondrial encephalopathy lactic acidosis and stroke like episodes, Fabry disease, homocystinuria, polymerase gamma, neurofibromatosis type 1, Down syndrome, Alagille syndrome

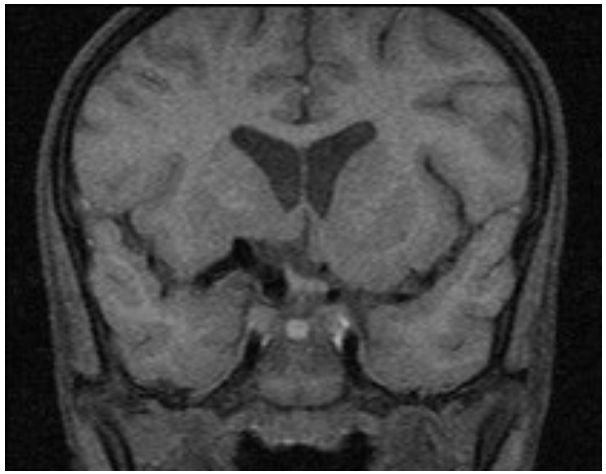
Other mimics[66]

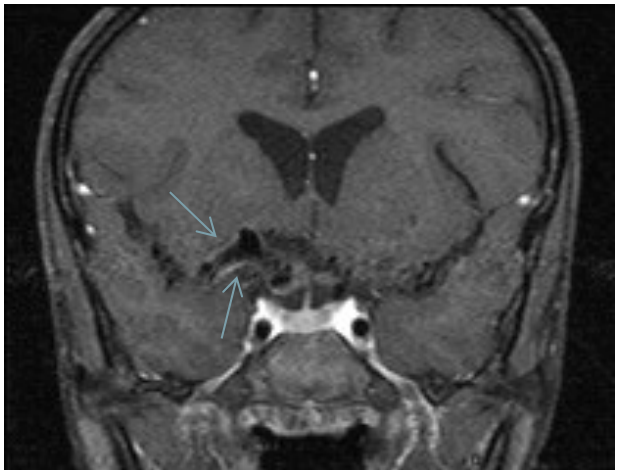
- Cerebral vasoconstriction such as reversible vasoconstrictive syndrome and ion channel diseases (calcium channelopathy, familial hemiplegic migraine), drug-induced vasoconstriction
- Malignancy (lymphoma)

HSV6 vasculopathy



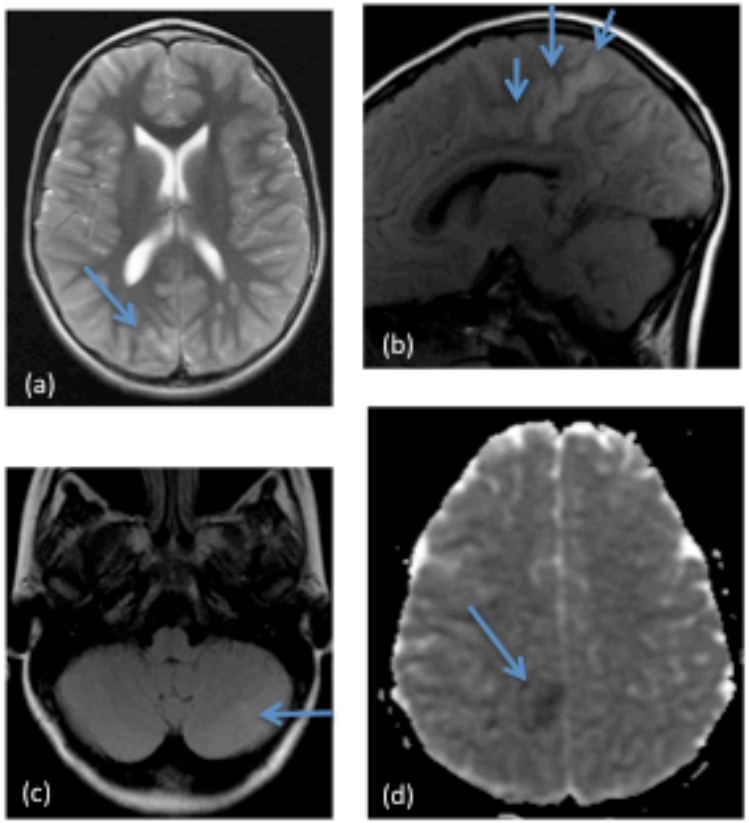


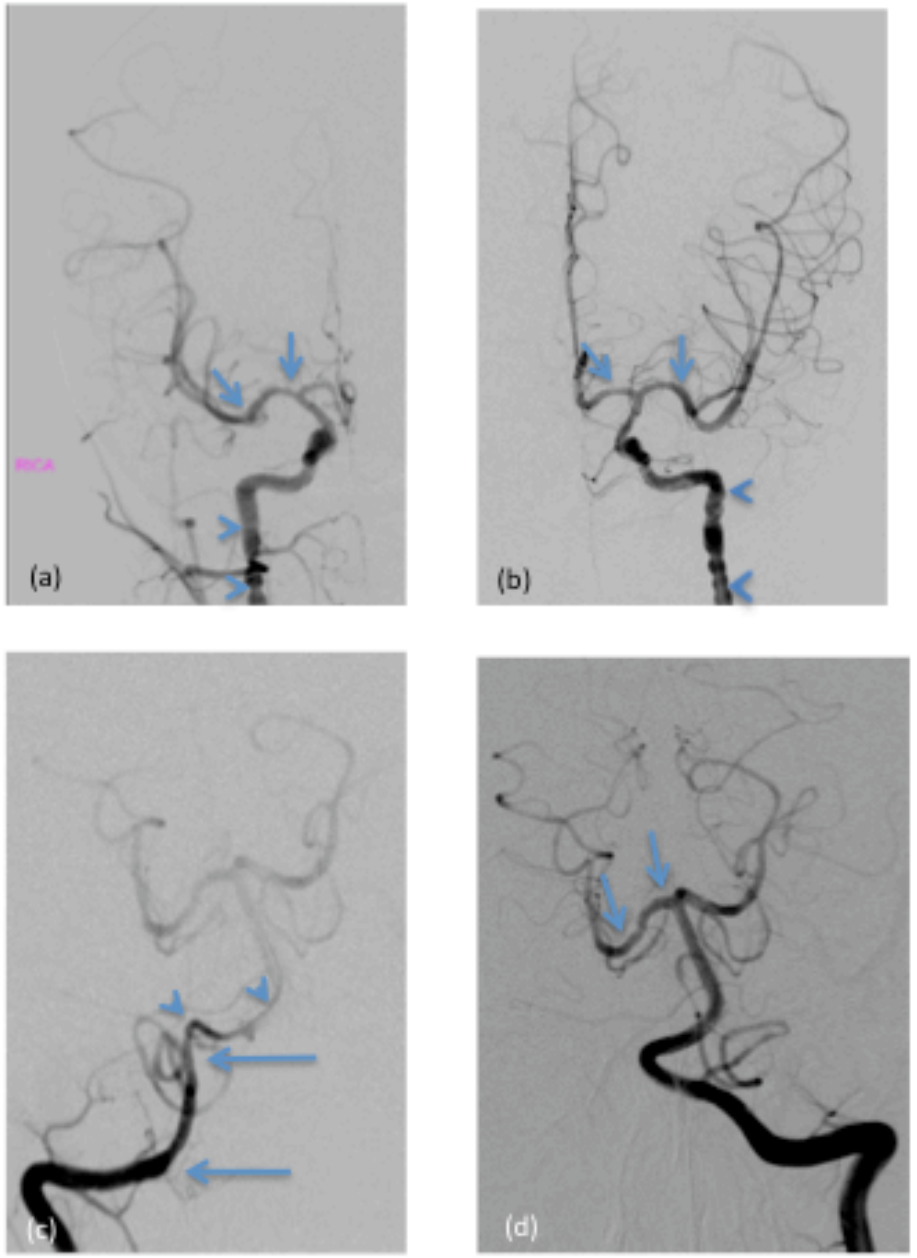




Pre-contrast

Post-contrast





13y M, thunderclap headache
No focal neurology
Normalised after 2/12
Final diagnosis: RCVS

Cerebrovascular imaging

- Luminal
  - MRA (time-of-flight/CEMRA)
  - CTA
  - Catheter angiography
- Wall

Luminal imaging: what are we looking for?

- “Beading” – not specific
- Multifocal disease
- Focal occlusive disease
- Dilatation
- Microaneurysms

*small vessel PACNS will by definition be angiogram negative

Is MRA useful?

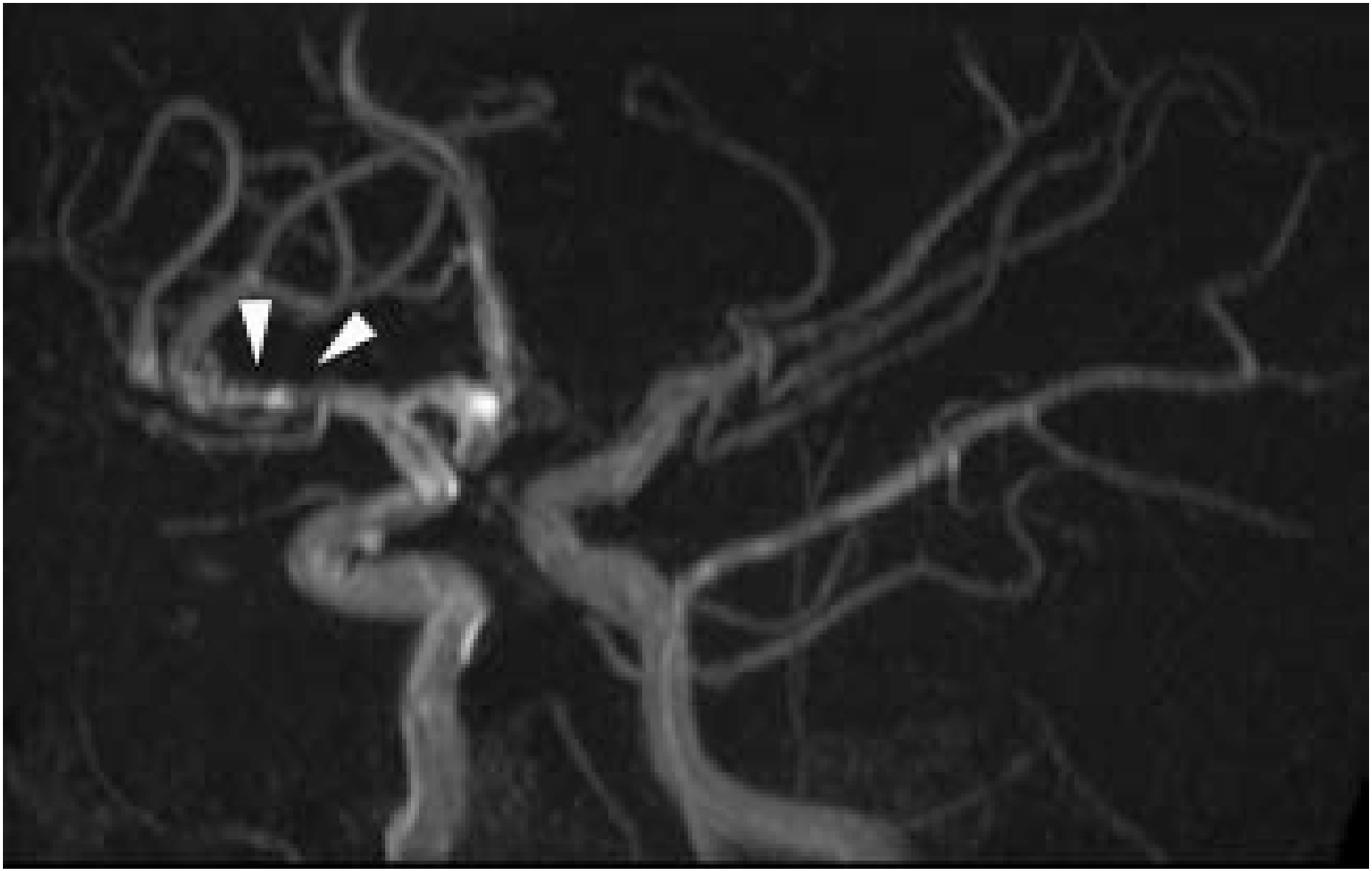
- Aviv et al 2006 (n = 42)
  - Time of flight MRA
  - 30/42 abnormal (all angiographically confirmed)
  - 83% carotid “T” involvement
  - >60% multiple proximal lesions
  - “benign” morphology in 22/30 with occlusive disease
    - ?overlap w patients who might be categorised as FCA

Table 4: Morphology of MRA stenoses

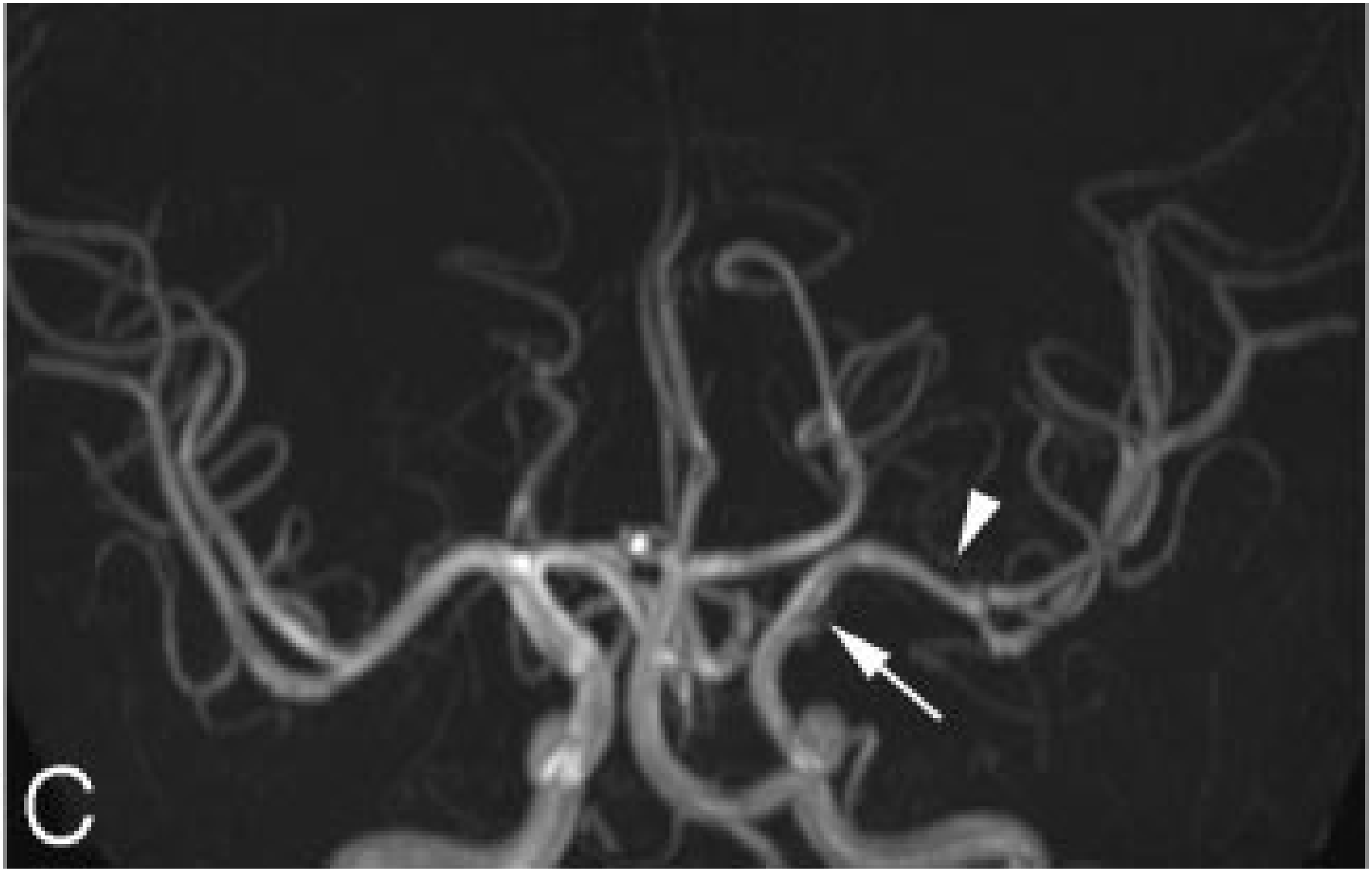
Morphology	Stenoses*
Smooth	56 (78%)
Irregular	14 (19%)
Concentric	68 (94%)
Eccentric	2 (3%)
Graduated	12 (17%)
Single	65 (90%)
Beading	8 (11%)

*multiple vessel involvement also counted as aggressive

Aviv et al 2006



“Aggressive”



“Benign”

Role of catheter angiography (CA)

- Along w histology considered a gold standard test for CNS vasculitis

BUT

- Low specificity
- Pathology & radiology terminology not interchangeable
- Sensitivity also an issue for small vessel PACNS

MRA vs CA in PACNS

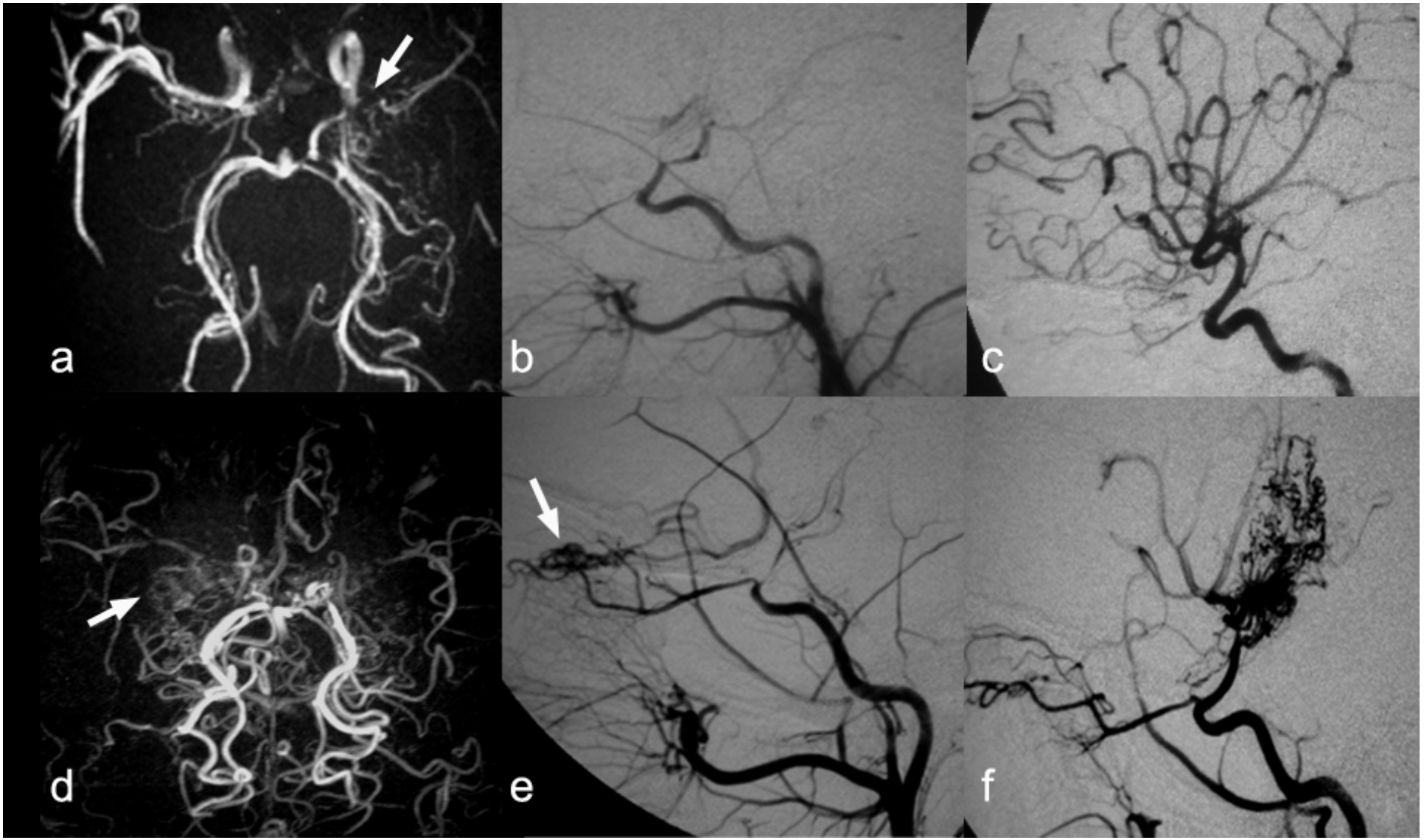
- Aviv et al 2007 (n = 25)
  - Proximal, multifocal, unilateral
  - Predominance of anterior circulation
  - MRA had PPV 71%, NPV 97% for CA abnormality
  - Recommend CA if MRI + and MRA -

MRA vs CA in PACNS

- Eleftheriou et al 2010 (n = 14)
  - Bilateral & proximal lesions
  - MRA: sensitivity 63%, specificity 89% for CA lesions
  - Overall sensitivity of MRA 94%
  - Most false negatives in posterior circulation

Does temporal evolution help/matter?

- Progressive arteriopathy significantly associated w AIS recurrence
- But does progressive arteriopathy = vasculitis?
- And does it necessitate immunosuppression??



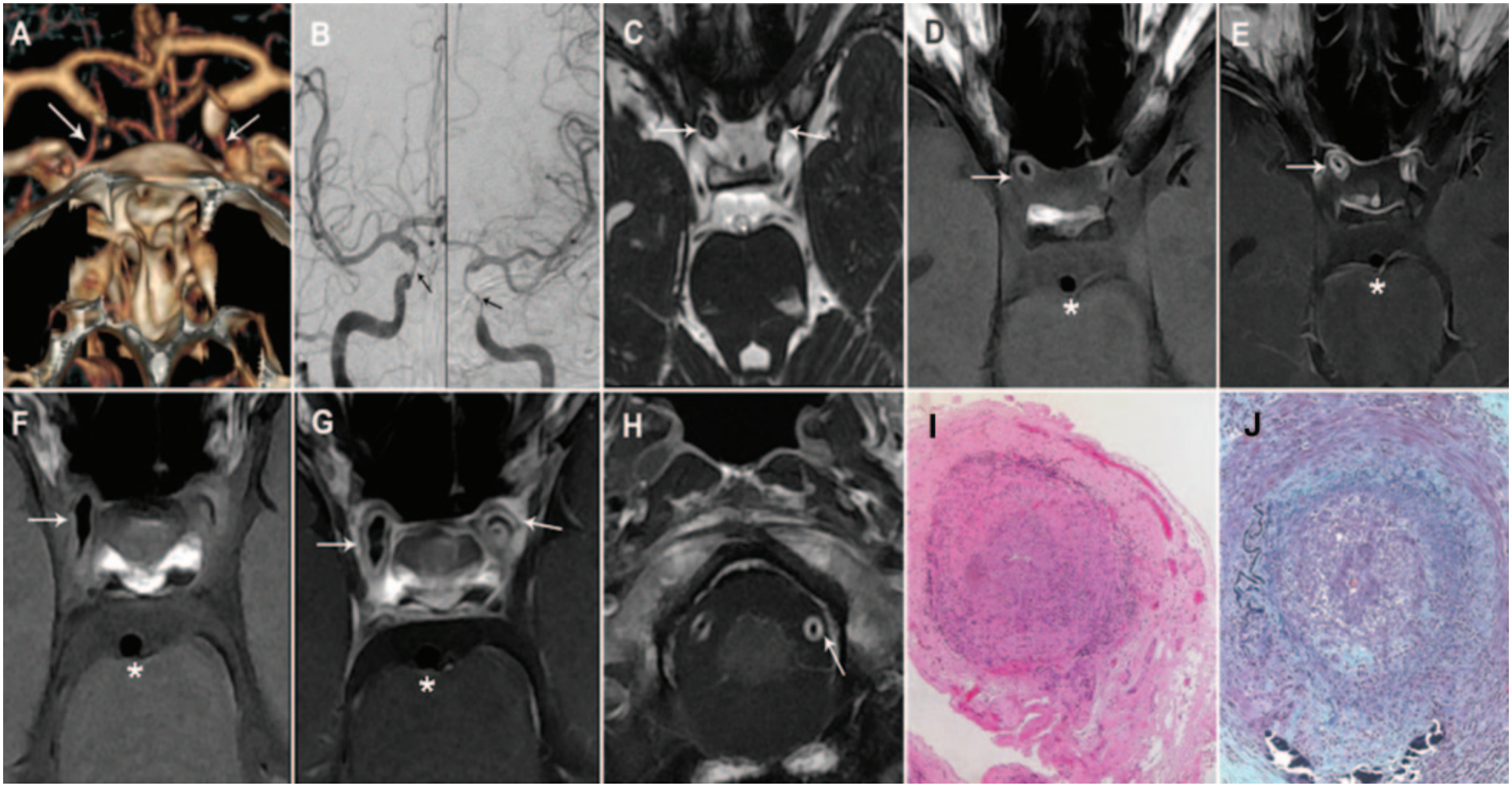
Inflammatory w/u negative; ?PACNS ?moyamoya

Vessel wall imaging

- Kuker et al 2007 (n = 27, 8 children)
  - diagnosis of cerebral vasculitis
  - 25/27 abnormal MRA
  - 25/27 wall thickening, 23/27 wall enhancement, usually at site of MRA/DSA abnormality

Vessel wall imaging

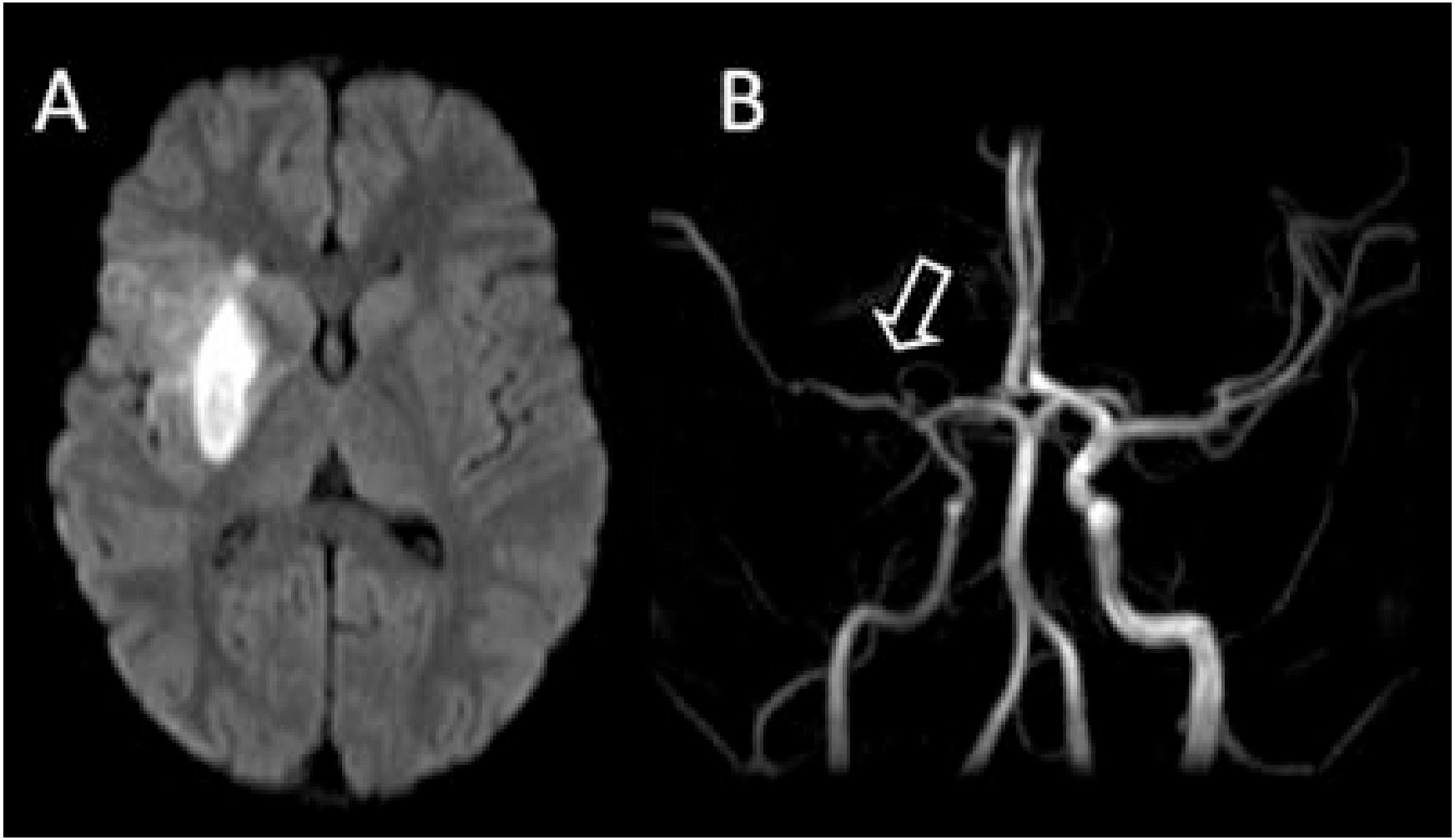
- Swartz et al 2009
  - 3T MRI, T1 FLAIR +/- gad, targeted to MRA abn site
  - 3 w clinical vasculitis had smooth concentric wall enhancement
  - Other patterns in atheroma/dissection
  - 2 moyamoya pts had wall thickening or enhancement
  - Spatial resolution still an issue
  - Sensitivity & specificity not established



From Swartz et al 2009

- Mandell et al 2012:
  - 7 patients with multifocal arterial narrowing
  - 3 w reversal of arteriopathy had no enhancement = RCVS
  - 4 w persistent arterial narrowing had enhancement; 3 diagnosed as PACNS, 1 as cocaine vasculopathy

- Payne et al 2011:
  - 5y w basal ganglia infarct
  - No other aetiology
  - Steroids for 3w
  - Initial vessel wall enhancement w reversed after steroids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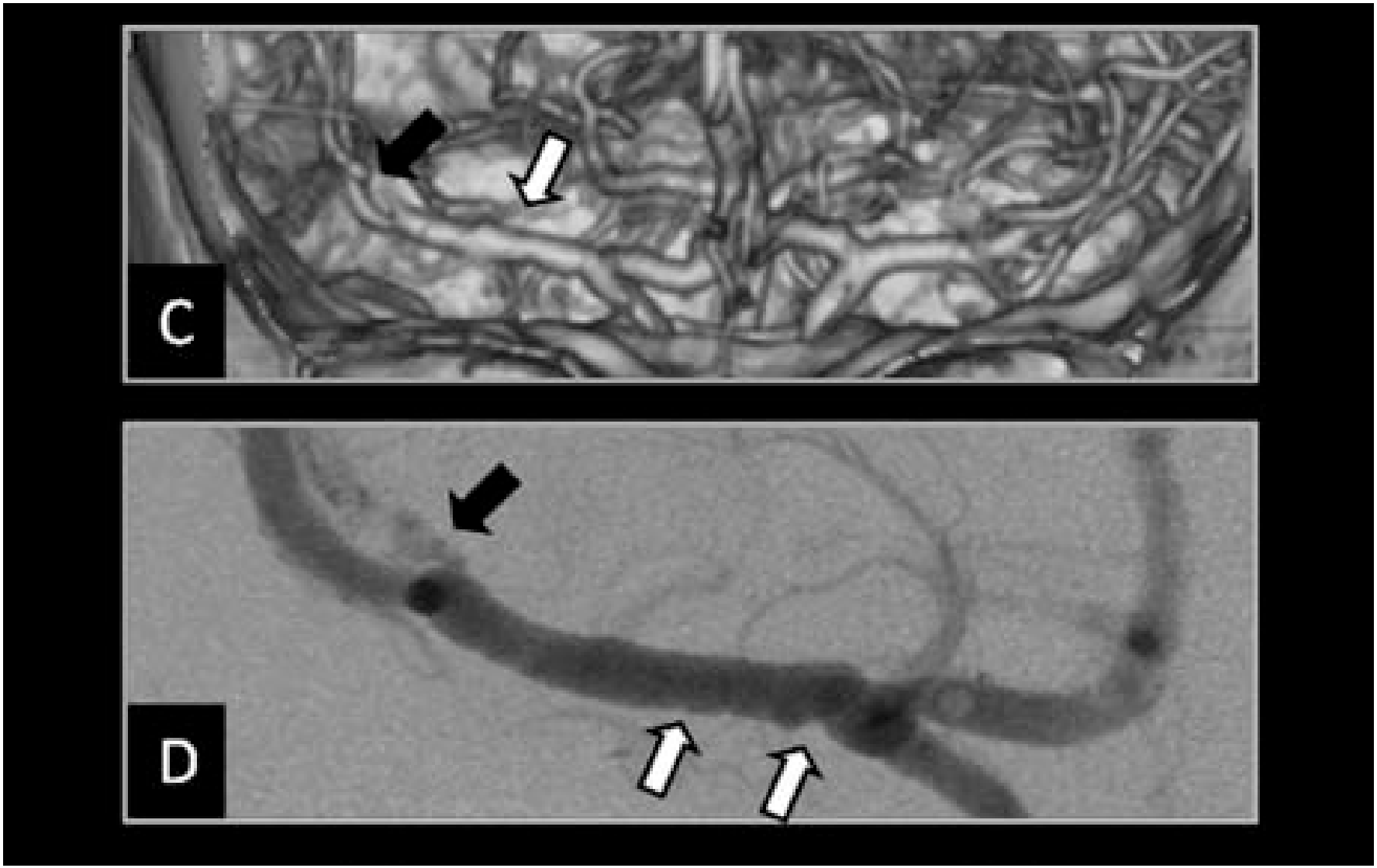
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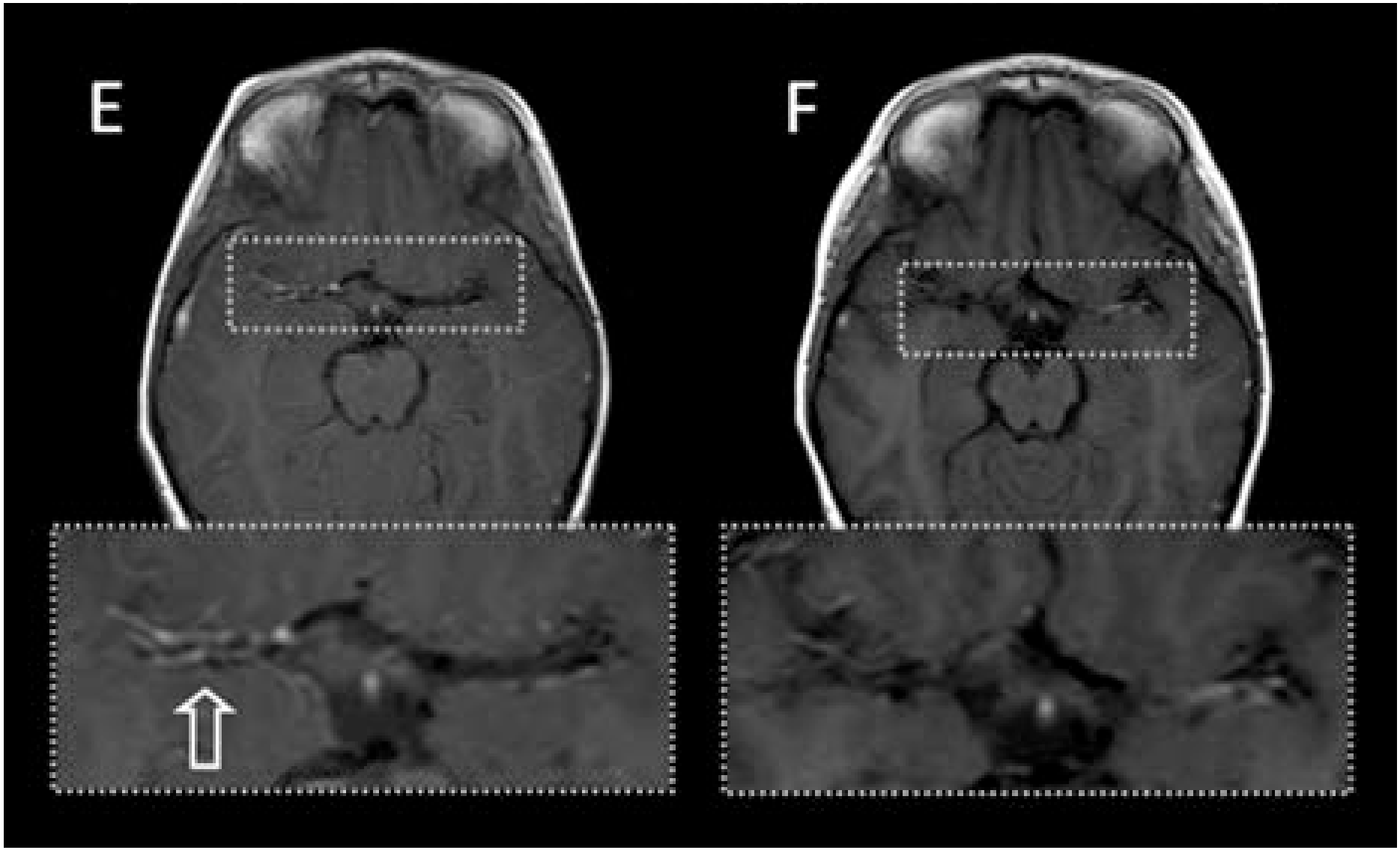
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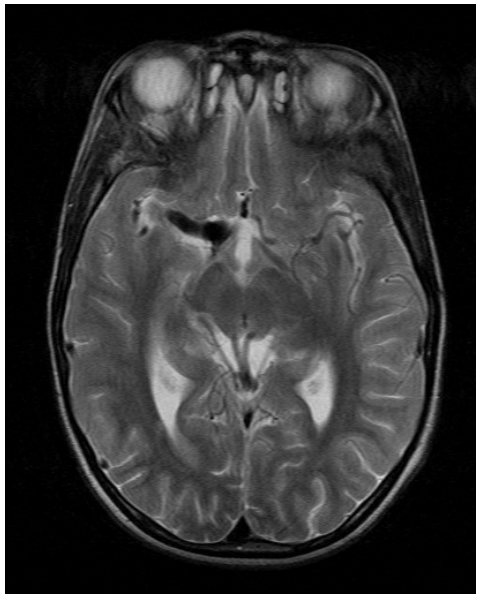
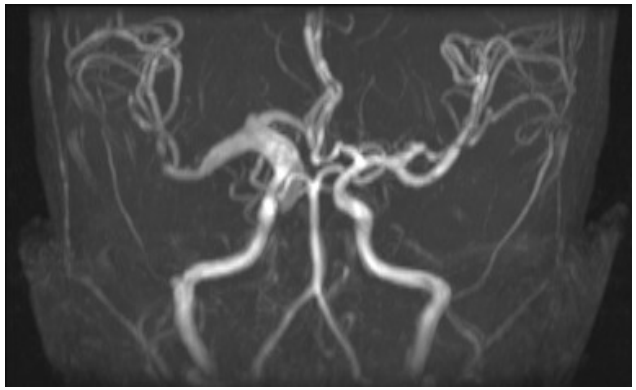
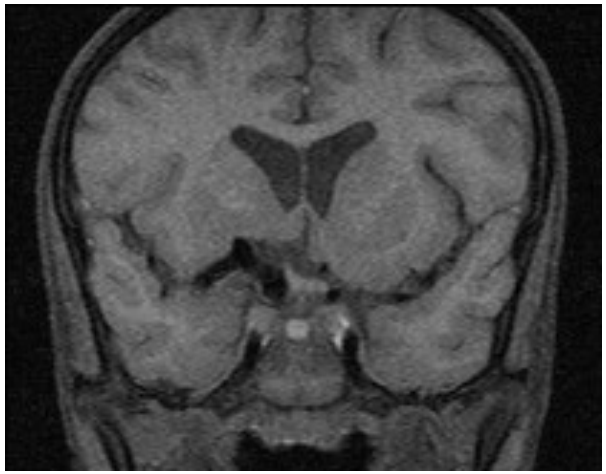
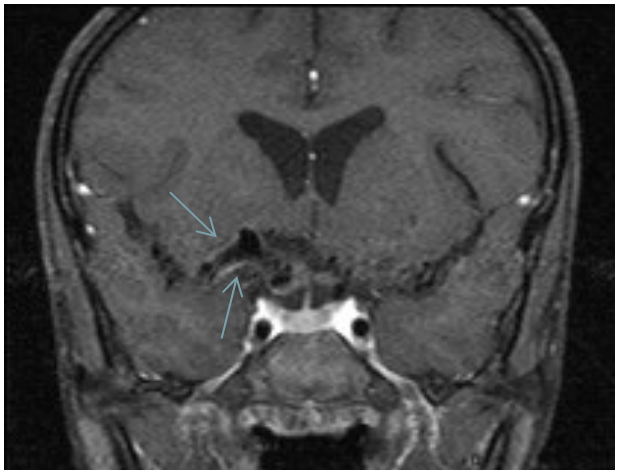
HIV +, VZV + in CSF









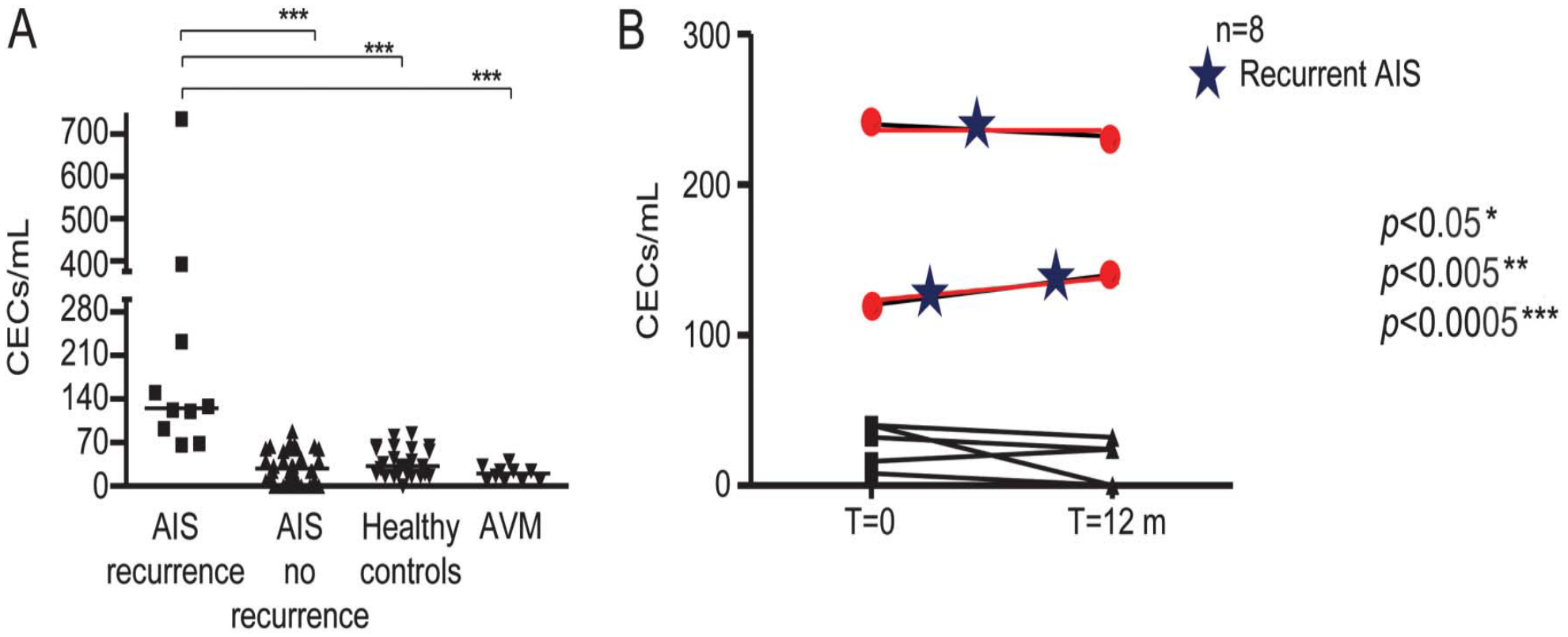
Pre-contrast

Post-contrast

Biomarkers of CNS vasculitis

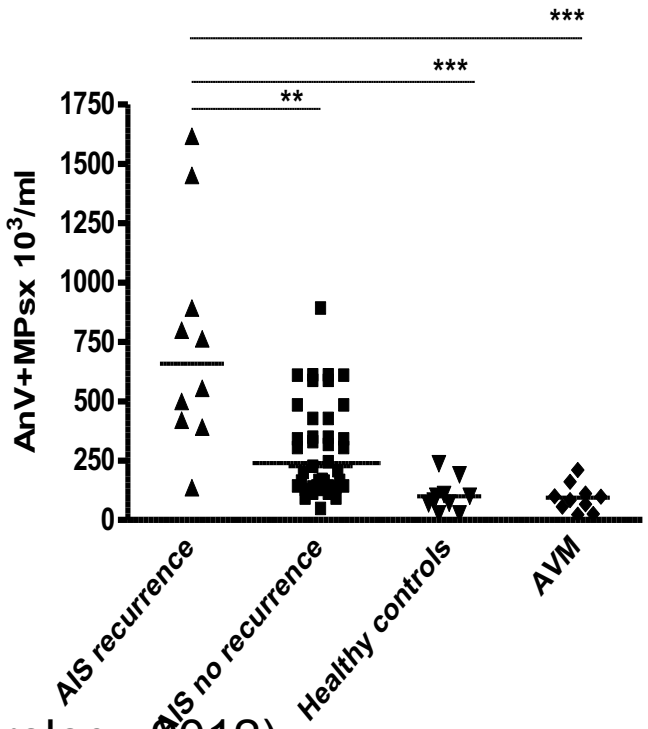
- Blood/CSF commonly negative
- Imaging – non-specific

CECs detect ongoing endothelial injury in children with AIS and arteriopathy



(Eleftheriou et al, Neurology 2012)

Circulating microparticles in children with AIS and arteriopathy



(Eleftheriou et al, Neurology 2012)

Personal approach

- High index clinical suspicion if
  - Prominent prodrome/diffuse features
  - Multifocal brain or arterial lesions
  - Clinical/radiological progression
  - Multiple size vessel involved
- Blood/CSF workup (incl. VZV Ab, neopterin)
- Ophthalmology, urinalysis etc
- Low threshold for angiography (inc. visceral)

Conclusions

- There are distinct clinical phenotypes of CNS vasculitis in children
- Diagnosis is challenging; imaging may overlap with non-inflammatory disorders

Reversible cerebral vasoconstriction syndrome

- Probably what used to be termed benign PACNS
- Thunderclap headache
- Segmental arterial constriction/dilatation
- Minority complicated by ischaemic/haemorrhagic stroke

Panel 3: Differential diagnosis of childhood primary CNS vasculitis

Secondary angiitis of the CNS

Infections

- Bacterial: *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae, Treponema pallidum,* and *Borrelia burgdorferi*
- Viral: Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, hepatitis-C virus, HIV, parvovirus B19, West-Nile virus, Enterovirus
- Fungal: *Candida albincans*, Aspergillus, Actinomyces

Rheumatic diseases in children

- Systemic lupus erythematosus
- Systemic vasculitis: Henoch Schoenlein purpura, Kawasaki disease, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss disease, polyarteritis nodosa
- Juvenile dermatomyosis
- Morphea or linear scleroderma
- Neuro-Behçet's disease
- Sjöegrens syndrome

Autoinflammatory diseases

- Inflammatory bowel disease
- Autoinflammatory syndromes

Non-vasculitis inflammatory brain diseases

Autoantibody-mediated inflammatory brain diseases

- NMDA-receptor-mediated encephalitis
- Neuromyelitis optica

Demyelinating diseases

- Acute demyelinating encephalomyelitis
- Optic neuritis
- Multiple sclerosis

T-cell-mediated inflammatory brain disease

- Rasmussen's encephalitis

Non-inflammatory vasculopathies

Vasculopathies

- Fibro-muscular dysplasia
- Moyamoya disease
- Intracranial dissection
- Radiation vasculopathy
- Drug-induced vasculopathy

Cerebral vasoconstriction

- CNS calcium channelopathies
- Reversible vasoconstrictive syndrome

Other diseases that mimic primary angiitis of the CNS

- Thromboembolic disease
- Haemoglobin disorders
- Malignancy
- Graft-versus-host reaction

Table 2. Childhood secondary Central Nervous System vasculitis and Central Nervous System vasculitis mimics

Secondary Central Nervous System vasculitis (Figure 4)
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Other mimics[66]
- Cerebral vasoconstriction such as reversible vasoconstrictive syndrome and ion channel diseases (calcium channelopathy, familial hemiplegic migraine), drug-induced vasoconstriction
- Malignancy (lymphoma)

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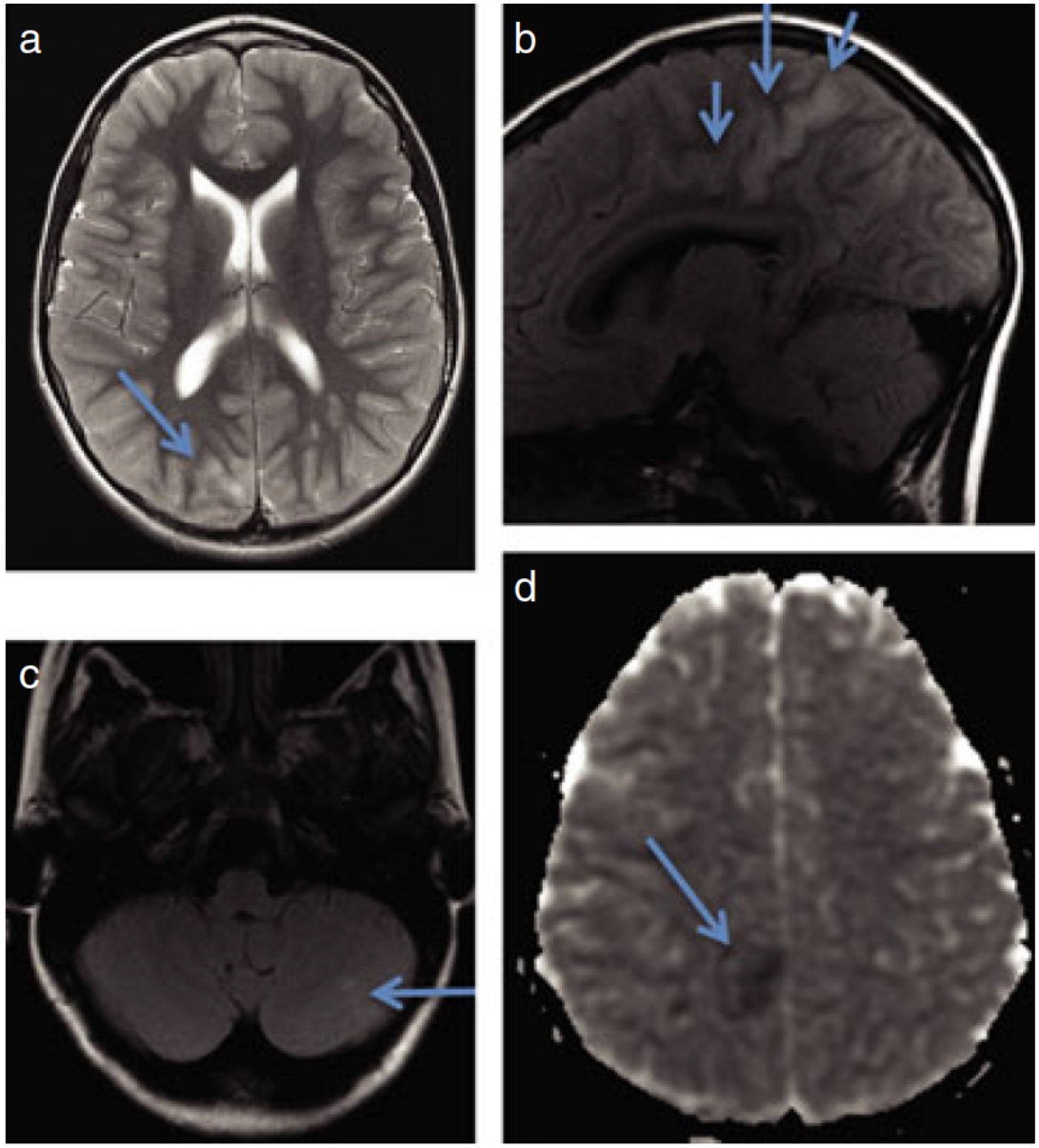
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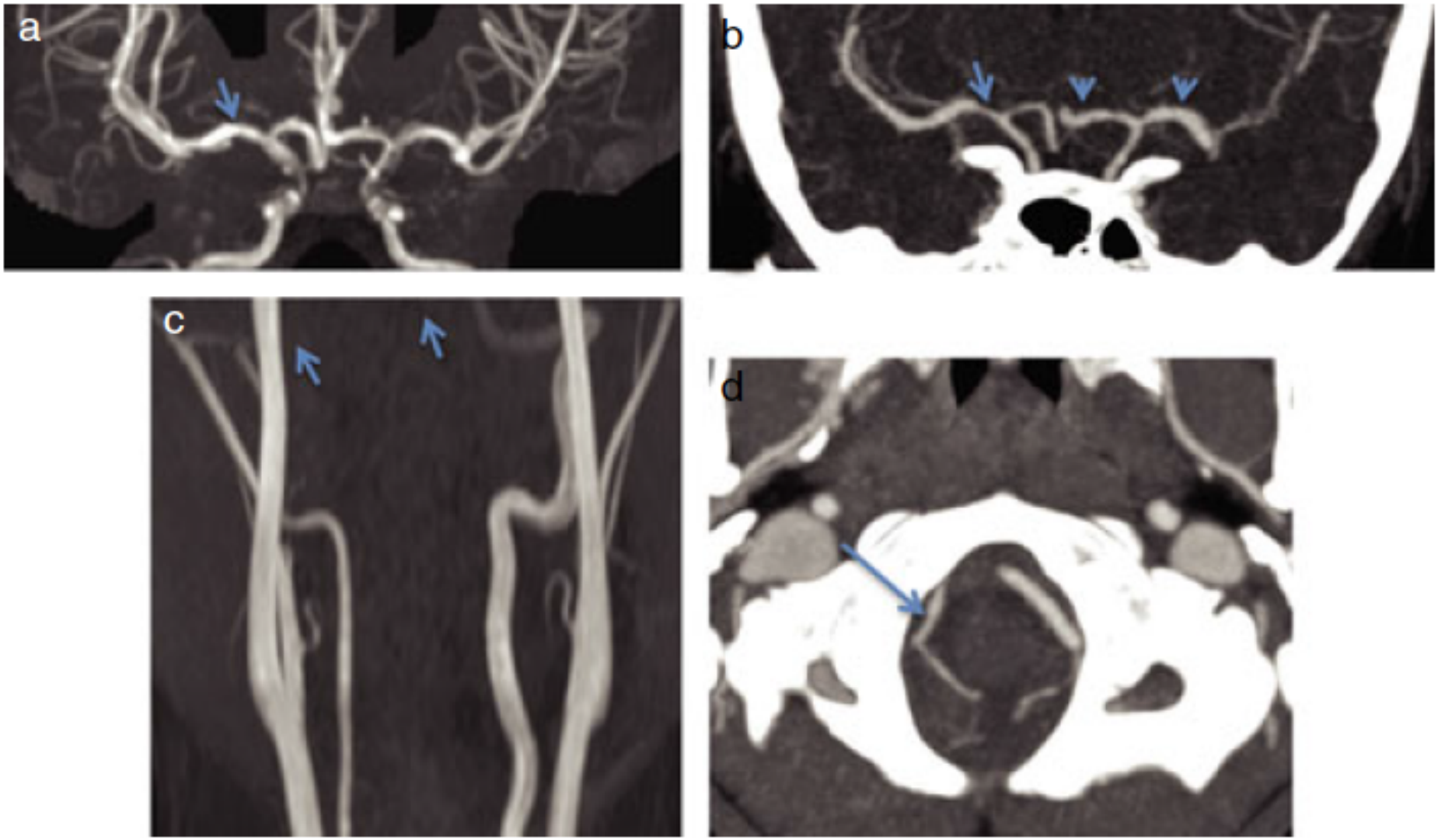
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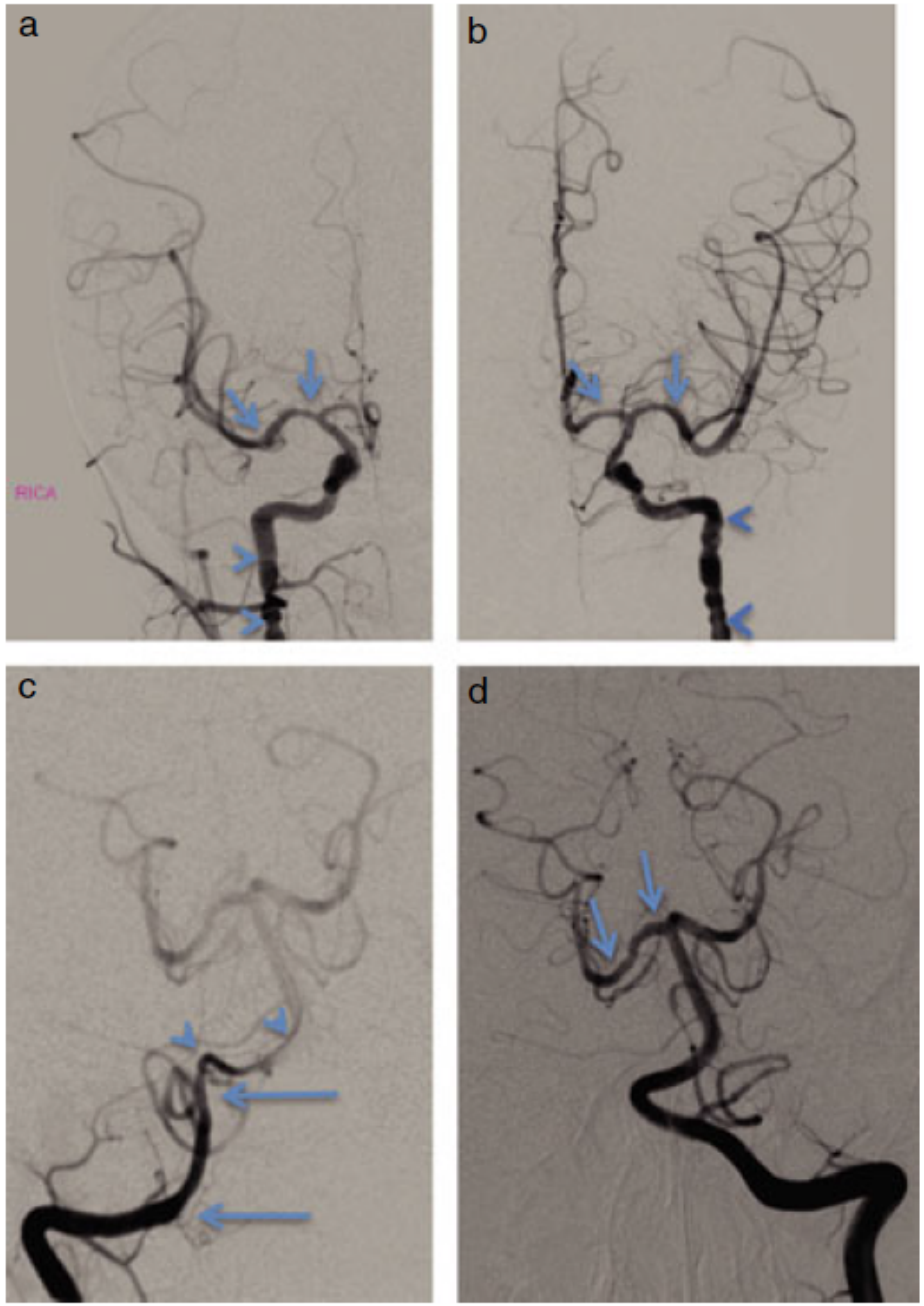
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Table 1. Childhood Primary Angiitis of the Central Nervous System: Diagnostic Criteria, Disease Subtypes, and Their Characteristics

Modified Calabrese criteria for childhood primary angiitis of the central nervous system
A newly acquired focal or diffuse neurological or psychiatric symptom in a patient $\leq$ 18 years of age **plus** characteristic angiographic and/or histopathological features of central nervous system angiitis
in the absence of an underlying systemic disorder that explains or mimics the features
Childhood primary angiitis of the central nervous system *subtypes*
Angiography-positive large vessel childhood primary angiitis of the central nervous system (Figure 1)
Nonprogressive childhood primary angiitis of the central nervous system
- Demographics: boys > girls
- Clinical: unilateral stroke
- Inflammatory markers in serum/cerebrospinal fluid: usually normal
- MRI: unilateral fluid-attenuated inversion recovery/T2, diffusion restricted lesions (acute)
- Angiography: unilateral proximal vessel stenoses, gadolinium wall enhancement (magnetic resonance angiography)
- Brain biopsy: not indicated

Progressive childhood primary angiitis of the central nervous system (Figure 2)
- Demographics: boys > girls
- Clinical: focal *and* diffuse neurological deficits
- Inflammatory markers in serum/cerebrospinal fluid: mild-moderately raised in up to 50%
- MRI: unilateral multifocal or bilateral fluid-attenuated inversion recovery/T2 and/or diffusion restricted lesions
- Angiography: proximal and distal stenoses at diagnosis or isolated proximal disease with evidence of progression > 3 months, gadolinium wall enhancement (magnetic resonance angiography)
- Brain biopsy: not indicated

Angiography-negative small vessel childhood primary angiitis of the central nervous system (Figure 3)
- Demographics: girls >> boys
- Clinical: seizures, focal and diffuse neurological deficits, and psychiatric symptoms
- Inflammatory markers in serum/cerebrospinal fluid: raised > 90%
- MRI: white and/or gray matter fluid-attenuated inversion recovery/T2 lesions, not restricted to vascular territories. Leptomeningeal and/or lesional enhancement
- Angiography: normal
- Brain biopsy: intramural and perivascular lymphocytic infiltrates

Table 1. Childhood Primary Angiitis of the Central Nervous System: Diagnostic Criteria, Disease Subtypes, and Their Characteristics

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Panel 3: Differential diagnosis of childhood primary CNS vasculitis

Secondary angiitis of the CNS

Infections

- Bacterial: *Mycobacterium tuberculosis, Mycoplasma pneumoniae, Streptococcus pneumoniae, Treponema pallidum,* and *Borrelia burgdorferi*
- Viral: Epstein-Barr virus, cytomegalovirus, varicella-zoster virus, hepatitis-C virus, HIV, parvovirus B19, West-Nile virus, Enterovirus
- Fungal: *Candida albincans*, Aspergillus, Actinomyces

Rheumatic diseases in children

- Systemic lupus erythematosus
- Systemic vasculitis: Henoch Schoenlein purpura, Kawasaki disease, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss disease, polyarteritis nodosa
- Juvenile dermatomyosis
- Morphea or linear scleroderma
- Neuro-Behçet's disease
- Sjöegrens syndrome

Autoinflammatory diseases

- Inflammatory bowel disease
- Autoinflammatory syndromes

Non-vasculitis inflammatory brain diseases

Autoantibody-mediated inflammatory brain diseases

- NMDA-receptor-mediated encephalitis
- Neuromyelitis optica

Demyelinating diseases

- Acute demyelinating encephalomyelitis
- Optic neuritis
- Multiple sclerosis

T-cell-mediated inflammatory brain disease

- Rasmussen's encephalitis

Non-inflammatory vasculopathies

Vasculopathies

- Fibro-muscular dysplasia
- Moyamoya disease
- Intracranial dissection
- Radiation vasculopathy
- Drug-induced vasculopathy

Cerebral vasoconstriction

- CNS calcium channelopathies
- Reversible vasoconstrictive syndrome

Other diseases that mimic primary angiitis of the CNS

- Thromboembolic disease
- Haemoglobin disorders
- Malignancy
- Graft-versus-host reaction