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# Central Nervous System Vasculitis: Immunopathogenesis, Clinical Aspects, and Treatment Options

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Roger E. Kelley, Ramy El-Khoury, and Brian P. Kelley

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## Introduction

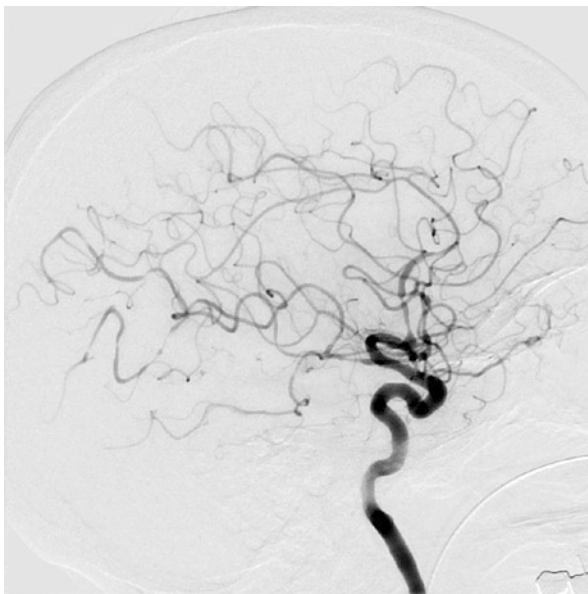
There continues to be significant challenges in determining the etiology of vascular inflammation of the nervous system. Not only can the clinical presentation be obscure, there is the differentiation of primary central nervous system (CNS) vasculitis from secondary vasculitis related to various systemic illnesses such as connective tissue disorders, sarcoid, infectious etiologies such neuroborreliosis, neoplastic vascular involvement, and an array of other autoimmune processes such as Susac syndrome and demyelinating disorders. Primary CNS vasculitis, also known as angiitis, is often denoted as primary angiitis of the CNS (PACNS). It is considered rare, but enhanced diagnostic measures have led PACNS to be a not uncommonly encountered component of the differential diagnosis in the inflammatory disorders of the CNS. Much has been made of the determination of PACNS by vasculitic changes most sensitively detected by a suggestive pattern on intra-arterial cerebral angiography (Fig. 4.1). However, it is now well recognized that the sensitivity of such imaging is certainly not 100% especially when one is encountering small vessel involvement. On the other hand, the index of suspicion tends to be much higher when there is a so-called smoking gun for inflammatory CNS disorders such as coexistent rheumatological disorders including systemic lupus erythematosus, Sjogren's syndrome, neuro-Behcet's disease, Wegener's granulomatosis, polyarteritis nodosa, Kohlmeier-Degos disease, Cogan's syndrome, sarcoid granulomatosis and angiitis, granulomatous (temporal) arteritis, and scleroderma. The overall differential diagnosis of central nervous system

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R.E. Kelley, MD (✉) • R. El-Khoury, MD • B.P. Kelley, BS  
Department of Neurology, Tulane University School of Medicine,  
1430 Tulane Avenue 8065, New Orleans, LA 70112, USA  
e-mail: [rkelly2@tulane.edu](mailto:rkelly2@tulane.edu); [relkhour@tulane.edu](mailto:relkhour@tulane.edu); [bkelly1@tulane.edu](mailto:bkelly1@tulane.edu)

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**Fig. 4.1** Cerebral arteriogram in patient diagnosed with primary central nervous system angiitis. There is diffuse vessel narrowing in this patient with a stroke-like presentation

**Table 4.1** Differential diagnosis of primary central nervous system vasculitis

1. Primary angiitis of the CNS	10. Progressive multifocal leukoencephalopathy
2. Reversible cerebral vasoconstriction syndrome	11. Lymphocytic angioendotheliosis
3. Fibromuscular dysplasia	12. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)
4. Systemic autoimmune disorders (Table 4.2)	
5. CNS lymphoma	13. Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS)
6. Multiple sclerosis	
7. Acute disseminated encephalomyelitis	
8. CNS infectious processes (Table 4.3)	14. Mitochondrial encephalopathy with lactic acidosis and stroke-like syndromes (MELAS)
9. Moyamoya disease	

vasculitis is summarized in Table 4.1. Potential autoimmune mechanisms are summarized in Table 4.2.

From a practical standpoint, one must determine if the presentation represents actual PACNS, when confined to the CNS, or the primary mimic of this disorder which is reversible cerebral vasoconstriction syndrome (RCVS). This has major implications, and it will determine whether or not potent immunosuppression, specifically for PACNS, is indicated or not.

**Table 4.2** Autoimmune disorders associated with central nervous system vasculitis with subcategories

Large vessel	Medium vessel
1. Giant cell arteritis	1. Polyarteritis nodosa
2. Takayasu arteritis	2. Kawasaki disease
Small vessel rheumatologic	
1. Systemic lupus erythematosus	3. Sjogren's syndrome
2. Rheumatoid arthritis	4. Scleroderma
Antineutrophil cytoplasmic antibody (ANCA) associated	
1. Wegener's granulomatosis	3. Microscopic polyangiitis
2. Churg-Strauss syndrome	
Immune-complex deposition associated	
1. Henoch-Schonlein purpura	2. Cryoglobulinemia
Other inflammatory or undetermined pathogenesis	
1. Neuro-Behcet's syndrome	4. Cogan's syndrome
2. Sarcoidosis disease	5. Churg-Strauss syndrome
3. Susac syndrome	

## Primary Angiitis of the Central Nervous System (PACNS)

### Overview

PACNS is based upon the determination of unexplained neurological or psychiatric manifestations with demonstration of arteritis of the CNS by either angiography and/or pathological confirmation. Childhood PACNS is similar except for an age range of 1 month of age or older up to 18 years of age [1]. In many patients, the clinical presentation is one of the unexplained stroke-like features along with headache, cerebrospinal fluid (CSF) pleocytosis, and lack of systemic manifestations. In such a clinical setting, routine cerebral angiography remains indicated despite the attractiveness of magnetic resonance angiography (MRA) or computed tomographic angiography (CTA) as less invasive alternative vascular imaging modalities. It has been proposed that the criteria for diagnosis be separated into definite and probable categories [2]. It has also been proposed that subcategorization into granulomatous angiitis of the central nervous system, benign angiopathy of the CNS, and atypical PACNS is also indicated [3].

In certain patients, there can be an insidious course with subtle manifestations predating a more definitive diagnosis by up to several years. This form of granulomatous angiitis is associated with small vessel infarction in different vascular territories along with a meningitic symptoms [4, 5]. There can also be spinal cord involvement [6]. Such small vessel involvement, especially in vessels smaller than 500  $\mu\text{m}$ , limits the sensitivity of even routine angiography with a reported detection rate ranging from 40 to 90% [1]. One study reported a sensitivity of cerebral angiography as low as 27% when compared to documentation by tissue biopsy [7]. In such circumstances, leptomeningeal enhancement on MRI brain scan can be particularly pertinent in helping to raise concern about such a vasculitis process and guiding planned biopsy [8].

## Diagnosis

It is expected that MRI brain scan will be of particular value in supporting or refuting CNS vasculitis. MRI brain scan abnormality, along with CSF pleocytosis, is found in greater than 90% of patients [2]. Conversely, a normal MRI brain scan and negative CSF exam are expected to have a high level of confidence in ruling out PACNS as an explanation for the symptoms. The helpful MRI clues to diagnosis are a characteristic vascular pattern in different distributions seen on either T2-weighted or fluid attenuation inversion recovery (FLAIR) images. This along with a leptomeningeal enhancement pattern can be particularly pertinent. However, leptomeningeal enhancement is uncommonly reported to occur in roughly 8% of patients [9]. Enhancement of parenchymal lesions in PACNS is reported to occur in up to one-third of patients [4].

It is reported that the CSF is abnormal in up to 80–90% of patients with PACNS [2], but the findings can be quite subtle and nonspecific such as a modest elevation of the white blood cell count or the total protein. However, CSF analysis also serves to determine if there may be a systemic process such as infection, connective tissue disorder, or malignancy. A pronounced CSF white blood cell elevation, especially with polymorphonuclear leukocytes, rather than a relatively modest lymphocytic pleocytosis, should raise particular concern about alternative explanations. In such circumstances, gram stain and bacterial culture, along with viral culture and appropriate viral polymerase chain reaction (PCR), as well as a fresh, large CSF sample for cytology, will be indicated. White matter signal intensity changes in such a clinical setting should also lead to serious consideration of a multiple sclerosis panel.

PACNS remains a diagnostic challenge, and this is probably compounded by the fairly routine substitution of routine intra-arterial cerebral arteriography with less invasive modalities specifically MRA and CTA which have lower diagnostic yield. This mandates higher levels of suspicion for PACNS when features in Table 4.3 are present. The sensitivity of brain/leptomeningeal biopsy varies from 36 to 83% [2]. The supportive histologic findings include lymphocytic cellular infiltrates, granulomatous inflammation, and vessel wall fibrinoid necrosis [6]. In the Mayo Clinic cohort [10], of 163 patients diagnosed with PACNS, 105 were diagnosed on the basis of cerebral angiographic findings, while 58 were diagnosed by biopsy. The authors were able to identify some differentiations in their cohort with biopsy-proven subjects more likely to present with cognitive impairment as well as had higher CSF protein, less frequent cerebral infarction pattern, more frequent enhancing lesions on

**Table 4.3** Features which can raise concern about primary angiitis of the central nervous system in a patient with stroke-like presentation

1. Unexplained ischemic stroke	4. Leptomeningeal enhancement
2. Multiple vascular territories involved	5. Cerebrospinal fluid pleocytosis
3. Accompanying headache	6. Suspicion of cerebral arterial narrowing, especially beading pattern, on angiography

MRI, as well as lesser mortality and morbidity. On the other hand, those identified by cerebral angiography had more frequent stroke-like presentations both clinically and by imaging along with greater mortality. It was theorized that this was attributable to larger vessel involvement in the angiogram-positive group.

## Treatment

The importance of accurate diagnosis is underscored by the dilemma of an unrecognized and untreated serious disease process, with potentially devastating consequences, versus empiric therapy with potent immunosuppressive agents which can have serious long-term side effects. The treatment for PACNS remains empiric with no randomized clinical trials available to provide convincing guidance. Because of the inflammatory nature of the disease process, immunosuppression is considered the underpinning of effective management. This must factor in the risks versus potential benefits of such therapy especially with the absence of specific biomarkers for disease activity. This is in distinction to giant cell arteritis where both the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) can be of value in monitoring the course of the disease and response to therapy [11].

Birnbaum and Hellman [2] outlined a therapeutic approach for PACNS in 2008 based upon presently available information. They combined cyclophosphamide at 2 mg/kg/day with prednisone at 1 mg/kg/day. In severe acute presentations, they initiated methylprednisolone intravenously with 1000 mg daily for 3 days. This reflected some alteration of the recommendation of Salavarani et al. [4] in which corticosteroid therapy alone was felt to be adequate. In a recent review from 2013 [12], the combination of a corticosteroid and cyclophosphamide is felt to be the “gold standard.” However, in light of concerns about the longer-term side effects of daily oral cyclophosphamide, intravenous pulse therapy is reported to be less toxic and of equivalent efficacy [13]. There is also increasing acceptance of limiting the course of oral cyclophosphamide therapy to no more than 3–6 months in light of these concerns over longer-term toxicity [14]. Over the longer term, it has been recommended that prednisone be tapered and discontinued over a 12-month period [2], and cyclophosphamide be replaced with lower-risk immunosuppressants such as azathioprine at 1–2 mg/kg/day, methotrexate at 20–25 mg/week, or mycophenolate mofetil at 1–2 gram/day [15]. Most patients are felt to go into remission after a 12–18-month course of immunosuppression [16], but treatment for up to 2–3 years may be necessary [2].

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## Reversible Cerebral Vasoconstriction Syndrome (RCVS)

### Overview

This is an increasingly recognized entity that has been invoked with various terminologies such as Call-Fleming syndrome [17] as well as a migraine-related vasospasm [18]. RCVS is characterized by severe headache in association with diffuse

segmental vasoconstriction of the cerebral arteries that are generally reversible within a 3-month time frame [19]. This “string of beads” pattern is most definitively detected by intra-arterial digital subtraction angiography (DSA). However, the yield of detection is reported to be as high as 80% by less invasive cranial tomographic angiography (CTA) or magnetic resonance angiography (MRA) [20]. RCVS, despite being viewed as a reversible process, is not only associated with what can be incapacitating severe headache, which has been termed thunderclap to underscore its severity [21, 22], it can also be associated with seizures, ischemic and hemorrhagic stroke, as well as subarachnoid hemorrhage not in association with cerebral aneurysm [23].

The incidence of RCVS is unknown as its detection is predicated on pursuit of cerebrovascular imaging in the clinical setting which is often arbitrary for a particular institution. There can also be a difference of opinion as to what constitutes RCVS depending upon the criteria used by the reporting physicians [23]. This is often dependent on the duration of the headache and any possible associated focal neurological deficit. Most patients have headache as the sole manifestation [24], and, unlike the headache associated with aneurysmal subarachnoid hemorrhage, the duration is usually no more than several hours [23].

## Associated Conditions

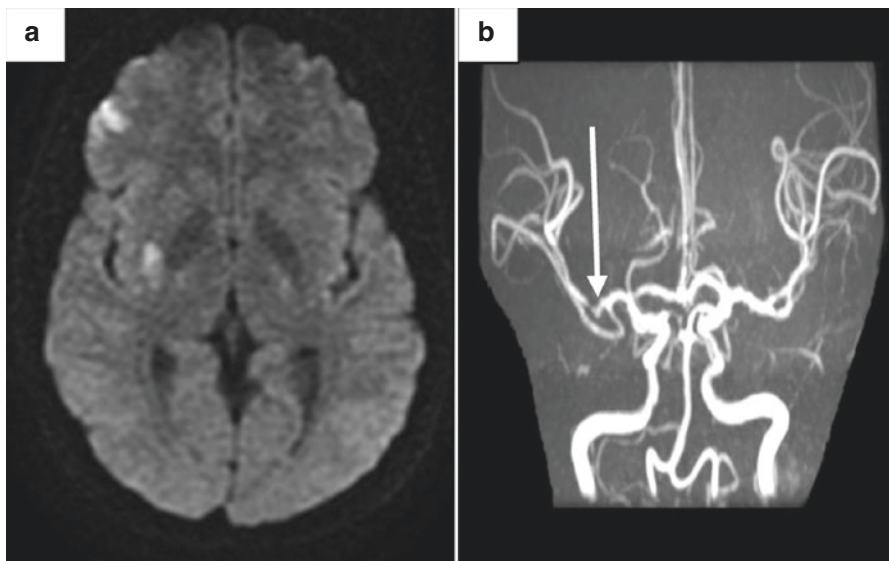
Table 4.4 summarizes conditions that can be associated with reversible cerebral vasoconstriction syndrome. There are particularly pertinent associations including migraine; postpartum period vascular complications, including that associated with preeclampsia and eclampsia; posterior reversible encephalopathy syndrome (PRES); and convexity subarachnoid hemorrhage. It has been reported that two-thirds of patients with postpartum RCVS have onset of symptoms within 1 week of delivery and typically after an uncomplicated delivery [25]. RCVS can overlap with PRES in between 8 and 39% of those affected [21, 26]. PRES is an encephalopathic condition associated with seizures, headache, and visual loss [27]. Like RSCV, the onset is usually sudden and is associated with reversible vasogenic edema seen either on CT or more readily defined on MRI brain scan, particularly T2-weighted and FLAIR images [28]. The DWI/ADC image pattern of hyperintensity on DWI and ADC has been reported to be most common with some subjects showing hyperintensity on DWI with hypointensity of ADC or normointensity on DWI and hyperintensity on ADC [29].

**Table 4.4** Conditions associated with reversible cerebral vasoconstriction syndrome

1. Migraine angiopathy	5. Post-carotid endarterectomy
2. Postpartum angiopathy	6. Cerebral venous thrombosis
3. Posterior reversible encephalopathy syndrome	7. Convexity subarachnoid hemorrhage
4. Vasoactive drugs including triptans, ergotamines, sympathomimetic agents, immunosuppressants	8. Head trauma
	9. Autonomic dysreflexia

PRES tends to be self-limited with resolution of the vasogenic edema within several days. However, despite the “reversible” connotation, one can see resultant cerebral infarction, associated with cytotoxic edema, as well as intracerebral hemorrhage [30]. PRES is associated with numerous conditions, including infection, markedly elevated blood pressure, autoimmune disease, immunosuppressants, cytotoxic agents, as well as eclampsia and preeclampsia. Naturally, the manifestations of PRES, as well as the outcome, might well reflect the underlying associated condition.

Migraine was previously thought to represent a vasoconstriction in the aura phase followed by vasodilatation in the headache phase, at least in regard to migraine with aura. However, this simplified approach has been abandoned to a considerable degree. Despite this, concerns about vessel narrowing in migraine, especially when there is focal neurological deficit, such as in hemiplegic migraine, have raised concerns about the potential for infarction (Fig. 4.2). This is of particular concern with vasoconstrictive agents such as triptans and ergot alkaloids. Of note, migraine is often seen in association with RCVS and terminologies previously used, such as migraine angiitis [31], or migrainous vasospasms [32] may have been reflective of this association. Also of interest, in terms of potential overlap mechanism, triptans and ergots have been reported to precipitate RCVS in certain patients [33] with potentially serious consequences [34]. In addition, migraine in association with RCVS is reported to increase the risk of cerebral hemorrhage [35].



**Fig. 4.2** (a) Diffusion-weighted image (DWI) on magnetic resonance imaging (MRI) brain scan of a 36-year-old woman with severe migraine-type headache in association with acute left side weakness. There are multiple areas of increased signal intensity in the distribution of the right middle cerebral artery (MCA). (b) Magnetic resonance angiography (MRA) revealed focal right MCA narrowing (*arrow*) believed reflective of migrainous arteriopathy

## Treatment

Any potential factor possibly contributing to RCVS should be as effectively removed as feasible. This would include discontinuation of vasoactive medications. Management of associated hypertension is imperative as are symptomatic management approaches to headache, avoidance of physical exertion, and relaxation measures for anxiety. There have been reports of response to vasodilating agents, such as verapamil or nimodipine, as well as to magnesium [23], but no systematic randomized control trials are presently available to support this in an evidence-based approach.

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## Giant Cell (Temporal) Arteritis

### Overview

This is a larger- and medium-size vessel inflammatory disorder typically seen in older subjects, beyond age 50, with the peak incidence at 70–80 years of age [36]. It is most commonly seen in Caucasians of European descent [37]. An association has been reported between HLA-DR4 and HLA-DRB1 suggestive of a genetic susceptibility [38]. The female to male ratio is reported to be 3:1 [39]. There is considerable overlap with a diffuse inflammatory disorder of the muscles, polymyalgia rheumatica (PMR). Roughly 50% of patients with giant cell arteritis (GCA) develop PMR either before, during, or after the time of presentation of GCA [40]. GCA is a T-cell-mediated disorder with recruitment of both T cells and macrophages to form a granulomatous infiltrate within the affected vessels [41]. On temporal artery biopsy, one sees inflamed vascular tissue with various cytokine and other inflammatory mediators [41]. Of interest, in terms of pathogenesis, Gilden and Nagel [42] have reported a relationship between varicella zoster virus (VZV) antigen and positive GCA pathology on temporal artery biopsy. In an extension of this study [43], they found VZV antigen in 74% of 82 GCA-positive biopsies. They theorize that GCA has a viral-mediated trigger.

It is expected that the incidence of GCA will increase as the population has greater longevity, and there is a present reported incidence of 27 cases per 100,000 for those 50 years of age and older [37]. The recognition is extremely important in a timely fashion in light of the potential for ischemic optic neuritis with irreversible blindness. This is reported to affect 10–15% of patients with GCA [44]. The protection of such an occurrence with early administration of steroid therapy is utmost urgency in the clinical setting.

### Manifestations

A patient presenting with new onset headache at 50 years or beyond should always raise concern about GCA. Localization to the superficial temporal artery region



**Table 4.5** Features of giant cell (temporal) arteritis

1. Moderate to severe head pain in region of the superficial temporal artery	6. Elevation of the erythrocyte sedimentation rate (ESR)
2. Age $\geq$ 50 years	7. Elevation of the C-reactive protein (CRP)
3. Predilection for female Caucasians	8. Systemic complaints which can include fever, malaise, and weight loss
4. Jaw claudication	
5. Neck pain	9. Temporal biopsy with characteristic granulomatous inflammation

along with tenderness to palpation of this region should heighten the degree of concern. These are the most common manifestations. There can be accompanying jaw claudication and neck pain. It is also important to recognize that there can be systemic manifestations including fever of unknown origin, lassitude, and malaise, as well as loss of appetite with weight loss. The vasculitic process can involve not only the temporal arteries but also the carotid distribution, the aortic arch, as well as the axillary, iliac, and femoral arteries [45]. There can be both arterial and venous occlusive events associated with such inflammation including both myocardial infarct and stroke [46]. Features of GCA are summarized in Table 4.5.

## Diagnosis and Treatment

The American College of Rheumatology criteria [38] factors in such features as head pain in the region of the superficial temporal artery, age  $\geq$  50, and elevation of the erythrocyte sedimentation rate (ESR) to  $> 40$  mm/h to formulate their criteria for diagnosis with a reported sensitivity of 93.5% and specificity of 91.2% [45]. However, Murchison et al. [47] reported that the use of these criteria alone, without confirmatory temporal artery biopsy findings, could miss up to 25% of cases. The ESR is often quite high at 80 mm/h or above, and the C-reactive protein (CRP) is often quite elevated. These are not 100% in terms of degree of detection, however. One study of 764 subjects [48] reported a sensitivity of the ESR of 84% and the CRP of 86% but with a specificity of 30%. Overall, the yield is quite high with only 4% of patients having normal ESR and CRP values at the time of diagnosis.

Because of the low specificity for the ESR and CRP, and the need to support ongoing steroid therapy if indeed the patient has GCA, then a temporal artery biopsy is mandatory. The granulomatous inflammatory findings expected on biopsy are detected in 85–95% of GCA cases [49]. The urgency to protect against potential blindness, with steroid therapy, can lead to misdiagnosis. Saedon et al. [50] reported that clinical criteria for diagnosis, without confirmatory biopsy findings, led to immunosuppressive treatment in 61% of 112 patients which raises some concern about possible unnecessary treatment in some subjects.

A generally accepted approach is the initiation of prednisone at 1 mg per kg of body weight per day. For those patients with worrisome visual symptoms, a 3-day course of daily 1000 mg intravenous methylprednisolone would be indicated. Assuming response, various tapering courses have been implemented. It has been

suggested that a reasonable approach is reduction of the dose of prednisone by 10–20% every 2 weeks down to less than 10 mg a day, and then a slower taper follows by 1 mg per month [40]. The course of tapering is obviously influenced by the ESR, and CRP results with such studies recommended monthly the first year, bimonthly the second year, and every 3–6 months for longer-term follow-up. Alternative agents for those patients either not responsive or intolerant of glucocorticoids include cyclophosphamide, methotrexate, azathioprine, and infliximab [51]. Antiviral therapy will certainly be investigated in light of the recent identification of an association with VZV [42, 43].

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## Polyarteritis Nodosa (PAN)

### Overview

PAN usually presents in the fourth or fifth decade but can present in childhood. Men are affected twice as commonly as women. There can be an association with hepatitis B or C infection [12]. There is typically multi-organ involvement. The systemic inflammatory process can be reflected in systemic signs such as fever, malaise, and weight loss. This can be supported by an elevated ESR, and renal involvement is usually accompanied by proteinuria as well as hypertension. Dermatological manifestations and peripheral neuropathy tend to be particularly common.

Despite potentially devastating effects, PAN is not uncommonly associated with CNS vascular involvement. In one report, 12% of 26 patients had only CNS involvement, while 34% had combined CNS and peripheral nervous system (PNS) involvement [52]. This systemic vasculitis is associated with necrotizing inflammatory vascular lesions of primarily small- and medium-size muscular arteries. There tends to be preferential involvement of vessel bifurcations. There is microaneurysm formation with the potential for hemorrhage as well as thrombosis with infarction [53]. Cumulative involvement of the brain can result in a multifocal encephalopathy in up to 40% of affected patients [54], but isolated cerebral infarction or hemorrhage can be the presenting manifestation. One can see a lacunar-type infarction pattern related to thrombotic microangiopathy [55]. Generally speaking, in light of the potential for smaller vessel involvement, cerebral arteriography is recommended for evaluation of patients suspected of having the disease.

### Diagnosis and Treatment

The spectrum of manifestation of a systemic vascular inflammatory process should raise suspicion for PAN in the differential diagnosis. Pathological confirmation is most readily determined when there is associated dermatological or PNS involvement available for biopsy. The diagnostic challenge of CNS involvement is lessened by the tendency for cerebral, or spinal, vasculitis to develop 2–3 years later than other manifestations.

The treatment is immunosuppression. In uncomplicated disease, corticosteroids can have a very positive impact on prognosis including survival [56]. In more aggressive disease, cyclophosphamide combined with steroid can have a positive impact [57]. Anecdotally, rituximab may provide benefit in refractory cases of PAN [12]. Antiviral therapy combined with immunosuppression is reported to be of particular benefit in hepatitis B- and C-related PAN [58] especially in severe disease [59].

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## **Antineutrophil Cytoplasmic Antibody (ANCA)-Associated CNS Vasculitis**

### **Overview**

Antibodies reflective of ANCA are directed against certain cytoplasmic proteins within neutrophils and appear to be part of the pathogenesis in certain vasculitides. This is an evolving process both in terms of insight into mechanism and terminology. For example, “Wegener’s granulomatosis” has been suggested to be replaced with “granulomatosis polyangiitis” (GPA). Churg-Strauss syndrome has been proposed to be replaced with eosinophilic granulomatosis with polyangiitis (EGPA). The other commonly cited ANCA-related vasculitic process is microscopic polyangiitis (MPA) [60].

CNS involvement by Wegener’s granulomatosis is quite uncommon [61]. It can be associated with either small to medium-sized cerebral vasculitis, meningitis, or orbital granuloma [62]. There can be extension of the granulomatous process to the cavernous sinus with resultant cavernous sinus syndrome [63]. Cerebral vasculitis is seen in up to 4% of patients and is reported to be the most frequent CNS manifestation [64].

MPA affects small vessels such as arterioles, capillaries, and venules and can be associated with cerebral infarction [65] although reports tend to be few and far between reflective of the rarity of such a disorder. There is the potential for lacunar-type infarct as well as hemorrhagic stroke, and support for the diagnosis can come from elevated ESR and CRP, positive ANCA, and pathological confirmation such as sural nerve biopsy [66].

EGPA affects small- and medium-size vessels. This is a systemic process typically affecting the lungs with asthma and eosinophilia and often with gastrointestinal involvement as well. The necrotizing small vessel vasculitis can also affect the CNS with resultant stroke, ischemic or hemorrhagic [54]. Although rare, it has been proposed that this diagnostic possibility be raised in patients with stroke and hyper-eosinophilia [12].

### **Diagnosis and Treatment**

Recognition of the clinical manifestations is key with such a systemic granulomatosis processes as Wegener’s, aka GPA, and Churg-Strauss, aka EGPA. Pathological confirmation of available tissue for biopsy is of utmost importance as aggressive immunosuppressive therapy can be of clear benefit in most patients. In EGPA, for

**Table 4.6** Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis types and patterns

Designation	Alternative name	Areas of involvement	CNS manifestations
Wegener's granulomatosis	Granulomatosis with polyangiitis	Small and medium blood vessels of multiple organs	Ischemic and hemorrhagic stroke small- and medium-size vessel pattern
Churg-Strauss syndrome	Eosinophilic granulomatosis with polyangiitis	Pulmonary with eosinophilic asthma, gastrointestinal, and other organs	Ischemic and hemorrhagic stroke with nodular small vessel polyangiitis, seizures, cranial nerve palsies
Microscopic polyangiitis		Micro-arteriolar necrotizing systemic pattern	Ischemic small vessel infarcts, sino-venous occlusion, hemorrhagic stroke, basilar meningitis

example, the small epineural arteriolar inflammatory process is often identified on peripheral nerve biopsy as neuropathy is a common manifestation of this illness [67] with CNS involvement much less common [68]. Characteristically, one sees necrotizing vasculitis with eosinophilic infiltration along with extravascular granulomas. In this disorder, corticosteroid therapy can be highly effective with one study demonstrating remission in 94% of patients during the first year of therapy [69].

More aggressive ANCA-associated inflammatory disease, especially when associated with cerebral vasculitis, often calls for more potent immunosuppression such as a combination of cyclophosphamide and high-dose glucocorticoids. Gaining acceptance as a replacement for cyclophosphamide is rituximab shown to be non-inferior in two ANCA-associated vasculitis studies [70, 71]. Both azathioprine and methotrexate can be alternatives for chronic immunosuppression [72].

It is important to point out that the role of ANCA autoantibodies in the pathogenesis is not clearly defined. For example, Wegener's granulomatosis can be associated with polyangiitis in ANCA-negative patients [73]. In addition, the presence of ANCA antibodies can overlap with other autoimmune disorders, such as Sjogren's syndrome, and possibly contribute to the spectrum of manifestations [74]. ANCA-associated vasculitic disorders are outlined in Table 4.6.

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## Takayasu Disease

### Overview

This is a larger-vessel granulomatous vasculitis with particular involvement of the aorta and its major branches. It is typically seen in patients less than 40 years of age [54]. It is much more commonly seen in women than men. Aortic imaging in patients suffering from large artery occlusive disease, with loss of pulses (pulseless

disease), is vital in diagnostic evaluation. Systemic manifestations can precede occlusive events and include fever, malaise, and loss of appetite. Elevated ESR and CRP call attention to the inflammatory nature of this rare disorder. The natural history can range from mild to severe [75]. Involvement of the carotid arteries can result in ischemic optic neuropathy and stroke. Corticosteroid therapy is traditionally the first line of immunosuppression. Unfortunately, the ongoing need for such therapy often leads to side effects. Agents used for steroid sparing include azathioprine, methotrexate, antitumor necrosis factor receptor agents, rituximab, and cyclophosphamide with some degree of response reported in open-label trials [76].

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## Neuro-Behcet's Disease

### Overview

Unlike Takayasu disease, Behcet's syndrome is more common in men. There is a triad of oral and genital ulcers with uveitis. There can be CNS involvement in up to 30% of cases which can include small vessel vasculitis and meningovascular inflammatory cell deposition. Neuro-Behcet's disease can be either acute or chronic progressive [77]. The acute form can be set off by cyclosporine A. The acute form is associated with a meningoencephalitis with focal lesions seen on T2-weighted and FLAIR MRI [78]. This form tends to be very steroid responsive and self-limited.

The chronic form is characterized by a slowly progressive neurological impairment with dementia, ataxia, and dysarthria [79]. There is an elevation of cerebrospinal fluid interleukin-6 activity [54]. High-dose methylprednisolone tends to be the first line of therapy with well-recognized resistance to such therapy along with cyclophosphamide and azathioprine. However, low-dose methotrexate may be of particular benefit for disease suppression in the chronic progressive form [80].

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## Cogan's Syndrome

### Overview

This rare autoimmune syndrome is characterized by bilateral interstitial keratitis with profound sensorineural hearing loss. There can be systemic vasculitic manifestations, and there are both typical and atypical presentations described [81]. There can be an association with both ANCA antibodies and rheumatoid factor suggestive of a potential overlap in terms of pathogenesis and potential contribution to vasculitis. There can be associated larger artery aneurysm formation which can include the carotid artery [82]. This is reflective of the larger vessel involvement seen in both Cogan's syndrome and Behcet's disease [83]. Of note, there is considerable overlap in the manifestations of these two disorders with both diagnosed on the basis of clinical manifestations with lack of confirmatory diagnostic testing. Despite its recognition as a cause of CNS vasculitis, it is felt that Cogan's syndrome is not only quite rare but uncommonly results in neurological manifestations [84].

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## Susac Syndrome

### Overview

The clinical trial of this rare, apparent autoimmune process consists of CNS involvement, branch retinal artery occlusions, and sensorineural hearing loss. As of a review published in 2012, 304 cases of this syndrome had been reported worldwide at that time [85]. There is an inflammatory process affecting microvessels of the brain, retina, and inner ear. It has most commonly been reported in young women and is felt to be underdiagnosed [86]. Retinal artery branch occlusions can be documented by fluorescein angiography, and compatible changes on MRI brain scan have been reported in patients presenting with the triad. Antiendothelial cell antibodies are found in some patients [86]. Response to immunosuppression has been reported with corticosteroid therapy as the usual initial first choice.

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## Cryoglobulinemia-Associated CNS Vasculitis

### Overview

Vasculitic involvement in cryoglobulinemia is characterized by the triad of purpura, weakness, and arthralgia [12]. The presentation can be quite insidious, but aggressive multi-organ involvement can be life threatening. This smaller vessel arteritis is related to the deposition of cryoglobulins within the vessel wall with activation of the complement cascade. Type I represents single monoclonal immunoglobulin formation related to B-cell lymphoproliferative disorders, while types II and III are often referred to mixed cryoglobulinemias. These are reflective of polyclonal IgG immunoglobulin formation with or without monoclonal IgM associated with rheumatoid factor activity [87]. Hepatitis C virus infection is observed to be the most common cause of mixed cryoglobulinemic vasculitis [88].

There can be associated cerebral infarction, and there is also the potential for the associated hyperviscosity to promote cerebral ischemia. The treatment consists of various forms of immunosuppression with the potential for rituximab to be particularly effective [89, 90]. Hyperviscosity in cryoglobulinemia is best managed with early plasma exchanges.

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## CNS Vasculitis in Association with Connective Tissue Disorders

### Overview

The following disorders fall into this category: systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (scleroderma), and Sjogren's syndrome. SLE is the best recognized for association with CNS vasculitis although alternative mechanisms can be related to coexistent antiphospholipid antibody syndrome,

resulting in a hypercoagulable state, as well as potential cardio-embolic events from Libman-Sacks endocarditis. The most common CNS presentation is a multifactorial encephalopathy which can include cognitive impairment with psychosis, seizures, headache, and chorea. The autoimmune-mediated pathology tends to be non-thrombotic in such a presentation but instead is a combination of deposition of immune complexes and vasculitis. SLE is prominently listed in the differential diagnosis of stroke in the young [91]. There can be vascular occlusion with ischemic stroke as well as hemorrhagic insults which can be related to vasculitic mediated aneurysm formation [92]. Involvement of the CNS is relatively common in SLE, but the exact frequency of involvement varies considerably among reported studies [54, 93].

Systemic sclerosis is not commonly associated with CNS vasculitis but is recognized for potential PNS effects. Amaral et al. [94] reported on 180 studies of systemic sclerosis and identified the following pattern of potential CNS involvement: headache in 23.73%, seizures in 13.56%, and cognitive impairment in 8.47% with anxiety/depression also commonly seen.

Rheumatoid arthritis (RA), like lupus, is now a much more indolent disease with advances in immunosuppression. Furthermore, the incidence of RA is reported to be declining [54]. Cerebral infarction can be seen related to vasculitis. Of note, there is the potential for atlantoaxial subluxation with resultant ischemia or compression to the brainstem. It is reported that this is a not uncommon cause of death attributable to RA [95].

Sjogren's syndrome, also known as keratoconjunctivitis sicca, can be associated with vasculitis of the CNS. It is reported that the vascular insult may be related to the presence of anti-Ro and antineuronal antibodies [54]. There have been reports of both ischemic and hemorrhagic strokes with this disorder. However, the risk appears to be quite small and, as mentioned previously, may be part of an autoimmune overlap such as with coexistent ANCA antibodies [74].

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## Infection-Related CNS Vasculitis

### Overview

The classic infectious CNS vasculopathy, from years past, was meningovascular syphilis. After effective eradication of this former common cause of stroke, there has been somewhat of a reemergence related to coinfection with human immunodeficiency virus (HIV) resulting in less resistance to CNS penetration by the spirochete. It is still fairly standard to obtain syphilis serology for any unexplained stroke, either ischemic or hemorrhagic, especially in a younger patient. A biologically false-positive test, such as the VDRL (Venereal Disease Research Laboratory) test or RPR (rapid plasma reagin) test, could be an indicator of the presence of antiphospholipid antibodies, while a true positive, such as that seen with a positive fluorescent treponemal antibody absorption (FTA-ABS) study, would point toward CSF evaluation for possible meningovascular syphilis. According to recent reports, the yield of such a pursuit is now greater with coexistent HIV disease.

**Table 4.7** Vasculopathy of the CNS associated with infection

1. Varicella zoster	7. Meningovascular from bacterial, fungal, and tuberculosis infection
2. HIV	
3. Neurosyphilis	8. Septic emboli from subacute bacterial endocarditis
4. Hepatitis C	9. Septic aortitis
5. Rickettsial	10. Q fever
6. Viral encephalitis	11. Mycoplasma
7. Ehrlichial vasculitis	12. Toxoplasma vasculitis

HIV can be associated with CNS vasculopathy with resultant infarction. There is often a heterogeneous pattern to the vascular involvement, related to coexistent disease, but there is the potential for either a primary granulomatous angiitis, eosinophilic vasculitis, or a necrotizing vasculitis [97, 98]. The pathogenesis of the vasculitis may involve overlap with autoimmune antibodies such as antinuclear antibodies and ANCA antibodies [98].

VZV can be associated with a combined meningoencephalitis and vasculitis [99]. There can be either small or larger vessel involvement. As mentioned previously, there is recently reported evidence of the potential for VZV to promote GCA [42, 43]. Despite the recognition that VZV can affect the CNS in a number of ways [100], a recent review of this topic [101] concluded that VZV-associated cerebral infarction is uncommon. When cerebral infarction does occur, the reported cerebral angiographic findings can include segmental constriction and occlusion often with post-stenotic vessel dilatation [102]. However, this would be reflective of larger vessel involvement with negative cerebral arteriography not necessarily excluding small vessel disease. Such VZV-associated infarcts are often treated with a combination of corticosteroids and acyclovir after support for such a process with a positive VZV polymerase chain reaction (PCR) result.

Other infection-related vasculitides include endovascular microbial disease related to bacterial endocarditis and septic aortitis, rickettsial, Q fever, ehrlichial, mycoplasma, toxoplasmosis, tuberculosis, fungal, parvovirus, cytomegalovirus, herpes simplex virus, human T-cell lymphotropic virus-1, Epstein-Barr virus, and West Nile virus [103] outlined in Table 4.7.

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## Neoplastic-Related CNS Vasculitis

### Overview

Vascular invasion with an inflammatory response can be seen in certain neoplastic disorders. Both Hodgkin's and non-Hodgkin's lymphoma have been implicated along with angioimmunolymphoproliferative disorder [3]. The clinical picture can mimic PACNS with the potential for both ischemic and hemorrhagic strokes. The presentation can be quite insidious for intravascular lymphomatosis also known as neoplastic angioendotheliosis [104]. The presentation can mimic disseminated



encephalomyelitis and encephalomyelopathy [105]. A clue to the variable presentations [106] is an unexplained elevation of the serum lactate dehydrogenase level [104, 107]. Naturally, the treatment is directed toward the neoplastic process, and outcome is reflective of response to therapy.

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