CASE REPORT

Reversible Cerebral Vasoconstriction Syndrome or Primary Angiitis of the Central Nervous System?

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ABSTRACT: ***Background:*** Reversible Cerebral Vasoconstriction Syndrome (RCVS) may present as thunderclap headache (TCH), accompanied by reversible cerebral vasospasm and focal neurological deficits, often without a clear precipitant. RCVS may be mistaken for Primary Angiitis of the Central Nervous System (PACNS) due to the presence of similar angiographic features of segmental narrowing of cerebral arteries. We discuss the clinical features of a young female migraine patient who developed TCH and was found to have RCVS following initial treatment with corticosteroids for PACNS, in the context of a systematic review of the available medical literature. ***Methods:*** A Medline™ search was performed to identify all case reports since 1966 describing RCVS and PACNS that provide sufficient clinical detail to permit diagnostic classification according to published criteria. RCVS included case studies in which there was angiographic or transcranial Doppler ultrasound evidence of near-to-complete resolution of cerebral vasoconstriction in the absence of a well-recognized secondary cause. PACNS included reports of histologically confirmed PACNS either through biopsy or necropsy. ***Results:*** Reversible Cerebral Vasoconstriction Syndrome occurs primarily in females and is characterized by sudden, severe headache at onset, normal CSF analysis, vasoconstriction involving the Circle of Willis and its immediate branches, and angiographic or TCD ultrasound evidence of near-to-complete vasospastic resolution within 1-4 weeks. It occurs typically in the context of vasoconstrictive drug use, the peripartum period, bathing, and physical exertion. ***Conclusion:*** Initial and follow-up (within 4 weeks) non-invasive angiographic studies are indicated in patients who present with TCH or who have clinical presentations that could be consistent with RCVS or PACNS in the absence of a well-recognized secondary cause, such as subarachnoid haemorrhage. Early reversibility of cerebral vasospasm is the key neuroradiological feature that supports the clinical diagnosis of RCVS.

RÉSUMÉ: Syndrome de vasoconstriction cérébrale segmentaire réversible ou angéite primitive du système nerveux central? ***Contexte :*** Une céphalée en coup de tonnerre (CCT) peut être la manifestation initiale du syndrome de vasoconstriction cérébrale segmentaire réversible (SVCSR), accompagnée par un vasospasme cérébral réversible et des déficits neurologiques focaux, souvent sans facteur précipitant évident. Le SVCSR peut être confondu avec l'angéite primitive du système nerveux central (APSNC) à cause de la présence de manifestations angiographiques similaires dans ces deux pathologies, soit des rétrécissements segmentaires au niveau d'artères cérébrales. Nous discutons des manifestations cliniques observées chez une jeune femme migraineuse qui a consulté pour une CCT et chez qui on a diagnostiqué un SVCSR après un traitement initial par des corticostéroïdes pour une APSNC. Nous présentons également une revue systématique de la littérature médicale actuelle sur ce sujet. ***Méthodes :*** Nous avons effectué une recherche dans la base de données Medline™ afin d'identifier toutes les observations qui décrivent le SVCSR et l'APSNC depuis 1966 et qui fournissent suffisamment de détails cliniques pour permettre une classification diagnostique selon les critères publiés. Nous avons relevé des études de cas de SVCSR comportant des données d'angiographie ou d'échographie Doppler transcrânienne (DTC) sur la régression complète ou presque complète de la vasoconstriction cérébrale, en l'absence d'une cause secondaire évidente. Nous avons identifié des comptes-rendus d'APSNC confirmées en anatomopathologie sur des spécimens obtenus soit par biopsie ou par autopsie. ***Résultats :*** Le SVCR survient principalement chez les femmes et il se caractérise par une céphalée subite, sévère d'amblée, une analyse du LCR normale, une vasoconstriction impliquant l'hexagone de Willis et ses branches immédiates et une régression complète ou quasi complète du vasospasme en 1 à 4 semaines constatée à l'angiographie ou à l'échographie DTC. Il survient typiquement dans le contexte de la prise de médicaments vasoconstrictifs, en période péripartum, lors d'un bain ou lors de l'activité physique. ***Conclusion :*** On devrait effectuer des études angiographiques non effractives au départ et au cours du suivi chez les patients qui consultent pour une CCT ou dont le tableau clinique est compatible avec un SVCSR ou une APSNC en l'absence d'une cause secondaire évidente, telle une hémorragie sous-arachnoïdienne. La réversibilité précoce du vasospasme cérébral est la manifestation neuroradiologique clé qui étaie le diagnostic clinique du SVCSR.

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Reversible Cerebral Vasoconstriction Syndrome (RCVS) is an under-recognized, often misdiagnosed condition, first described according to its current definition by Call et al (1988) to categorize patients with sudden severe headaches, idiopathic cerebral ischemia and concomitant fully reversible vasoconstriction prominently involving the Circle of Willis or its immediate branches.[1] Until recently RCVS was understood through the eponymous nomenclature of Call-Fleming Syndrome.[2] Reversible Cerebral Vasoconstriction Syndrome is most common in women ages 20-50 years old and has been observed in relation to the post-partum period,[3] eclampsia,[4] bathing,[5,6] pheochromocytoma,[7] and associated with the use of certain vasoactive drugs.[8-12] Often there is no identifiable precipitant.

Due to the inadequately understood pathophysiological mechanisms underlying reversible cerebral vasospasm, a number of other disorders tantamount to RCVS have been identified according to clinical context, including: benign angiopathy of the CNS;+drug induced vasospasm; post-partum angiopathy; crash migraine and migrainous angiitis.[8,13-16] A lack of a shared nosology both within and across disciplines has limited the clinical recognition, pathophysiological understanding and treatment of this syndrome. Since its first description, recent efforts are being made towards the development of a unified classification of the associated conditions.[2]

The International Classification of Headache Disorders, 2nd Edition (ICHD-2)[17] define headaches associated with benign/reversible angiopathy of the CNS similar to Call et al (1988): Diffuse, severe headache of abrupt or progressive onset; with or without neurological deficits and/or seizures; 'strings and beads' appearance on angiography in the absence of subarachnoid haemorrhage; but add, according to Criteria D, that headache (and neurological deficits, if present) resolves spontaneously within two months. This necessity for resolution of neurological deficits fails to acknowledge case examples of patients with spontaneous angiographic resolution, yet lingering neurological deficits secondary to cerebral vasospasm induced ischemic events.[1,15,18,19] Dodick and other co-authors[2,20,21] provide more detailed characteristics of the syndrome, namely: sudden onset TCH; normal or near normal complete blood cell count, erythrocyte sedimentation rate, and CSF analysis; angiographic evidence of segmental cerebral vasospasm involving arteries of the Circle of Willis or its immediate branches; variability as to the presence and degree of neurological deficits; and substantial angiographic improvement within four weeks of symptom onset with complete resolution often not observed for several months. This specificity is invaluable for distinguishing between RCVS and Primary Angiitis of the Central Nervous System (PACNS). Furthermore, the flexibility of including cases in which neurological deficits are permanent permits the inclusion of cases that would otherwise have defied classification.

Reversible Cerebral Vasoconstriction Syndrome has generally come to be recognized as a subclass of thunderclap headache-associated conditions (Table 1).[2,20] Although traditionally associated with subarachnoid haemorrhage, TCH are now indicative of an expanding list of secondary causes, including: unruptured aneurysms;[22-24] cerebral venous sinus thrombosis;[25-29] pituitary apoplexy;[30-33] cervicocephalic arterial dissection;[34] hypertensive crisis;[35] spontaneous intracranial hypotension;[36-38] posterior leukoencephalopathy syndrome;[39,40] and retroclival haemorrhage.[20,41] In the absence of an identifiable secondary cause (or known aetiology including reversible segmental vasospasm), primary TCH has become a diagnosis of exclusion.[2] Many cases of TCH are unresolved with CT and lumbar puncture (LP) necessitating further angiographic investigation.[21] Even with radiographic evidence of segmental vasoconstriction, RCVS may be confused with PACNS due to this shared feature of cerebrovascular narrowing and ectasia.

Table 1: Causes of Thunderclap headache

Subarachnoid haemorrhage
Cerebral venous sinus thrombosis
Carotid artery dissection
Pituitary apoplexy
Spontaneous intracranial hypotension (secondary to CSF leak)
Acute hypertensive crisis
Spontaneous retroclival hematoma
Sentinel headache
Ischemic stroke
3rd ventricle colloid cyst
Intracranial infection
Reversible cerebral vasoconstriction syndrome
Primary thunderclap headache (without reversible vasoconstriction)
Primary cough, sexual, and exertional headache

Vasculitis is a spectrum of disorders characterized by inflammation of systemic and CNS blood vessels of varying size, typically caused by deposition of antigen-antibody immune complexes or other immune-mediated events. All CNS vasculitides have the potential to result in cerebral ischemia and infarction. Early recognition and treatment are vital to a favourable clinical outcome.[42] Primary Angiitis of the Central Nervous System (PACNS), exclusively involving the central nervous system vasculature, has previously been described as: 'granulomatous angiitis of the brain'; 'granulomatous angiitis of the nervous system'; and 'isolated angiitis of the CNS'.[43] The differential diagnosis includes a large number of primary and secondary disorders. Biopsy of CNS leptomeninges, cerebral

+ In a cohort study of 16 patients diagnosed with benign angiopathy of the CNS, Hajj-Ali et al. (2002) suspected the underlying pathophysiological process in 10 of the 16 cases that had angiographic follow-up was mediated by vasoconstriction rather than vasculitic mechanisms.

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lesion, and cortex is often considered as the diagnostic gold standard. Primary Angiitis of the Central Nervous System is characterized histologically by perivascular and transmural lymphocytic or histiocytic infiltration, affecting the small vessels of the leptomeninges more so than the cortex, with the branches of the Circle of Willis only rarely affected. The infiltrate is typically granulomatous, including giant cells, but is nongranulomatous in about 15% of cases.[44] Fibrinoid necrosis is seen in the majority of cases.[45] Cerebral biopsy is limited, however, by sampling error and its invasiveness despite its minimal risk for complications (<2%).[46,47]

The hallmark angiographic features of PACNS are alternating ectasia (beading) and stenosis. Nonetheless, this pattern is not specific to the disorder as it is present in other conditions; including RCVS.[43] Angiography has moderate sensitivity but lacks specificity. In a comprehensive review of the diagnostic and clinical features of PACNS, Calabrese et al (1992) highlighted that in 38.6% of histologically confirmed cases of PACNS, cerebral angiography was completely normal, with the classic presentation of beading and ectasia manifest in just 25% of cases.[44] Furthermore, the angiographic differentiation of RCVS and PACNS is very difficult. There are no published reports that examine the value of vessel wall enhancement as a distinguishing characteristic. A diagnosis of PACNS may be one of exclusion, after other clinical entities have been ruled out through thorough history, lab work, CSF analysis, and other clinically-guided investigations.[48] CSF analysis, while being helpful (elevated protein and pleocytosis may suggest PACNS) is of limited value as a normal analysis does not exclude diagnosis. In one study, 25% of histologically proven cases in a previous study had a normal CSF white count, and 61% had protein levels either normal or less than 100 mg/dl.[13]

Methods

A Medline™ (1966-2006) search of English language case reports describing RCVS and PACNS was performed using the terms: 'thunderclap headache'; 'Call-Fleming syndrome'; 'cerebral vasospasm'; 'cerebral vasoconstriction'; 'migraine'; 'migrainous vasospasm'; 'posterior leukoencephalopathy'; 'post-partum cerebral angiopathy'; 'post-partum cerebral arteriopathy'; 'benign angiitis of the nervous system'; 'drug-induced vasospasm'; 'primary angiitis of the central nervous system'; 'primary cerebral vasculitis'; 'primary CNS vasculitis'; 'granulomatous angiitis of the brain'; 'granulomatous angiitis of the nervous system'; and 'isolated angiitis of the CNS'. All terms were investigated as keyword and title searches. The objective of the search was to identify all case reports since 1966 that provide sufficient clinical detail to permit diagnostic classification according to published criteria. The data was divided into two distinct groups (See Tables 2 and 3):

1. RCVS included case studies in which there was angiographic or transcranial Doppler (TCD) ultrasound evidence of near-to-complete resolution of cerebral vasoconstriction in the absence of a well-recognized secondary cause such as subarachnoid haemorrhage or other forms of intracerebral and intraventricular haemorrhage* (Table 2). We made one exception to these inclusion criteria for a case in which there was initial angiographic evidence of beading and ectasia and no evidence of vasculitis, infection or other possible cause at autopsy.[49]
2. PACNS included reports of histologically confirmed PACNS either through biopsy or necropsy (Table 3). All cases with evidence suggesting systemic involvement, infection, neoplasm, sarcoidosis, amyloid angiopathy, other vasculopathies, and those with primary CNS vasculitis limited to the spine were excluded.

Case Report

The patient is a 40-year-old woman with a longstanding history of recurrent migraine headaches since her teens. These headaches usually involved the vertex and occipital region and were associated with nausea, vomiting, photo- and phonophobia but no visual aura. A month or so prior to her initial visit to the ER, however, she experienced a change in the headache pattern characterized by increasing headache frequency and severity. On presentation to a local hospital, she reported that she had experienced an occipital thunderclap headache six days prior, described as the worst headache ever and reaching a maximum intensity of 10/10 within one minute of onset. On examination, she was in considerable pain, diaphoretic and vomiting. She had mild neck stiffness, but no fever, weakness, numbness, or visual disturbances. Her neurological exam was unremarkable. A CT scan of the head was negative and she declined a lumbar puncture, reportedly because of her physical discomfort. She was discharged with follow-up arranged at an outpatient neurology clinic.

Seven days later the patient returned to the hospital complaining of leg weakness and falls. She was initially sent home, but recalled the next day after a CT of the head and subsequent diffusion-weighted MRI imaging identified acute cerebral infarctions in both anterior cerebral artery territories, and an additional cerebral infarction involving the right anterior choroidal artery territory. On examination, she was oriented, but her attention fluctuated. Mental status examination revealed deficits across multiple domains, including executive functioning, visuospatial abilities, verbal fluency and recall. She demonstrated weakness and apraxia confined to the left arm. Romberg's test was positive. A presumptive diagnosis of cerebral vasculitis was made following an MRA (ATECO◊) that revealed tapering of the posterior cerebral arteries (P1 territory) and the supraclinoid portion of internal carotid arteries (ICAs), and severe narrowing of the basilar artery (Figure 1). An echocardiogram and carotid Doppler were normal. CSF analysis was negative and a vasculitis workup indicated she was anticardiolipin antibody (aCL) positive. Her erythrocyte sedimentation rate (ESR) was within normal limits. Of note, the patient had prior diagnoses of iron deficiency anaemia and hypothyroidism. Her thyroid-stimulating hormone (TSH) was

*In some instances, vasospasm may result in ischemia of intracranial vessel walls, followed by necrosis and subsequent reperfusion rupture when vessel patency is restored. It is impossible to determine, however, whether or not the vasospasm preceded the haemorrhage or vice versa, unless of course there is conclusive evidence of vasospasm prior to the onset of haemorrhage.

◊ATECO = Autotriggered Elliptical Centric-Ordered 3D gadolinium-Enhanced MRI Angiography.

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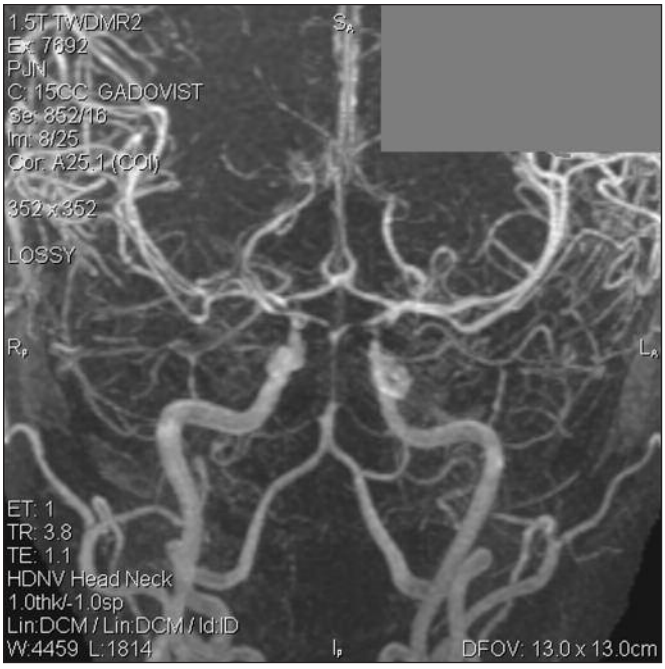

Figure 1: *The MR Angiography demonstrates segmental narrowing of the basilar artery, the P1 segments of the posterior cerebral arteries, and the supraclinoid segment of distal internal carotid arteries.*

elevated at 14 μmol/L (normal: 2-10 μmol/L) on admission. The patient was treated with prednisone, warfarin was deferred pending the outcome of repeat antiphospholipid testing and she made favourable progress. Repeat routine serology was unremarkable and follow-up aCL testing was negative arguing against the presence of an antiphospholipid syndrome contributing to a thrombotic state. She was then referred for outpatient neurological consultation in our centre.

Clinical examination six weeks later revealed only a slight flattening of the right nasal labial fold, reduced toe tapping in both legs, and impaired tandem gait. A follow-up MRI at the same time demonstrated considerable reconstitution of the basilar blood flow and resolution of the carotid narrowing. An MRA performed 16 weeks after the original demonstrated complete resolution of the angiographic abnormalities and no evidence of persistent cerebral arterial segmental narrowing (Figure 2). A diagnosis of RCVS was made, and as no systemic evidence of vasculitis was noted, prednisone therapy was discontinued. Migraine headaches continued to occur at a frequency of 1-2 episodes per month.

Results

Reversible Cerebral Vasoconstriction Syndrome (RCVS)

Sixty-six cases met the criteria of near-to-complete angiographic or transcranial doppler (TCD) ultrasound evidence of reversible vasospasm. Angiography was employed in the vast majority of cases. The TCD ultrasound documented the initial finding of cerebral vascular narrowing in only four cases and provided sole evidence of resolution of vasospasm in 10 cases. The patients were predominantly female (M:F 1:6.3), ranging in age from 11-63 years old (mean 36 years). The majority of cases of RCVS occurred within the postpartum period (33%) or following the ingestion of a vasoconstrictive substance (36%) that included: ergot derivatives; sympathomimetic agents; and serotonergic agents. A number of postpartum subjects had concomitant ingestion of a vasoactive drug (12%). Calado et al (2004)[50] reported a case arguing the co-occurrence of PACNS and RCVS in the postpartum period. They present evidence of reversible vasospasm in conjunction with histologically confirmed PACNS. Three cases of reversible vasospasm occurred in the third trimester. Reversible Cerebral Vasoconstriction Syndrome was reported in the context of physical exertion in nine cases (14%). Activities included: intercourse (preorgasmic and orgasmic); swimming; deep water diving; and bowel movement.

Thunderclap headache, according to the ICHD-2[17] is defined as severe head pain of sudden onset, reaching maximum intensity in less than one minute and lasting from 1 hour to 10 days. Seventy-one percent of the subjects with RCVS described their headache akin to severe and/or sudden and 91% reported the occurrence of some form of headache towards the onset of their symptoms. To meet the criteria for Primary TCH, the head pain must not be attributable to any other disorder, and normal CSF and brain imaging are required.[17] We encountered 13 case

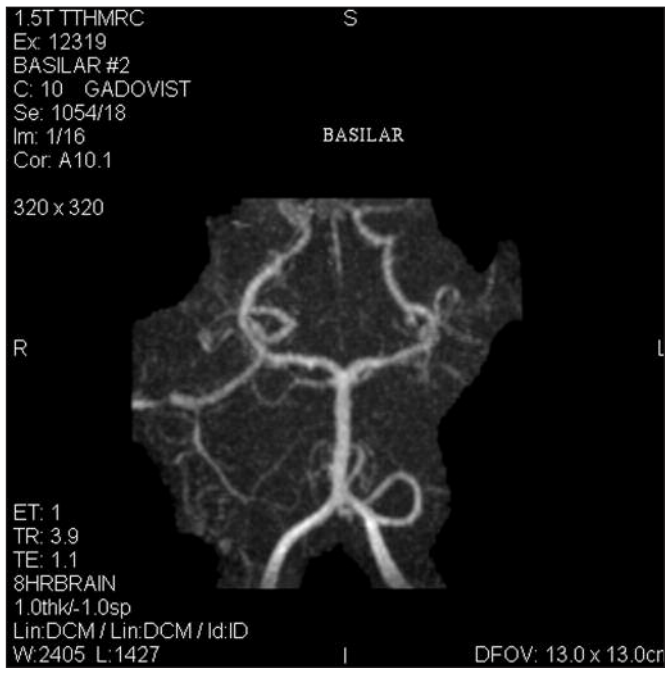

Figure 2: *Follow-up MR Angiography. The MR Angiography demonstrates full resolution of previously affected areas: basilar artery, the P1 segments of the posterior cerebral arteries, and the supraclinoid segment of distal internal carotid arteries.*

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Table 2: Reversible Cerebral Vasospasm, Case Reports since 1966

Study Publication	Ss	Sex	Age	Suspected Condition(s) by Treating Physicians	Onset Context	Vasocons. Drug♫	Chronic H/A Hx§	H/A Description at Onset	Highest BP	ESR mm/h	FND*	Sz♥	RPLS♠	Other Clinical Features	Abnorm. CT/MRI¶	CSF• R	CSF• W	CSF• %L	CSF• P	CSF• G	Cerebral Biopsy¤	Abnorm. Angio◊	CoW Affected⌂	Angio Resol.▫	Repeat Date	CCB♣	Clinical Resol.†
J Neurol Neurosurg Psych 1984; 47:73	1	♀	39	PACNS, migrainous vasospasm	-	-	+	Sudden, severe, pulsatile	130/80	-	+	+	-	-	n/a	7	6	100%	-	-	-	+	?	+	19d	-	+
Cephalalgia 1984; 4:171	1	♀	25	Ergometrine induced RCVS	CMV rhinopharyngitis, drug intake	+	+	Severe, throbbing	120/70	55	-	-	-	↑LFTs, CMV (+)	-	-	-	-	155	-	n/a	+	+	+	30d	-	+
Neurology 1987; 37:1555	1	♀	35	Pre-eclampsia & cerebral vasospasm	35 weeks gestation	-	-	-	180/90	-	+	-	-	Pre-eclampsia, ↑LFTs	+	46	-	-	474	-	n/a	+	+	+	2y	-	-
Stroke 1988; 19:1159	1	♀	48	RCVS	-	-	-	Severe	200/100	-	+	+	+	WBC 14 x 10^9/L	+	-	-	-	-	-	-	+	+	+	21d	-	-
	2	♀	37	Fibromuscular dysplasia, RCVS	-	-	+	Severe	normal	-	+	-	-	-	+	10	-	-	51	-	n/a	+	+	+	18d	+	-
	4	♂	34	Arteritis, RCVS	hospitalized for rash	-	-	Severe	-	45	+	-	-	Post antibiotic rash	-	2	16	100%	51	-	n/a	+	+	+	4m	-	+
Arch Neurol 1988; 45:63	1	♀	31	Migraine with vasospasm	-	-	+	Migraine	-	-	+	-	-	-	+	-	-	-	47	-	n/a	+	+	+	15d	+	+
Medicine 1988; 67:20	8	♀	26	PACNS	postpartum	-	-	Severe, worst	178/110	-	+	-	-	WBC 14.9 x 10^9/L	-	175/hpf	-	-	92	-	n/a	+	?	+	6m	-	+
Eur J Neuro 1989; 29:102	1	♀	22	Postpartum RCVS	postpartum, drug intake	+	-	Headaches	220/120	18	+	+	-	-	+	-	42	40%	47	-	n/a	+	?	+[a]	4w	-	+
Angiology 1991; 42:152	1	♀	33	Migrainous vasospasm	sleeping	-	+	Awakened, intense, throbbing	-	-	-	-	-	-	+	n/a	n/a	n/a	n/a	n/a	n/a	+[a]	+	+	3d	-	+
Neurology 1991; 41:1145	1	♀	27	Cerebral vasospasm	postpartum	-	-	Headache, persistent	170/100	54	+	-	-	Death, no vasculitis at necropsy	+	1	-	-	-	-	-	+	+	n/a	n/a	+	D
Arch Intern Med 1991; 151:2290	10	♂	31	migraine, PACNS	-	-	-	Sudden, severe	160/100	-	-	-	-	-	-	10/hpf	-	-	-	-	n/a	+	?	+	6m	-	+
	11	♀	37	PACNS	-	-	-	Sudden, severe	normal	-	-	+	-	-	-	-	10/hpf	n/a	57	-	n/a	+	?	+	5m	-	+
Obstet Gynecol 1991; 78:941	2	♀	21	Bromocriptine & sympathomimetic induced headache	postpartum, drug intake	+	-	Sudden, later severe	116/86	-	+	+	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	3m	-	+
Stroke 1992; 23:1364	1	♀	28	Ergonovine induced postpartum RCVS	postpartum, drug intake	+	-	Sudden, severe	normal	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+	3m	+	n/a
Cephalalgia 1993; 13:289	1	♀	47	Migrainous vasospasm, Ergot induced vasospasm, PACNS	drug intake	+	+	Worsening, severe	-	-	+	-	-	-	+	-	-	-	86	-	n/a	+	+	+	5w	+	-
Am J Perinatol 1993; 10:243	1	♀	36	Postpartum eclampsia & RCVS	postpartum	-	-	Sudden, severe	200/120	-	+	+	-	Postpartum eclampsia	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+[a]	+	+[a]	5d	+	+
Stroke 1993; 24:2108	1	♀	32	Isometheptene induced postpartum RCVS	postpartum, drug intake	+	+	↑Severity	normal	-	+	+	+	RPLS	+	-	-	-	-	-	n/a	+	+	+[a]	6d	-	+
AJNR 1995; 16:1344	1	♀	28	Preeclampsia & RCVS	34 weeks gestation	-	-	Headache	180/100	-	+	-	-	Pre-eclampsia	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	26d	+	+
Stroke 1995; 26:128	1	♀	20	Bromocriptine induced postpartum RCVS	postpartum, drug intake	+	+	Severe	-	-	-	+	-	Status epilepticus	+	-	-	-	70	38	n/a	+	+	+	3m	-	+
Headache 1995; 35:1	1	♀	55	TCH	drug intake	+	-	Abrupt, severe	-	-	-	-	-	-	+	13	-	-	-	88	n/a	+	+	+	5w	+	+
Amer J Obstet Gynecol 1996; 175:1386	1	♀	23	Postpartum RCVS	postpartum	-	-	Throbbing	190/120	-	+	+	-	-	-	161	7	86% MN	67	-	n/a	+	+	+/-	21d	+	+
Arch Neurol 1998; 55:712	1	♂	43	Sumitriptan & Midran induced RCVS	drug intake	+	-	Sudden, severe	-	-	+	-	-	-	+	39	12	n/a	95	-	n/a	+	-	+	39d	+	+
Intensive Care Med 1999; 25:532	1	♀	20	Sumatriptan & Ergotamine induced Postpartum RCVS	postpartum, drug intake	+	-	Severe	130/80	-	+	+	-	Status epilepticus	+	-	-	-	-	360	n/a	+	+	+	10d	-	+
Internal Medicine 1999; 38:54	1	♀	34	RPLS	-	-	-	-	normal	-	+	-	+	HRT, thrombolysis	+	-	-	-	-	-	n/a	+	+	+	36d	-	+
	2	♀	19	RPLS	-	-	-	Sudden	-	-	+	-	+	Thrombolysis	+	-	-	-	-	-	n/a	+	+	+	27d	-	-
Cephalalgia 1999, 19:118	1	♂	49	TCH	swimming, drug intake	+	+	Sudden, severe	-	-	-	-	-	Hep A&B	n/a	-	-	-	68	-	n/a	+	+	+	15d	-	+
	2	♂	47	PACNS, TCH	intercourse	-	-	Sudden, severe	-	-	-	-	-	-	-	8	-	-	-	-	n/a	+	+	+	4w	-	+
J Neuroimaging 2000; 10:230	1	♀	27	Ergonovine induced postpartum RCVS	postpartum, drug intake	+	-	Headaches	HTN	-	+	-	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	14d	-	+
Cephalalgia 2000; 20:135	1	♀	58	TCH RCVS	Post IV Technetium pertechnetate	-	-	Hyperacute, explosive	-	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+	5d	+	-
Neurology 2000; 54:2003	1	♀	27	Postpartum RCVS	postpartum	-	-	Severe	160/80	38	+	+	+	-	+	n/a	n/a	n/a	n/a	n/a	n/a	+[a]	+[a]	+[a]	22d	+	+
	2	♀	25	Postpartum RCVS	postpartum	-	-	Sudden	150/100	-	+	+	+	-	+	150	-	-	49	-	n/a	+	+	+	22d	+	+
Neurology 2001; 57:743	1	♀	37	Ergotamine or Ritonovir induced RCVS	antiretroviral treatment, drug intake	+	-	Sudden, severe	normal	-	+	-	-	HIV	+	-	-	-	-	-	n/a	+	+	+	90d	-	-
AJNR 2001; 22:1550	1	♀	37	Migraine, carotid dissection	-	-	+	↑Severity of migraine	-	-	-	-	-	-	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	Minutes	-	n/a
Gynecol Obstet Invest 2002; 53:65	1	♀	34	Postpartum eclampsia & RCVS	postpartum	-	-	Headache	186/92	-	-	+	-	HELLP syndrome	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	20d	-	+
Cerebrovasc Dis 2002; 13:288	1	♀	26	Ergometrine induced postpartum RCVS	postpartum, drug intake	+	-	Headache, severe	214/116	-	-	+	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	3m	+	+
J Child Neurol 2002; 17:470	1	♀	11	Familial Hemiplegic Migraine & RCVS	-	-	+	Severe, throbbing	-	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+	2w	-	+
Headache 2002; 42:297	1	♀	29	Postpartum RCVS	postpartum	-	-	Severe	normal	37	-	-	-	-	-	-	7	100%	-	-	n/a	+	+	+	19d	+	+
Neurology 2002; 58:130	1	♀	46	Serotonergic induced RCVS	drug intake	+	+	Sudden, worst	normal	-	+	-	-	5 mm ICA aneurysm	+	-	-	-	-	-	-	+	+	+[b]/+	3m/6m	-	+
	2	♀	45	Serotonergic induced RCVS	drug intake	+	-	Sudden, explosive	normal	101	+	-	-	ICA aneurysm, carcinoid lung tumor	+	-	-	-	-	-	n/a	+	+	+[b]/+	3m/14m	-	+
	3	♂	34	Serotonergic induced RCVS	speed boating, drug intake	+	-	Explosive	normal	-	+	+	-	-	+	-	-	-	-	-	-	+[a]	+	+[b]	3m	-	+
Neurology 2002; 59:1772	1	♀	60	Migrainous RCVS	swimming, drug intake	+	+	Severe	normal	-	-	-	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	71d	-	+
Cerebrovasc Dis 2003; 15:230	1	♀	47	RPLS, RCVS	Post-transfusion	-	-	Severe	140/80	-	+	+	+	Pancytopenia, ↓Ca, ↓Mg	+	-	-	-	-	-	n/a	+	+	+	9m	-	-
Headache 2003; 43:72	1	♀	23	Hemiplegic migraine & RCVS	38 weeks gestation, drug intake	+	+	Throbbing	138/70	-	+	-	-	FV Leiden allele	-	17	17	6%	-	-	n/a	+	+	+[a]	<1w	+	+
Cephalalgia 2003; 23:218	1	♀	63	TCH & RCVS	-	-	-	Sudden, worst	150/100	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+[b]/+	2d/17d	+	+/-
Cephalalgia 2003; 23:854	1	♀	51	Bathing headache, TCH, RPLS	bathing	-	-	Sudden, explosive	172/84	-	-	-	+	PMHx: thyroid cancer	+	30	10	100%	-	-	n/a	+	+	+	15d	+	+
Cephalalgia 2003; 23:994	1	♀	46	PACNS, TCH, RCVS & RPLS	bowel movement	-	+	Sudden, severe, TCH	200/120	-	-	+	+	RPLS	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	11d	-	+
Clin Exp Rheumatol 2003; 21 (S32):S1	1	♀	43	CNS vasculitis, RCVS	-	-	-	Severe, excrutiating	-	-	-	-	-	-	+	-	-	-	-	-	n/a	+	+	+[a]	8w	+	-
Cerebrovasc Dis 2004; 18:340	1	♀	33	Postpartum RCVS & PACNS	postpartum	-	-	Severe, pulsatile	144/75	-	+	+	-	ANA 1:240, PACNS & RCVS	+	-	-	-	75	-	+	+	?	+[a]	6w	+	-
Neuroradiology 2004; 46:1022	1	♀	42	Postpartum RCVS	postpartum	-	-	-	-	-	+	+	-	Intracranial balloon angioplasty	+	-	-	-	-	-	-	+	+	+[a]	10d	+	-
Epilepsia 2004; 45:551	1	♀	43	Hypercalcemia induced RCVS, RPLS	-	-	-	-	-	-	+	+	+	PTH, ↑Ca, status epilepticus, breast	+	-	-	-	-	-	n/a	+	+	+	1m	-	-
Headache 2004; 44:244	1	♀	44	Sexual headache & RCVS	orgasm	-	+	Sudden, excrutiating	-	-	-	-	-	Asymptomatic arachnoid cyst	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	40d	-	+
Arch Neurol 2004; 61:411	1	♀	37	Postpartum RCVS & RPLS	postpartum	-	-	Sudden, severe	190/100	-	-	-	+	-	+	-	-	-	-	-	n/a	+	+	+/-	2d	-	+
	3	♀	23	Postpartum RCVS & RPLS	postpartum	-	+	Sudden, severe	200/100	-	-	+	+	-	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+[a]	7d	-	+
	4	♀	31	Postpartum RCVS & RPLS	postpartum	-	-	Sudden, excrutiating	200/100	-	-	-	+	ncidental extracranial ICA dissectio	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	6m	-	+
Headache 2004; 44:710	1	♂	36	Sexual headache & RCVS	orgasm	-	-	Severe, explosive	normal	-	-	-	-	-	+	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	6m	-	+
CMAJ 2004; 171:593	1	♀	31	oxymetazoline induced RCVS	drug intake	+	-	Sudden, worst	normal	-	-	-	-	-	-	-	-	-	-	-	n/a	+	+	+	6w	+	+
Neurology 2004; 63:2128	1	♀	43	Sumitriptan induced RCVS	drug intake	+	+	-	-	-	+	-	-	-	-	-	-	-	-	-	n/a	+	+	+	7d	-	n/a
Cephalalgia 2005; 25:191	6	♀	50	Bathing headache	bathing, micturition	-	-	Sudden, excrutiating	normal	-	-	-	-	-	-	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+[b]/+	12d/4w	+	+
Arthritis Rheum 2005; 52:3314	1	♀	53	PACNS, oxymetazoline induced RCVS	intercourse, drug intake	+	+	↑Severity	-	-	-	-	-	-	+	-	-	-	-	-	n/a	+	+	+	2w	-	+
Cephalalgia 2005; 26:530	1	♀	51	TCH, RCVS, RPLS	bowel movement	-	+	Sudden, intense, worst	220/110	-	+	-	+	-	+	32	-	-	-	-	n/a	+	+	+[b]/+	16d/17d	-	+
Canadian J Neurol Sci 2006	1	♂	13	TCH & RCVS	deep water diving	-	-	Sudden, severe	-	-	-	-	-	-	-	1375	-	-	-	-	n/a	+	+	+	10d	-	+
Obstet Gynecol 2006; 107:446	1	♀	17	Postpartum RCVS	postpartum	-	-	Abrupt, severe	130/80	-	+	+	+	-	+	-	-	-	-	-	-	+	+	+	3m	-	+
J Neurol Neurosurg Psych 2006; 77:88	1	♂	35	ICA vasospasm	-	-	-	-	-	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+	<1m	+	+
Neurology 2006; 67:159	1	♀	45	SSRI (Venlafaxine) induced RCVS	drug intake	+	-	Moderate	normal	-	+	-	-	↑CRP	+	-	-	-	62	-	n/a	+	+	+	3w	-	-
	2	♀	41	SSRI (Paroxetine) induced RCVS	drug intake	+	-	Pounding	-	-	+	-	-	-	+	-	-	-	-	-	n/a	+	+	+	6d	+	-

Table 2 - LEGEND: RCVS, reversible cerebral vasoconstriction syndrome; TCH, thunderclap headache; PACNS, primary angiitis of the central nervous system; RPLS, reversible posterior leukoencephalopathy syndrome; ∞ Vasocons. Drug, report of vasoconstrictive medication taken prior to angiography; § Chronic H/A Hx, history of recurrent tension headaches or migraines; * FND, focal neurological deficits excluding seizure; ♥ Sz, seizure activity of any type; ♣ RPLS, reversible posterior leukoencephalopathy syndrome; [n] Abnorm CT/MRI, CT/MRI evidence of ischemia and/or edema; • Abnorm CSF, abnormal cerebrospinal fluid analysis, R = >0 RBCμl, W = >5 WBC/μl, L = lymphocytes, MN = mononuclear cells, N = neutrophils, P = protein >45 mg/dl, G = glucose >75 or <45 mg/dl; ¤ Cerebral Biopsy, histiological evidence of perivascular or transmural lymphocytic and/or histiocytic infiltration; ⌂ CoW Affected, segmental cerebral vasoconstriction affecting the Circle of Willis or its immediate branches, including the distal internal carotid arteries; ◊ Abnorm Angio, angiographic evidence of segmental cerebral vasoconstriction; □ Angio resolution, angiographic evidence of near to complete resolution of cerebrovascular narrowing; ♠ CCB, calcium channel blocker; † Clinical resolution, no residual neurological deficits; [a] Transcranial Doppler U/S evidence of either vasoconstriction or resolution; +/-, very mild residual clinical deficits not impairing daily functioning; D, death

reports with TCH and no evidence of a recognized secondary cause (including RCVS). Only three met full criteria for a diagnosis of primary TCH, all of which occurred in the context of bathing.[5] Although bathing-triggered RCVS was identified in just two cases, 11 cases of bathing-induced TCH without evidence of reversible vasospasm were reported, arguing for its inclusion as a variant of primary TCH.[4] In seven of these cases, cerebral angiography was not performed; while in the other six cases, angiography was negative for segmental narrowing of the vasculature. Therefore, not all the cases of bathing headache without RCVS were sufficiently characterized to determine if RCVS was responsible.

A history of chronic headache, typically either migraine or tension type headache was reported in 30% of RCVS cases. Severe hypertension occurred in 21% of subjects (systole or diastole ≥180 or ≥110 mmHg, respectively), and 30% had moderate to severe hypertension (systole or diastole ≥160 or ≥100 mmHg, respectively). Focal neurological deficits were evident in 61% of cases, while seizures occurred in 33%. Common clinical features included nausea/vomiting; visual disturbances, i.e. blurred vision, vision loss, and visual field deficits; paresis, primarily hemiparesis; aphasia; sensory changes, i.e. dysesthesias, paresthesias, and hypesthesias; and cognitive status changes, ranging from confusion to coma. One subject died. Blood work was generally unhelpful although the ESR was reportedly elevated in six instances. In the 50 cases where LP results were provided the RBC and WBC counts were entirely normal in 68% and 82%, respectively. CSF leukocytosis, when present, was usually less than 20 WBC/μl. Protein was elevated >45 mg/dl in 30%, with only two cases of protein greater than 100 mg/dl.

Positive CT or MRI findings were present in 71% of cases where head imaging was performed. In two instances follow-up angiography demonstrated reversibility of affected vessels, but also identified vasospasm in previously unaffected territories.[51,52] The Circle of Willis or its immediate branches, including the distal segments of the internal carotids was involved in 89% to 98% of cases. Near-to-complete resolution of the segmental vasoconstriction was demonstrated in 86% of cases within 12 weeks of the initial study and 59% reported reversibility within four weeks. Fifteen documented resolution of vasospasm in less than one week.

Clinical recovery from symptoms was achieved by 71% of subjects; conversely nearly 1/4 had significant residual neurological deficits. A calcium channel blocker (usually nimodipine) was used for the management of cerebral vasospasm in 25 cases in which only 64% had near-to-complete clinical resolution. The overall rate of clinical resolution was 71%, while the recovery rate of those not treated with calcium channel blockers was 78%, suggesting that this class of drugs was used in the more severely affected patients.

The literature review of RCVS-associated conditions highlighted significant co-morbidity with other syndromes including: hypertensive encephalopathy; pre/eclampsia; and reversible posterior leukoencephalopathy (RPLS), either in the presence or absence of thunderclap headache.[51] Severe hypertension, RPLS, and pre/eclampsia occurred in 20%, 23% and 5% of cases, respectively. Reversible Cerebral Vasoconstriction Syndrome may explain the neurological manifestations of these syndromes in a number of instances. Hypertensive encephalopathy has long been recognized in conjunction with RPLS and pre/eclampsia.[53] Reversible posterior leukoencephalopathy is a syndrome of nausea, vomiting, visual changes, altered mental status, seizures, and MRI evidence of vasogenic oedema within the posterior circulation.[39] It occurs both in the presence and absence of severe hypertension.[54-56] Forty percent of RCVS cases with concurrent RPLS had a blood pressure ≥190/100 mmHg. The theory that reversible vasospasm is a cause of RPLS is suspected by a number of authors and supported by cases of angiographic evidence of "rapid" reversibility and complete resolution of segmental cerebral narrowing.[39,40,57] Interestingly, Call et al's (1988) first case description of RCVS meets the criteria for RPLS, in which the patient experienced visual changes, a focal seizure, and had low density lesions bilaterally in the occipital and parietal lobes on CT head imaging.[1] Conversely, we also uncovered cases of RPLS in which cerebral angiograms failed to demonstrate cerebral vasoconstriction, arguing for the existence of aetiologies for RPLS other than cerebral vasospasm.[55,58]

Primary Angiitis of the Central Nervous System

Our search revealed 83 patients diagnosed histologically with PACNS by biopsy (73%) or post-mortem (27%). Cases were evenly distributed between the sexes (M:F 1:1), ranging in age from 3-78 years (mean 40 years). The clinical contexts were quite variable and preceding infection was rare. Symptoms

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Table 3: Primary angiitis of the central nervous system, case reports since 1966

Publication	Ss	Sex	Age	Suspected Condition(s) by Treating Physicians	Onset Context	Sx onset to Dx	H/A Description at Onset	Highest BP	Temp °C	WBC x109/L	ESR mm/h	FND*	Abnorm. CT/MRI[n]	Leptomeningeal Enhancement	CSF• R	CSF• W	CSF• %L	CSF• P	CSF• G	Cerebral Biopsy¤	Dx at Autopsy	Abnorm. Angio◊	CoW Affected⌂	Angio Resol.□	Repeat Date	Steroid Rx	Clinical Resol.†
Neurology 1976; 26:797	1	♀	67	PACNS	-	9m	Severe, generalized	150/92	38.3	-	46	+	n/a	n/a	800	205	86%	-	-	n/a	+	n/a	n/a	n/a	n/a	-	D
J Neurol Sci 1976; 29:335	1	♂	47	PACNS	-	2y	-	-	-	14.9	75	+	n/a	n/a	-	100	67% MN	490	-	-	+	-	n/a	n/a	n/a	+	D
Am J Roentgenol; 1977 129:463	1	♀	70	PACNS	Fall & LOC in her room	12w	-	190/110	-	-	-	+	+	n/a	6	-	-	188	77	n/a	+	+	-	-	6w	+	D
J Neurol 1977; 215:175	3	♂	42	PACNS	-	5w	Diffuse	160/110	-	-	30	+	n/a	n/a	-	120	↑	-	-	n/a	+	-	n/a	n/a	n/a	+	D
	4	♀	44	PACNS	Viral pneumonia, iridocyclitis, ileitis	16m	-	160/90	+	-	29	+	n/a	n/a	-	180	80%	200	103	n/a	+	-	n/a	n/a	n/a	+	D
	5	♂	71	PACNS	-	<1w	-	190/100	-	-	18	+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	-	D
Arch Pathol Lab Med 1977; 101:382	2	♂	47	PACNS	-	7w	Headache	-	+	-	95	+	n/a	n/a	166	62	90%	66	-	n/a	+	+	-	n/a	n/a	+	D
Arch Neurol 1979; 36:433	1	♂	25	Viral encephalitis, PACNS	URI	6m	Severe, intermittent	-	-	-	44	-	n/a	n/a	5	52	100% MN	170	44	n/a	+	n/a	n/a	n/a	n/a	-	D
Ann Neurol 1979; 5:490	1	♀	50	PACNS	Sore throat 2 weeks prior	20d	Headache	-	-	-	38	+	n/a	n/a	-	-	-	55	43	+	n/a	-	n/a	n/a	n/a	+	+
J Comput Assist Tomogr 1979; 3:536	1	♂	34	Brain Tumor, PACNS	Found unconscious	10w	-	-	-	-	-	+	+	n/a	-	60	100% MN	-	-	+	n/a	-	n/a	n/a	n/a	+	-
Arch Neurol 1981; 38:129	1	♂	19	PACNS	-	25m	-	-	-	-	2	+	+	n/a	202	121	63%	75	80	n/a	+	-	n/a	n/a	n/a	+	D
J Neurol 1984; 231:38	1	♀	38	Temporal tumor, PACNS	-	<1m	Severe, persistent	-	-	8.3	15	+	+	n/a	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	+	-
Ann Intern Med 1985; 102:210	1	♀	64	PMR, PACNS	-	18m	-	-	38.9	-	44	-	+	n/a	Traumatic	-	-	107	-	+	n/a	-	n/a	n/a	n/a	+	?
J Neurol Neurosurg Psychiatry 1985; 48:1054	1	♂	43	PACNS	-	15m	-	-	-	-	-	+	+	n/a	-	163	100%	200	-	+	n/a	-	n/a	n/a	4m	+	-
Postgrad Med J 1987; 63:1085	1	♀	15	PACNS	BCP started 2w previous	3d	Generalized	-	-	10.8	25	+	+	n/a	-	30	0%	89	90	n/a	+	n/a	n/a	n/a	n/a	+	D
J Neurology 1987; 234:344	1	♀	64	PACNS	Post lumbar infarct, lamanectomy	7m	Increasing	-	-	-	-	+	+	-	-	-	-	150	-	+	n/a	-	n/a	n/a	n/a	+	+
J Neurol Neurosurg Psychiatry 1988; 51:1126	1	♂	69	PACNS	-	3m	Global	-	-	-	22	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	-	n/a	n/a	n/a	+	+
	2	♂	65	PACNS	-	6w	-	-	-	-	30	-	+	n/a	-	12	67%	142	76	+	n/a	-	n/a	n/a	n/a	+	+
	3	♂	44	Meningoencephalitis, PACNS	-	3w	-	-	39	11.6	41	+	+	n/a	3000	800	92%	119	39	+	n/a	+	-	+	2m	+	-
	4	♂	78	Multi-infarct state, PACNS	-	2w	-	-	-	-	47	+	+	n/a	-	-	-	81	115	n/a	+	n/a	n/a	n/a	n/a	-	D
	5	♂	60	Cerebellar glioma, PACNS	-	5m	-	-	-	-	28	+	+	n/a	-	169	100%	100	-	n/a	+	-	n/a	n/a	n/a	+	D
Medicine 1988; 67:20	5	♂	74	PACNS	-	18m	-	-	-	3.8	50	+	-	n/a	1	38	97%	169	-	+	n/a	-	n/a	n/a	n/a	+	+
Neurology 1989; 39:167	1	♂	35	PACNS	-	<1m	Severe, throbbing	-	-	12.8	16	+	-	n/a	-	-	-	102	-	+	n/a	+	+	+	18m	+	+
	2	♀	50	PACNS	-	<3w	Acute, pounding, episodic	-	-	14.8	14	+	-	n/a	78	-	-	30	79	+	n/a	+	?	n/a	n/a	+	+/-
	3	♀	40	PACNS	-	8y	-	-	-	11.4	8	+	-	n/a	-	-	-	-	-	+	n/a	+	+	-	1y/2y	+	+
	4	♀	37	PACNS	-	<1w?	Sudden	-	-	9.9	23	+	-	n/a	2	-	-	53	-	+	n/a	+	+	+	5m	+	-
	5	♂	68	PACNS	-	n/a	Recurrent	-	-	9.5	2	+	+	n/a	410	100	100%	78	81	+	n/a	+	+	n/a	n/a	+	+
Med Sci Law 1989; 29:172	1	♂	41	PACNS	-	n/a	Persistent	-	+	-	↑	-	+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	-	D
Can J Neurol Sci 1990; 17:151	1	♂	8	MS, PACNS	-	8m	Occasional headaches	-	-	-	-	+	+	-	-	-	-	-	-	+	+	-	n/a	n/a	n/a	+	D
Surg Neurol 1990; 33:206	1	♂	61	PACNS	-	7w	Sudden, severe	-	-	13	4	+	+	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	-	n/a	n/a	n/a	+	-
J Neurol 1991; 238:235	1	♂	40	PACNS	-	1m	Mild, worsening	-	-	16.4	27	+	+	- nc	-	30	100%	90	-	+	n/a	-	n/a	n/a	n/a	+	-
Indian J Pathol Microbiol 1992; 35:365	1	♂	60	PACNS	-	<2w	Headache	-	-	-	-	+	+	n/a	-	mild	-	slight	-	n/a	+	n/a	n/a	n/a	n/a	-	D
Neurol Med Chir 1992; 32:834	1	♂	43	PACNS	-	18m	Progressive	-	36.7	13.3	8	+	+	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	+	+	n/a	n/a	+	?
SAMJ 1993; 83:618	1	♂	Adol	PACNS	-	7m	Headache	-	-	-	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	-	n/a	n/a	n/a	+	-
	2	♂	40	PACNS	-	3m	Severe, throbbing	-	-	-	-	+	+	-	-	↑	n/a	-	-	+	n/a	-	n/a	n/a	n/a	+	-
Arch Neurol 1993; 50:925	1	♀	53	PACNS	-	55d	Severe, throbbing	-	-	-	28	+	+	+	53	74	92%	144	-	+	n/a	-	n/a	n/a	n/a	+	-
Neurol Med Chir 1993; 33:386	1	♂	22	Tumor, PACNS	-	6m	Dull	-	37.5	-	-	-	+	n/a	-	61	95% MN	134	-	n/a	+	-	n/a	n/a	n/a	+	D
AJNR 1993; 14:26	1	♀	53	SAH, chronic meningitis, PACNS	-	30d	Severe	-	-	-	-	+	+	+	<60	122	85%	144	-	+	n/a	n/a	n/a	n/a	n/a	+	-
AJNR 1994; 15:331	1	♂	45	PACNS	-	17m	Posterior neck ache	-	-	-	-	+	+	-	-	↑	-	-	-	+	n/a	-	n/a	n/a	n/a	+	?
Stroke 1994; 25:1693	1	♂	45	PACNS	-	11m	-	130/80	-	-	-	+	+	-	-	-	-	123	-	+	n/a	-	n/a	n/a	n/a	+	D
J Neurosurg 1994; 81:472	1	♀	61	PACNS	-	?	Progressive	180/70	37.2	3.7	-	+	+	-	-	↑	-	-	-	+	n/a	n/a	n/a	n/a	n/a	+	+
Neurology 1995; 45:1462	1	♀	52	PACNS	3w post febrile illness	<3m	Headaches	-	-	-	44	-	+	-	80	30	100%	150	-	+	n/a	-	n/a	n/a	n/a	+	+
Neurology 1995; 45:1731	1	♂	47	Benign focal vasculitis, ?PACNS	Playing tenis	3w	Intense	-	-	-	4	+	+	-	-	-	-	68	-	+	n/a	n/a	n/a	n/a	n/a	-	+/-
Arch Pathol Lab Med 1995; 119:334	1	♂	70	PACNS	Fall & hip fracture	8w	-	216/110	39	-	-	+	n/a	n/a	n/a	n/a	n/a	n/a	n/a	+	+	+	n/a	n/a	n/a	-	D
	2	♂	32	PACNS	-	5w	Intermittent, throbbing	-	39.3	-	16	+	+	+	-	356	93%	100	-	n/a	+	+	+	n/a	n/a	+	D
	3	♂	41	PACNS	-	1-2y	Headache	-	-	-	19	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	-
J Neurol 1996; 243:662	1	♀	67	PACNS	-	6w	-	-	-	-	85	+	n/a	n/a	-	21	68%	136	-	n/a	+	n/a	n/a	n/a	n/a	+	D
Neurology 1997; 49:1696	1	♂	48	Primary demyelinating disease, PACNS	-	3y	-	-	-	-	30	+	+	-	-	21	100%	98	-	+	n/a	n/a	n/a	n/a	n/a	+	-
Clin Exp Rheumatol 1998; 16:77	1	♀	25	Tumor, PACNS	-	5y	Headache	-	-	5.6	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	?
Neurology 1998; 51:1774	1	♀	76	viral meningoencephalitis, PACNS	ICH surgical evacuation 9m prior	9m	-	-	-	-	-	+	+	-	-	228	100%	134	-	+	n/a	n/a	n/a	n/a	n/a	+	+
J Neurosurg 1998; 88:133	1	♂	10	Preaneurysmal vasculitis, PACNS	-	7y	Headache	-	-	-	-	+	+	n/a	-	-	-	-	-	-	+	+	-	-	serial 2w/3	+	D
J Neurol Neurosurg Psychiatry 1998; 65:956	1	♀	46	Migraine, Meniere's, PACNS	-	30m	Recurrent headache	-	-	mild ↑	-	+	+	n/a	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	-
J Postgrad Med 2000; 46:272	1	♀	20	TB meningitis, CNS lymphoma, PACNS	-	7m	Episodic	-	-	-	-	+	+	+	-	↑	↑	↑	-	+	n/a	n/a	n/a	n/a	n/a	+	+
Neurol India 2000; 148:149	1	♂	31	Intracranial hypertension, PACNS	-	5m	Episodic	-	+	-	8	+	n/a	n/a	-	100	100%	235	20	-	+	-	n/a	n/a	n/a	-	D
	2	♂	18	Status epilepticus, PACNS	-	4y	-	-	-	-	-	+	n/a	n/a	2000	40	100%	140	-	-	+	n/a	n/a	n/a	n/a	-	D
	3	♂	31	Stroke, AVM, TB meningitis, PACNS	-	5½y	Episodic	-	-	-	10	+	+	n/a	-	110	98%	97	40	-	+	n/a	n/a	n/a	n/a	+	D
J Rheumatol 2000; 27:1297	1	♀	6	Tumor, PACNS	-	<1w?	-	-	-	-	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	-*	n/a	n/a	n/a	+	+
Eur Neurol 2001; 45:184	1	♀	44	PACNS	-	2w	-	-	-	-	-	+	+	-	-	-	-	47	-	+	n/a	-	n/a	n/a	n/a	+	+
Eur Neurol 2001; 16:162	1	♂	32	myelopathy, PACNS	-	8½y	-	-	-	-	-	+	+	-	-	25	100%	187	-	+	n/a	+	-	n/a	n/a	+	-
AJNR 2001; 22:577	1	♀	29	PACNS with spinal involvement	-	?	Subacute, severe	-	-	-	-	+	+	-	-	12	80%	70	-	+	n/a	-	n/a	n/a	n/a	+	+
	2	♂	50	PACNS with spinal involvement	-	6m-2y	-	-	-	-	-	+	+	-	-	30	80%	140	-	+	n/a	-	n/a	n/a	n/a	+	-
Neurology 2001; 56:837	1	♀	10	PACNS	-	6w	-	-	-	-	-	+	+	-	-	-	-	-	-	+	n/a	+	-	n/a	n/a	+	-
	2	♀	16	PACNS	Cough, sore throat, headache	1m	Severe, increasing	-	-	11.9	20	+	+	-	-	747	74%	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	+
AJNR 2002; 23:1561	1	♂	42	PACNS	-	9d	-	110/70	-	-	3	+	+	-	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	+	+
Comput Med Imaging Graph 2002; 26:265	1	♀	8	PACNS	-	?	-	-	-	-	↑	+	+	-	-	-	-	↑	-	+	n/a	+	n/a	n/a	n/a	+	+
J Neurophthalmol 2003; 23:127	1	♀	38	viral meningoencephalitis, PACNS	-	6w	-	-	-	-	-	+	+	+	-	250	↑	50	-	+	n/a	n/a	n/a	n/a	n/a	+	-
J Neuroophthalmol 2003; 23:148	1	♀	68	PACNS	-	<1w	-	-	-	-	-	+	+	+	-	38	↑	223	-	+	n/a	-	n/a	n/a	n/a	+	?
J Neurol 2003; 250:444	1	♀	42	PACNS & RPLS	-	?	Headache	-	-	-	-	+	+	-	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	+	+
Cerebrovasc Dis 2004; 18:340	1	♀	33	Postpartum RCVS & PACNS	Postpartum	27d	Severe, pulsatile	144/75	-	-	-	+	+	-	-	-	-	75	-	+	n/a	-	?	-[a]	6w	+	-
J Pediatr 2004; 145:693	1	♂	12	Childhood PACNS	-	>3m	Persistent	-	-	-	-	+	+	-	-	16	89%	-	-	+	n/a	-	n/a	n/a	n/a	+	-
	2	♀	3.75	Childhood PACNS	-	>2y	-	-	+	15	83	-	+	-	-	425	<25%	-	-	+	n/a	-	n/a	n/a	1y	+	+
Clin Exp Rheumatol 2004: 2116 Suppl 32:S13	1	♂	40	Neurosarcoidosis, PACNS	-	?	Increasing, severe	-	-	-	-	-	+	-	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	n/a	n/a
Clin Exp Rheumatol 2004: 2216 Suppl 36:S70	1	♀	39	Susac's Syndrome, PACNS	-	3y	-	-	-	-	-	+	+	-	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	+	-
AJNR 2005; 36:642	1	♀	25	PACNS	-	2y	Sudden	-	-	-	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	-
Arthritis Rheum 2005; 52:2159	1	♀	10	PACNS	-	6w	-	-	-	25	25	+	+	-	-	9	↑	47	-	+	n/a	-	n/a	n/a	n/a	+	+
	2	♀	9	PACNS	-	2m	-	-	38.2	20.2	95	+	+	-	-	51	43%	-	-	+	n/a	-	n/a	n/a	n/a	+	+
	3	♀	16	PACNS	-	1m	Headaches	-	+	16.3	20	+	+	-	-	747	74%	75	-	+	n/a	-	n/a	n/a	n/a	+	+
	4	♀	5	PACNS	-	<2w	-	-	-	11.5	108	+	+	-	-	-	-	60	-	+	n/a	-	n/a	n/a	n/a	+	+
Neurol Med Chir 2005; 45:156	1	♀	27	Tumor, PACNS with xanthoma cells	-	4w	Headache	-	-	-	-	+	+	+	-	8	0%	-	-	+	n/a	n/a	n/a	n/a	n/a	+	+
Intern Med 2005; 44:883	1	♀	42	PACNS	-	2y	-	-	-	-	-	-	+	-	-	6	n/a	77	-	+	n/a	-	n/a	n/a	n/a	+	-
Can J Neurol Sci 2005; 32:243	1	♀	10	PACNS	-	6w	-	-	-	-	-	+	+	-	-	-	-	-	-	+	n/a	-	n/a	n/a	n/a	n/a	-
Ann Rheum Dis 2006; 65:408	1	♂	76	PACNS & Antiphospholipid Syndrome	-	?	Headaches	-	-	-	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	-	n/a	n/a	n/a	+	-
	2	♂	62	PACNS & Antiphospholipid Syndrome	-	?	-	-	-	-	-	+	+	-	n/a	n/a	n/a	n/a	n/a	+	n/a	n/a	n/a	n/a	n/a	+	+

PACNS, primary angiitis of the central nervous system; RCVS, reversible cerebral vasoconstriction syndrome; RPLS, reversible posterior leukoencephalopathy syndrome; * FND, focal neurological deficits; [n] Abnorm. CT/MRI, CT/MRI evidence of ischemia, hemorrhage, edema or mass lesion; • CSF, abnormal cerebrospinal fluid analysis, R = >0 RBC/µl if no report of traumatic tap, W = >5 WBC/µl, L = lymphocytes, MN = mononuclear cells, N = neutrophils, P = protein >45 mg/dl, G = glucose >75 or <45 mg/dl; ¤ Cerebral Biopsy, histiological evidence of perivascular or transmural lymphocytic and/or histiocytic infiltration; ⌂ CoW Affected, segmental cerebral vasoconstriction affecting the Circle of Willis or its immediate branches, including the distal internal carotid arteries; ◊ Abnorm. Angio, angiographic evidence of cerebral vasoconstriction; □ Angio Resol., angiographic evidence of near to complete resolution of cerebrovascular narrowing; † Clinical Resol., no residual neurological deficits; [a] Transcranial Doppler U/S evidence of either vasoconstriction or resolution; +/-, very mild residual clinical deficits not impairing daily functioning; D, death

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included vision changes, cognitive impairment, paresis, dysesthesias, dysphasia, ataxia, loss of consciousness, coma and seizures.[59] Primary Angiitis of the Central Nervous System presented with headaches of varying degrees in slightly more than half (55%). Focal neurological deficits were documented in 89% of cases, while seizures occurred in just over 1/4. Less than 10% of cases were accompanied by sudden severe headache suggestive of TCH. The underlying cause in five of these instances was sudden infarction, sentinel headache, subarachnoid haemorrhage or CNS infection that would exclude the diagnosis of RCVS. One case was diagnosed concomitantly as RCVS. The disease progression is typically slow and insidious and evolves over weeks to months. In 61% of cases the time of symptom onset to diagnosis was greater than six months. The diagnosis was made greater than two years in 20% of studies. Conversely, five cases were diagnosed within one week of symptom onset, further highlighting the variability of disease presentation. The morbidity and mortality of the disease is considerable as 29% of the subjects reviewed died and only 34% showed clinical recovery.

Laboratory studies revealed an elevated serum white cell count in 20% of cases (range 9.9 to 20.2 x 10^9/L). The ESR was raised in 40% of studies, ≥15 and ≥20 mm/h for males and females, respectively; with a peak of 108 mm/h in one instance.

CSF analysis revealed pleocytosis (≥5 white cells/mm^3) and elevated protein in 65% and 70% of cases, respectively, where lumbar puncture was performed. The white count was ≤200 cells/mm^3 in 88% of reports and lymphocytes predominated (82%) in most instances of pleocytosis. Protein was ≤200 mg/dl in 96% of studies, while glucose and red cell counts for the most part were within normal limits.

Table 4: Typical features distinguishing RCVS[1,2,20,21] and PACNS[13]

RCVS	PACNS
Sudden onset TCH at presentation	Typically no TCH, but headaches often present
ESR normal	Slow, insidious progression
Normal or near-normal CSF analysis	+/- ESR elevation
+/- abnormal MRI	CSF pleocytosis (lympho cytes) & protein elevation
No MRI leptomeningeal enhancement	Abnormal MRI
Segmental cerebral vasoconstriction involving the CoW and/or its immediate branches	+/- MRI leptomeningeal enhancement
Angiographic or TCD ultra sound evidence of near to complete resolution of cerebral vasospasm	Segmental cerebral vasoconstriction not resolved within 2 months of initial angiography.
+/- clinical resolution of neurological deficits	Diagnostic biopsy

Radiologically, all histologically proven cases demonstrated evidenced of a MRI anomaly suggestive of ischemia, haemorrhage, edema or mass lesion. The sensitivity of MRI, however, is insufficient to exclude a diagnosis of PACNS as MRI may be negative early in the disease.[60] Leptomeningeal enhancement occurred in only 15% of studies with MRI. It was unclear from a number of reports if contrast enhancement was used.

The pathognomonic angiographic feature of beading and ectasia was present in just 27% of cases in which cerebral angiography was performed,[5] and affected the Circle of Willis or its immediate branches in 1/2 of these instances. In the few studies with repeat angiography only two demonstrated angiographic resolution at two months and five months, respectively. There was one other study, as mentioned previously, where PACNS and RCVS were suspected to co-occur.[50]

Diseases other than RCVS that can mimic PACNS angiographically include malignant lymphoma,[61] sarcoidosis,[62] herpes viridae, mycoplasma, HIV infections and other vasculitides.[13] It is beyond the scope of this paper to review these conditions in detail. Moyamoya disease is a non-inflammatory vasculopathy that like RCVS involves the spontaneous occlusion of the Circle of Willis. A case reported by Ishimori et al (2006) included reversible vasospasm within the differential diagnosis, however they concluded it was unlikely as there was no angiographic evidence of reversibility at two months follow-up.[63] Primary Angiitis of the Central Nervous System and cerebral amyloid angiopathy are generally recognized as two distinct diseases, yet they may coexist and may be indistinguishable clinically.[64] Cerebral amyloid angiopathy usually requires pathological confirmation. It is unclear if chronic inflammation leads to amyloid deposition or there is a vasculitic response to primary amyloidosis.[44]

Patients were treated with corticosteroids in 88% of PACNS cases, where sufficient information regarding treatment was provided. Nine of the ten cases not prescribed steroids died. Mortality was 17% in patients treated with corticosteroids. This observation is consistent with a review by Harrison (1976)[65] in which all 17 of the first reported PACNS cases not receiving corticosteroids had a fatal outcome.

Discussion

A recent narrative review of reversible cerebral vasoconstriction syndromes by Calabrese et al (2007)[66] published during the data analysis phase of this work also discussed the features distinguishing RCVS and PACNS. The results of our systematic review are largely concordant with their recommendations; however based upon our analysis of the extant literature we recommend a shorter interval between the initial and follow-up vascular imaging studies.

The illustrated clinical scenario is compatible with RCVS or PACNS. The TCH at onset; absence of systemic involvement and infection; normal CSF; and complete reversibility of angiographic abnormalities favours a diagnosis of RCVS despite the occurrence of cerebral infarction. In this case there was no evidence for drug-induced RCVS. The diagnosis of RCVS was made retrospectively after the other competing diagnostic

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entities were excluded and repeat angiography demonstrated resolution of vascular abnormalities.

With respect to the management of TCH and inconclusive CT head imaging and CSF analysis, further investigation based on current protocols is largely determined by the index of suspicion of the treating physician. Two separate long-term studies, roughly a decade apart, of 71 and 93 patients with idiopathic TCH demonstrated that none went on to have SAH or serious neurological sequelae at an average of 3.3 and 5 years follow-up, respectively.[67,68] In a recent review of Thunderclap headache, Schwedt et al[2] recommend an MRI, followed by either an MRA or CT angiography (CTA), as soon as possible to identify potentially reversible secondary causes of TCH. Calabrese et al[66] point out that the most definitive evidence for RCVS is the demonstration of near-complete reversibility within 12 weeks. Our analysis also suggests that a firm diagnosis of RCVS cannot be made until follow-up angiography or other vascular imaging is performed. Based upon our systematic review, we believe that there is sufficient evidence to recommend that physicians managing patients with RCVS seek evidence of angiographic reversibility within one-four weeks of clinical presentation. Cerebral vasospasm may not be entirely resolved at that time, however there may be significant reversibility in vessels initially affected as suggested in Akins et al (1996) and Singhal (2004)[51,52] In our analysis of the available literature, evidence of reversibility was documented in 86%, 59%, and 15% of RCVS cases at three months, four weeks, and seven days, respectively. Reversibility has also been shown to occur within minutes.[69] This variability in time points demonstrating vasoconstriction reversibility does not appear entirely related to the disease process, but rather to the time at which follow-up vascular imaging was instigated. Establishing reversible vasoconstriction within four weeks of diagnosis will be of tremendous practical value to guide patient management. Furthermore, it will help distinguish RCVS from PACNS (See Table 4) since angiographic resolution in histologically confirmed cases of PACNS with repeat cerebral angiography (7 of 83 reports) has been demonstrated in two instances (29%) as early as two and five months after clinical presentation (See Table 3).

Non-invasive MRA or CTA is preferred to conventional catheter-based angiography, and its associated complications, as RCVS tends to affect the circle of Willis or its immediate branches, which are adequately visualized with the former modalities. Alternatively, serial TCD ultrasound carried out over the course of one to two weeks may prove to demonstrate high specificity and sensitivity for RCVS and cerebral vasculitis, respectively (See Gomez et al, 1991 & Ikeda et al, 2001).[70,71] Clearly, both the timing and the diagnostic performance of non-invasive vascular imaging and conventional angiography in this setting requires the performance of a prospective clinical study.

There is little evidence of any effective treatment for RCVS, but it typically has a good outcome in the majority of patients. Some case reports suggest the possible benefit of calcium channel blockers, such as nimodipine.[8,72] As with all calcium channel blockers, blood pressure monitoring is necessary to avoid hypotension, decreased cerebral perfusion, and watershed infarction. In the context of thunderclap headache, normal CSF, absence of systemic manifestations and vasospasm restricted to the Circle of Willis or its immediate branches, nimodipine may be used with caution and corticosteroids may be withheld for one week to look for early signs of angiographic reversibility.

Failing the demonstration of rapid reversibility, one must consider treatment for PACNS. Treatment guidelines, however, have yet to be established due to the lack of controlled clinical trials. Traditionally, therapy has consisted of prednisone with or without the addition of cyclophosphamide depending on the severity of clinical presentation. Younger[42] argues that cyclophosphamide should be reserved for patients with histologically confirmed PACNS who progress or fail to improve with corticosteroids and who can be safely monitored for serious medication side effects.

The key features that distinguish RCVS from PACNS are described in Table 4. Reversible Cerebral Vasoconstriction Syndrome predominantly occurs in females and is characterized by sudden, severe headache at onset, normal CSF analysis, reversible vasoconstriction involving the Circle of Willis and its immediate branches, and angiographic or TCD ultrasound evidence of near-to-complete vasospastic resolution within one-four weeks. It occurs primarily in the context of vasoconstrictive drug use, the peripartum period, bathing, strenuous physical exertion, and sex, but also occurs in isolation. It may help explain the phenomena of primary TCH. Reversible Cerebral Vasoconstriction Syndrome may also be associated with hypertensive encephalopathy, pre-eclampsia and eclampsia, and RPLS warranting consideration of cerebral angiography in the presence of these conditions to explore the possibility of vasospasm.

Primary Angiitis of the Central Nervous System, on the other hand, is rarely accompanied by TCH and generally follows a slow and insidious course. An elevated ESR, which occurs in 40% of histologically proven cases, may help to distinguish PACNS from RCVS. CSF analysis often reveals pleocytosis and/or elevated protein. Magnetic resonance imaging is not sensitive enough to exclude a diagnosis of PACNS if clinical suspicion is high, particularly early in the disease process. Histologically proven cases of PACNS often fail to show the classic angiographic pattern of beading and ectasia. In the instances where segmental narrowing is demonstrated, the Circle of Willis and its immediate branches are involved in half. Near-to-complete normalization on follow-up angiography has not been shown to occur in less than two months from the initial study in cases verified pathologically. Diagnostic certainty of PACNS is obtained only through biopsy.

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