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Is it CNS Vasculitis or Something Else?

Leonard H Calabrese

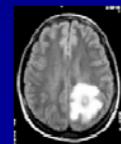
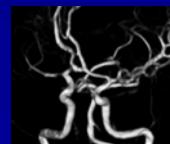
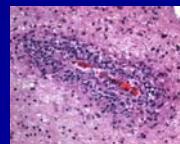
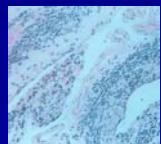
Professor of Medicine

Cleveland Clinic Lerner College of Medicine

RJ Fasenmyer Chair of Clinical Immunology

Department of Rheumatic and Immunologic Disease

Cleveland Clinic



Disclosures

- COI managed by the Cleveland Clinic Innovation Management & Conflict of Interest Program
- Is it CNS Vasculitis or Something Else?
 - NO RELEVANT CONFLICTS
- <http://cc-clcoirpt51.cc.ad.cchs.net/COIPProd>.

General References

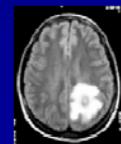
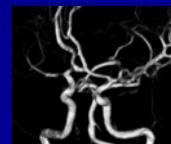
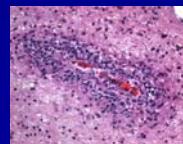
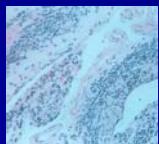
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- Salvarani C et al Primary central nervous vasculitis: Analysis of 101 patients. *Ann Neurol* 62:442-451,2007
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Outline

- 1. PACNS – the disease**
Definition, clinical, laboratory, neuroradiographic and pathologic features
- 2. Rheumatologic encounters with PACNS**
 - A) Influence of clinical context on pretest probability
 - B) Clinical case studies demonstrating perils of diagnostic accuracy
- 3. Best Practices**

CNS Vasculitis

- Rare disorder but increasingly recognized
- CNS tissues relatively inaccessible and diagnosis often inferential
- Originally viewed as uniform and highly fatal
- Now recognized as heterogeneous and treatable if detected early



Diagnostic Criteria

Calabrese and Mallek 1988

- A neurologic deficit that remains unexplained after a vigorous diagnostic work up
- Either
 1. High probability angiogram for vasculitis or
 2. Biopsy evidence of vasculitis within the CNS
- Exclusion of all those conditions capable of producing secondary arteritis or mimicking the angiographic features of arteritis

Exclusions (Mimics)

Systemic Inflammatory Conditions

- Systemic vasculitis
- Sjogren's
- Sarcoid
- Paraneoplastic

Coagulation Disorders

- Emboli – SBE, myxoma, AF
- SBE
- Hypercoag disorders

Infections

- Viral (HCV,HBV,VZV,HIV)
- Fungal
- Bacterial
- Neuroborreliosis

Miscellaneous

- Brain disease with abnormal MRI- CNS lymphoma, micro vascular ischemia, demyelinating, others
- Genetic – CADASIL , MELAS, HERNS, COL4A1, others
- Occulo-otic - Susac's AMPI, others

Hajj-Ali & Calabrese CH29 Primary Central Nervous System Vasculitis, Inflammatory Diseases of the Blood Vessels 2nd Edition 2012

Diagnostic Approach

- History and physical
- Laboratory testing
- Lumbar puncture
- Neuroimaging
- Angiography
- Biopsy

AXIOM 7 AXIOMS of CNS Vasculitis

ax·i·om noun

- 1. A self-evident truth that requires no proof**
- 2. A universally accepted principle or rule**

PACNS Clinical AXIOM 1

There is no specific clinical finding or set of findings of sufficient pre-test probability ‘to secure a diagnosis’ of PACNS

Clinical Manifestations at Presentation

(Salvarani C et al Ann Neurol 2007)

Characteristics	All Patients (N=101), n (%)	Patients Diagnosed by Biopsy (n=31), n (%)	Patients Diagnosed by Angiography (n=70), n (%)
Headache	64 (63)	16 (52)	48 (69)
Altered cognition	50 (50)	22 (71)	28 (40)
Hemiparesis	44 (44)	6 (19)	38 (54)
Persistent neurological deficit or stroke	40 (40)	8 (26)	32 (46)
Aphasia	28 (28)	11 (36)	17 (24)
Transient ischemic attack	28 (28)	5 (16)	23 (33)
Ataxia	19 (19)	5 (16)	14 (20)
Seizure	16 (16)	2 (7)	14 (20)
Visual symptom (any kind)	42 (42)	9 (29)	33 (47)
Visual field defect	21 (21)	5 (16)	16 (23)
Diplopia (persistent or transient)	16 (16)	5 (16)	11 (16)
Blurred vision or decreased visual acuity	11 (11)	0 (0)	11 (16)
Monocular visual symptoms or amaurosis fugax	1 (1)	0 (0)	1 (1)
Papilledema	5 (5)	2 (7)	3 (4)
Intracranial hemorrhage	8 (8)	2 (7)	6 (9)
Amnestic syndrome	9 (9)	4 (13)	5 (7)
Paraparesis or quadripareisis	7 (7)	4 (13)	3 (4)
Parkinsonism or extrapyramidal sign	1 (1)	0 (0)	1 (1)
Prominent constitutional symptom	9 (9)	4 (13)	5 (7)
Fever	9 (9)	4 (13)	5 (7)
Nausea or vomiting	25 (25)	6 (19)	19 (27)
Vertigo or dizziness	9 (9)	3 (10)	6 (9)
Dysarthria	15 (15)	2 (7)	13 (19)
Unilateral numbness	13 (13)	0 (0)	13 (19)

PACNS Clinical

Highest Pre-test Probability

- Chronic Meningitis
- Recurrent Focal Deficits
- Unexplained Focal & Diffuse Neurologic Dysfunction

Clinical Features of Isolated Angiitis of the Central Nervous System

- Headaches
- Encephalopathy
- Behavioral changes
- Focal motor / sensory abnormalities
- Ataxia
- Cranial neuropathies
- Visual changes (field cuts, scotomata)
- Myelopathy
- Radiculopathy

Lumbar Puncture AXIOM 2

A lumbar puncture is the key laboratory test in the evaluation of PACNS and should only be omitted in the presence of risk from CNS mass effect

Lumbar Puncture

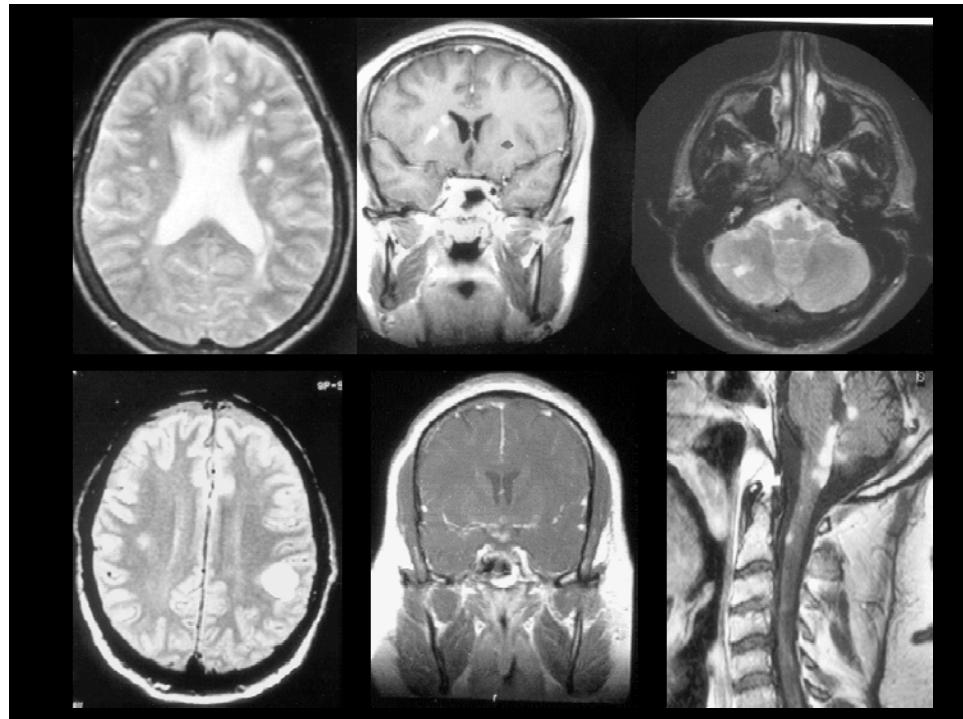
- **Essential element of diagnosis for must rule out conditions**
- **C&S, cytology, routine**
- **Sensitivity varies according to the subset: GACNS > 95%, All patients documented by biopsy or angiography 89% (Salvarani C et al Ann Neurol 2007)--- High negative predictive value SNOUT**
- **95% Cells <200/hpf, protein <300 mg%**

Non Vascular Neuroimaging AXIOM 3

Non vascular imaging in the diagnosis of PACNS is highly sensitive and thus of high negative predictive value (SNOUT) but of low specificity. Thus it can not confirm the diagnosis (low SPIN)

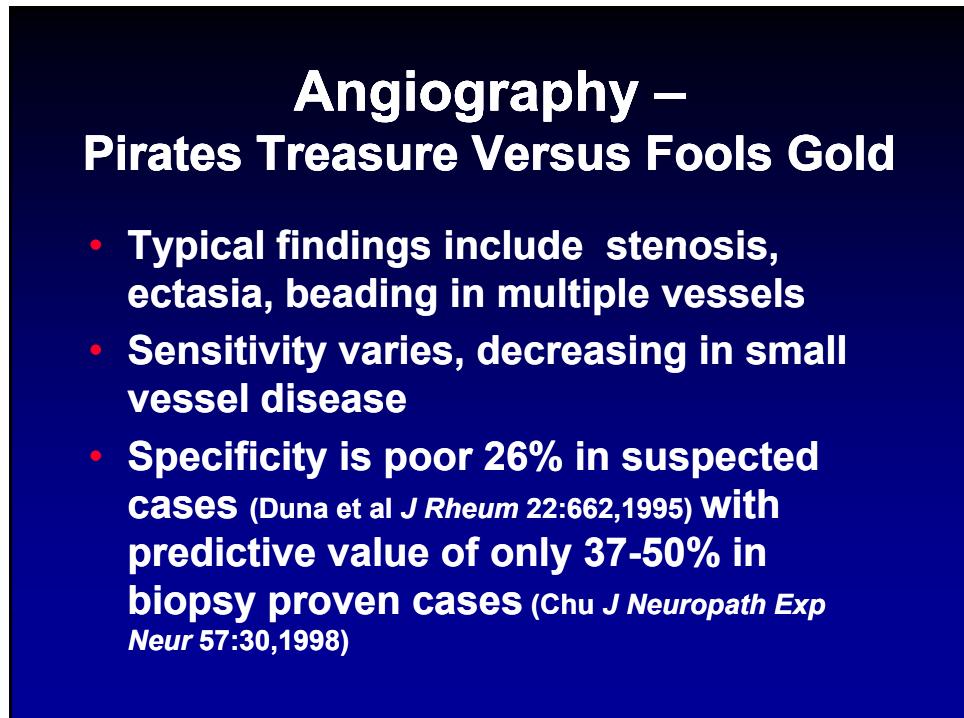
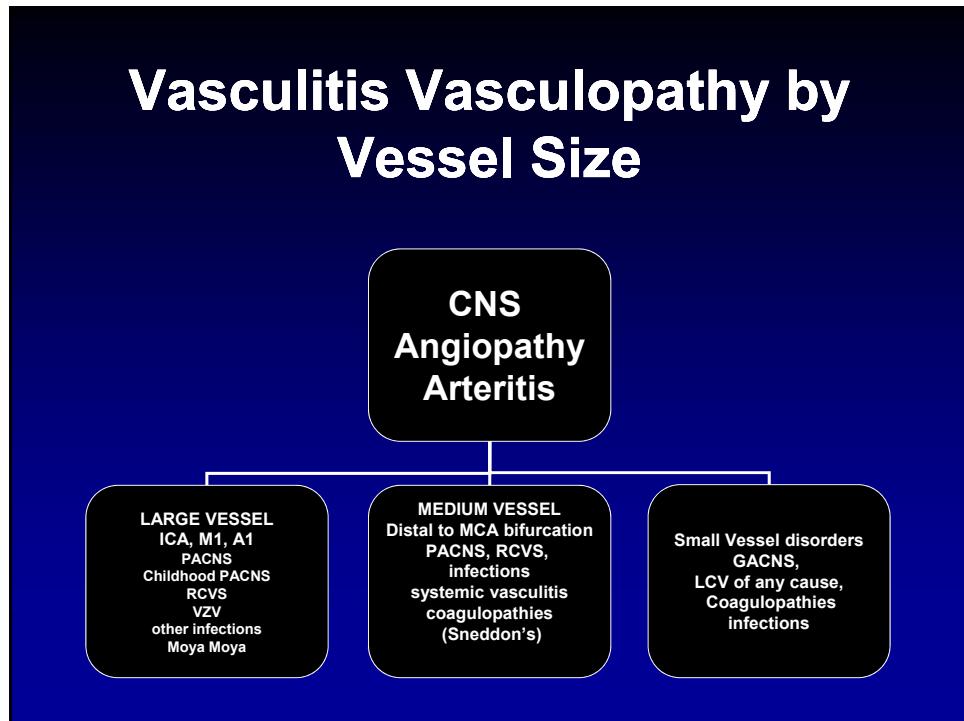
Non Vascular Neuroimaging

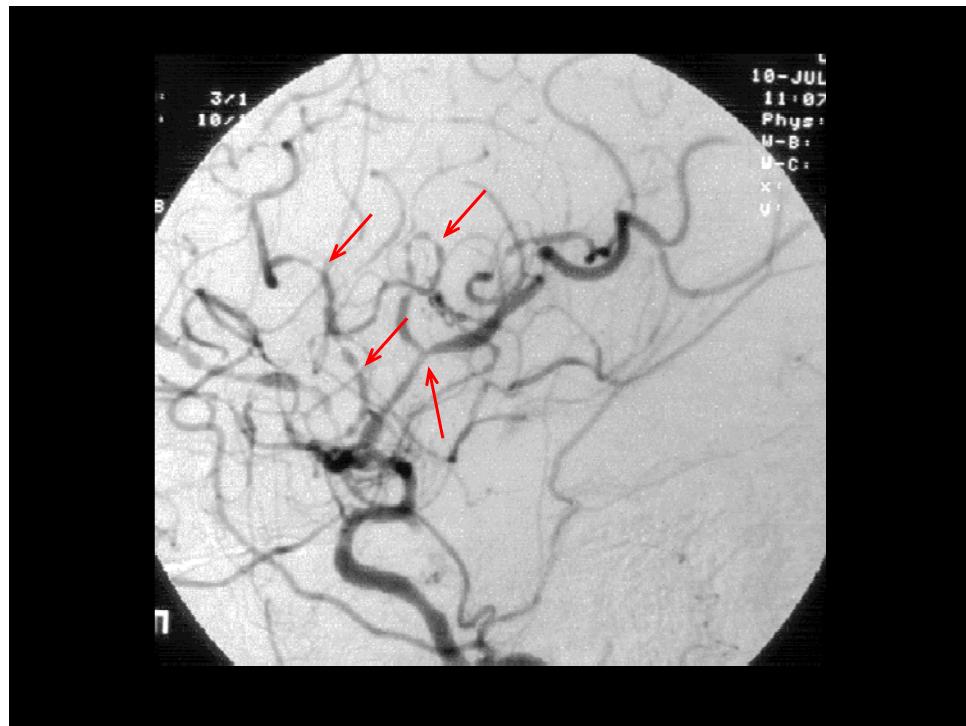
- CT, MRI, SPECT, PET
- Highly sensitive 97%
(Salvarani C et al Ann Neurol 2007)
- No specific findings
 - Multiple ischemic lesions
 - Hemorrhages
 - Leukoencephalopathy
 - Gad enhancing lesions
(parenchyma or leptomeninges)
- MRI test of choice with Gad and DWI
(White ML et al AJNR 2007)



Vascular Imaging Direct or Indirect AXIOM 4

**There is NO angiographic study of
100% specificity for the diagnosis
of CNS vasculitis**





Brain Biopsy AXIOM 5

Brain biopsy is underutilized and is a valuable but imperfect diagnostic tool

Brain Biopsy Two Reasons to Biopsy

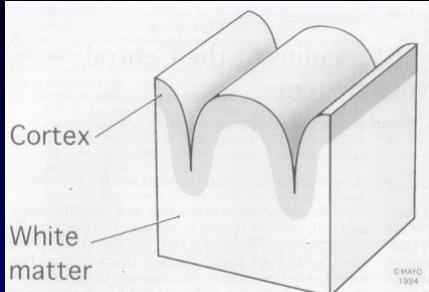
1. To “rule in” (positive predictive value)

High specificity

- **Predictive value of 90-100% in 30 consecutively biopsied cases**
(Chu J Neuropath Exp Neur 57:30,19980)
- **Shortcoming is low sensitivity 60-75%**

2. Rule out ‘other conditions’

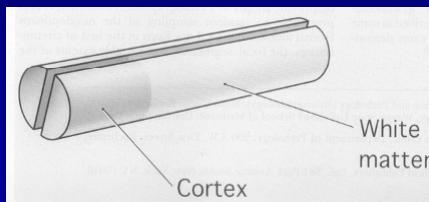
- **Mimics detected in 39% (Alrawi A et al Brain biopsy in PACNS. Neurology 53:858-860,1999)**



Cortex
White matter

OPEN with overlying leptomeninges
Preferred for 'blind biopsy or suspected GACNS
1 cm³; non dominant temporal lobe
Compassing 1 gyrus

Stereotactic
Preferred for targeted biopsy
Can include leptomeninges



Cortex
White matter

Parisi and Moore *Sem Neurol* 14:341, 1994

AXIOM 6 Must Rule Outs

- While all alternative possibilities (i.e. diagnosis) in Bayesian reasoning are treated equally. All diagnosis are not clinically equal.
- Must rule outs :
 - Infection
 - Malignancy

Must Rule Outs

Infections

- Viral – VZV, HCV, HIV, CMV, LCM other
- Mycobacteria- M Tb
- Fungi- cocci, others
- Rickettsial
- Spirochete - syphilis borreliosis
- Parasite – acanthamoebae

Cancer

- Intravascular lymphoma
- CNS lymphoma (NHL)
- Leptomeningeal metastasis of a solid tumor

AXIOM 7

Failure to respond or progress on cyclophosphamide and glucocorticoids suggests an alternative diagnosis rather than refractory disease

Part 2

Rheumatologic encounters with PACNS

- A) Influence of clinical context
on diagnostic reasoning**
- B) Clinical case studies
demonstrating perils of
diagnostic accuracy**

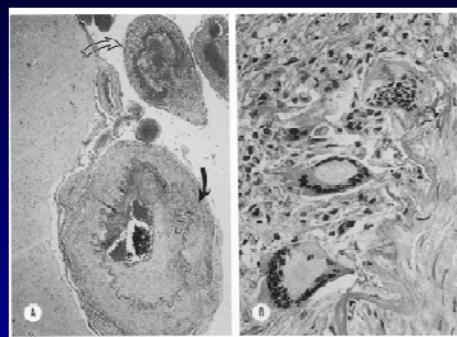
Rheumatology and PACNS 3 Scenarios

- **Scenario 1**
 - Positive Biopsy
 - Confirm and treat
- **Scenario 2**
 - Positive “angiogram”
 - Confirm and treat
- **Scenario 3**
 - Suspicious clinical setting and/or suspicious neuroimaging and input is requested regarding likelihood and/or diagnostic approach

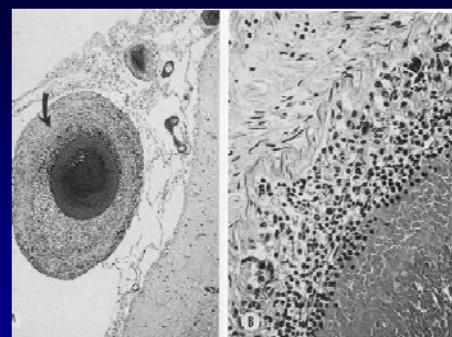
Rheumatology and PACNS Scenario 1

You are consulted for a patient on the neurology service who has just undergone a brain biopsy and is reported as 'consistent with vasculitis'. You are asked to initiate therapy.

The Role of Biopsy



Granulomatous



Non-granulomatous /
lymphocytic

Calabrese L Duna G Lie JT *JT A&R* 1997

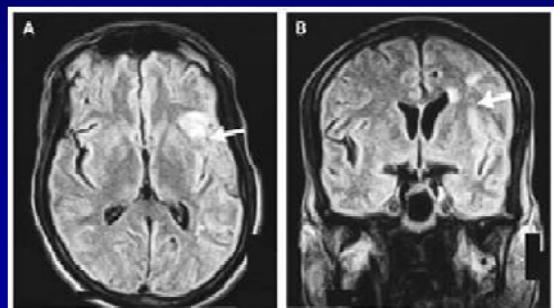
What is a “Positive” Brain Biopsy

- True vasculitis = transmural inflammation + vascular wall damage
- Perivasculitis ≠ vasculitis
 - Injury of multiple types in brain is angiocentric: infection, hypoxia, trauma other
- Is there concomitant beta amyloid present?
- Have the “must rule outs” been considered

Miller D Am J Surg Path 33:35-43,2009

Case 1- Summary

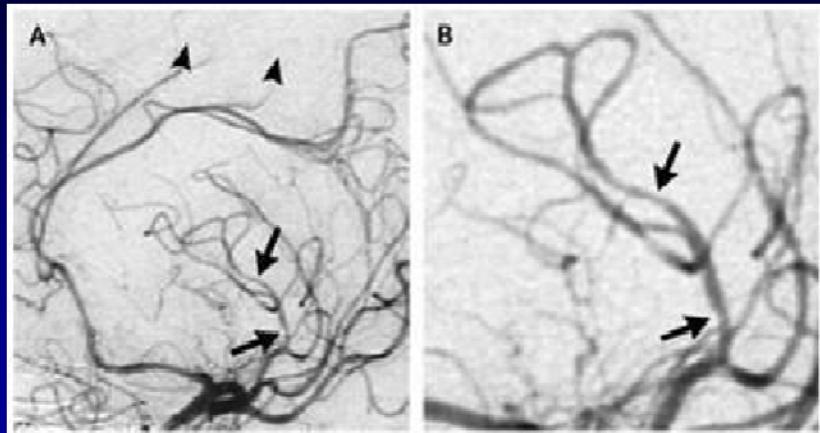
A 30 year old man from Belize with 1 month of fevers headache, aphasia and leptomeningeal enhancement



“meningoencephalitis versus vasculitis.”

N Engl J Med 2005;352:919-24.

Case 1



Case 1

CSF

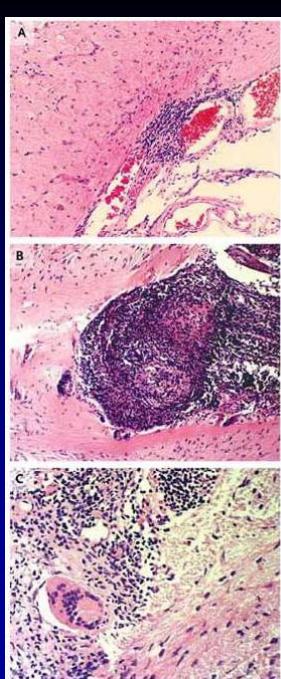
WBC 30 cells/mm³ 100% lymphocytes

Protein 130mg%

Glucose 33m%

Pathology

Granulomatous, angiocentric inflammation with giant cells



Case 1

Three weeks later, the laboratory reported positive cerebrospinal fluid cultures for isoniazid-sensitive *M. tuberculosis*.

Red Flags

- Have the **must rule outs** been considered?
- CSF atypical with hypoglycorrachia
- Epidemiologic clues from a tropical region

Considerations in the Presence of a “Positive” Biopsy Must Rule Outs

- Infection

Are there epidemiologic clues?

- Granulomatous – mycobacteria, acanthomebae, H zoster, Borrelia
- HIV HCV syphilis - pro forma screening

- Malignancy – especially in lymphocytic perivasculitis

- CNS lymphoma – can present with intense peri-vascular inflammation with equivocal LM findings of malignancy

Scenario 2

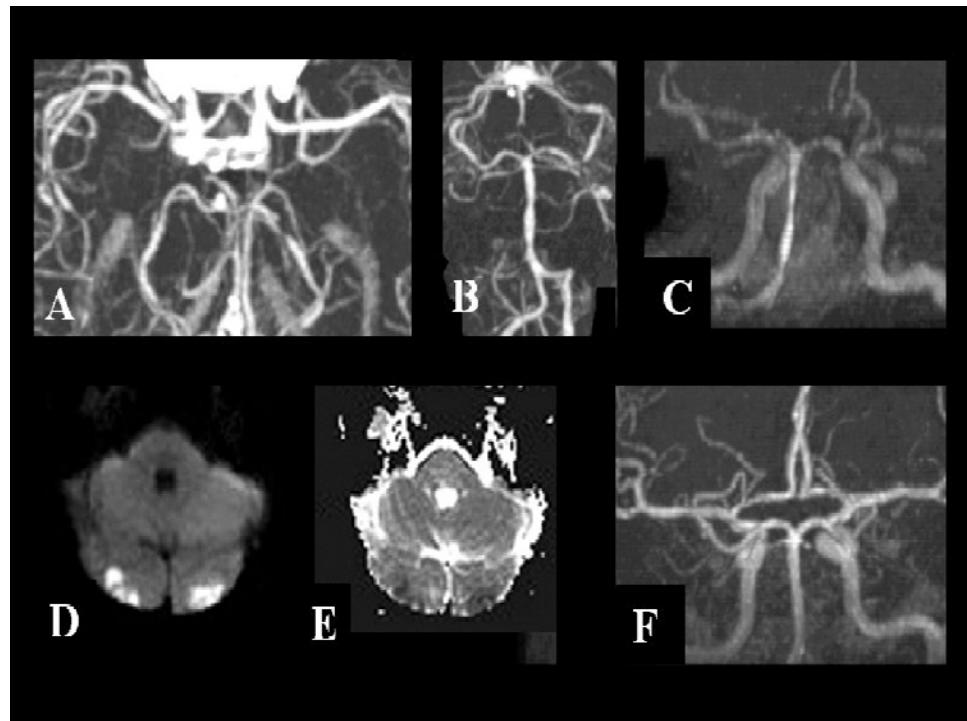
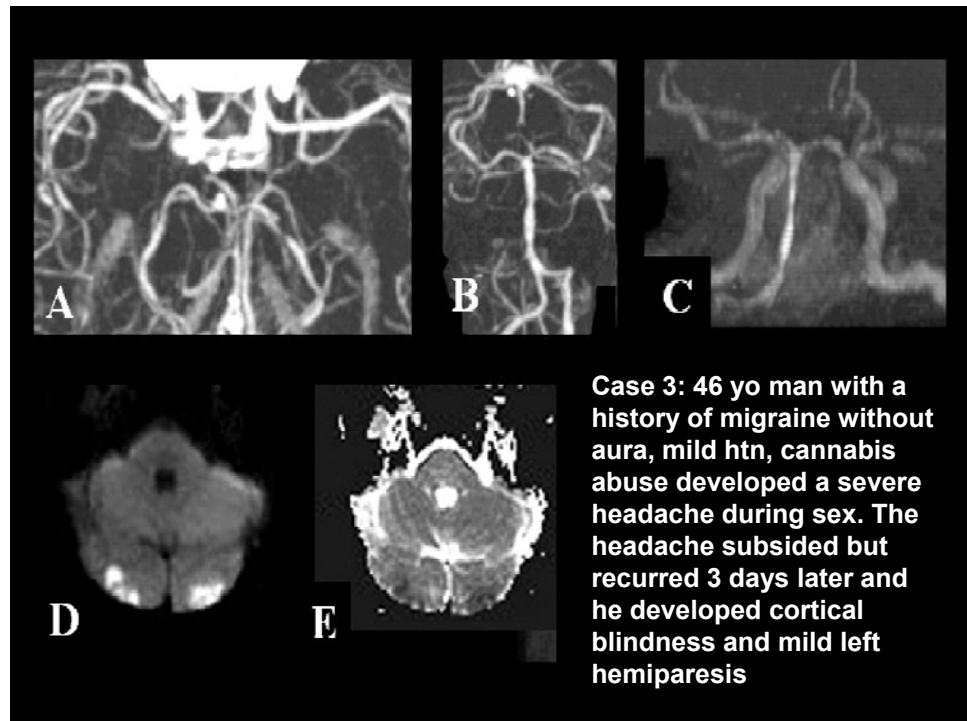
You are called to see and treat a patient who has been diagnosed as having CNS vasculitis based on a “positive” angiogram (direct or indirect)

Natural Sign of Danger



Exclusions in the Setting of a “High Probability” Angiogram

- **Vasospastic disorders**
- **Emboli**
- **Hypercoaguable disorders**
- **Infections**
- **Malignancy**
- **Atherosclerosis**
- **Miscellaneous vascular diseases**
 - **Inherited and acquired vascular syndromes**



RCVS--- Reversible Cerebral Vasoconstrictive Syndromes

- The most important mimic of angiographically documented CNS vasculitis
- Remarkably ‘common’
- Readily diagnosed
- Often confused, misdiagnosed and mismanaged

Benign (Idiopathic) Thunderclap Headache and Vasoconstriction

- Instantaneous severe headache peaking in 1-2 minutes - “worst headache of my life” “my head is going to blow off”
- May be spontaneous or precipitated by exercise, sex, cough, bathing, Valsalva
- May occur isolated or occur repeatedly over 7- 14 days
- Generally benign but can be associated with neurologic signs/sxs

Dodick TCH. *Headache* 2002;42:309-15. Schwedt TJ, Dodick DW. *Lancet Neurol* 2006;5:621-31.

<i>Table 1. Conditions Associated with Reversible Cerebral Vasoconstriction Syndromes*</i>	
Pregnancy and puerperium	
Early puerperium, late pregnancy, eclampsia, preeclampsia, and delayed postpartum eclampsia	
Exposure to drugs and blood products	
Phenylpropanolamine, pseudoephedrine, ergotamine tartrate, methergine, bromocryptine, lisuride, selective serotonin reuptake inhibitors, sumatriptan, isometheptene, cocaine, ecstasy, amphetamine derivatives, marijuana, lysergic acid diethylamide, tacrolimus (FK-506), cyclophosphamide, erythropoietin, intravenous immune globulin, and red blood cell transfusions	
Miscellaneous	
Hypercalcemia, porphyria, pheochromocytoma, bronchial carcinoid tumor, unruptured saccular cerebral aneurysm, head trauma, spinal subdural hematoma, postcarotid endarterectomy, and neurosurgical procedures	
Idiopathic	
No identifiable precipitating factor	
Associated with headache disorders, such as migraine, primary thunderclap headache, benign exertional headache, benign sexual headache, and primary cough headache	

*Adapted from reference 1: Singhal AB, Bernstein RA. Postpartum angiopathy and other cerebral vasoconstriction syndromes. *Neurocrit Care.* 2005;3:91-7.

2 January 2007 | *Annals of Internal Medicine* | Volume 146 • Number 1 | 35

Key Elements for Diagnosis

1. **DSA / CTA / MRA: multifocal vasoconstriction**
2. **Severe, acute, recurrent ‘thunderclap’ headache with or without additional neurologic signs or symptoms**
3. **No evidence for aneurysmal SAH**
4. **Normal CSF (protein <80, cells <10)**

The diagnosis cannot be confirmed until:

- A. **Reversibility is documented (typically < 12 wks)**
- B. **Autopsy – no mimics (PACNS, athero, aSAH)**

Calabrese, Dodick, Schwedt & Singhal (*Annals Int Med* 2007)

Distinguishing RCVS from PACNS

Feature	RCVS	PACNS
Headache	Recurrent TCH	Insidious, chronic
Infarct pattern	'Watershed'	Small, scattered
Lobar Hemorrhage	Common	<u>Very Rare</u>
Cortical SAH	Common	<u>Very Rare</u>
Reversible edema	Common	—
Angiogram	Sausage on a string (smooth)	? Irregular, notched, ectasia

Treatment of RCVS

- No controlled trials of any therapy
- Effective therapy may be none (TCH), calcium channel blockers alone or glucocorticoids
- Choice of agent(s) is best gauged by disease severity and course
- Failure to demonstrate dynamic change should prompt search for another diagnosis

Case – Positive Angiogram

46 year old male 4 months
of progressive confusion,
memory loss, headache
and visual blurring

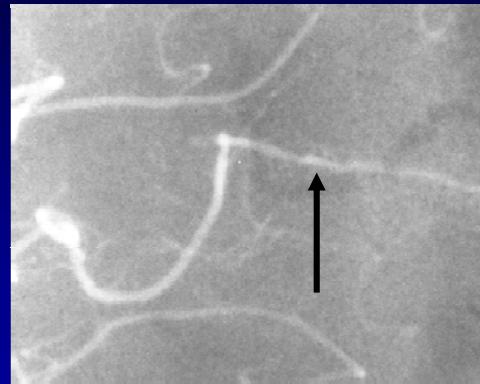
CSF protein 156 mg%,
6 WBC/mm

MRI generalized atrophy
and punctate infarctions

Angiogram - “arteritis”

Infection, emboli TEE,
malignancy work up
negative

Rx CTX and prednisone

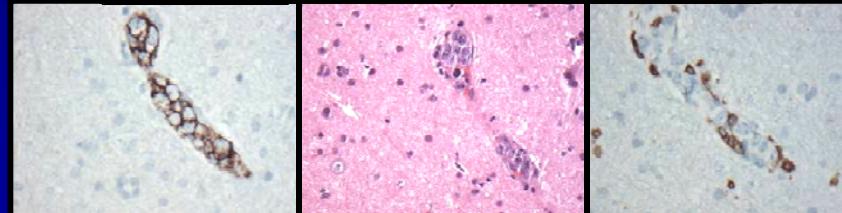
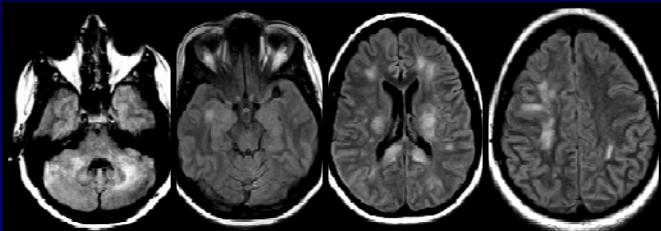


Red Flags

- **Angiographic diagnosis**
- **No tissue confirmation (not performed)**
- **Failure to respond to cyclophosphamide**

Intravascular Lymphoma

Another important mimic of PACNS
 Headaches, punctate infarctions, CSF abnormal,
 angio mildly abnormal
 Diagnosis by CSF cytology, brain biopsy

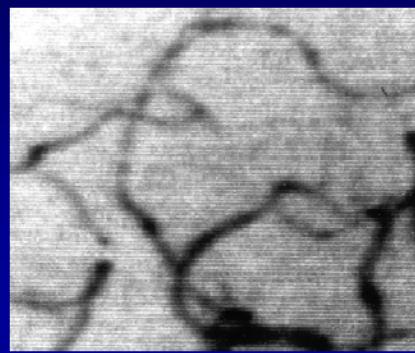


Case 5

41 yo woman with a 10 year history of migraines with aura collapsed on a treadmill with a right sided hemiparesis. Hospitalization yielded an MRI with bilateral lacunar infarcts, CSF with a protein of 55 mg% and 0 cells. A rheumatologic evaluation for CTD and hypercoaguable states was negative.

ANGIO #1

Treatment IVMP/CYTX with improvement but 4 months later had increased symptoms and repeat angio was worse. Several more lacunar lesions noted. Calcium channel blocker was added with some improvement but 8 months latter a third angio showed progression.



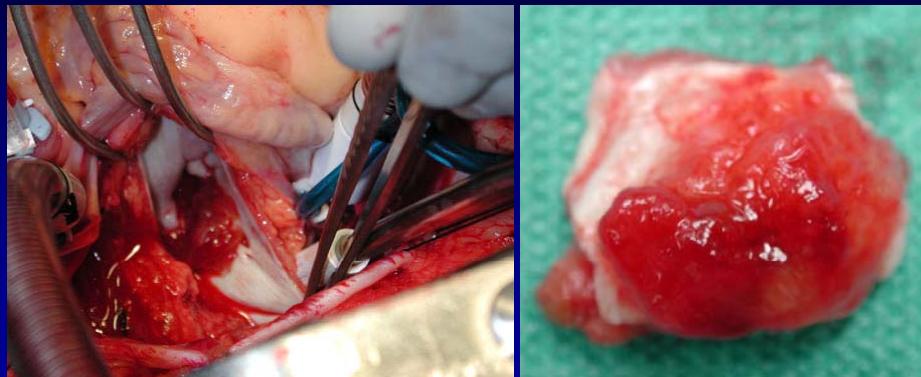
Red Flags

- **Angiographic diagnosis**
- **No tissue confirmation (not performed)**
- **“non inflammatory” spinal fluid**
- **Failure to respond to cyclophosphamide**
- **Multiple strokes presentation mandates a detailed hypercoaguable and embolic work up**

Case 5 continued

- **Normal hypercoaguable panel**
- **Normal TTE**
- **She returns on maximal therapy with new onset pain in the right lower leg with a diminished pulse. An angiogram reveals a smooth narrowing of the peroneal artery ending in an occlusion**

TEE Atrial Myxoma as PACNS



Evaluation of Hypercoaguable and Thromboembolic Disease

- **APS or CAPS**
 - ACL Ab, anti-B2 Ab, LAC
- **Other hypercoaguability studies**
 - protein C and protein S deficiency, factor V Leiden, homocysteine, hyperviscosity
- **Systemic Disorders**
 - Sneddon's syndrome, cancer, nephrosis, TTP, decompression syndrome
- **Emboli TTE,TEE, bubble study**
 - Atrial fibrillation or, atrial myxoma
 - Endocarditis
 - Cholesterol emboli
 - Paradoxical embolism

Other Conditions with Cerebral Angiographic Abnormalities

- **Reversible Cerebral Vascular Syndrome******
- **Premature intracranial atherosclerosis ******
- **Moyamoya disease**
- **Angiotropic and intravascular lymphoproliferative disorders**
- **Radiation vasculopathy**
- **Many others**

Scenario 3

**Suspicious clinical setting and/or
suspicious neuroimaging and input is
requested regarding likelihood and/or
diagnostic approach**

Last Case

- A 59-year-old Caucasian male presented with left-sided visual loss that progressed to the other side
- Fluorescein angiography showed bilateral “retinal vasculitis” and two branch vein occlusions in the left eye
- He was started on glucocorticoids for six months and responded well

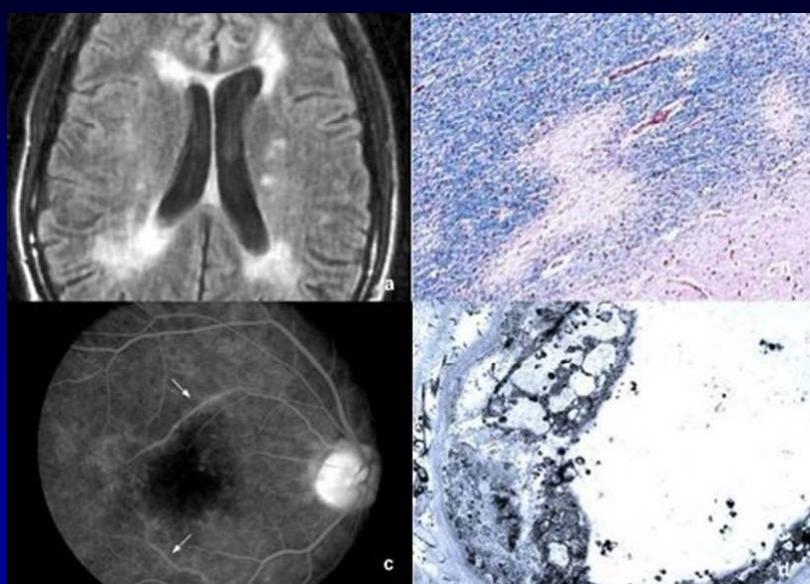
Last Case - Failure to Respond to Therapy

- He developed cognitive difficulties, personality changes, memory disturbances and imbalance
- CSF analysis showed elevated protein at 94 mg/dl (15-45 mg/dl) and 3 white blood cells
- MRI brain showed extensive white matter changes with enhancement
- Conventional cerebral angiography was normal

Case

- Workup did not reveal any infectious, cancer or autoimmune etiology
- Family history
 - Father: blindness for one month before death at age 30
 - Cousin: diagnosis of “brain tumor”
- Brain biopsy of bilateral temporal lobes and dura mater showed perivascular chronic inflammation

Case

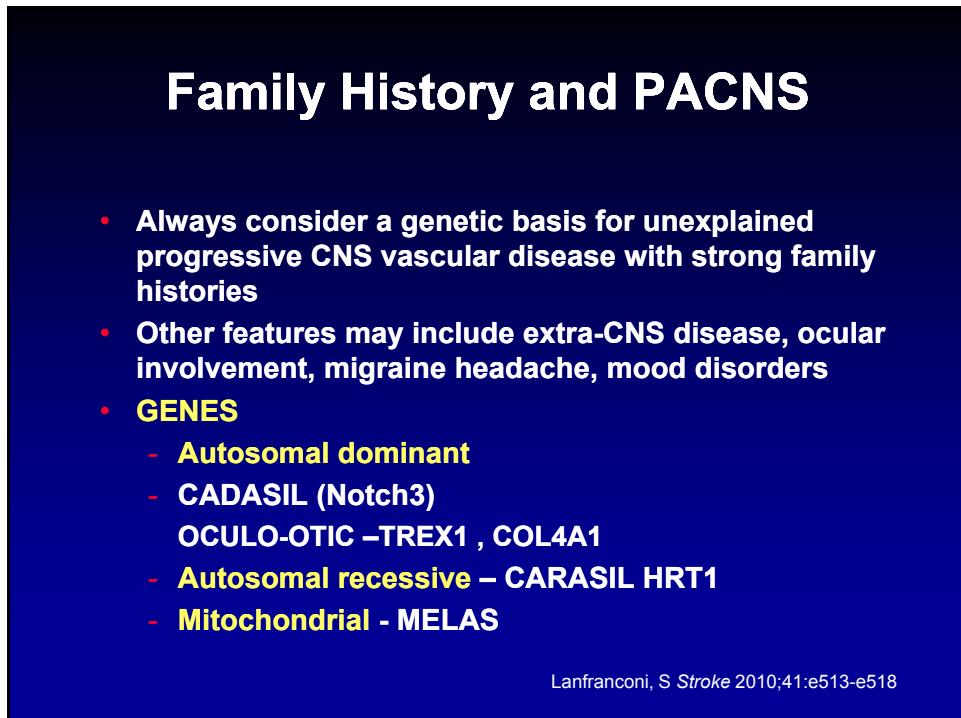
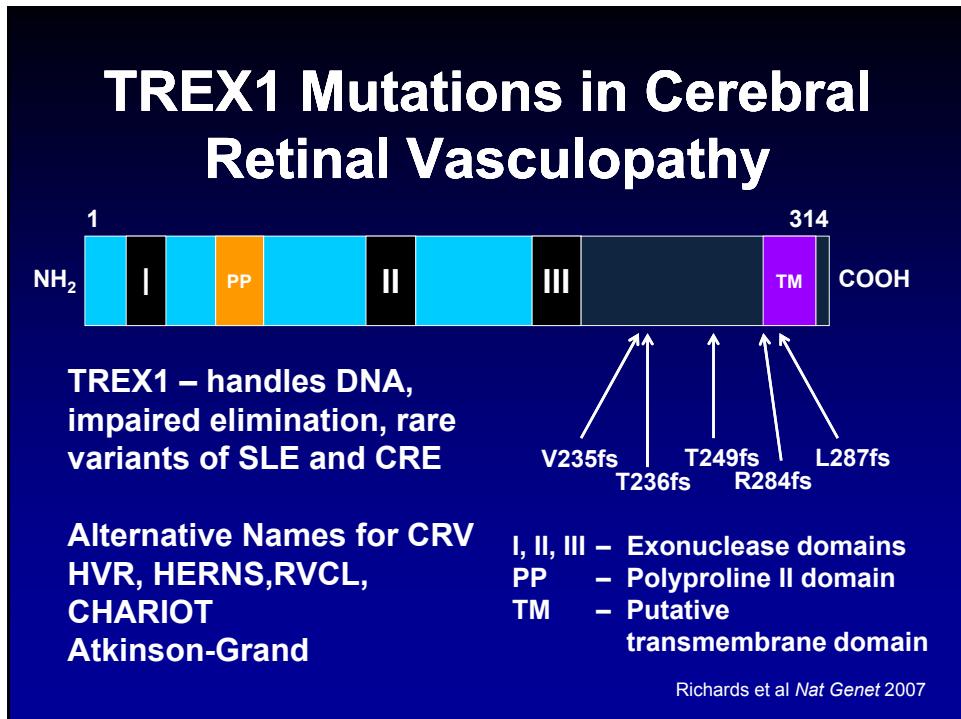


Case

- With disease progression and evidence of possible inflammation on biopsy, he was started on monthly intravenous cyclophosphamide (CYC) and high dose glucocorticoids
- He did not experience any improvement on this immunosuppressive regimen and developed progressive neurologic decline

Last Case Red Flags

- Non diagnostic brain biopsy (not true vasculitis)
- Lack of response to cyclophosphamide
- Family history of neurological symptoms



Treatment and Outcome

- No controlled data
- Subject to historical bias
- RCVS-
 - Observation, a calcium blocker, steroids?
- Biopsy proven disease – based on burden of morbidity
- PACNS with granulomatous pathology - CTX/GC ‘Wegener’s protocol’
- Role for biologics? Anti-TNF, Rituximab
(Salvarani C, Brown RD Jr, Calamia KT, et al. *Arthritis Rheum* 2008; 59:291–296.)

Best Practices

Are Red Flags Present

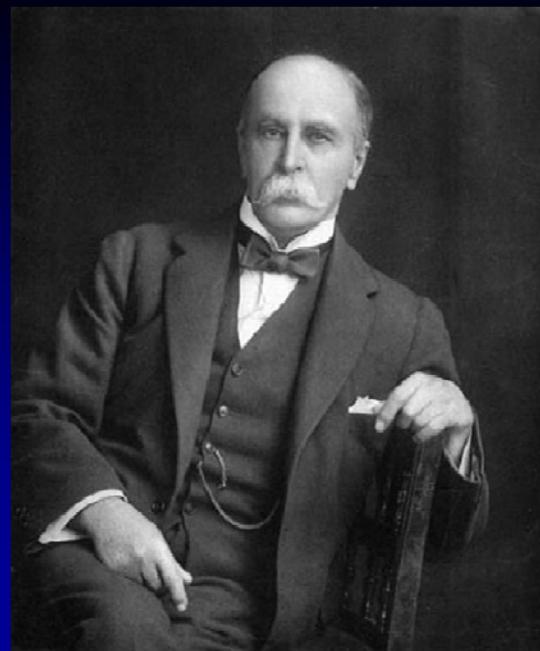
- Diagnosis made in the absence of an LP
- Diagnosis made on angiographic grounds with a normal LP
- Patient has been treated empirically and is not responding

General

- The approach to PACNS in most cases requires a team of interested clinicians
- The diagnosis is never solely biopsy or angiography based -- Clinical

**The value of
experience is
not in seeing
much, but in
seeing wisely**

Osler



**Believe nothing, no matter where
you read it, or who has said it, not
even if I have said it, unless it
agrees with your own reason and
your own common sense. *Buddha***

