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Primary Angiitis of the Central Nervous System and Reversible Cerebral Vasoconstriction Syndrome

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Abstract Primary angiitis of the central nervous system (PACNS) is one of the most devastating pathologic processes that affect the central nervous system (CNS). It results in exclusive inflammation and destruction of CNS blood vessels. Progressive debilitating unexplained neurological deficit associated with abnormal cerebrospinal fluid (CSF) analysis findings is the typical picture of the disease. CNS biopsy is the gold standard diagnostic test. Immunosuppressive therapy is the core treatment. Reversible cerebral vasoconstriction syndrome (RCVS) is a main mimic of PACNS. RCVS is characterized clinically by recurrent thunderclap headache with or without neurological deficit and normal CSF analysis findings and angiographically by reversible diffuse segmental vasospasm of intracranial vessels. A stepwise diagnostic approach should be followed to differentiate PACNS from RCVS and exclude the other clinical, radiographic, and angiographic mimics.

Keywords Primary angiitis of the central nervous system · Reversible cerebral vasoconstriction syndrome

Introduction

"Central nervous system vasculitis" is a broad definition for diseases that result in inflammation and destruction of the blood vessels of the brain, spinal cord, and meninges. We broadly classify central nervous system (CNS) vasculitis into primary and secondary CNS vasculitis. In primary CNS vasculitis, the vasculitis is confined to the CNS; in such cases the term "primary angiitis of the central nervous system" (PACNS) is applied.

The differential diagnosis of secondary CNS vasculitis is broad and includes the involvement of the CNS, in a vasculitic pattern, secondary to wider systemic inflammatory diseases such as connective tissue disease, systemic vasculitis, and chronic inflammatory disease, or infectious diseases such as varicella zoster.

In 1959, Cravioto and Feigin [1] were the first to recognize the entity of PACNS and revealed part of the ambiguity about a new pathologic disease after examination of brains on autopsy. PACNS attracted more attention when reports of successful treatment were reported in the 1980s [2]. After that and as a result of progress in diagnostic modalities and more awareness of the disease, more than 500 cases were reported in the medical literature by 2007 [3••].

Epidemiology

PACNS is rare disorder. A retrospective analysis of 101 cases revealed that the average annual incidence rate of PACNS is 2.4 cases per million person-years [4]. The disease has been reported more commonly in white males, with the median age at onset being 50 years [4–6]. Children have been also affected [7–9].

Clinical Features

The diffuse nature of the involvement of the inflammation of the CNS in PACNS results in nonspecific clinical presentation of the disease. Headache is the commonest presenting symptom. It is usually insidious with subacute onset,

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followed by encephalopathic symptoms, dementia, cognitive dysfunction, and behavioral and personality changes. Recurrent multiple strokes and transient ischemic attacks occur in 30–50 % of patients [4, 10, 11]. Rarely, cranial neuropathies, seizure, ataxia, and coma have been reported [4, 10–12]. The clinical course is usually subacute and chronic. In short, PACNS patients may present with any focal or nonfocal neurological symptoms as a result of diffuse and often patchy involvement of the brain, spinal cord, and their coverings [3••].

Systemic symptoms such as fever, weight loss, and malaise are lacking, and if present should alert the clinician to look for a systemic process.

Subsets of PACNS

Different radiographic and pathologic subsets have been recognized in PACNS. This classification has not been validated, but rather represents authors' observations. The prototype subset, which was originally described, is granulomatous angiitis, referred to as granulomatous angiitis of the CNS (GACNS). This subset is extremely rare. GACNS is characterized by a typical granulomatous inflammatory process affecting the vessel walls on histological examination.

Another finding on pathologic examination includes involvement of the vessel wall by a lymphocytic inflammation without granulomatous components; this group has been classified as lymphocytic PACNS.

Further, a group of patients are diagnosed by angiography without a pathological confirmation. This is referred to as angiographically defined PACNS. In this category, careful exclusion of the mimics of PACNS should be performed; in addition, an inflammatory component of the cerebrospinal fluid (CSF) should be confirmed. Spinal cord vasculitis and mass lesion presentations have been rarely reported as has amyloid-related angiitis [13–16].

Diagnostic Criteria of PACNS

Nonspecific clinical presentation of PACNS makes the diagnostic process more challenging. Furthermore, the absence of sufficiently sensitive and specific diagnostic tests which can confidently confirm the diagnosis or safely exclude it and other mimics makes it a real diagnostic dilemma. In 1988, Calabrese and Mallek [5] proposed a set of diagnostic criteria (Table 1) to assist in the diagnosis of PACNS. Depending on these criteria, to diagnose PACNS, patients should meet all of the following: (1) the presence of an acquired otherwise unexplained neurological or psychiatric deficit; (2) the presence of either classic angiographic or histopathological features of angiitis within the CNS; and (3) no evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease. In essence, these criteria affirm the exigency of exclusion of a long list of differentials before the diagnosis of PACNS is accurately confirmed. This necessarily imposes an extensive workup, which has been continuously updated and widened according to the new emerging diagnostic tools and nosologic entities.

Reversible Cerebral Vasoconstriction Syndromes

Reversible cerebral vasoconstriction syndrome (RCVS) comprises a group of diverse conditions, all characterized by reversible multifocal narrowing of the cerebral arteries heralded by sudden (thunderclap), severe headaches with or without associated neurological deficits [17]. Historically, RCVS was previously described under several miscellaneous cerebral vasculopathic disorders such as migrainous vasospasm [18], postpartum angiopathy [19], drug-induced cerebral angiopathy [20], and Call–Fleming syndrome [21]. In the rheumatology literature, RCVS was originally recognized as a vasculopathy that highly mimics PACNS and was referred to as benign angiopathy of the CNS.

Table 1 Diagnostic criteria of primary angiitis of the central nervous system (*PACNS*) and reversible cerebral vasoconstriction syndrome (*RCVS*)

PACNS	RCVS
The presence of an acquired otherwise unexplained neurological or psychiatric deficit	Severe and acute headache (often thunderclap) with or without focal deficits or seizures
The presence of either classic angiographic or histopathological features of angiitis within the CNS	Direct or indirect angiography documenting multifocal segmental cerebral artery vasoconstriction
No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease	No evidence of aneurysmal subarachnoid hemorrhage
	Normal or near-normal CSF analysis findings (protein concentrations below 80 mg/dL, fewer than 10 white blood cells per microliter)
	Reversibility of angiographic abnormalities within 12 weeks after onset

CNS central nervous system, *CSF* cerebrospinal fluid

Benign angiopathies of the CNS were distinguished from PACNS by the monophasic course and reversible vascular abnormalities [22, 23]. In 2007, Calabrese et al. [17] proposed the concept of RCVS to encompass all syndromes that have unifying clinical, laboratory, and radiologic features, and they proposed clinical features and diagnostic criteria. Since 2007, many case series and reports have been published that further describe the different features of RCVS [24, 25••, 26•, 27•].

Epidemiology

In contrast to PACNS, RCVS has a female predilection, with a mean age at onset of 42 years, which ranges from 18 months to 76 years [25••, 26•, 27•, 28]. Owing to the absence of epidemiologic studies; the true incidence of RCVS has not been estimated. But, on the basis of our practice and published series, we intuit that RCVS is not an uncommon disease [24, 25••, 26•, 27•].

Clinical Features

The proliferating case reports and series have persistently shown a characteristic clinical picture of RCVS. Sudden onset of single or recurrent thunderclap headache (TCH) described as "explosive-onset" or "worst ever" is the typical presentation in 78–100 % of cases [24, 25••, 26•, 27•]. Various maneuvers that increase intracranial pressure such as defecation, urination, coughing, and climax have been mentioned to exacerbate or trigger the attacks of headache [17, 29]. In addition to headache, neurological deficits, either transient or persistent, occurred in 43 % of cases in the largest case series [25••]. Seizure was also reported in 17 % of cases in the same series. Different precipitating factors such as serotonergic or adrenergic agents [28, 30–33], recreational drugs [20, 25••], and postpartum state [19, 24, 25••] have been commonly described in temporal association with RCVS in around half of patients [24, 25••, 26•, 27•]. In contrast to PACNS, RCVS generally has a self-limiting and monophasic course with a better outcome [17, 34••]; headaches are usually resolved within 3 weeks, with no new symptoms 1 month after presentation.

Diagnostic Criteria of RCVS

The diagnostic criteria of Calabrese et al. have been used since 2007 (Table 1). To diagnose RCVS, all of the following should be fulfilled: (1) severe and acute headache (often thunderclap) with or without additional neurological signs or symptoms; (2) direct or indirect angiography documenting multifocal segmental cerebral artery vasoconstriction; (3) no evidence of aneurysmal subarachnoid hemorrhage; (4) normal or near-normal CSF analysis findings (protein concentrations below 80 mg/dL, fewer than ten white blood cells per microliter); and (5) reversibility of angiographic abnormalities within 12 weeks after onset. If death occurs before the follow-up studies are completed, autopsy rules out conditions such as vasculitis, intracranial atherosclerosis, and aneurysmal subarachnoid hemorrhage, which can also manifest themselves as headache and stroke [17].

Evaluation of Patients Suspected of Having PACNS or RCVS

Extensive workup is usually performed to exclude common causes of neurological deficits, PACNS mimics, and secondary causes of CNS vasculitis. We will review the diagnostic modalities that are essential when evaluating patients suspected of having PACNS or RCVS.

Laboratory Workup

In both PACNS and RCVS, the levels of acute phase reactants such as C-reactive protein, erythrocyte sedimentation rate, complete blood count, and complete metabolic profile are normal.

The presence of anemia or elevated levels of acute phase reactants should alert the treating physician to a secondary process. Investigations for rheumatologic, autoinflammatory, autoimmune, malignant, and infectious diseases by more specific serologic tests should be properly implemented according to the existing clinical setting. These serologic tests give negative results in PACNS and RCVS.

Cerebrospinal Fluid Analysis

Unless contraindicated, CSF analysis is an indispensable diagnostic tool which should be performed on all patients suspected of having PACNS or RCVS. CSF analysis is a relatively safe procedure that is very useful in excluding infections and malignancies. The CSF analysis findings in most biopsy-proven PACNS cases include a lymphocyte-predominant pleocytosis, elevated protein level, and normal glucose level [4, 35, 36]. Cultures and serologic tests for infections should be performed in all patients. The extent of excluding infectious processes should be tailored to risk factors and the exposure of the patient.

On the other hand, a normal CSF profile is the rule in RCVS. Mild abnormalities in the CSF can be present when subarachnoid or intracerebral hemorrhages exist in RCVS [17, 23, 24, 25••].

Neuroimaging

In PACNS, ischemic infarctions are the commonest lesions, occurring in 53 % of cases [4]. They are often multiple and bilateral, and affect different vascular territories of differing size, and in various stages of healing, involving the cortex, subcortex, and leptomeninges [37–39]. Other commonly visualized lesions include nonspecific high-intensity lesions in the white matter demonstrated by T2-weighted magnetic resonance imaging (MRI) with a fluid-attenuated inversion-recovery sequence [40]. Additional lesions include mass lesions, meningeal enhancement, and intracranial hemorrhages that are seen in 5 %, 8 %, and 9 % of cases, respectively [4]. MRI is a very sensitive diagnostic tool for initial evaluation of PACNS, with sensitivity approaching 100 % [4, 10, 41, 42]. In other words, the probability of PACNS is extremely low if MRI images are normal.

In RCVS, MRI images can be normal in up to 20 % of patients. Ischemic infarctions are the commonest lesions in RCVS, occurring in 39 % of cases in the series of Singhal et al. [25••]. Infarctions can be multiple, bilateral, and symmetrical. Brain edema, either alone or accompanied by other lesions, is a common finding [25••, 34••]. As computed tomography has been demonstrated to be more sensitive at identifying intracranial hemorrhages, it plays a more important role in approaching RCVS cases since intracranial hemorrhages are commoner in RCVS than in PACNS [24, 25••, 27•]. About one third of RCVS cases in the series of Singhal et al. [25••] and the series of Ducros et al. [27•] showed convexity subarachnoid hemorrhage (cSAH) lesions. In RCVS, the cSAH is a nonaneurysmal subarachnoid hemorrhage, limited to a few sulci unilaterally or bilaterally. It is manifested as a hyperintense lesion on fluid-attenuated inversion-recovery MRI and a hypointense lesion on T2-weighted MRI [34••]. Intracerebral hemorrhage occurred more frequently in RCVS than in PACNS, and was chiefly described as single and lobar and in association with other lesions [25••, 27•]. Different lesions may coexist in the same patient [25••]. Characteristically, all brain lesions have the tendency to occur at the watershed areas, between the anterior and posterior circulations [25••, 34••]. The series of Ducros et al. [27•] described variable timing for lesions to be visualized with the brain imaging tools; edema, cSAH, and intracerebral hemorrhage were seen early during the first week, whereas ischemic lesions appeared in the second week of presentation [26•, 27•, 34••].

Cerebrovascular Imaging

Diffuse, bilateral, and alternating areas of stenosis and dilatation seen by direct or indirect (e.g., magnetic resonance or computed tomography) angiography referred to as "beading" can be found in both RCVS and PACNS [17, 25••, 34••], but are not specific to either. In RCVS, the sensitivity of indirect magnetic resonance angiography and computed tomography angiography, when direct angiography is used as the gold standard, is 70 % [24, 34••, 43]. Beading in RCVS is usually dynamic; areas of spasm and severity will change with time and completely resolve within 3 months [34••]. In PACNS, stenosis is usually fixed, and may affect a single vessel only, in contrast to RCVS, where the involvement of intracerebral vessels is diffuse and bilateral. The sensitivity and specificity of direct angiography to detect the typical findings in PACNS are 27 % and 30 %, respectively [44, 45].

Sensitivity is limited by the resolution of angiography. Other nonspecific angiographic findings in PACNS include tapering of the vessel lumen of a single vessel or many vessels and fusiform arterial dilatations, multifocal vascular occlusions, development of collateral circulation, or delayed contrast-medium enhancement and washout time [3••].

High-resolution MRI is an emerging technique that may improve the specificity of magnetic resonance angiography in distinguishing PACNS from RCVS. High-resolution MRI has the ability to visualize the wall of cerebral blood vessels as well as the lumen [46, 47]. Preliminary data have revealed that RCVS patients have no to minimal wall enhancement, in contrast to PACNS patients, where the enhancement is stronger and occurs in most patients (Fig. 1) [47, 48]. Although these findings are very exciting, this technique remains in its infancy and larger studies are needed to validate these findings.

Pathologic Examination of the Brain

Brain biopsy is the gold standard test that confirms the diagnosis of PACNS. The low sensitivity combined with its invasive nature dampens the clinician's enthusiasm for this diagnostic tool. False-negative biopsy findings occur in 25 % of autopsy-proven cases [2, 49]. The explanation for this low sensitivity is twofold; first, because of the skipping vasculitic lesions; second, because of the inaccessibility of the affected lesions. Biopsy ideally should target the radiologically affected areas if they are amenable to biopsy. Including leptomeninges, especially where meningeal enhancement is seen, increases the diagnostic yield. Alternatively, tissue is usually harvested from the nondominant temporal lobe with overlying leptomeninges if affected lesions are not amenable to biopsy. Despite the reluctance of some treating physicians to order a brain biopsy, an open wedged procedure is considered a low-risk procedure in PACNS [50]. Stereotactic biopsies have been increasingly used as well. The goals of the biopsy are to confirm the diagnosis of PACNS and to exclude other mimics. Even when histological features of vasculitis are present, appropriate infectious staining and molecular testing must be performed to rule out infectious

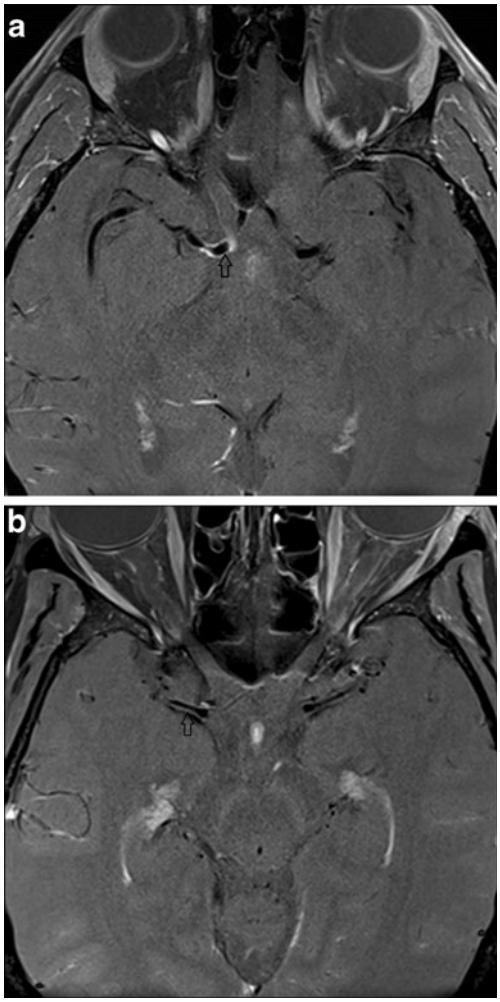

Fig. 1 High-resolution magnetic resonance imaging brain axial section after administration of gadolinium contrast medium. **a** Vasculitis patient showing vessel wall enhancement and thickening (*arrow*), and **b** reversible cerebral vasoconstriction syndrome patient showing no vessel wall enhancement

and malignant mimics, particularly if there is evidence of lymphocytic involvement. The commonest histological finding in PACNS is lymphocytic inflammatory reaction with a variable number of plasma cells, histiocytes, neutrophils, and eosinophils. Segmental granulomatous vasculitic lesions with multinucleated giant cells occur in less than 50 % of cases, and necrotizing vasculitis occurs in 25 % of cases. Intimal fibrosis usually signifies healed lesions [3••].

In RCVS, histological examination typically shows normal vessels [34••]. Brain biopsy should not be performed for the diagnosis of RCVS unless there is doubt about the diagnosis.

Differential Diagnosis

Differential diagnosis of PACNS is broad owing to the nonspecific clinical and diagnostic features. The rarity of PACNS makes consideration of other diseases more important. Diseases with multifocal cerebral thromboembolisms (e.g., endocarditis, left atrial myxoma, carotid atherosclerosis, antiphospholipid antibody syndrome, and other hypercoagulable disorders) should be excluded early in the disease course.

Radiologically, many diseases can mimic the neuroimaging findings of PACNS, and these should be excluded. These include brain tumors (e.g., intravascular lymphoma, gliomatosis cerebri), demyelinating diseases (e.g., multiple sclerosis), genetic conditions (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), chronic hypertension, and Susac's syndrome [6, 51–53]. Specific disease features will help in the final diagnosis. For example, central snowball lesions at a special topographic area such as corpus callosum coupled with eye and ear involvement are characteristic of Susac's syndrome. Bilateral external capsule and temporal lobe hyperintensities have high sensitivity and specificity for diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [3••].

Further, multiple entities can mimic the cerebrovascular abnormalities seen in PACNS. In our experience, RCVS is the commonest angiographic mimic of PACNS. The typical TCH presentation in RCVS as compared with the insidious headaches in PACNS, coupled with the associated triggers and normal CSF analysis findings, favors the diagnosis of RCVS (Table 2). Moreover, premature intracranial atherosclerosis is a very common diagnosis that mimics the cerebral angiographic abnormalities seen in PACNS. Atherosclerosis is usually distinguished by the presence of risk factors, the infrequency of headache, and normal CSF analysis findings [3••]. Radiation vasculopathy should be considered when a history of cranial irradiation is present [54, 55]. Likewise, fibromuscular dysplasia and Moyamoya disease are other causes of cerebrovascular abnormalities that should be excluded. These are easily distinguished from PACNS as they affect the proximal intracranial and extracranial vessels [3••].

Secondary CNS vasculitis should be differentiated from PACNS. This differentiation has a major influence on the management, especially when an infection is the cause of vasculitis. Immunosuppressive therapy, which is the fundamental therapy for PACNS, has a catastrophic outcome when infection is the cause of vasculitis. Many infections have been known to cause angiocentric inflammatory disease and must be ruled out early by blood tests, CSF analysis, and biopsy [40]. CNS vasculitis is one of the most serious complications of varicella zoster virus (VZV) infection [56]. Two distinct variants have been reported. A history of characteristic dermatomal rash associated with or followed by neurological deficits in old patients is the typical case in the large-vessel variant of VZV vasculitis. It has a propensity to

Table 2 Differentiating PACNS and RCVS

	PACNS	RCVS
Gender and mean age at onset	Male, 50 years	Female, 42 years
Clinical presentation	Insidious with subacute onset of headache with focal and nonfocal deficit	Acute onset of thunderclap headache with or without neurological deficit
Clinical course	Chronic, relapsing	Remission within 1 month, monophasic
CSF findings	Lymphocytic pleocytosis and elevated protein levels	Normal
Common neuroimaging findings	Ischemic, high intensity T2/FLAIR lesions	Ischemic, edema, cSAH, ICH
	Abnormal MRI images in 100 % of cases	Normal MRI images in 20 % of cases
Vascular findings	Normal in one third of cases	Abnormal in all cases
Histological findings	Vasculitic changes	Normal
Immunosuppressive therapy	Essential	Not indicated
Prognosis	Improved with immunosuppressive therapy	Excellent

cSAH convexity subarachnoid hemorrhage, *FLAIR* fluid-attenuated inversion recovery, *ICH* intracranial hemorrhage

affect the middle cerebral artery and occasionally the internal carotid artery. Angiographic lesions are similar to those of PACNS [57]. In the small-vessel variant, patients have a picture indistinguishable from PACNS that is only differentiated by dogmatizing the molecular evidence of viral infection. Either positive CSF VZV polymerase chain reaction or VZV antibodies are sufficient to confirm the VZV vasculitis [56]. The spectrum of CNS disease in human immunodeficiency virus (HIV) infection is wide and complex. HIV has a predilection to affect the CNS primarily, even though opportunistic CNS infections and other diseases, resulting from immunodeficiency, account more for the CNS involvement in HIV patients [58]. CNS vasculitis presenting separately or combined with other processes such as encephalitis has been reported owing to HIV itself or secondary to related infections and malignancies [58]. Other presentations include diffuse arteritis, angiocentric lymphoproliferative lesions, and classic GACNS [59]. Neurosyphilis is frequently reported in association with HIV-positive patients; CNS vasculitis is one of the manifestations [60, 61]. Other infections such as hepatitis C, tuberculosis, Lyme disease, and neurocysticercosis should be distinguished from PACNS. Appropriate history of exposure and eliciting host risk factors are important features of the workup in all patients suspected of having PACNS [59, 62, 63].

CNS vasculitis has been reported in many systemic vasculitides and autoinflammatory systemic diseases. In general, it is very unlikely to be the sole and first presentation for the primary disease. It usually occurs years after the primary diagnosis has been established (e.g., after 5 years in Behçet's syndrome) [64]. Nevertheless, other explanations for the occurring neurological dysfunction, either primary or secondary phenomena, must be considered first. Opportunistic infections, drug side effects or toxicity, and metabolic dysfunction are secondary phenomena of particular importance, especially in those patients with multisystemic involvement of the primary disease or who are using immunosuppressive therapy [65]. Polyarteritis nodosa [66], microscopic polyangiitis [67], Behçet's syndrome [68, 69], granulomatosis with polyangiitis [70], and eosinophilic granulomatosis with polyangiitis [71, 72] are the commonest systemic vasculitides reported to affect the CNS vessels [65]. Systemic lupus erythematosus, Sjögren's syndrome, rheumatoid arthritis [73, 74], and mixed connective tissue diseases may also target the CNS vessels. Autopsy studies in individuals with systemic lupus erythematosus revealed that CNS vasculitis is rare [75].

In the case of RCVS, all causes of TCH are usually sought and excluded in the first encounter. Aneurysmal subarachnoid hemorrhage is the commonest cause [76]. Unlike RCVS, the subarachnoid hemorrhage secondary to aneurysmal rupture is diffuse, not limited to a few sulci. The finding of an aneurysm confirms the diagnosis of aneurysmal subarachnoid hemorrhage. Perimesencephalic hemorrhage, which is the commonest cause of nonaneurysmal subarachnoid hemorrhage, should also be excluded [76]. Associated neck or face pain raises suspicion of cervical arterial dissection. Other entities that can present with TCH, such as pituitary apoplexy, cerebral venous sinus thrombosis, colloid cyst, and spontaneous intracranial hypotension, should be considered in the proper situation [77]. Other primary headache syndromes such as primary TCH and migraine have special characteristics in the history and cerebrovascular studies (the findings being normal) that help to differentiate them from RCVS.

Management and Outcome

PACNS has been historically reported as a devastating disorder with a dreadful outcome [1]. The use of immunosuppressive therapy in the 1980s [2] was a distinctive milestone in the development of PACNS management which has apparently

improved survival since that time [36]. Owing to the absence of controlled studies, therapeutic regimens have been extrapolated from the management of small-vessel and medium-sized-vessel systemic vasculitides and are based on the practice of experts [40, 78]. Aggressive therapy with glucocorticoids and intravenously or orally administered cyclophosphamide has been used for GACNS. After induction of remission, typically in 3–6 months, cyclophosphamide therapy is switched to maintenance therapy with other agents such as mycophenolate mofetil or azathioprine. For other variants of PACNS, glucocorticoids are used initially, and other immunosuppressive agents are added depending on the extent of the disease and the associated deficits [3••, 65]. No data are available on the duration of treatment; however, we continue maintenance immunosuppressive therapy if there are no contraindications or adverse effects. Follow-up to assess the disease activity and side effects of medications should be performed periodically. Disease activity is evaluated using the clinical situation, CSF analysis, MRI, and cerebrovascular studies. Of important note, for any emerging neurological dysfunction, opportunistic infections, drug side effects or toxicity, and metabolic dysfunction related to the therapy should also be excluded before a relapse is diagnosed.

Secondary vasculitis should be managed in the context of the primary causing disease. When it is secondary to infection, antimicrobial agents are the core treatment; immunosuppressive therapy may be added in some situations. For example, the combination of acyclovir and glucocorticoids is the core of treatment in VZV-related CNS vasculitis [57].

Other adjuvant therapies are usually used for symptomatic treatment and prevention of further complications associated with the vasculitis itself or the medications. Risk factor modifications to prevent premature and accelerated atherosclerosis, proper precautions for opportunistic infections and side effects associated with immunosuppressive medications, vitamin D and calcium supplements to prevent steroid-induced osteoporosis, antiplatelet medications for stroke prevention, analgesics, and antipsychotics are examples.

In general, RCVS is a self-limiting disorder, with complete recovery within 1 month [34••]. Avoiding exacerbating factors and precipitants are an important part of the management plan. Orally administered calcium channel blockers such as verapamil and nimodipine are commonly used medications [34••, 79], but there is no evidence that they alter outcomes in RCVS [25••]. Calcium channel blockers help in controlling the headaches in RCVS. In many patients the episode resolves without any treatment. Other therapeutic interventions such as intravenously administered magnesium sulfate and prostacyclin or intra-arterially administered calcium channel blockers have been reported with variable success and need further investigation [34••, 79]. Many investigators caution against any cerebral intra-arterial manipulation giving the risk of rebound reperfusion injury, which can be devastating [80]. The outcome of RCVS patients is certainly more favorable than that of PACNS patients. Excellent clinical outcome with a modified Rankin score of 0–1 occurs in 78 % of cases, whereas severe deficit (modified Rankin score of 4–5) was reported in 9 % of cases and death was reported in 2 % of cases [25••].

Conclusion

The great merit for better understanding of PACNS in the last decade is returning to recognition of RCVS. This new era has witnessed a flourishing in the medical literature of many studies that have demystified the various features of both PACNS and RCVS. Still, large-scale epidemiologic and case–control studies should be designed to expatiate on the different aspects of those diseases, such as epidemiologic properties, pathogenesis, diagnostic tools, management strategies, and follow-up algorithms. Substantial work is currently being done to study the pathogenic and diagnostic role of blood and CSF biomarkers in RCVS. Studies on the diagnostic and follow-up roles of high-resolution MRI and the International Study of Primary Angiitis of the Central Nervous System (INTERSPACE) are other examples. Multidisciplinary cooperation is essentially required to face these challenges and achieve considerable progress in the coming years.

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- • Of importance
- •• Of major importance

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