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ADULT PRIMARY CENTRAL NERVOUS SYSTEM VASCULITIS

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Vasculitides and connective tissue diseases associated with a diagnosis of CNS vasculitis at the Mayo Clinic over a 17-year period

Salvarani C et al, Arthritis Rheum 2006

Condition	Number of patients
Isolated CNS vasculitis	73
ANCA-associated vasculitis	13
Systemic lupus erythematosus	9
Beçhet's disease	8
Giant cell arteritis	2
Undefined vasculitis	3
Sjögren syndrome	2
Rheumatoid arthritis	2
Undefined connective tissue disease	1

Noninfectious granulomatous angiitis with a predilection for the nervous system

Humberto Cravioto, M.D., and Irwin Feigin, M.D.

Neurology - 1959 -

Recognition of this disorder as a distinct entity **dates back to 1959 when Cravioto and Feigin** described several cases of "non-infectious" granulomatous angiitis with a predilection for the nervous system with a fatal outcome

Definition

- ***Granulomatous*** **angiitis of the CNS**
- ***Giant cell arteritis*** **of the CNS**
- ***Isolated*** **angiitis of the CNS**
- ***Primary*** **angiitis of the CNS (PACNS)**
- ***Primary*** **CNS vasculitis (PCNSV)**

"A peculiar and uncommon type of vasculitis that is exclusively confined to the brain and spinal cord"

Lie JT, Human Pathology 1992

Pathophysiology

Studies evaluating immunological abnormalities in PCNSV

Authors, year	Patients	Methods	Results
CSF analysis			
Mandel-Brehm et al, 2019	8 with biopsy-proven PCNSV (1 GV and 7 LV), 4 with RCVS, and 11 noninflammatory controls.	Using mass spectrometry, **exploratory CSF proteomic analysis.** Validation of the findings by Western blot and commercial ELISA.	**Deregulation of the alternative complement cascade in the CSF of biopsy-proven PCNSV compared to noninflammatory controls**: alterations of several regulators of the C3 and C5 convertases and components of the terminal cascade.
Deb-Chatterji et al, 2021)	20 with PCNSV (18 with active disease) and 16 with non-inflammatory conditions.	Using an array-based multiplex system, **quantification of serum and CSF levels of activated and regulatory complement system proteins.**	Unchanged levels in PCNSV compared to non-inflammatory conditions of C3a, C5a, and SC5b-9, C4a, Ba and Bb, complement-inhibitory proteins factor H and factor I**: no evidence of increased complement activation in PCNSV**.

DIAGNOSTIC CRITERIA AND IMAGING

Diagnostic Criteria

Calabrese LH and Mallek JA, Medicine 1987

1) history or clinical findings of an acquired neurologic deficit, which remained unexplained after a thorough initial basic evaluation

2) classic angiographic or histopathologic features of angiitis within the central nervous system

3) no evidence of systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary

Diagnostic criteria

Salvarani et al, Ann Neurol 2007

- angiographic changes required to indicate a high probability of vasculitis are:

  - *alternating areas of smooth-wall segmental narrowing and dilatation of cerebral arteries*
  - *arterial occlusions affecting many cerebral vessels*
  - *absence of proximal vessel atherosclerosis or other recognized abnormalities*

- one abnormality in several arteries or several abnormalities in one artery are less consistent with CNS vasculitis


Multiple stenoses of the right and left posterior cerebellar arteries and right posterior cerebral artery

Cerebral angiogram results in 84 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=84)	Biopsy confirmed (N=14)	Angiogram confirmed (N=70)
Angiogram consistent with vasculitis**			
Number of patients (%)	76 (90.5%)	6 (42.9%)	70 (100%)
Angiographically bilateral vasculitis			
Number of patients (%)	71 (93.4%)	5 (83.3%)	66 (94.3%)
Large vessel changes consistent with vasculitis			
Large vessel changes, No. of patients (%)	54 (71.1%)	4 (66.7%)	50 (71.4%)
Unilateral	7 (9.2%)	0 (0%)	7 (10%)
Bilateral	47 (61.8%)	4 (66.7%)	43 (61.4%)
Small vessel changes consistent with vasculitis			
Small vessel changes, No. of patients (%)	70 (92.1%)	6 (100%)	64 (91.4%)
Unilateral	8 (10.5%)	0 (0%)	8 (11.4%)
Bilateral	62 (81.6%)	6 (100%)	56 (80%)

DIAGNOSTIC LIMITATIONS OF ANGIOGRAPHY

Salvarani et al, Ann Neurol 2007; Vollmer at al, Arch Neurol 1993; Duna et al, J Rheumatol 1995; Harris et al, AJNR 1994

- Because of the invasive nature of CNS biopsy, angiography is often used for the diagnosis of cerebral vasculitis
- the use of angiography as a gold standard for diagnosis has limitations
- overall, the sensitivity of angiography varies between 40% and 90% and cerebral angiograms have a specificity as low as 30%

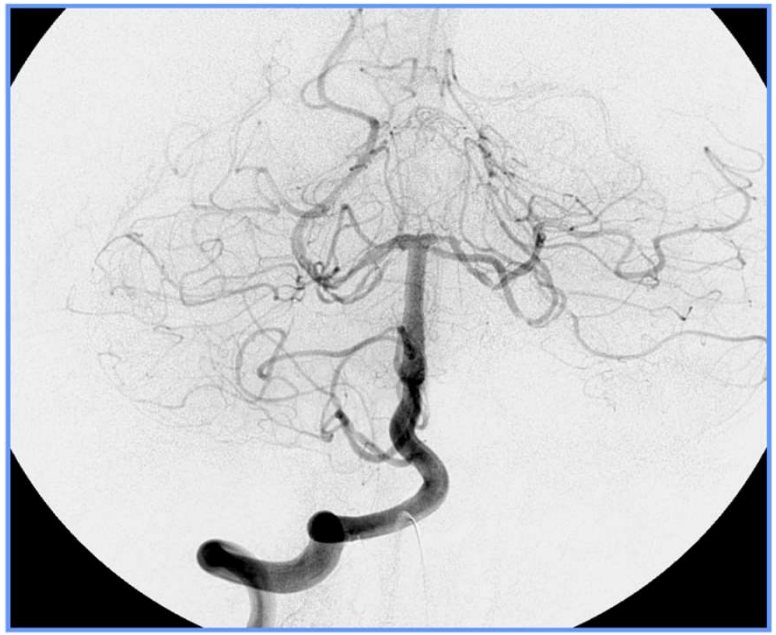
DIAGNOSTIC LIMITATIONS OF ANGIOGRAPHY

Salvarani et al, Current Opin Rheumatol 2012; Lancet, 2012

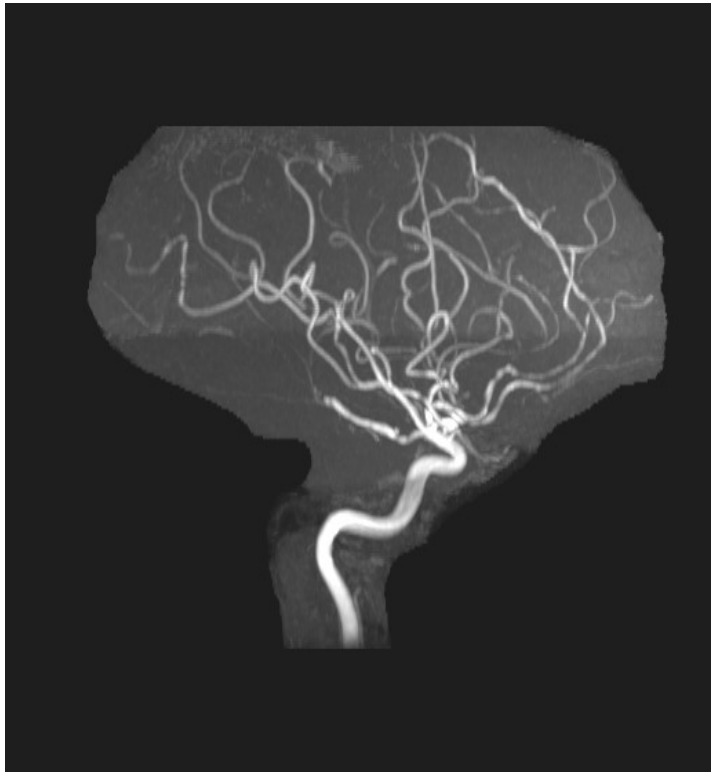
- Angiographic changes typical of vasculitis may be seen in:

- *vasospasm*
- *CNS infections*
- *lymphomas*
- *cerebral arterial emboli*
- *atherosclerosis*

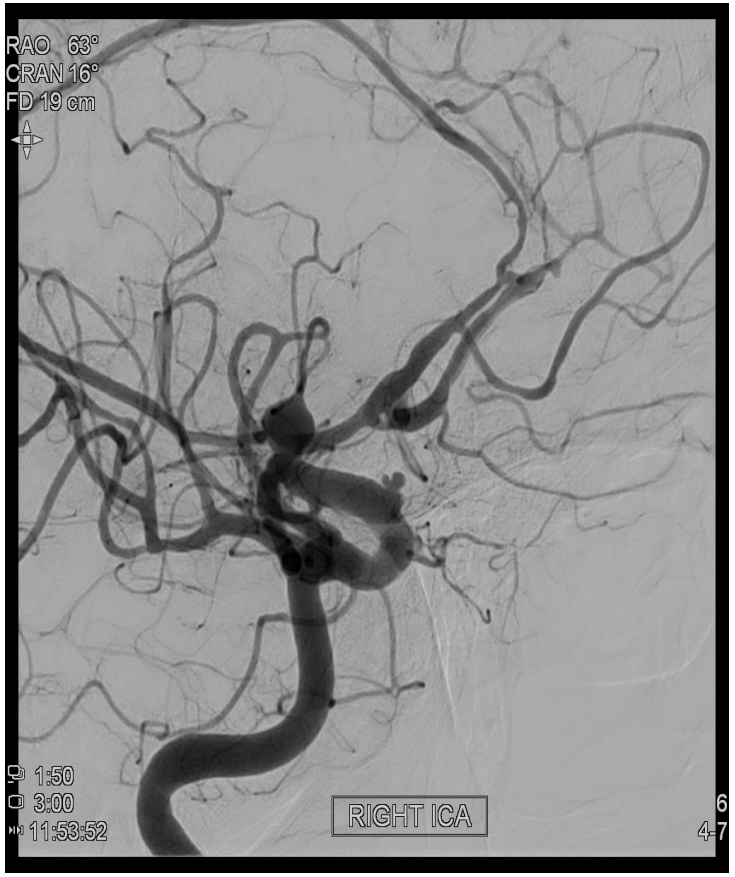
- Normal angiography may reflect vascular involvement in small vessels below the resolution of angiography



33-year old male with
biopsy-confirmed PCNSV



27-year old female
with postpartum RCVS



40-year old male with intracranial
atherosclerosis
2 cerebral biopsies: negative
cerebral autopsy: atherosclerosis of
small cerebral and leptomeningeal
arteries and multiple infarcts

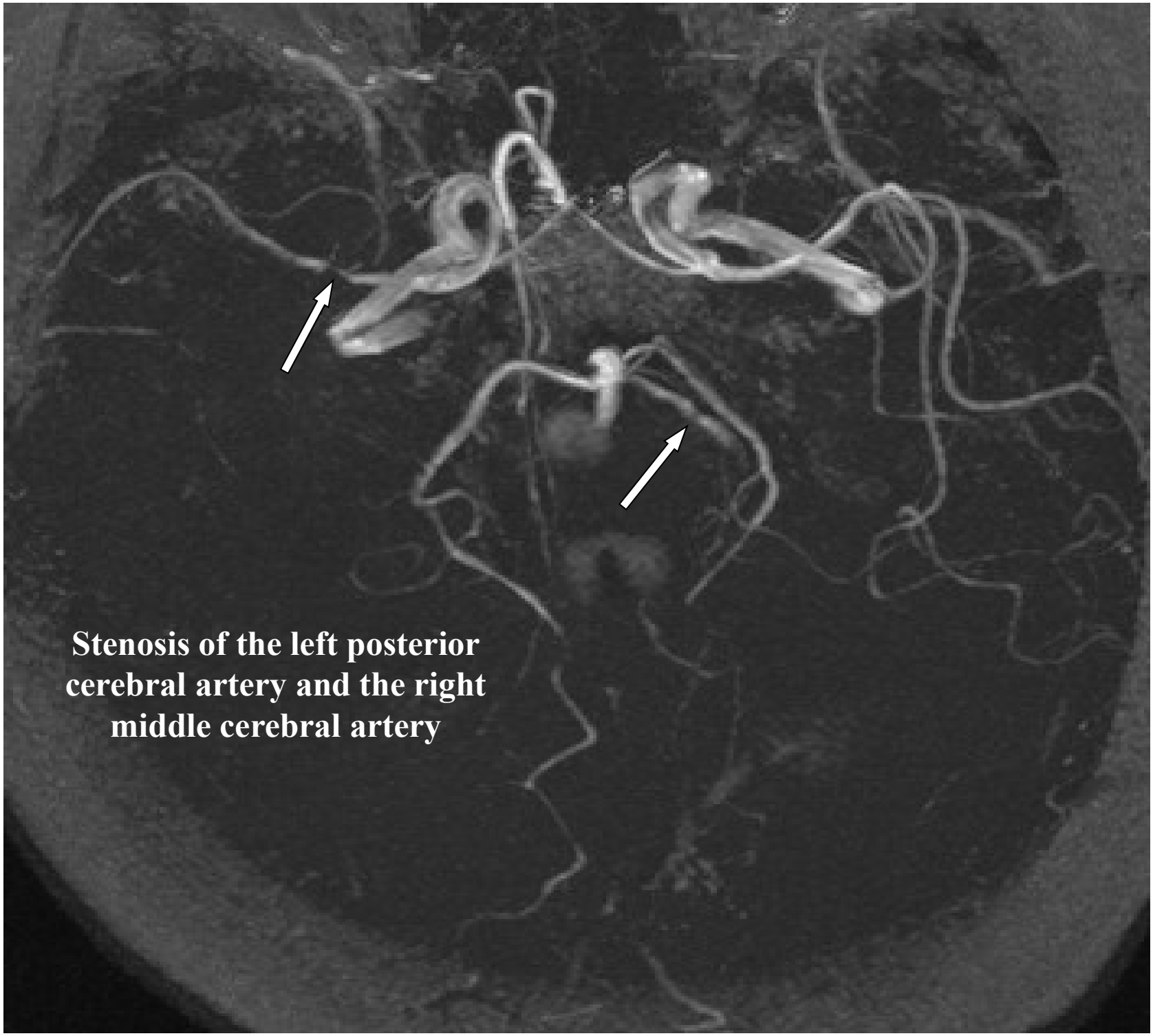
Magnetic Resonance Angiography

Salvarani et al, Ann Neurol 2007; Eleftheriou et al, Dev Med Child Neurol 2010

- MRA is a reasonable initial approach to investigate patients with suspected PCNSV

- MRA is less sensitive than conventional angiography in detecting lesions involving:
  - *the posterior circulation*
  - *distal vessels*

- if the clinical suspicion is high but MRA is normal, a standard cerebral angiography is warranted


Stenosis of the left posterior cerebral artery and the right middle cerebral artery

KEY POINTS

- the diagnosis of PCNSV should not be based on the findings of a positive angiography alone

- Angiography results should always be interpreted in conjunction with clinical, laboratory or MRI findings

Diagnostic criteria proposed by Birnbaum and Hellmann

Arch Neurol 2009

- Definite diagnosis:

  - confirmation of vasculitis on cerebral biopsy

- Probable diagnosis:

  - high-probability angiogram with abnormal findings on MRI and CSF profile consistent with PCNSV

- Patients with high-probability angiogram but normal CSF may have either RCVS or PCNSV:

  - evaluation of medical history, demographic and clinical findings

Magnetic Resonance Imaging

Salvarani et al, Ann Neurol 2007; Lancet 2012; Current Opin Rheumatol 2012

- MRI is highly sensitive (97-100%) but non specific
- Abnormal MRI findings include:

- *cortical and subcortical infarction*
- *parenchymal and leptomeningeal enhancement*
- *intracranial hemorrhage*
- *tumor-like mass lesions*
- *areas of increased signal intensity on FLAIR or T2-weighted images*

MRI examination results in 90 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=90)	Biopsy confirmed (N=27)	Angiogram confirmed (N=63)
Minimal/age-consistent white matter changes			
Number of patients (%)	3 (3.3%)	1 (3.7%)	2 (3.2%)
Any infarct present			
Number of patients (%)	48 (53.3%)	9 (33.3%)	39 (61.9%)
Single infarct			
Number of patients (%)	7 (7.8%)	2 (7.4%)	5 (7.9%)
Multiple infarcts-bilateral			
Subcortical (%)	7 (7.8%)	2 (7.4%)	5 (7.9%)
Cortical (%)	1 (1.1%)	1 (3.7%)	0 (0%)
Both (%)	26 (28.9%)	2 (7.4%)	24 (38.1%)
Intracerebral or subarachnoid hemorrhage			
Number of patients (%)	7 (7.8%)	2 (7.4%)	5 (7.9%)
Gadolinium Enhancing Lesions (Intracerebral or Meninges)			
Number of patients (%)	33 (36.7%)	18 (66.7%)	15 (23.8%)

Neuroimaging Techniques

Salvarani et al, Lancet 2012, Clin Exp Rheumatol 2008; Zuccoli et al, Clin Exp Rheumatol 2011; Swartz et al, Neurology 2009; Mandell et al, Stroke 2012; Obusez et al, AJNR2014

- Advances in neuroimaging techniques used to study the wall of intracranial vessels could improve the detection of inflammation:

  - vessel wall thickening

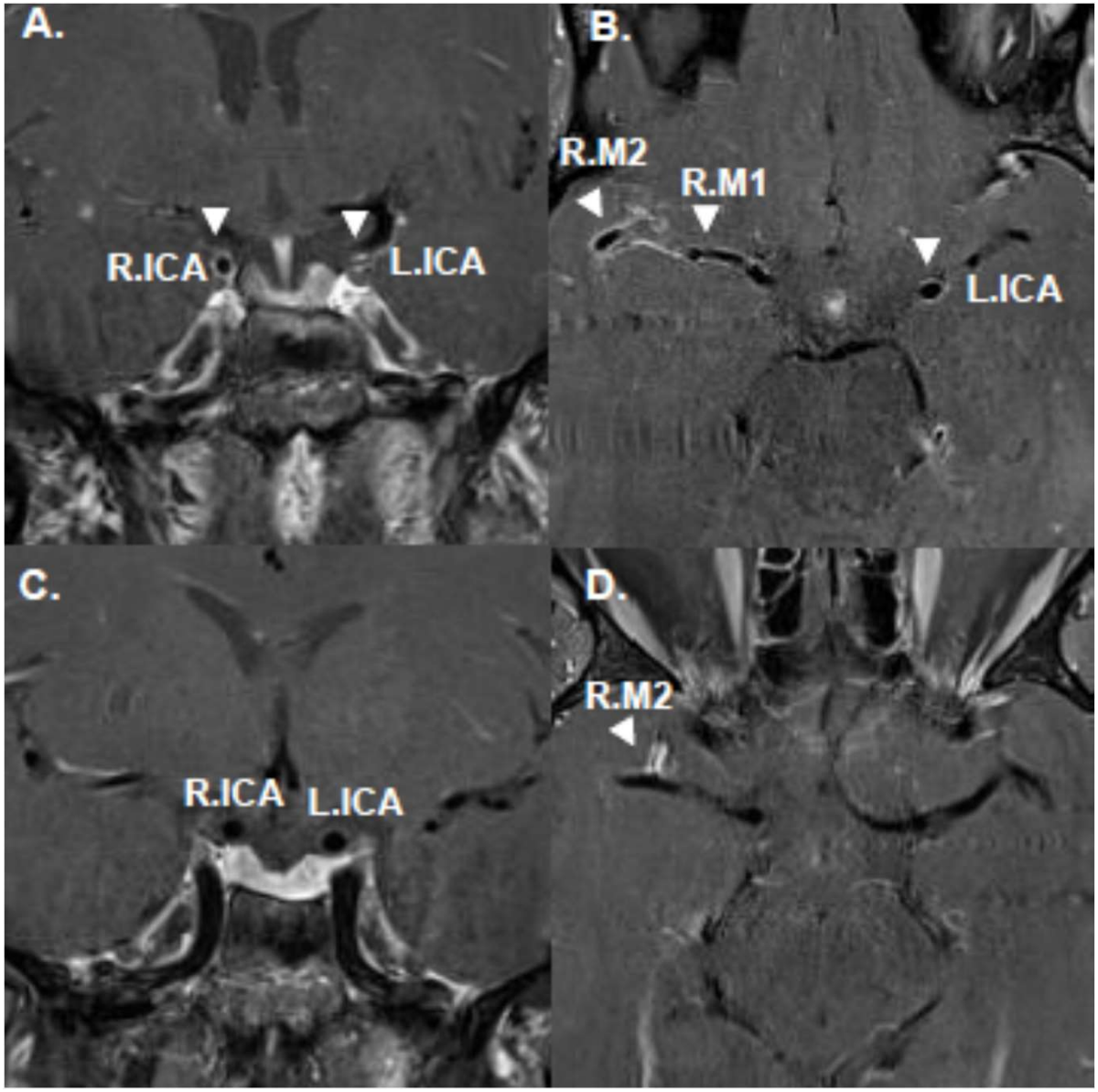
  - intramural enhancement

  - enhancement can extend into the adjacent tissue (perivascular enhancement)

- 3T-HR MRI vessel wall imaging may differentiate between RCVS and CNS vasculitis:

- *multiple areas of concentric wall thickening with absent/minimal enhancement in VS*
- *multiple areas of concentric marked wall enhancement and thickening in vasculitis*

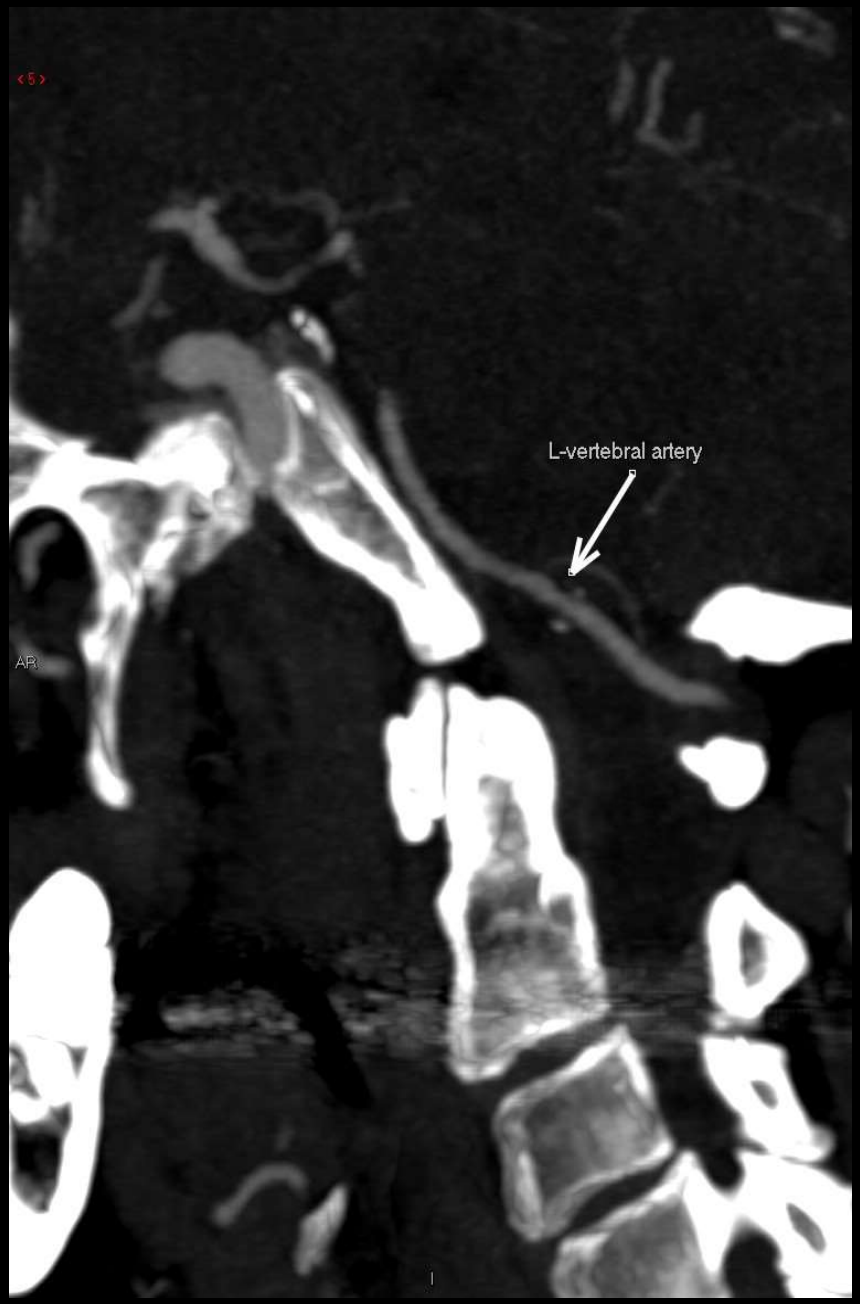
- 3T-HR MRI is also useful for assessing therapy response

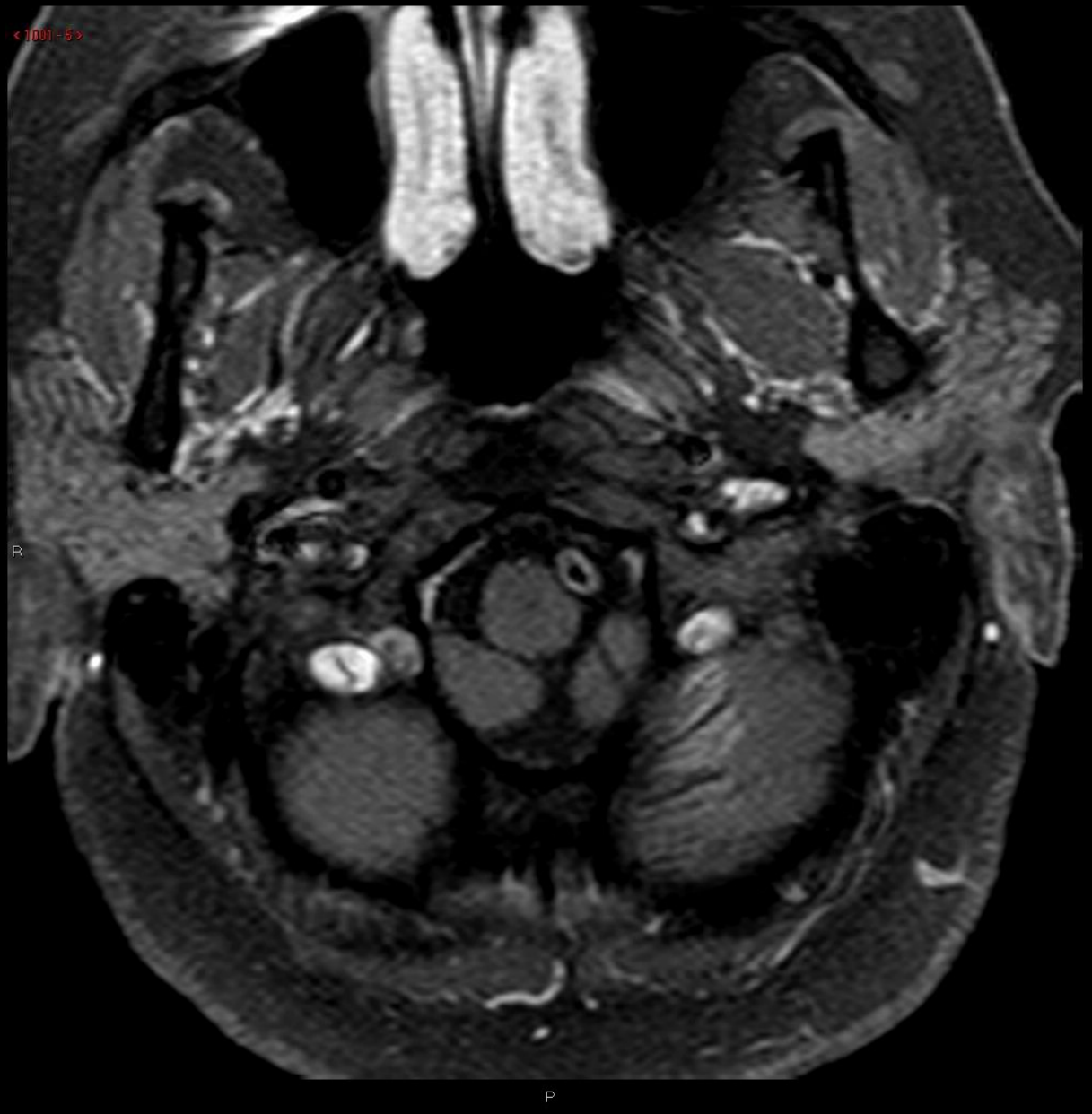


A 25-year-old woman with good response to therapy wirth CYC and GCs.

Baseline 3T-HRMRI post-gadolinium (A: Coronal image and B: Axial image). A, B: Multiple strong smooth, concentric wall enhancements (arrow-heads) in the R ICA, M1, M2 and the left ICA.

Follow-up 3T-HRMRI post-gadolinium at 19 months (C: Coronal image and D: Axial image). C, D: Strong smooth, concentric wall enhancement (arrow-head) remained in the right M2 segment. Interval resolution of vessel wall enhancement was observed in the bilateral ICA and the right M1 segments





Intracranial atherosclerosis affects the artery eccentrically and it less commonly cirumferential, however may cause unifocal or multifocal circumferential enhacement that could be confused with vasculitis

Meningeal-Brain Cerebral Biopsy

- Cerebral and meningeal biopsy is the gold standard for the diagnosis:
  - *1% risk of permanent neurological sequelae*
  - *biopsy of a radiographically abnormal area is preferable*
  - *an optimal biopsy should include adequate samples of dura, leptomeninges, cortex and white matter*
- Vasculitis affects arteries in a segmental way:
  - *a negative biopsy does not exclude diagnosis (sensitivity: 67%-74%)*
- it is imperative that the tissue be systematically sampled for light microscopy, microbiology, immunohistological,and possibly ultrastructural studies

Parisi and Moore, Semin Neurol 1994; Salvarani et al, Lancet 2012, Autoimmun Rev 2020; Miller et al, Am J Surg Pathol 2009; Giannini et al, Acta Neuropathol 2012; De Boysson and Pagnoux, Stroke 2026

EPIDEMIOLOGY AND HISTOPATHOLOGY

Epidemiology

Salvarani et al, Ann Neurol 2007

Incidence Rate in Olmsted County (MN, USA)

Average annual incidence rate*:

2.4 cases per 1,000,000 person years (95%CI: 0.3-4.4)

**Adjusted to the US white 2000 population*

CNS Histopathology

Miller et al, Am J Pathol 2008; Giannini et al, Acta Neuropathol 2012; Salvarani et al, Autoimmun Rev 2019

- a granulomatous inflammatory pattern was found in 34/58 pts (59%), a lymphocytic in 13 (22%), an acute necrotizing in 10 (17%), and a granulomatous/necrotizing in 1 (2%)

- beta-amyloid peptide deposition was present in 19/58 (33%) biopsies showing a granulomatous vascular pattern and in 2 with necrotizing

CNS Histopathology

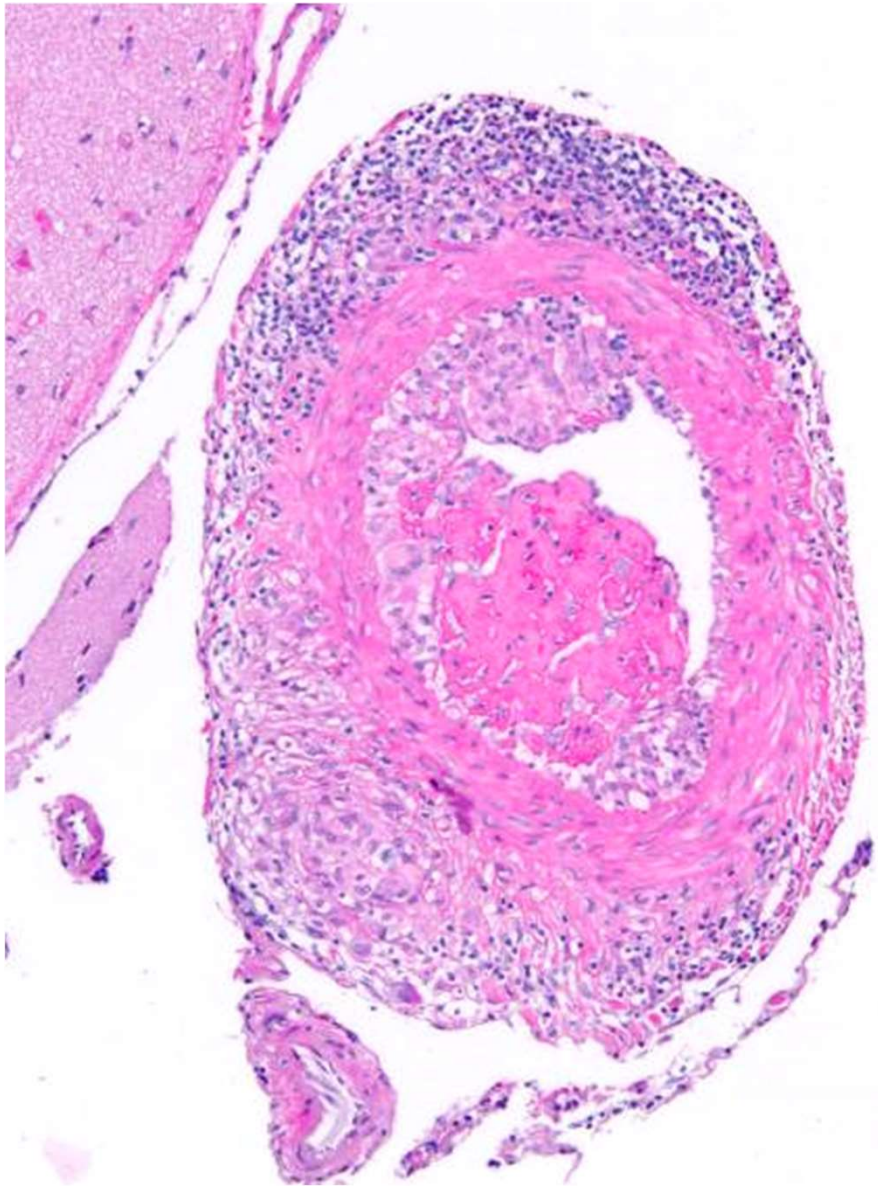
Salvarani et al, Arthritis Rheum 2011, Arthritis & Rheumatol 2015, Autoimmun Rev 2019

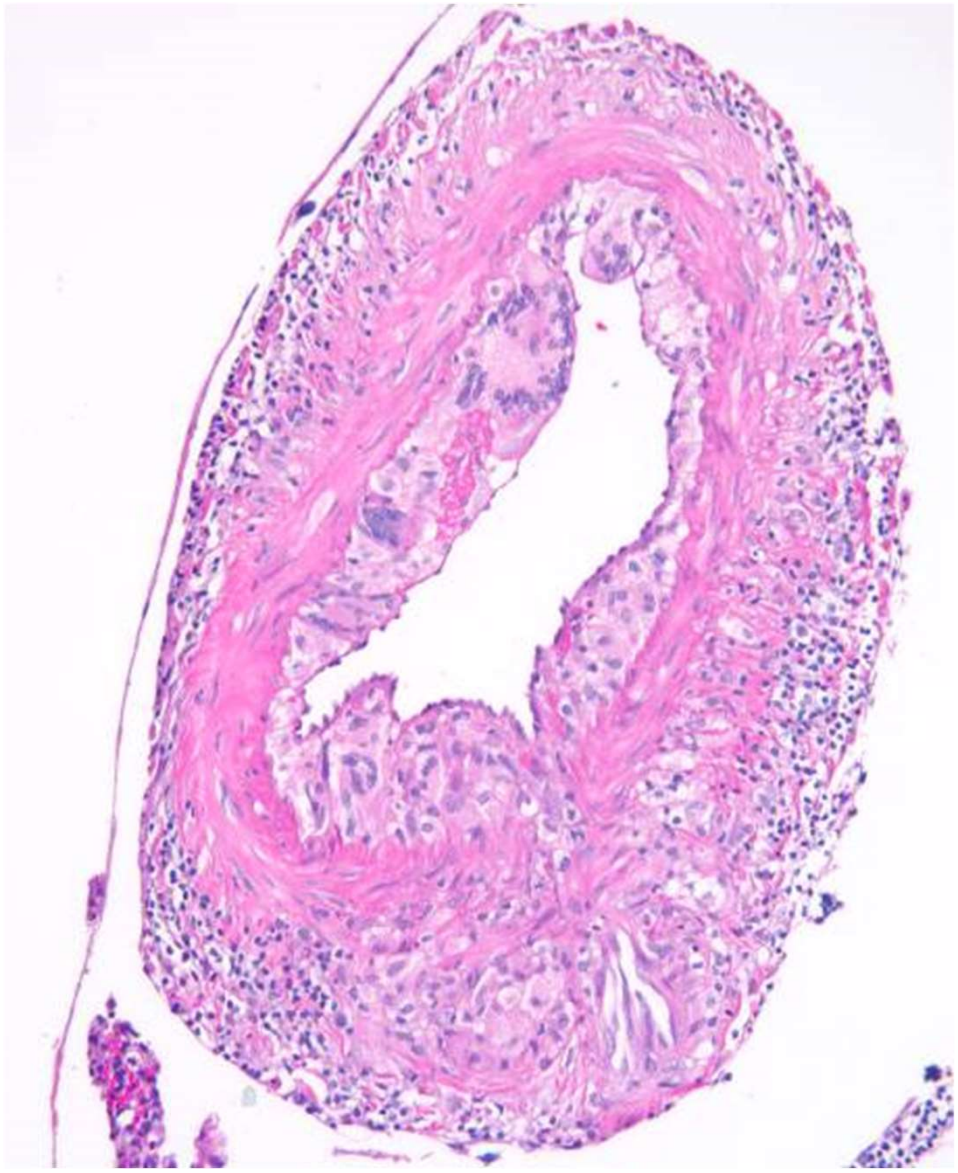
- Necrotizing vasculitis was associated with intracranial hemorrhage at presentation

- Pts with lymphocytic vasculitis had a lower level of disability at last follow-up compared to those with granulomatous and/or necrotizing vasculitis (mRS 4-6: 0 versus 38%, p = 0.006)

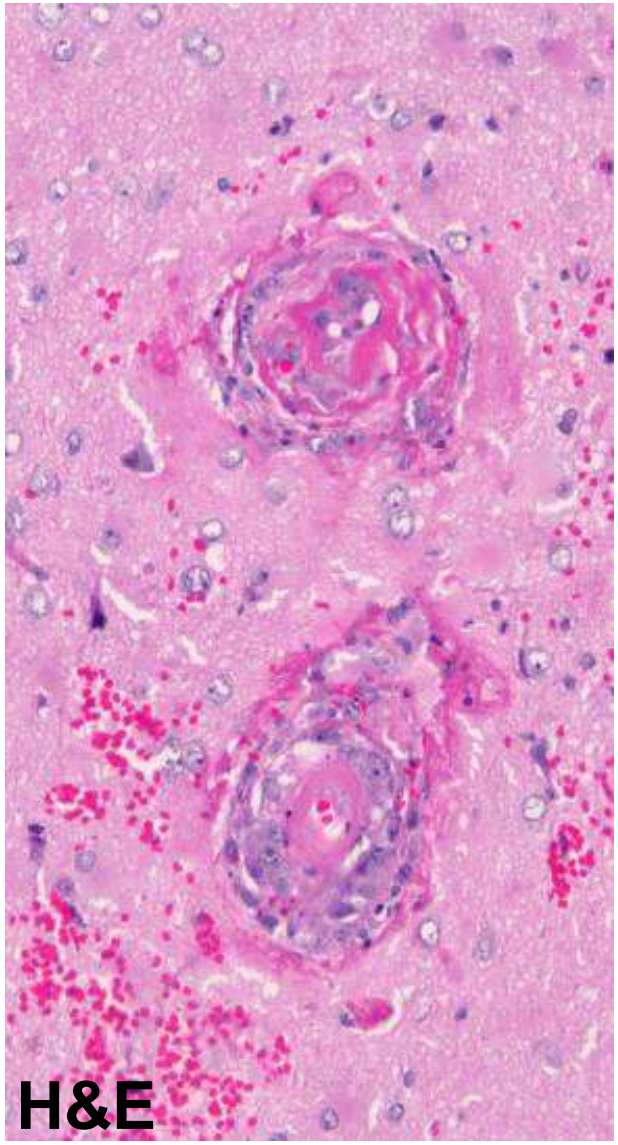
- No patients died in the group with lymphocytic vasculitis at last follow-up compared to 12/45 (27%) in the other 2 groups (p = 0.05)

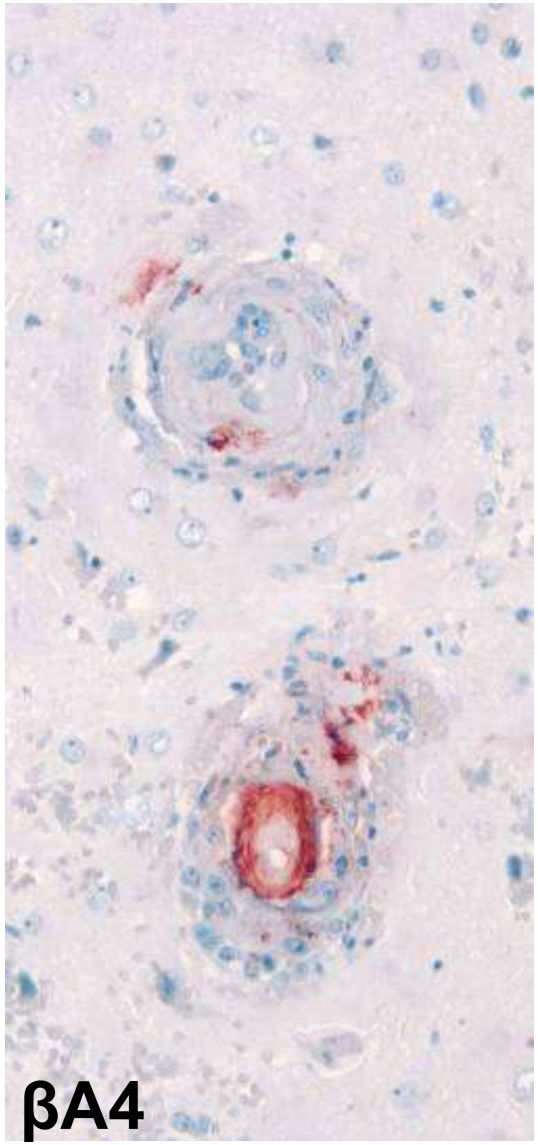
Granulomatous Vasculitis

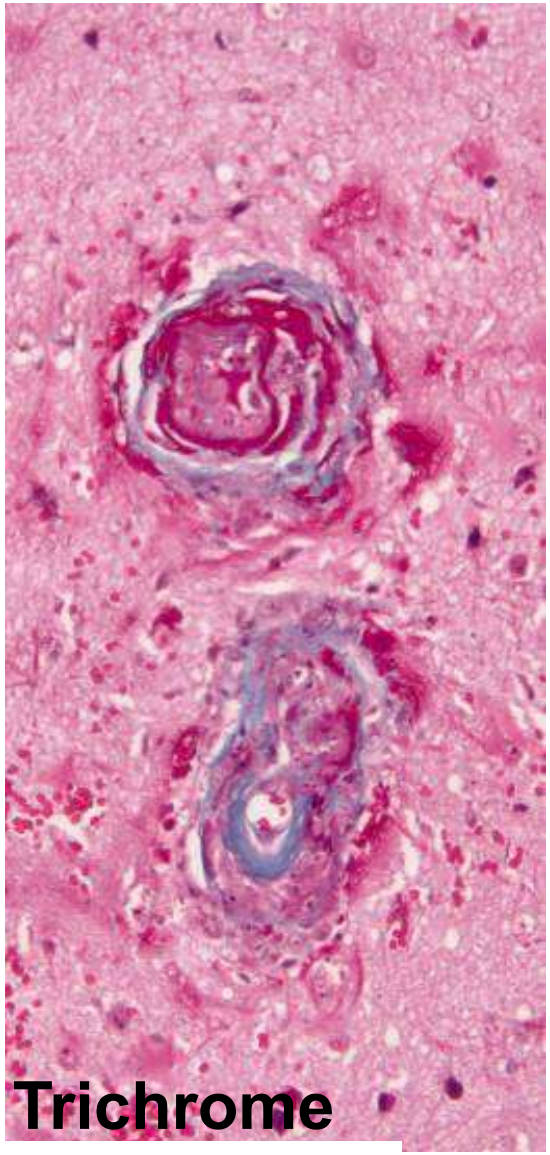




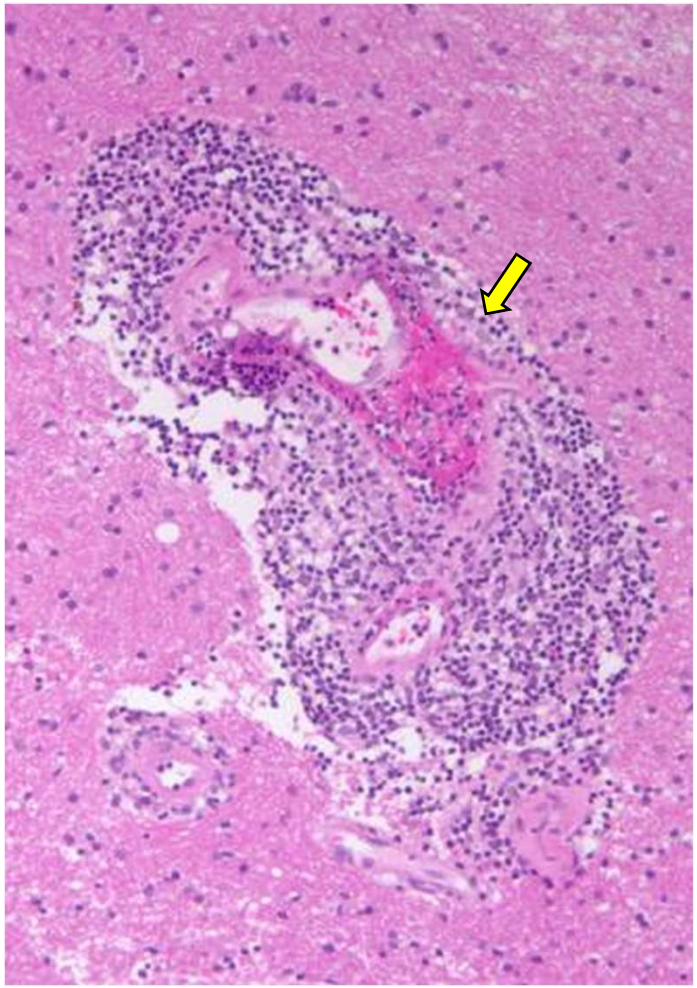
Granulomatous Vasculitis with Amyloid Angiopathy

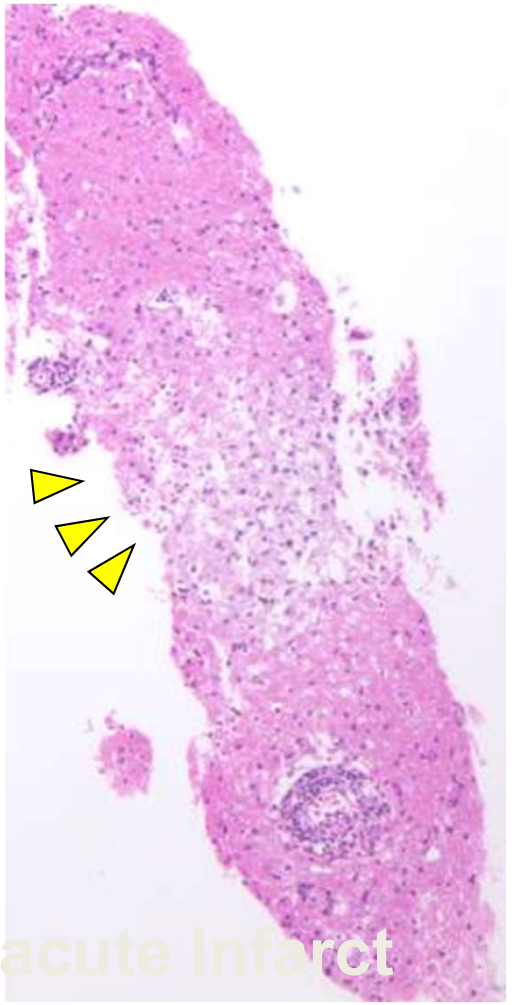




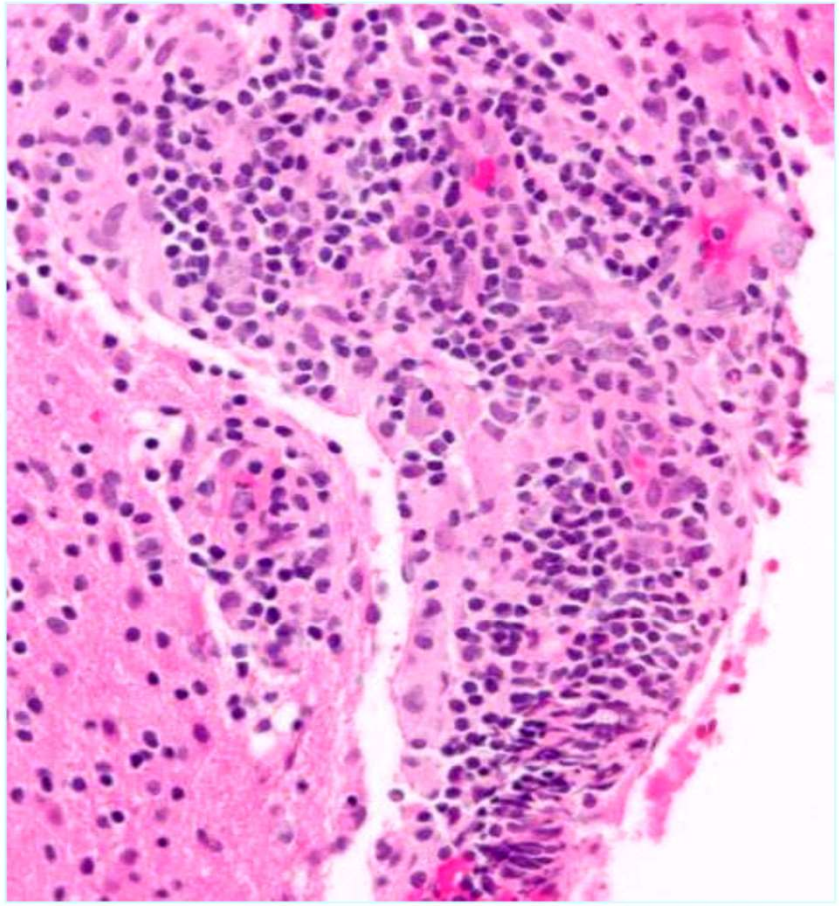


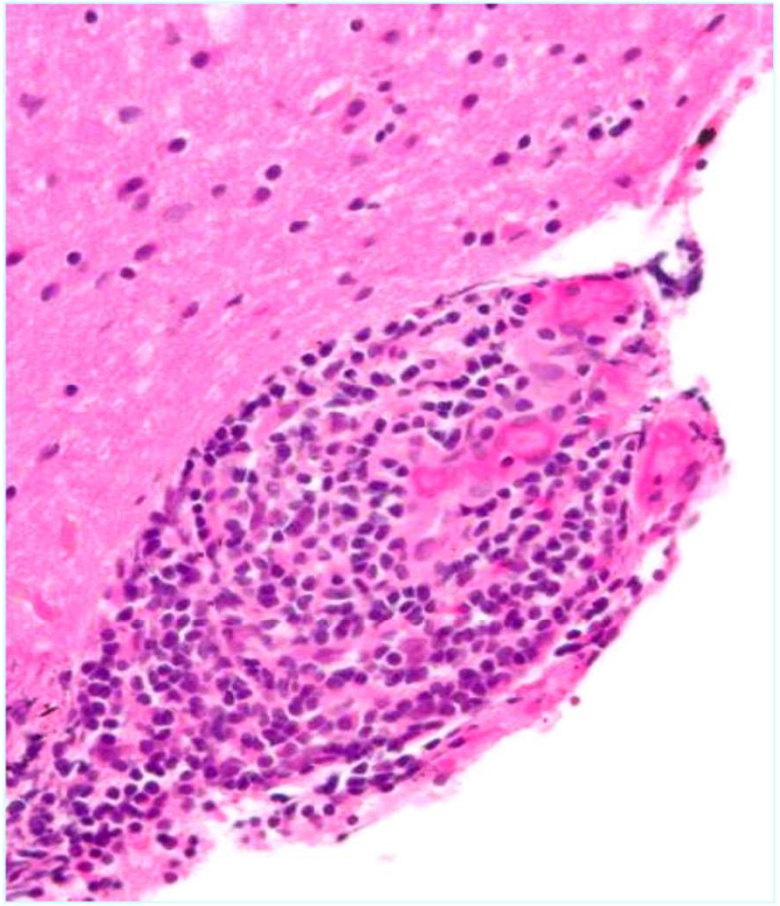
Necrotizing Vasculitis





Lymphocytic Vasculitis





Clinical Manifestations, Laboratory, Treatment and Outcome

Demographics in 101 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=101)	Biopsy confirmed (N=31)	Angiogram confirmed (N=70)
Gender			
Male/Female, number	43/58	17/14	26/44
Age at Diagnosis, years			
Median (Range)	47 (17-84)	46 (26-84)	47 (17-81)
Time from Onset to Diagnosis, years			
Median (Range)	0.1 (0.0-5.2)	0.2 (0.0-4.7)	0.1 (0.0-5.2)

Frequencies of Initial Main Presenting Symptom in 101 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=101)	Biopsy confirmed (N=31)	Angiogram confirmed (N=70)
Headache	30 (29.7%)	9 (29%)	21 (30%)
Altered Cognition	10 (9.9%)	7 (22.6%)	3 (4.3%)
Persistent neurologic deficit or stroke	39 (38.6%)	7 (22.6%)	32 (45.7%)
Aphasia	2 (2%)	2 (6.5%)	0 (0%)
Focal TIA's	6 (5.9%)	2 (6.5%)	4 (5.7%)
Ataxia	1 (1%)	0 (0%)	1 (1.4%)
Seizures	3 (3%)	0 (0%)	3 (4.3%)
Intracranial hemorrhage	7 (6.9%)	2 (6.5%)	5 (7.1%)
Paraparesis or quadriparesis	1 (1%)	1 (3.2%)	0 (0%)
Prominent constitutional symptoms	1 (1%)	0 (0%)	1 (1.4%)
Vertigo / Dizziness	1 (1%)	1 (3.2%)	0 (0%)

Results of Selected Laboratory Tests at Diagnosis in 101 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=101)	Biopsy confirmed (N=31)	Angiogram confirmed (N=70)
ESR, mm/hr			
Median (Range)	9.0 (0-110)	9.5 (0-110)	9.0 (1-107)
Serum CRP			
Normal/Elevated (18 patients tested)	12/6	3/3	9/3
Serum Rheumatoid Factor			
Negative/Positive (64 patients tested)	62/2	16/0	46/2
Serum Anti-cardiolipin antibody			
Negative/Positive (58 patients tested)	57/1	12/0	45/1
Serum Anti-nuclear Factor			
Negative/Positive (79 patients tested)	71/8	20/5	51/3

Cerebrospinal fluid findings in 77 patients with PCNSV

Salvarani et al, Ann Neurol 2007

	All Patients (N=77)	Biopsy confirmed (N=27)	Angiogram confirmed (N=50)
Leukocyte count (cell/mL)			
Median (Range)	5 (0-535)	17 (0-535)	4 (1-373)
Elevated Leukocyte count (>5 mononuclear cells/mL)			
Number of patients (%) (73 patients tested)	36 (49.3%)	19 (70.4%)	17 (37%)
Total Protein Concentration (mg/dL)			
Median (Range)	72 (15-1034)	98 (44-1034)	54 (15-166)
Elevated Total Protein Concentration (>45 mg/dL)			
Number of patients (%) (73 patients tested)	53 (72.6%)	26 (96.3%)	27 (58.7%)
Elevated Total Protein or Leukocyte Count or RBC			
Number of patients (%) (known for 74 patients)	66 (89.2%)	26 (96.3%)	40 (85.1%)

Therapy

Salvarani et al, Ann Neurol 2007; Current Opin Rheumatol 2012; Lancet 2012; Arthritis & Rheumatol 2015; Medicine, 2015

- No RCTs of medical management exist
- Treatment has been derived from therapeutic strategies used in other vasculitides
- Earlier reports suggested a poor prognosis in the majority of the cases

Adult PCNSV Treatment and Course

Salvarani et al, Arthritis & Rheumatol 2015

- In a cohort of 163 patients:

- *favorable response: in 85% of pts treated with GCs alone and in 80% of pts treated with GCs+CYC*
- *flares in 26% of pts, but were not associated with higher disability at last follow-up*
- *pts with gadolinium-enhanced lesions were associated with more frequent flares (OR 1.8)*
- *poor response to therapy: large-vessel involvement (OR 6.14) and cerebral infarcts at the diagnosis (OR 3.32)*

Therapy

Salvarani et al, Ann Neurol 2007; Lancet 2012; Neurology 2014; Arthritis & Rheumatol, 2015; Medicine, 2015; Semin Arthritis Rheum, 2015; Autoimm Rev 2019, 2020; de Boysson et al, J Rheumatol 2013; Rheumatology 2017; Stroke 2018

- Long-term remission (≥ 12 months after discontinuing therapy) in 21.5% of pts: negatively associated with gadolinium enhancing lesions (OR 0.20)
- In the Mayo and French series, maintenance therapy (AZA and MMF) was introduced in 34% and 49% of pts, mainly following CYC
- In the 2 series, maintenance therapy was associated with less disability and death at last follow-up, and lower relapse rate
- The results of the two studies, although limited by the retrospective design, support the use of maintenance therapy

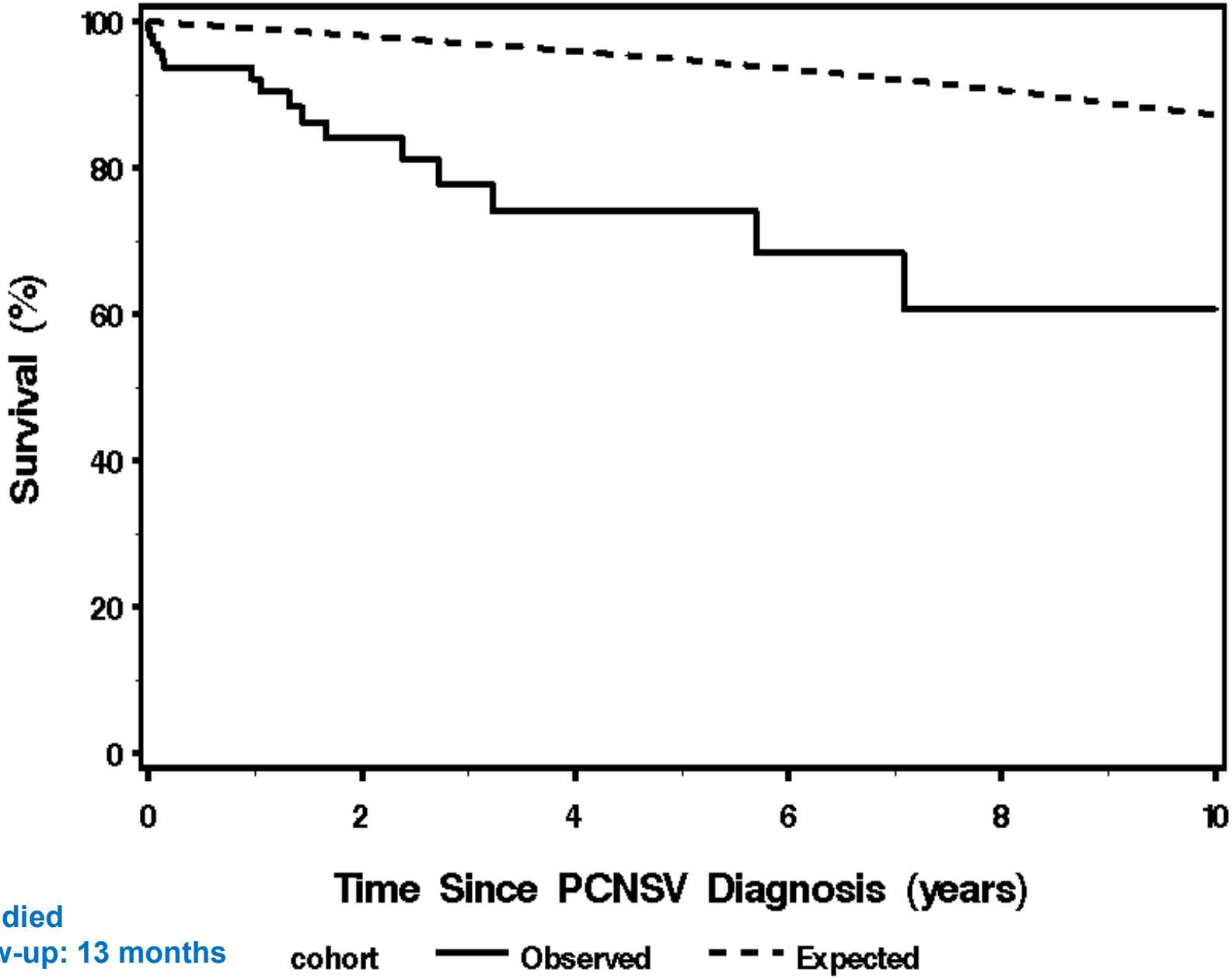
Therapy

Salvarani et al, Ann Neurol 2007; Lancet 2012; Neurology 2014; Arthritis & Rheumatol, 2015; Medicine, 2015; Semin Arthritis Rheum, 2015; Autoimm Rev 2019; de Boysson et al, J Rheumatol 2013; Rheumatol 2017, Stroke 2018

- The 26 pts treated with MMF at diagnosis or during flares had less severe disability at last follow-up than the 84 receiving CYC and PDN (mRS 1-3: 85% vs 63%, p = 0.05)
- TNFα blockers and rituximab have succesfully been used to treat some cases resistant to GCs and ISs
- Treatment course: 12-18 months
- Serial MRI and MRA, and neurological and CSF examinations are useful to monitor disease course

Age- and sex-adjusted survival of patients with PCNSV versus estimated survival of the US white population

Salvarani et al, Ann Neurol 2007



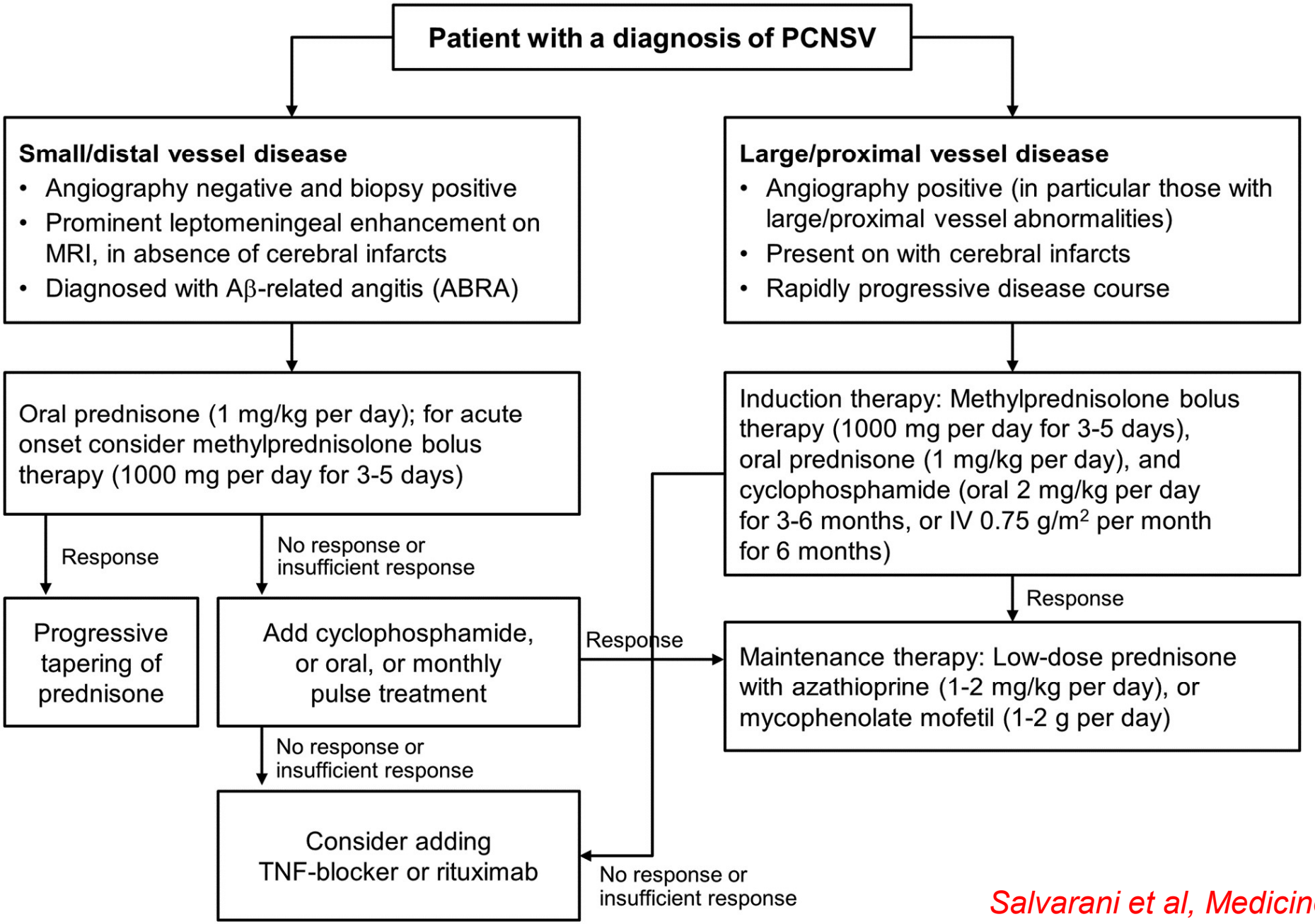
- **P < 0.001**
- **17/101 (17%) died**
- **Median follow-up: 13 months**

Characteristics associated with increased mortality (Univariate Cox model)

Salvarani et al, Arthritis & Rheumatology, 2015

Characteristics	HR	95% CI	P
Age (per 10-year difference)	1.39	1.05-1.85	0.022
Male vs female	0.80	0.34-1.88	0.61
Main symptom at presentation			
Headache or constitutional symptom	1.00		
Focal manifestation vs headache or constitutional symptom	2.42	0.69-8.52	0.17
Cognitive disorder vs headache or constitutional symptom	3.40	0.82-14.0	0.090
Diagnosis by angiography only compared with biopsy	**3.28**	**1.09-9.82**	**0.034**
MRI findings			
Infarct vs no infarct	**4.44**	**1.61-12.2**	**0.004**
Gadolinium-enhanced lesions or meninges vs normal or minimal changes	**0.20**	**0.06-0.67**	**0.009**
Large-vessel involvement vs small vessel involvement	**4.98**	**1.47-16.9**	**0.01**
Increased cerebrospinal fluid protein level (> 70 mg/dl)	1.29	0.49-3.39	0.61
Cerebral amyloid angiopathy, presence vs absence	0.17	0.02-1.33	0.092
Prednisone alone vs cyclophosphamide and prednisone	1.03	0.46-2.35	0.94
Rapid (< 1 mo) vs slow onset (> 1 mo)	1.27	0.55-2.94	0.57

Suggested Treatment Algorithm for Adult PCNSV



Salvarani et al, Medicine, 2015

SUBSETS OF PCNSV

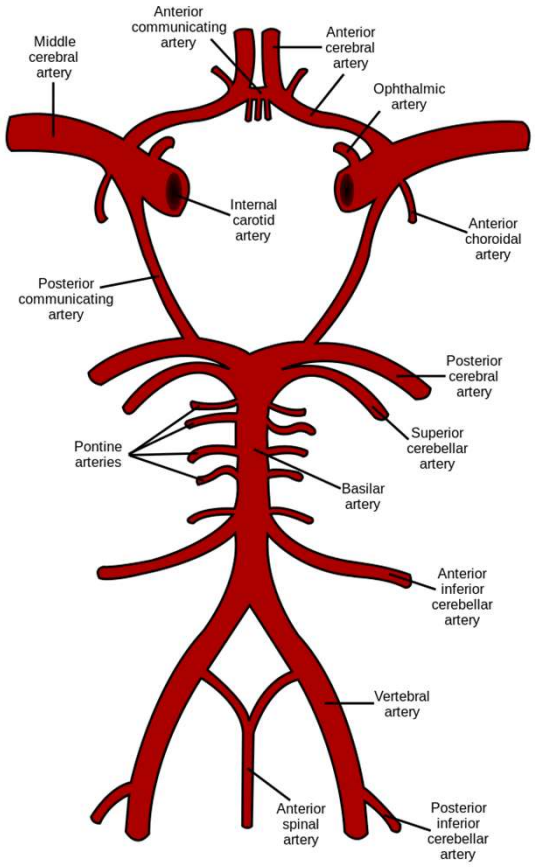
PCNSV: is it a single disease?

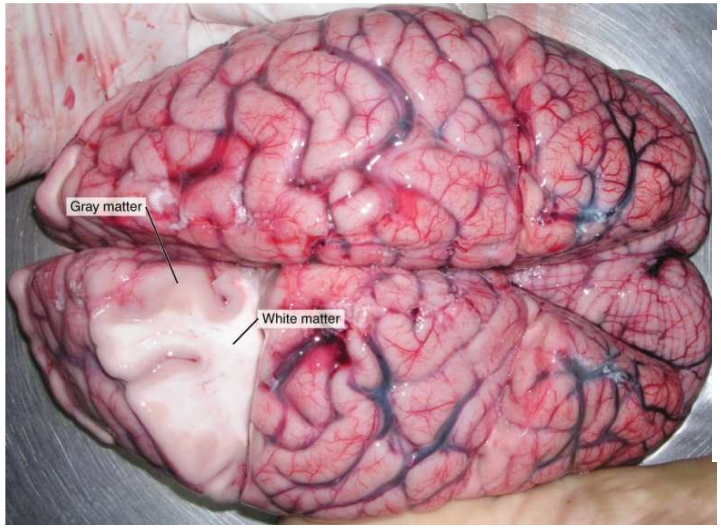
Hunder, Salvarani and Brown, Ann Neurol 2010; Salvarani et al, Lancet 2012, Medicine 2015

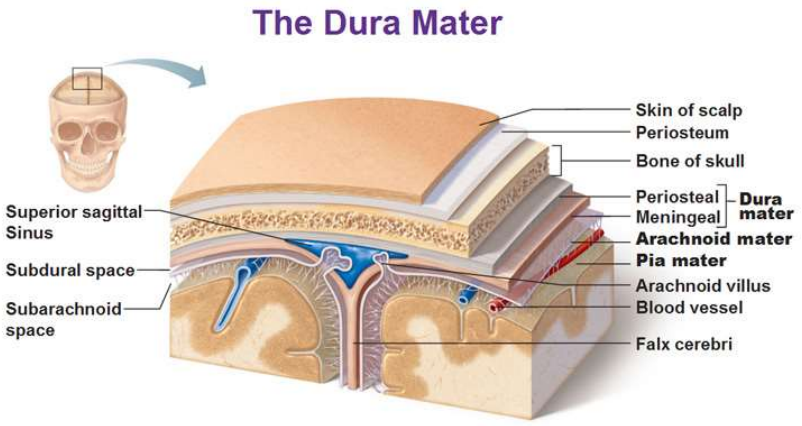
PCNSV is a heterogeneous condition and outcomes are related to:

- Size of the vessels involved in the inflammatory process:

- *large/proximal vessels versus small/distal vessels*





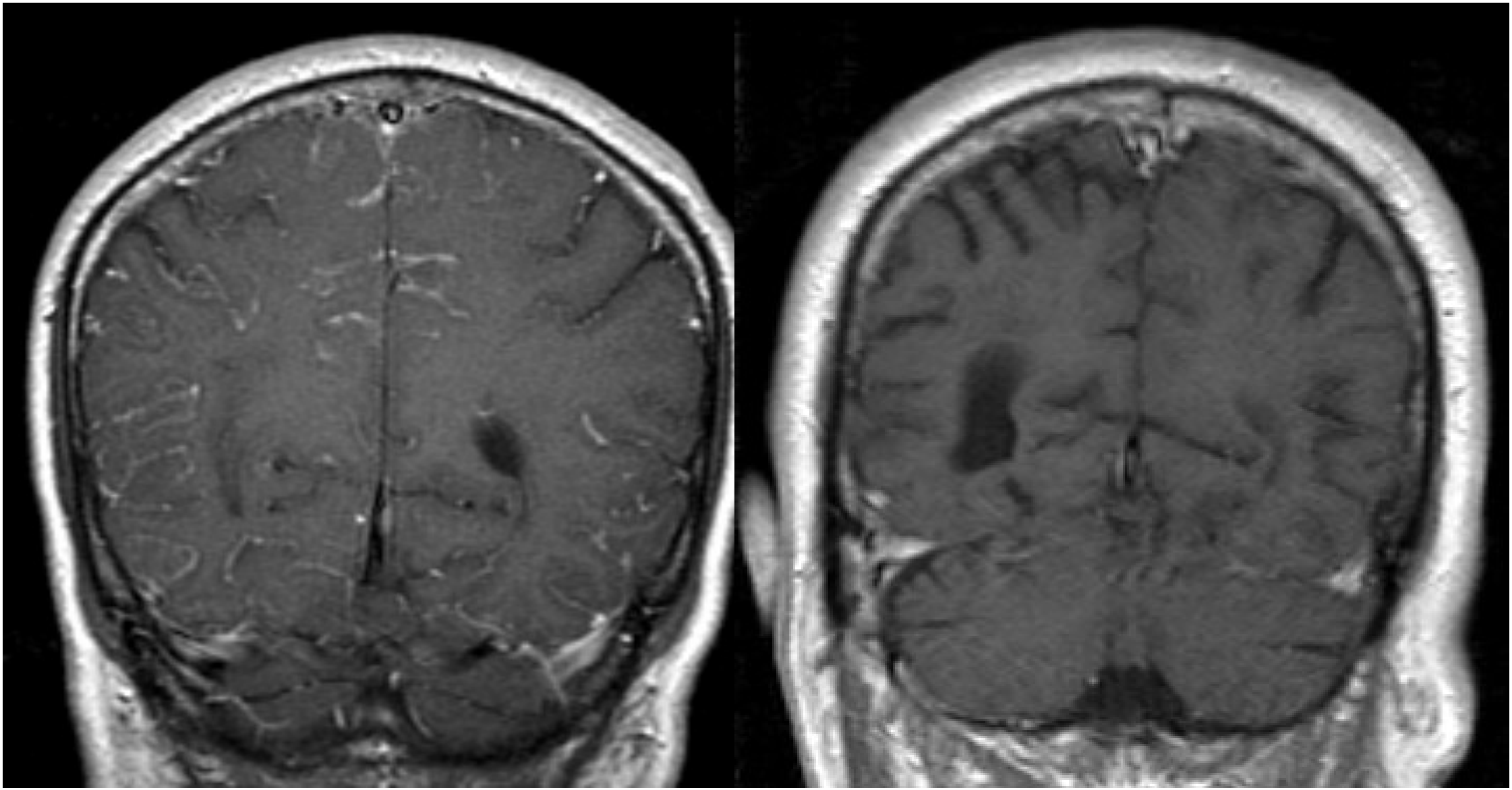


Small-Vessel Vasculitis

Salvarani et al, Arthritis Rheum 2008, Medicine 2008 and 2015,Rheumatology 2008, Neurology 2013

Characteristics:

- rapid onset of neurologic deficits
- frequent cognitive dysfunction at presentation
- more CSF abnormalities (marked elevation in total protein level)
- frequent presence at MRI of meningeal or parenchymal enhancing lesions
- MRA and cerebral angiography often negative
- CNS biopsy showing vascular inflammation
- association with amyloid angiopathy (ABRA)
- good response to GCs and/or immunosuppressive therapy
- favorable neurologic course



Aβ-related angiitis (ABRA)

Salvarani et al, Rheumatology 2008, Lancet 2012, Neurology 2013, Medicine 2016;
Scolding et al, Brain 2005; Hermann et al, Neurology 2011; Piazza et al, Ann Neurol 2013

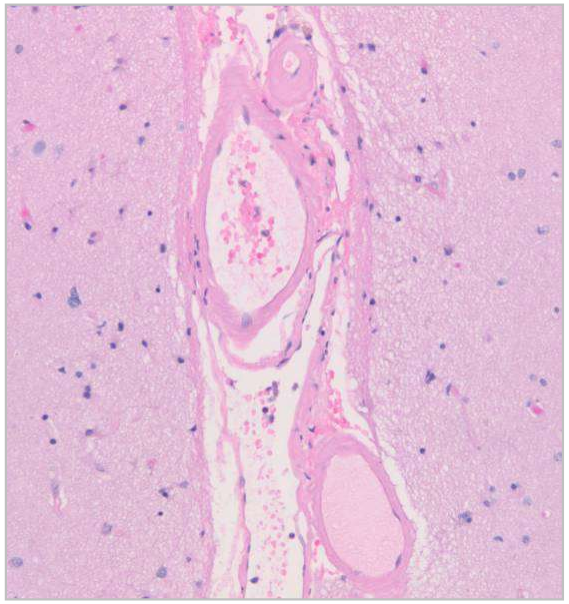
- Vascular inflammation in ABRA more than Aβ deposition has a major role in determining disease manifestations at presentation
- ABRA represents a defined subset of PCNSV characterized by:

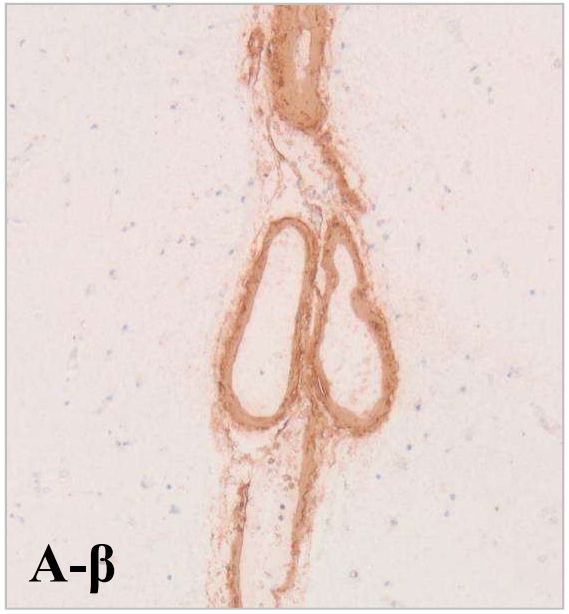
- *older age at disease onset*
- *high frequency of cognitive dysfunction and seizures/spells*
- *high spinal fluid protein levels*
- *high frequency of ehnancing leptomeningeal lesions*
- *favorable response to GCs alone or combined with CYC*

- An immune response directed against Aβ (presence of Abs anti-Aβ in the CSF) may represent a common disease mechanism shared by ABRA and amyloid-related imaging abnormalities (ARIA) reported in AD immunotherapy

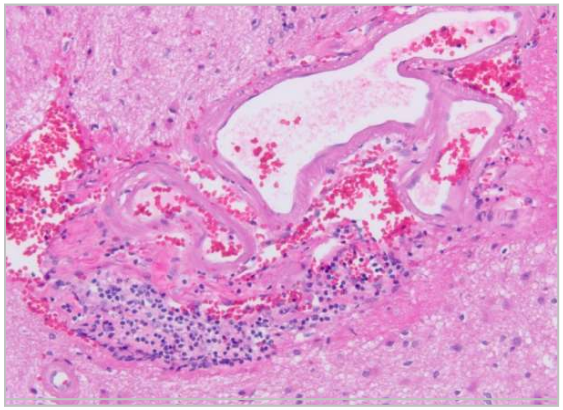
Vascular Cerebral βA-Deposition Spectrum

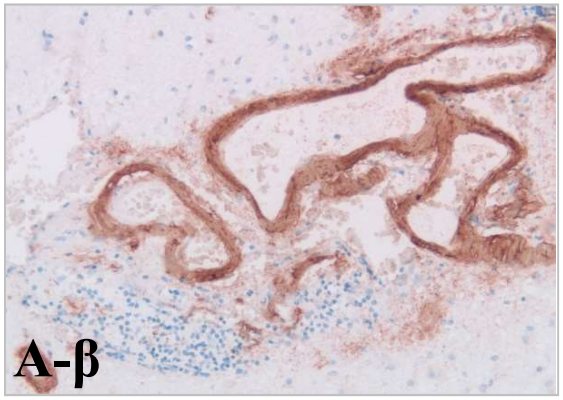
CAA

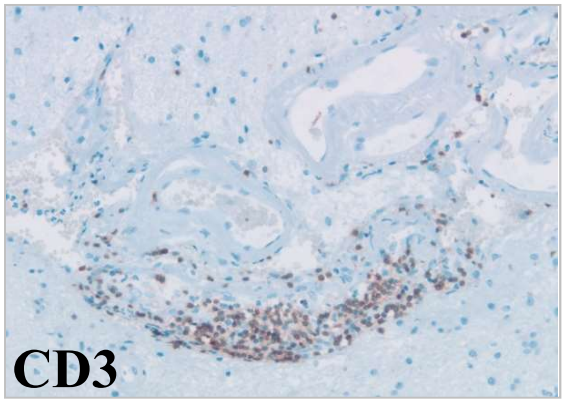




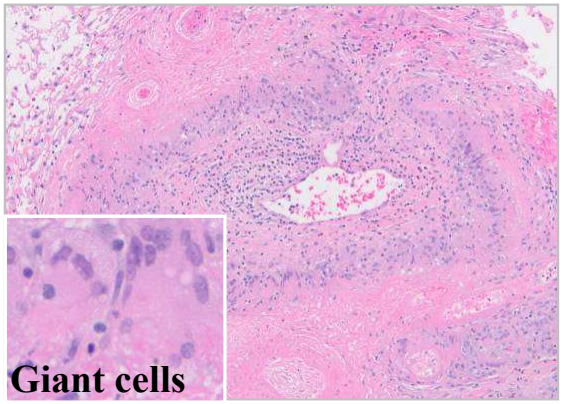
CAA-RI
perivascular inflammation

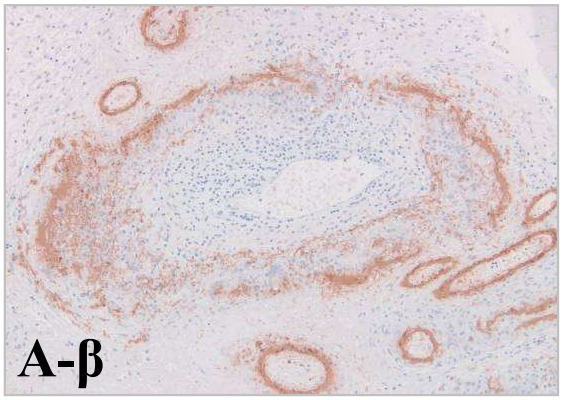


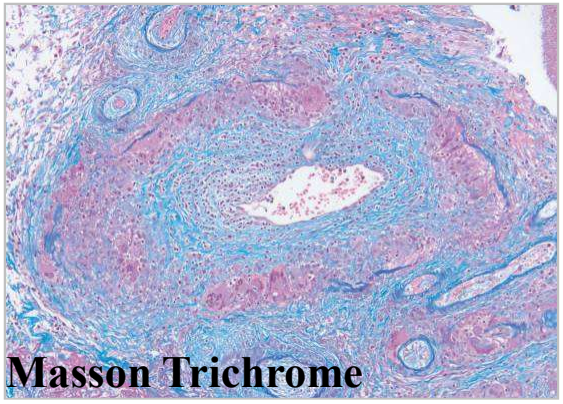




ABRA



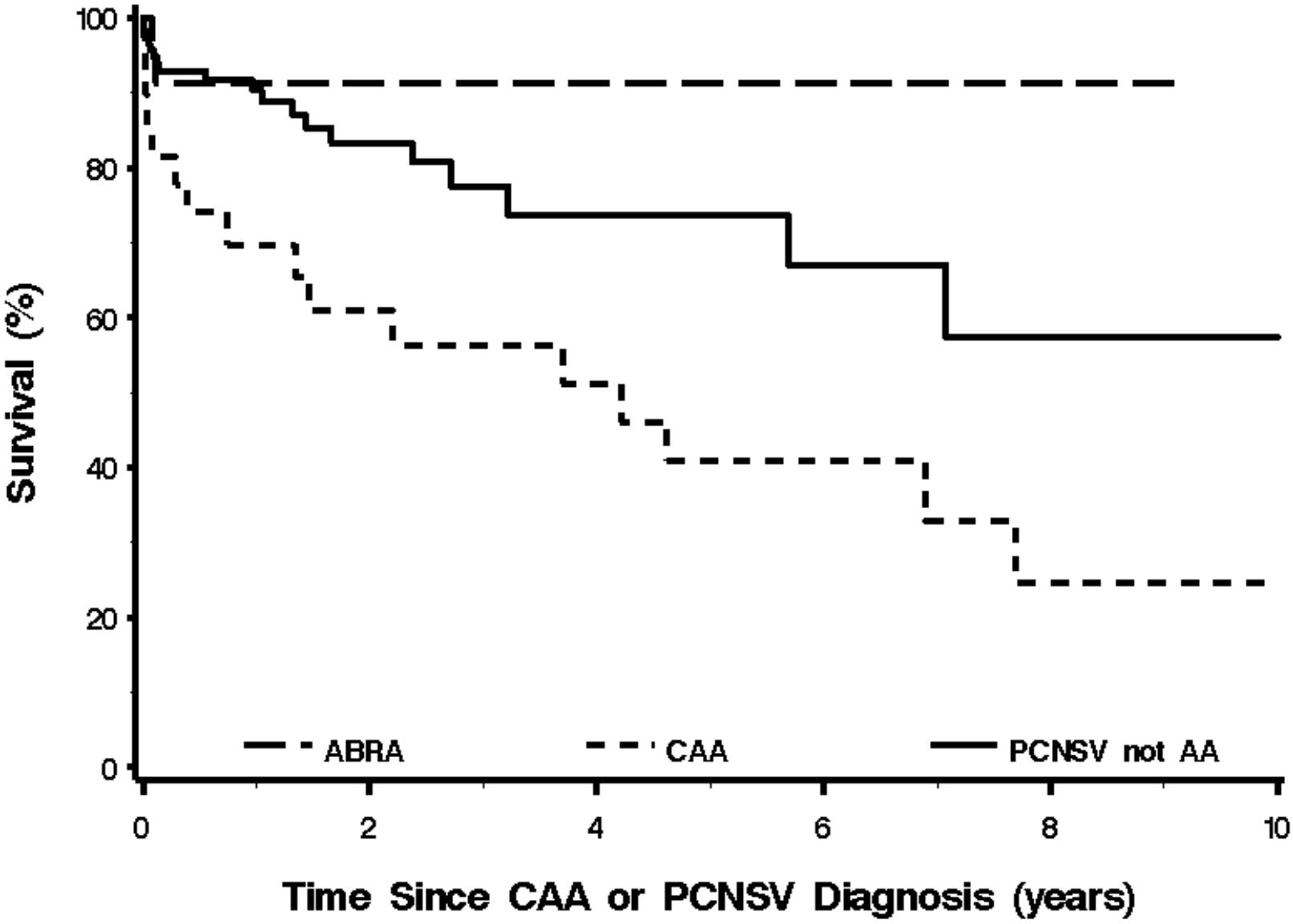




Treatment and outcome

Salvarani et al, Neurology 2013

	ABRA (n=28)	CAA (n=40)	PCNSV (n=118)
Initial treatment			
Prednisone alone	10 (36%)	-	51 (43%)
Prednisone + CYC	9 (32%)	-	53 (45%)
No therapy	5 (18%)	-	1 (1%)
Patients responding to the treatment	*19/23 (83%)*	*-*	*95/116 (82%)*
Patients without relapse/recurrence	*23 (82%)*	*-*	*86 (73%)*
Rankin disability score at last follow-up			
0-3 (no, mild-moderate)	*22 (79%)*	*13 (32%)*	*91 (77%)*
4-6 (severe, death)	*6 (21%)*	*27 (67%)*	*27 (23%)*


100
80
60
40
20
0
Survival (%)
ABRA
CAA
PCNSV not AA
0
2
4
6
8
10
Time Since CAA or PCNSV Diagnosis (years)

Long-term remission, relapses and maintenance therapy in adult primary central nervous system vasculitis: A single-center 35-year experience

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Table 5
Outcomes of the 71 patients with pathological evidence of vasculitis according to the histopathological pattern and the presence of ABRA[a].

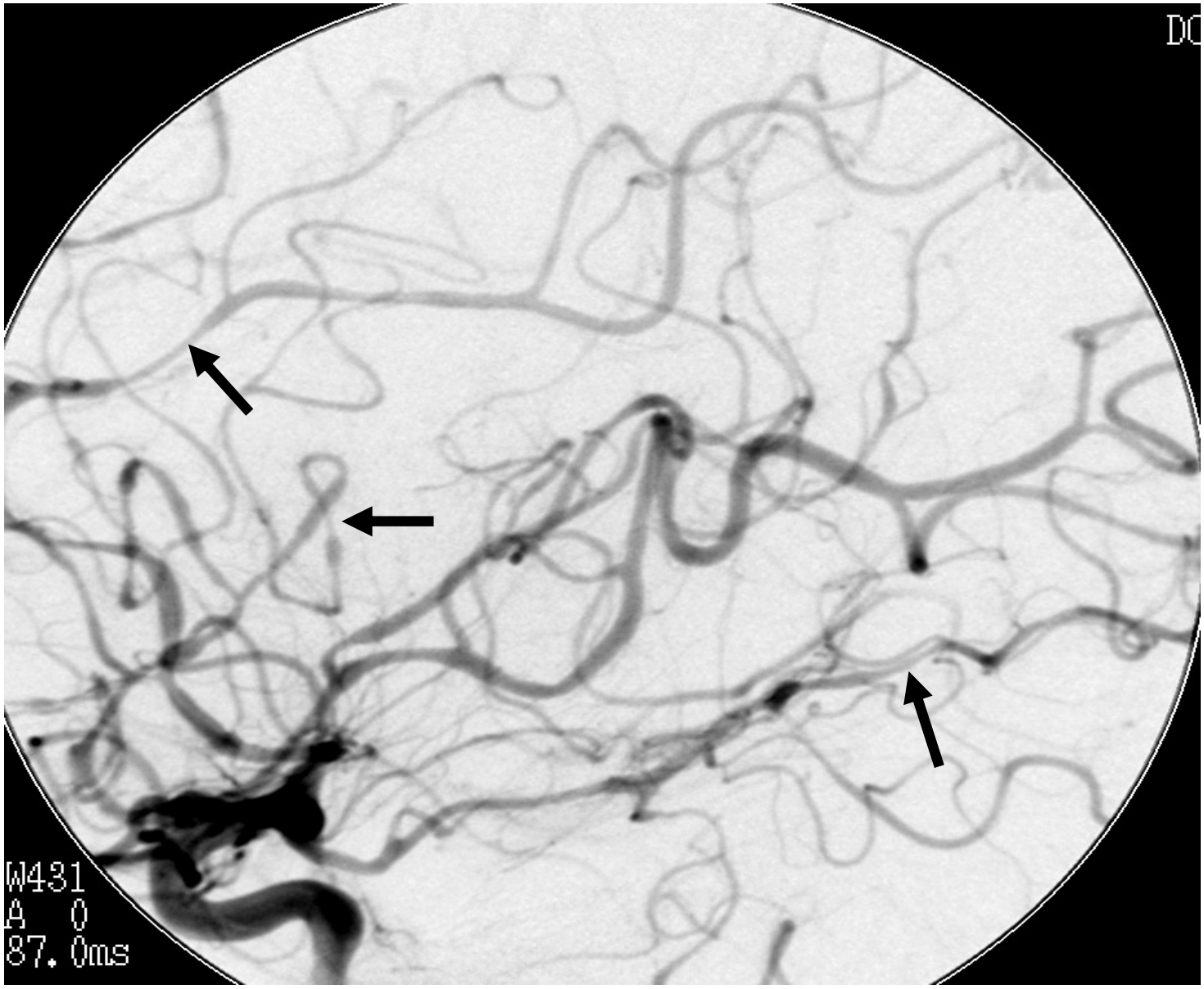
Outcome	Lymphocytic (n = 17)	Granulomatous (n = 44)	Necrotizing (n = 10)	ABRA (n = 24)	Without aβ deposits (n = 47)
Relapses	7/15 (47)	15/42 (36)	4/9 (44)	7/23 (30)	19/43 (44)
Response to therapy[b]	11/13 (85)	28/35 (77)	7/7 (100)	19/23 (83)	37/42 (88)
Therapy suspension	4/16 (25)	14/42 (33)	4/9 (44)	9/23 (39)	13/44 (29.5)
Long-term remission	0/17	9/44 (20)	2/10 (20)	5/24 (21)	6/47 (13)
Rankin score 4–6	0/17	18/44 (41)	3/10 (30)	10/24 (42)	11/47 (23)
Deaths	0/17	15/44 (34)	1/10 (10)	8/24 (33)	8/47 (17)

Rapidly progressive PCNSV

Salvarani et al, Rheumatology 2011

- 11 cases (8.4%) had a rapidly progressive course of PCNSV: Rankin 5 (severe disability) or 6 (stroke death) at diagnosis or within 6 months after the diagnosis:

- *frequent presence of paraparesis/quadriparesis at presentation*
- *angiographic evidence of bilateral, large-vessel vasculitis*
- *MRI evidence of multiple and bilateral cerebral infarctions, involving both the cortex and subcortex*
- *granulomatous or necrotizing histopathological patterns*
- *poor response to treatment*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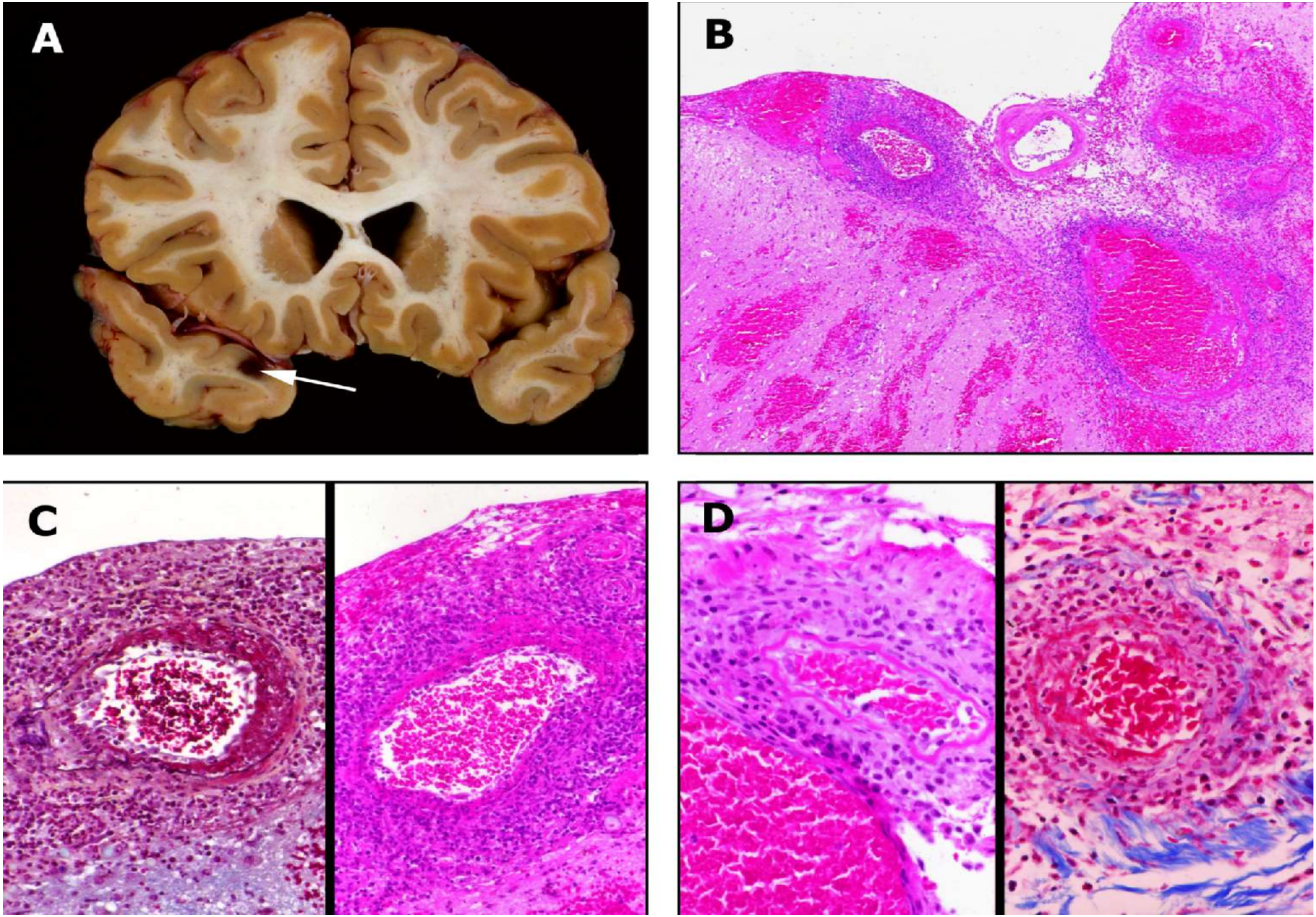

A
B
C
D

Other subsets of PCNSV

- 12.2% of patients had evidence of IH at presentation:

- intracerebral hemorrhage was more common than subarachnoid hemorrhage

- association with necrotizing vasculitis

Salvarani et al, Arthritis Rheum 2011

- about 4-7% of patients present with a solitary tumor-like mass lesion:

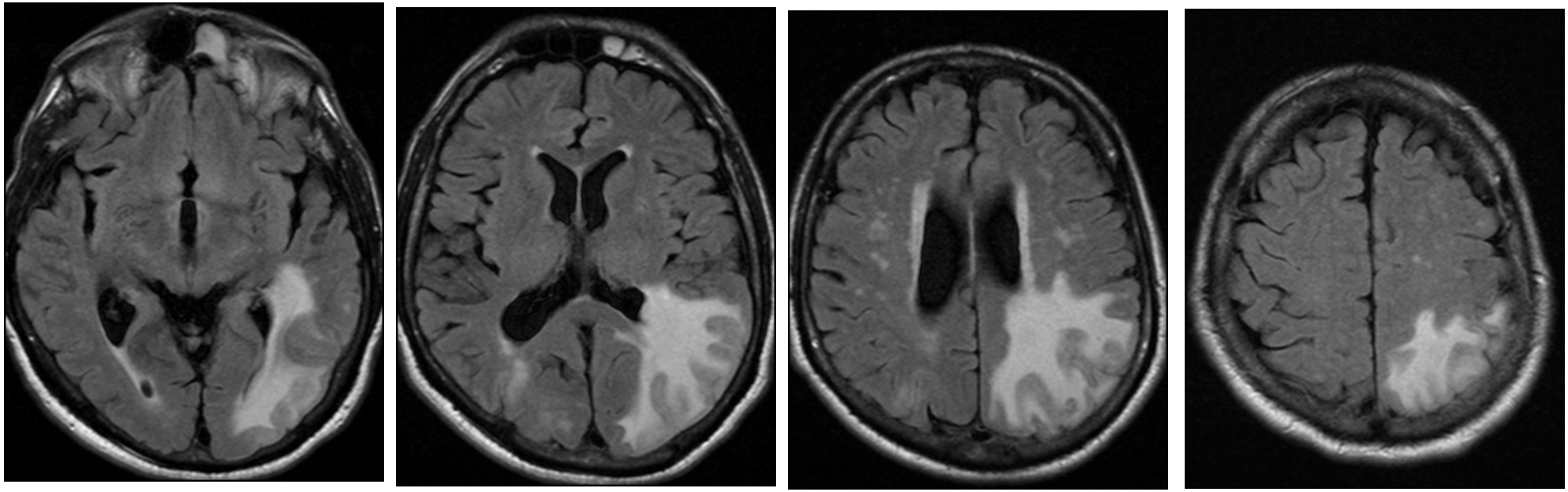
- Mayo Clinic PCNSV series: 13/191 (6.8%) over a 35-year period

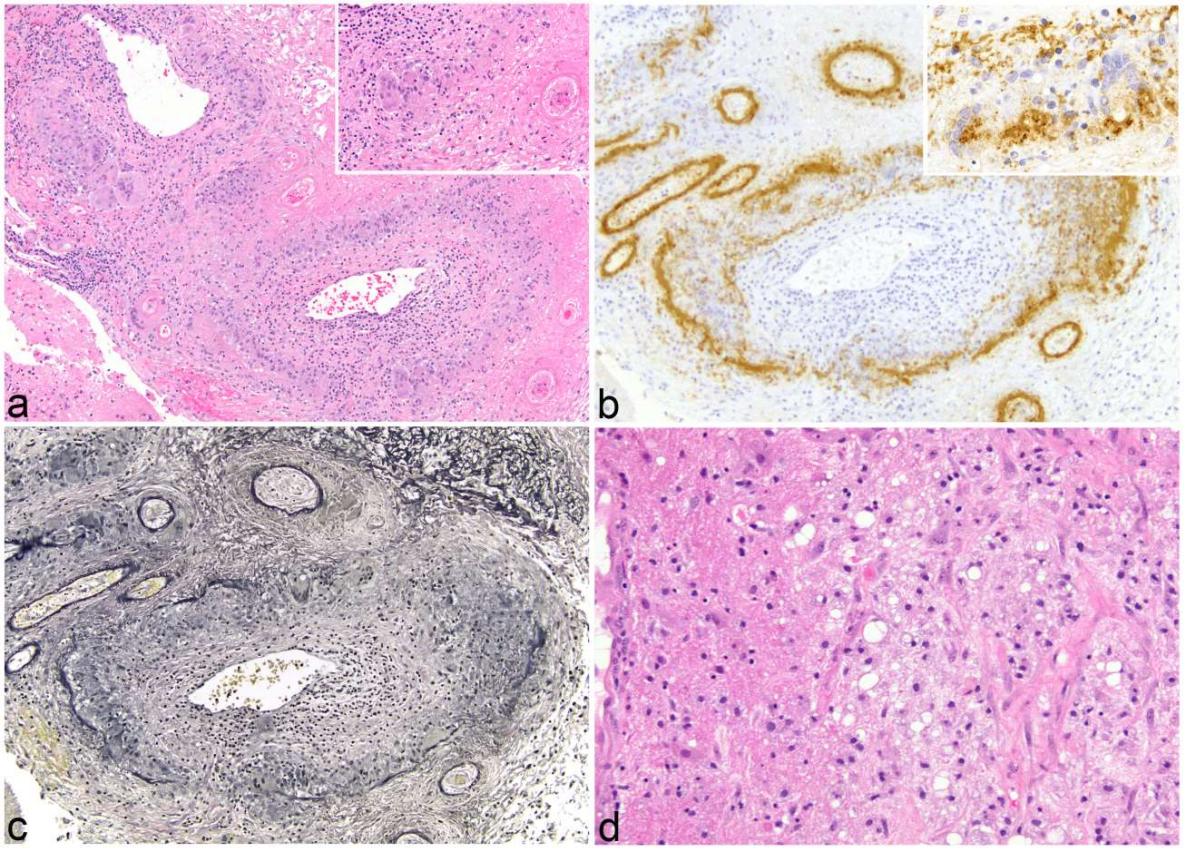
- more frequently seizures at presentation (46%)

- association also with CAA (29%), Mayo Clinic series: ABRA 53.8%

- immunosuppressive therapy is associated with a favourable outcome and may obviate the need for surgery

Molloy et al, Ann Rheum Dis 2008; de Boysson et al, Stroke 2016; Salvarani et al, J Autoimmun 2018





MRI and pathologic findings of a case with ABRA and tumor-like presentation:

MRI showing infiltrative white matter process mimicking low grade glioma. FLAIR-weighted MRI images show infiltrative white matter T2 hyperintesity in left temporal/parietal lobes with associated mass effect; mild contralateral infiltrative T2 hyperintensity is also present. The images are negative for enhancement

It illustrate extensive vasculitic involvement of leptomeningeal arteries (a) with granulomatous inflammation with giant cells (inset). Severe beta-amyloid deposition is present in the vascular wall (b) and amyloid is present inside the giant cells.The Verhoeff-Van Gieson stain for elastic fibers highlights the destruction of the internal elastic lamina (c). Subacute organizing infarct with dense macrophage infiltration contributes to the mass-like appearance of the lesion (d). Magnification a x100, b,c,d x140, inset a x200, inset b x400

Salvarani et al, J Autoimmun 2018

Other subsets of PCNSV

- spinal cord involvement is present in 5% of the cases:
  - *thoracic cord is predominantly affected*
  - *it is associated with brain vasculitis*
  - *good response to immunosuppressive therapy*

Salvarani et al, Neurology 2008

- about 6% of patients associate lymphomas:
  - *HL more frequent than NHL*
  - *association with granulomatous vasculitis*
  - *simultaneous diagnosis suggesting a paraneoplastic immunological mechanism*
  - *more frequent presence of leptomeningeal enhancement*
  - *more severe cerebral vasculitis with increased disability and mortality*

Salvarani et al, Neurology 2018

DIFFERENTIAL DIAGNOSIS

Discriminating Features of PCNSV and RCVS

Characteristics	PCNSV	RCVS
Precipitating factor	None	Onset in postpartum phase or after exposure to vasoactive substances
Onset	More insidious, progressive course	Acute onset followed by a monophasic course
Headaches	Chronic and progressive	Acute, thunderclap type
CSF findings	Abnormal	Normal to near normal
MRI	Abnormal in almost all patients	Normal in 70% of patients
Angiography	It may be normal, otherwise diffuse abnormalities often indistinguishable from RCVS	Always abnormal, strings of beads appearance of cerebral arteries, abnormalities reversible within 6-12 weeks
Cerebral biopsy	Vasculitis	No vasculitic changes
Drug treatment	Prednisone with/without cytotoxic agents	Nimodipine

Salvarani et al, Lancet 2012

Salvarani C, Brown RD and Gene GG, Lancet 2012

Panel: Causes of secondary CNS vasculitis

Viral infections
Varicella zoster virus, HIV, hepatitis C virus, cytomegalovirus, parvovirus B19

Bacterial infections
Treponema pallidum, Borrelia burgdorferi, Mycobacterium tuberculosis, Mycoplasma pneumoniae , Bartonella henselae, Rickettsia spp

Fungal infections
Aspergillosis, mucormycosis, coccidioidomycosis, candidosis

Parasitic infections
Cysticercosis

Systemic vasculitides
Wegener's granulomatosis, Churg-Strauss syndrome, Behçet's disease, polyarteritis nodosa, Henoch-Schönlein purpura, Kawasaki disease, giant-cell arteritis, Takayasu's arteritis

Connective tissue diseases
Systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, dermatomyositis, mixed connective tissue disease

Miscellaneous
Antiphospholipid antibodies syndrome, Hodgkin's and non-Hodgkin lymphomas, neurosarcoidosis, inflammatory bowel disease, graft-versus-host disease, bacterial endocarditis, acute bacterial meningitis, drug-induced CNS vasculitis (cocaine, amphetamine, ephedrine, phenylpropanolamine)

Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment

Lancet Neurol 2009; 8:731–40

Don Gilden, Randall J Cohrs, Ravi Mahalingam, Maria A Nagel

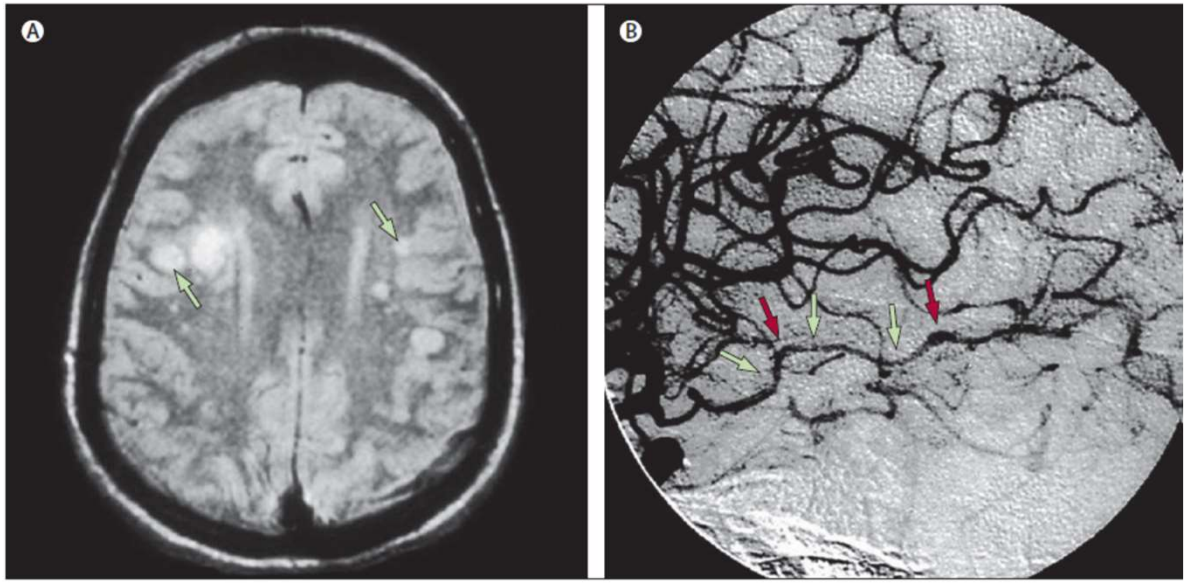


Figure 2: MRI scan and cerebral angiogram of patients with VZV vasculopathies

Characteristics:

- VZV is the only human virus shown to replicate in arteries
- Vasculopathies caused by VZV are indicative of a productive virus infection in cerebral arteries after either reactivation of VZV or primary infection
- The pathology of intracerebral VZV vasculopathy is characterized by granulomatous arteritis
- It can cause ischemic infarction of the brain and spinal cord and can be unifocal or multifocal with deep-seated and superficial infarctions
- Involvement of both large and small arteries is more common than that of either alone
- Anti-VZV IgG antibody in the cerebrospinal fluid is found more frequently than VZV DNA

Take Home Messages

- PCNSV is an heterogeneous disorder
- neurological manifestations commonly include headache, altered cognition, persistent neurologic deficit, or stroke
- serological markers of inflammation are usually normal
- CSF is typically abnormal
- the diagnosis is unlikely in case of a normal brain MRI
- Lymphomas (more often HL) may be diagnosed simultaneously with PCNSV, suggesting a paraneoplastic immunological mechanism

Take Home Messages

- Pts with lymphoma have a more severe cerebral vasculitis with increased neurological disability and mortality
- about 7% of patients present with a solitary tumor-like mass lesion responding to immunosuppressive therapy
- Biopsy of CNS tissue showing vasculitis is the only definitive test
- Angiography is often used for diagnosis even though it has only moderate sensitivity and specificity
- Angiography results should always be interpreted in conjunction with clinical, laboratory or MRI findings

Take Home Messages

- The size of the vessels involved is varied and influences outcomes and responses to treatment
- 83% of patients respond to the treatment (GCs alone or GCs + CYC)
- MMF may represent an effective treatment less toxic than CYC
- RTX may be an effective therapeutic option in pts refractory to conventional ISs
- Maintenance therapy with AZA, MMF or MTX is effective
- Early recognition is important because treatment with GCs with or without cytotoxic drugs is effective in most of the patients and may prevent serious outcomes

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Divisione di Reumatologia e Cattedra di Reumatologia,
Università of Modena and Reggio Emilia e Policlinico Universitario di Modena


Thank
You!
Sunset on the sea from
the roof terrace of my
house in Kavousi,
Phalasarna, Crete