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## **Diagnostic and therapeutic approach to adult central nervous system vasculitis**

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## ABSTRACT

The clinical manifestations of central nervous system (CNS) vasculitis are highly variable. In the absence of a positive CNS biopsy, CNS vasculitis is particularly suspected when markers of both vascular disease and inflammation are present. To facilitate the clinical and therapeutic approach to this rare condition, CNS vasculitis can be classified according to the size of the involved vessels. Vascular imaging is used to identify medium vessel disease. Small vessel disease can only be diagnosed with a CNS biopsy. Medium vessel vasculitis usually presents with focal neurological signs, while small vessel vasculitis more often leads to cognitive deficits, altered level of consciousness and seizures. Markers of CNS inflammation include cerebrospinal fluid pleocytosis or elevated protein levels, and vessel wall, parenchymal or leptomeningeal enhancement. The broad range of differential diagnoses of CNS vasculitis can be narrowed based on the disease subtype. Common mimickers of medium vessel vasculitis include intracranial atherosclerosis and reversible cerebral vasoconstriction syndrome. The diagnostic workup aims to answer two questions: is the neurological presentation secondary to a vasculitic process, and if so, is the vasculitis primary (i.e., primary angiitis of the CNS) or secondary (e.g., to a systemic vasculitis, connective tissue disorder, infection, malignancy or drug use)? In primary angiitis of the CNS, glucocorticoids and cyclophosphamide are most often used for induction therapy, but rituximab may be an alternative. Based on the available evidence, all patients should receive maintenance immunosuppression. A multidisciplinary approach is necessary to ensure an accurate and timely diagnosis and to improve outcomes for patients with this potentially devastating condition.

Abbreviations : ABRA – amyloid-beta related angiitis, CAA – cerebral amyloid angiopathy, CSF – cerebrospinal fluid, CNS – central nervous system, ICAD – intracranial atherosclerotic disease, MVV – medium vessel vasculitis, PACNS – primary angiitis of the central nervous system, RCVS –

reversible cerebral vasoconstriction syndrome, SVV – small vessel vasculitis, VZV – Varicella Zoster virus.

## **Introduction**

The diagnosis and treatment of primary angiitis of the central nervous system (PACNS) are challenging. Most clinicians only see a few patients with PACNS during their career, and no randomized controlled studies or consensual recommendations exist to guide clinical management. Our knowledge of the disease is based on single<sup>1-5</sup> and multi-center cohorts<sup>6</sup> of limited size. Multiple conditions can mimic central nervous system (CNS) vasculitis.<sup>7-9</sup> Even after an appropriate workup, in the absence of a positive CNS biopsy, the diagnosis of PACNS can remain uncertain, with various treatment strategies reported.<sup>10-12</sup>

The existence of PACNS subtypes contributes to the polymorphous clinical and radiological presentations of the disease.<sup>13</sup> Multiple cohorts refer to large, medium, and small vessel PACNS, but definitions vary across publications.<sup>5, 14, 15</sup> For intracranial arteries, we consider that medium vessel disease is diagnosed on vascular imaging, while small vessel disease can only be identified with a CNS biopsy. Based on this classification, the reported proportions of PACNS subtypes is isolated medium vessel vasculitis (MVV) in 45-69% of patients, isolated small vessel vasculitis (SVV) in 23-30%, and both MVV and SVV in 6-32%.<sup>4, 16, 17</sup> We use this classification to provide clinicians with an updated approach to the diagnosis and treatment of PACNS.

In this review, we aimed to: (1) describe the clinicoradiological manifestations and differential diagnoses of CNS vasculitis; (2) discuss the etiologies of CNS vasculitis, and (3) provide an up-to-date review on PACNS treatment.

## Section 1: When should I suspect CNS vasculitis?

No single clinical manifestation is sensitive or specific for CNS vasculitis. MVV tends to present with focal neurological signs, while SVV is more likely to lead to cognitive deficits, altered level of consciousness, and seizures.<sup>4, 16-18</sup> Headaches are reported in 51% of patients with PACNS.<sup>18</sup> A history of unusual subacute or chronic headaches prior to stroke onset increases the likelihood of CNS vasculitis. The clinical course of CNS vasculitis is most often subacute, but catastrophic presentations with rapidly successive infarcts or chronic presentations with aseptic meningitis and recurrent infarcts are possible.<sup>19, 20</sup> In a patient with otherwise unexplained neurological findings, CNS vasculitis is particularly suspected when both vascular disease and markers of CNS inflammation are present.

### *CNS vascular disease*

Although not specific for a vasculitic process, multifocal arterial stenoses – sometimes accompanied by post-stenotic dilation or beading – are the most common direct signs of arterial disease in MVV.<sup>21</sup> Rarely, MVV leads to arterial occlusion or development of aneurysms.<sup>22</sup> Steno-occlusive arterial lesions involve at least two cerebral arteries in 72% of patients with medium vessel PACNS.<sup>23</sup> Computed tomography angiography (CTA) and magnetic resonance angiography (MRA) can directly visualize medium vessel disease, but digital subtraction angiography (DSA) has superior sensitivity for detecting distal or posterior arterial lesions.<sup>23-25</sup> The sensitivity of time-of-flight MRA for vasculitic arterial stenoses is higher at 3T than 1.5T.<sup>26</sup> Importantly, normal vascular imaging does not rule out CNS vasculitis, as CTA, MRA and DSA do not image small vessels, which have a diameter

of less than 500  $\mu\text{m}$ .<sup>27</sup> Direct visualization of small vessels is only possible with a CNS biopsy. (Fig. 1)

Cerebral vasculitis typically presents with both acute and chronic multi-territorial infarcts. In the French PACNS cohort, 75% of patients had acute infarcts and 92% had subacute or chronic infarcts on brain magnetic resonance imaging (MRI) at the time of diagnosis.<sup>23</sup> Hemorrhagic manifestations are present on MRI in up to 64% of cases and may result from hemorrhagic transformation of ischemic lesions or rupture of inflamed vessels.<sup>23</sup> When the disease is restricted to small vessels, brain MRI can reveal small punctate infarcts with normal vascular imaging. SVV can also lead to white matter hyperintensities and cerebral microbleeds. PACNS presents as a tumor-like lesion in 7-12% of patients. Pseudotumoral PACNS most often results from isolated SVV.<sup>28, 29</sup> Spinal cord involvement is documented in 5% of patients in the Mayo Clinic PACNS cohort and tends to occur simultaneously or several months after cerebral vasculitis.<sup>30</sup>

### *CNS inflammatory findings*

Definite diagnosis of cerebral vasculitis requires the visualization of CNS vessel wall inflammation, which is only possible with a CNS biopsy and is mainly limited to small vessels. In patients with isolated medium vessel involvement and/or a negative biopsy, the combination of vascular disease and markers of CNS inflammation allows the clinician to infer the presence of CNS vasculitis.

In medium vessel disease, smooth and concentric enhancement of the vessel wall on MRI can result from vascular inflammation and can support the diagnosis of MVV.<sup>31, 32</sup> In the context of vasculitis, enhancement is thought to result from increased permeability of endothelial cells, with

secondary leakage of gadolinium into the vessel wall.<sup>32</sup> However, overreliance on vessel wall MRI findings can lead to overdiagnosis of CNS vasculitis. Non-vasculitic arteriopathies (e.g. atherosclerosis, dissection, vasospasm), partially recanalized thrombi and mechanical thrombectomy can lead to vessel wall enhancement.<sup>32-34</sup> Conversely, misidentification of vessel wall enhancement can result from incomplete blood flow suppression, crossing arteries, microhemorrhages, or adjacent venous, meningeal or parenchymal enhancement.<sup>33</sup> The significance of vessel wall enhancement in the absence of arterial stenoses is unknown. The specificity of vessel wall enhancement has not been established in comparison with a pathological gold standard.<sup>31</sup> Leptomeningeal or non-ischemic parenchymal gadolinium enhancement suggest the presence of CNS inflammation and are more frequent in SVV (73%) than in MVV (36%).<sup>16</sup>

Cerebrospinal fluid (CSF) pleocytosis and elevated protein levels can result from vasculitis-related CNS inflammation. In a systematic review and meta-analysis of patients with PACNS, 48% had a CSF white blood cell count  $> 4/\text{mm}^3$  and 65% had a CSF protein level  $> 450 \text{ mg/l}$ .<sup>18</sup> SVV is more likely to present with abnormal CSF findings than MVV.<sup>14, 16</sup> Mild CSF anomalies should be interpreted with caution, as ischemic stroke unrelated to vasculitis is associated with CSF pleocytosis in up to 13-18% of patients, with white blood cell counts usually ranging from 5 to  $15/\text{mm}^3$ .<sup>35, 36</sup> Based on our experience and reported cohorts, the CSF white blood cell count seldom exceeds  $200/\text{mm}^3$  in PACNS.<sup>1, 12, 17</sup> In addition, minor elevations in CSF protein levels are not specific to CNS vasculitis, as they can occur with all strokes.<sup>37</sup> Oligoclonal bands are detected in the CSF of 21-26% of patients with PACNS but can also occur in all etiologies of ischemic stroke.<sup>17, 36, 38</sup>

## **Section 2: What disorders can mimic CNS vasculitis?**

The differential diagnosis of CNS vasculitis is broad but can be narrowed based on the clinical and radiological presentation.

### *Mimics of CNS MVV*

Table 1 details a selection of the main non-vasculitic mimics of CNS MVV.

While reversible cerebral vasoconstriction syndrome (RCVS) is often compared to CNS vasculitis, the presence of thunderclap headaches in > 90% of patients with RCVS usually helps to differentiate the two disorders.<sup>39, 40</sup> Specific triggers (e.g. nasal decongestants, postpartum, sexual activity) are associated with RCVS. In CNS vasculitis, initial brain MRI is always abnormal, and patients more often present focal neurological signs and ischemic stroke. In RCVS, initial brain MRI is normal in > 50% of patients and can identify convexity subarachnoid hemorrhage or vasogenic edema, which are infrequent in CNS vasculitis. Arterial stenoses peak two weeks after the onset of RCVS symptoms and resolve within three months, while they usually persist in CNS vasculitis.<sup>41, 42</sup>

In our experience, intracranial atherosclerotic disease (ICAD) is commonly misdiagnosed as CNS vasculitis, particularly when it presents in young adults with recurrent strokes. The likelihood of ICAD increases with the number and severity of vascular risk factors, as well as with the presence of related complications (e.g. left ventricular hypertrophy, hypertensive/diabetic retinopathy or nephropathy). ICAD is more common in Asian, Black and Hispanic populations.<sup>43</sup> Atherosclerotic stenoses tend to develop at arterial bifurcations and can be associated with calcifications.<sup>44</sup> However, the absence of extracranial atherosclerosis or calcifications does not rule out ICAD. On vessel wall MRI, the presence of a lipid core, an intraplaque hemorrhage or negative remodeling can support the

diagnosis of ICAD.<sup>32</sup> Eccentric vessel wall enhancement is more common in ICAD but can also occur in MVV.<sup>32, 45</sup>

### *Mimics of CNS SVV*

Table 2 details a selection of the main non-vasculitic mimics of CNS SVV.

The suspicion for a non-inflammatory mimic of CNS SVV increases with a normal lumbar puncture: small vessel PACNS is associated with elevated CSF white blood cells ( $> 4/\text{mm}^3$ ) or protein levels ( $> 450 \text{ mg/L}$ ) in at least 75% of cases.<sup>18</sup> Both vascular and non-vascular diseases can mimic CNS SVV. Sudden-onset neurological deficits, small infarcts and microbleeds suggest a vascular disease. Etiologies include severe forms of sporadic small vessel disease (e.g. deep perforator arteriopathy), hereditary pathologies (e.g. cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [CADASIL]), drugs (e.g. cocaine, amphetamines), prothrombotic states (e.g. antiphospholipid syndrome, malignancies, disseminated intravascular coagulation), and neoplastic vasculopathies (e.g. intravascular lymphoma).

Non-vascular inflammatory (e.g. autoimmune encephalitis) or metabolic (e.g. mitochondrial encephalopathy with lactic acidosis and stroke) diseases can present with headaches, rapidly evolving neurological symptoms and white matter lesions, mimicking CNS SVV. Susac syndrome leads to ischemic strokes and is associated with markers of CNS inflammation.<sup>46</sup> However, Susac syndrome is not classified as a CNS vasculitis, as its clinical manifestations are thought to result from immune-mediated endothelial cell injury rather than vessel wall inflammation.<sup>47</sup>

### **Section 3: What are the etiologies of secondary CNS vasculitis?**

Table 3 lists the etiologies of secondary CNS vasculitis, which can result from infectious, auto-immune, auto-inflammatory, paraneoplastic, genetic and drug-induced disorders.

Infections can lead to CNS vasculitis as a result of septic emboli (e.g. infectious endocarditis), contiguous spread from the subarachnoid space (e.g. bacterial meningitis), direct invasion of endothelial cells (e.g. varicella Zoster virus [VZV]), or an immune response to the infectious agent (e.g. hepatitis B-induced polyarteritis nodosa).<sup>48</sup> Infectious endocarditis can present with intracranial arterial stenoses and markers of inflammation in the CSF.<sup>49</sup> Two-thirds of VZV vasculitis cases occur after an episode of shingles, and one-third are isolated to small vessels.<sup>50,51</sup> An elevated CSF to serum ratio of anti-VZV IgG antibodies can suggest the diagnosis in patients with a recent history of shingles and a negative CSF VZV PCR.<sup>52</sup> (Fig. 2) Vasculitis frequently occurs in patients with tuberculous meningitis and is often associated with hydrocephalus and low CSF glucose.<sup>53</sup> Aspergillosis and mucormycosis mainly develop in immunocompromised patients and can lead to hemorrhagic CNS vasculitis.<sup>48</sup> One biopsy-proven case of pediatric pseudotumoral CNS vasculitis has been reported after COVID-19.<sup>54</sup>

CNS involvement can occur in primary vasculitides that affect large, medium and small vessels. Giant cell arteritis is associated with an increased risk of stroke, particularly in the posterior circulation.<sup>55,56</sup> Giant cell arteritis preferentially affects the V3 and proximal V4 segments of the vertebral artery,

possibly due to the higher amount of elastic tissue in their media and adventitia in comparison with other intracranial arteries.<sup>57,58</sup> In granulomatosis with polyangiitis, two patterns of CNS involvement are recognized: a granulomatous pattern, with cerebral and/or spinal cord pachymeningitis, and a vasculitic pattern, where CNS vasculitis frequently co-exists with necrotizing glomerulonephritis.<sup>59</sup> Neuro-Behçet causes meningoencephalitis and cerebral venous thrombosis more often than arteritis and can present with neutrophilic pleocytosis in the CSF. Retinal vasculitis can be associated with neuro-Behçet and tends to involve both arteries and veins.<sup>60</sup>

Many systemic auto-immune or auto-inflammatory conditions are associated with CNS disease through parenchymal or vascular inflammation, hypercoagulability, involvement of other organs, or complications of immunosuppressive treatments. Systemic lupus erythematosus can lead to ischemic stroke through accelerated atherosclerosis, antiphospholipid syndrome, Libman-Sacks endocarditis, and, more rarely, vasculitis.<sup>61</sup> Similarly, neurological symptoms can occur in Sjogren's syndrome due to CNS vasculitis but also to non-vasculitic mechanisms or co-existent auto-immune conditions (e.g. neuromyelitis optica).<sup>62,63</sup> Neurosarcoidosis can present with granulomatous CNS vasculitis and is more likely than PACNS to affect the brainstem, basal cistern meninges, hypothalamus, and spinal cord.<sup>64</sup>

Paraneoplastic CNS vasculitis is suspected when CNS vasculitis occurs simultaneously with lymphoma, leukemia, or solid cancers.<sup>65,66</sup> Treatment with immune checkpoint inhibitors can be complicated by CNS vasculitis.<sup>67</sup> There are rare reports of biopsy-proven CNS vasculitis in relation with the use of cocaine, amphetamines, and cannabis, often with hemorrhagic manifestations.<sup>68,69</sup> However, in patients using those drugs, other mechanisms such as accelerated atherosclerosis or vasospasm are more frequent.

In cerebral amyloid angiopathy (CAA)-related inflammation, an auto-immune reaction targets cerebrovascular amyloid-beta deposits. Amyloid-beta-related angiitis (ABRA) refers to a subset of patients with CAA-related inflammation, where this auto-immune reaction involves the vessel wall. ABRA is diagnosed when vasculitic changes colocalize with amyloid-beta peptides on CNS biopsy.<sup>70</sup> This pattern was found in 32% of patients with a previous diagnosis of biopsy-confirmed PACNS in the Mayo Clinic cohort.<sup>71</sup> When compared to biopsy-confirmed PACNS, patients with ABRA are older and more likely to present with leptomeningeal enhancement, intracerebral hemorrhage, and a granulomatous vasculitic pattern.<sup>72</sup> On MRI, ABRA is suspected when markers of CNS SVV co-occur with signs of CAA, such as cortical microbleeds or intracerebral hemorrhage, superficial siderosis, dilated perivascular spaces, and posterior predominant white-matter hyperintensities.<sup>70, 73</sup> (Fig. 3) CAA-related inflammation typically leads to asymmetrical vasogenic edema and is more common in patients with a homozygous APOE4 genotype.<sup>74, 75</sup>

#### **Section 4 : What is the workup for suspected CNS vasculitis?**

The diagnostic workup in suspected CNS vasculitis aims to answer two questions: is the neurological presentation due to a vasculitic process, and if so, is the vasculitis primary (i.e., PACNS) or secondary?<sup>76</sup> As defined by Birnbaum and Hellman, a definite diagnosis of PACNS can only be made with a positive CNS biopsy.<sup>77</sup> In the absence of a tissue confirmation, the diagnosis of PACNS is at best probable.

A thorough multidisciplinary clinical evaluation should be performed, looking for signs of extra-CNS involvement. An ophthalmological exam should be considered in all patients, as many mimickers and secondary etiologies of CNS vasculitis can involve the eye. Fluorescein angiography can reveal peripheral retinal vascular disease in patients with an otherwise normal fundus examination.<sup>78</sup> An audiogram can demonstrate patterns suggestive of specific immune-mediated disorders affecting the brain, eye and ear, such as low to mid frequencies sensorineural hearing loss in Susac syndrome.<sup>79</sup> Table 4 lists a suggested workup and tests that can be considered based on the clinical presentation. Intravascular lymphoma can be isolated to the CNS and should be considered when serum lactate dehydrogenase levels are elevated.<sup>80</sup> In the absence of a contraindication, a lumbar puncture should always be performed to evaluate for the presence of CNS inflammation and alternative infectious or neoplastic conditions. A CSF VZV PCR should systematically be obtained. CSF cytology, flow cytometry and T-cell receptor clonality assays can be considered when the clinical presentation is also compatible with CNS lymphoma.<sup>81</sup>

Head CTA or MRA should always be obtained to document the presence and burden of medium vessel disease at initial presentation. In patients with medium vessel disease on non-invasive vascular imaging, DSA provides limited additional information and carries a small risk of neurological complications.<sup>82</sup> In patients with a normal CTA or MRA, DSA can identify distal or posterior medium vessel disease.<sup>23-25</sup> Repeat vascular imaging is sometimes necessary to clarify the diagnosis. Arterial stenoses are completely reversible in RCVS and post-SAH vasospasm, and often progress in untreated CNS vasculitis. Whole body imaging can reveal signs of extra-neurological findings (e.g. infection, cancer, systemic vasculitis), which may narrow the differential diagnosis and provide an extra-CNS target to biopsy.

## Section 5 : When should CNS biopsy be considered?

The histopathological diagnosis of CNS vasculitis requires the presence of inflammatory cells within the vessel wall. Perivascular inflammation is not specific for vasculitis.<sup>83</sup> Histological PACNS subtypes include granulomatous, lymphocytic and necrotizing CNS vasculitis. Although these subtypes may overlap, necrotizing CNS vasculitis tends to be associated with more severe presentations and hemorrhagic manifestations.<sup>13</sup> However, intracerebral hemorrhage can lead to secondary necrosis within the vessel wall. Necrotizing vasculitis can only be diagnosed in biopsy areas without hemorrhage or parenchymal necrosis.<sup>13</sup> Biopsy specimens should be analyzed for infectious etiologies of CNS vasculitis. In CNS lymphoma, immunostains can reveal atypical lymphocytes with high mitotic activity both within and around blood vessels.<sup>81</sup> Congo red staining differentiates PACNS from ABRA.<sup>70</sup>

CNS biopsies in patients with suspected PACNS are associated with a low risk of severe complications (ranging from 0-4%).<sup>84-87</sup> This risk should be weighed with the potential complications of immunosuppression in patients with alternative non-inflammatory disorders. In patients with SVV, the diagnosis of PACNS is only possible with a positive CNS biopsy. Moreover, patients with positive biopsies tend to have normal angiograms, likely because their disease is isolated to small vessels.<sup>88</sup> In patients with unremitting or relapsing disease, a positive biopsy decreases diagnostic uncertainty and facilitates the decision to intensify treatment.

A CNS biopsy can reveal an alternative diagnosis in 30-39% of patients with suspected PACNS.<sup>84, 85</sup> In a meta-analysis of three observational studies, CNS biopsies for suspected PACNS led to the diagnosis of vasculitis or an alternative disorder in 75% of patients.<sup>86</sup> A biopsy may be negative due

to the segmental nature of vasculitic lesions, or to isolated involvement of proximal medium vessels, which are not sampled per procedure. Strategies to increase the yield of CNS biopsies include: (1) targeting radiologically abnormal sites; (2) selecting patients with radiological evidence of small vessel involvement (small infarcts, leptomeningeal or non-ischemic parenchymal enhancement, microbleeds and/or pseudotumoral lesions); (3) targeting a peripherally located and enhancing artery on vessel wall imaging; (4) sampling at least 1 cm<sup>3</sup> of tissue; and (5) assessing tissue representativeness during the procedure. <sup>13, 86, 89, 90</sup>

## **Section 6 : What are the treatments and outcomes of cerebral vasculitis?**

In secondary etiologies of cerebral vasculitis, the treatment is tailored to the underlying disease. For most systemic auto-immune or inflammatory conditions, CNS involvement predicts a worse prognosis and justifies more aggressive immunosuppression. <sup>91, 92</sup> In the absence of prospective and randomized trials, the treatment of PACNS is based on retrospective cohort studies and the well-established drug regimens that are used in systemic vasculitides. Infectious etiologies of CNS vasculitis should be ruled out prior to introducing immunosuppressants. In patients with mild or chronic presentations, we suggest completing the workup prior to initiating treatment. The impact of corticosteroids on CNS biopsy results in PACNS is unknown. However, corticosteroids increase the likelihood of false negative biopsies in certain PACNS mimics, such as giant cell arteritis and CNS lymphoma. <sup>93, 94</sup>

The treatment of PACNS should probably include an induction (to achieve remission) followed by a maintenance phase (to maintain remission and prevent relapses). Remission may be defined as the absence of new or worsening disease activity attributable to PACNS, after initiation of treatment.

The minimum period needed to define remission after treatment introduction varies across cohorts.<sup>4,6</sup> Similarly, there is no consensual definition for a PACNS relapse. A relapse may be defined as the association of new clinical PACNS manifestations that occur after remission, are associated with new abnormalities on imaging, and lead to a change in treatment.<sup>6</sup> Whether isolated clinical (e.g. recrudescence of headaches with a stable brain MRI) or radiological events (e.g. silent brain infarct or asymptomatic new leptomeningeal enhancement) should define a relapse is unknown.

Induction therapy consists of high-dose glucocorticoids, usually accompanied by an immunosuppressive agent. Intravenous methylprednisolone pulses (500-1000 mg/day) are sometimes used for 3-5 days, with no evidence to suggest they are superior to oral corticosteroids alone. Oral glucocorticoids (mainly prednisone or an equivalent) are initiated at 1 mg/kg per day (not exceeding 80 mg/day). This dose is maintained for 15-21 days, followed by a slow tapering over at least a one-year period. In the two largest PACNS cohorts, induction with cyclophosphamide was not associated with higher odds of remission or lower relapse rates.<sup>4, 6</sup> However, patients with or without cyclophosphamide were probably not comparable, i.e. patients who received cyclophosphamide probably had a more severe presentation. In light of its benefit in systemic vasculitides, it is reasonable to use cyclophosphamide in the induction phase of PACNS.<sup>95-97</sup> We usually prefer intravenous to oral cyclophosphamide, due to its association with reduced cumulative drug doses and lower odds of myelosuppression.<sup>98</sup> Intravenous cyclophosphamide can be prescribed monthly at 0.7 g/m<sup>2</sup>/month (not exceeding 1200 mg) for at least six months and is adjusted for the leukocyte nadir and adverse events. In patients with a severe initial presentation, the first three infusions can be delivered every 15 days at 0.6 g/m<sup>2</sup> followed by three to six infusions every three weeks at 0.7 g/m<sup>2</sup>.

Preliminary evidence suggests that rituximab may be effective in inducing remission when PACNS is refractory to glucocorticoids and cyclophosphamide, or when cyclophosphamide is contraindicated.<sup>10, 99</sup> In systemic vasculitides, rituximab is nowadays more frequently used than cyclophosphamide to achieve remission. Two rituximab regimens can be used: 375 mg/m<sup>2</sup> once weekly for four doses, or 1000 mg every two weeks for two doses. In systemic vasculitides, there is no evidence to suggest that either regimen is superior in terms of efficacy or safety.<sup>100</sup>

Maintenance therapy should be initiated after completing the induction treatment and achieving remission, usually one month after the last infusion of cyclophosphamide or rituximab. Azathioprine (2 mg/kg/day in two oral intakes, not exceeding a total of 150 mg/day) is the most commonly used agent, followed by methotrexate (0.3 mg/kg/week, usually 20-25 mg/week, associated with folic acid) and mycophenolate mofetil (2000 to 3000 mg/day in two oral intakes). Similarly to systemic vasculitides, one infusion of 500 to 1000 mg of rituximab can be used for maintenance every six months, although data are scarce in PACNS.

In the French PACNS cohort, maintenance therapy was associated with higher odds of prolonged remission and good functional status.<sup>6</sup> The optimal duration of maintenance therapy (excluding glucocorticoids) is unknown. Maintenance therapy should probably be prescribed for at least 24 months to reduce the risk of a relapse. The rapidity of the glucocorticoid taper and the total duration of treatment should be adjusted based on the severity of the initial presentation, disease evolution, and drug tolerability.

Relapses are reported in 30-59% of patients with PACNS.<sup>4-6</sup> New-onset neurological manifestations may result from an undiagnosed PACNS mimic, PACNS sequelae (e.g. remote

seizure), a PACNS relapse, or complications of immunosuppression (e.g. CNS infection).<sup>101</sup> If the disease relapses after discontinuation of treatment, new induction and maintenance regimens should be initiated, and a longer course of maintenance immunosuppression is reasonable. If the disease relapses while the patient is receiving maintenance therapy, glucocorticoids should be re-initiated or increased, and a change of maintenance agent should be discussed. In cases where the relapse is clinically severe, a new induction regimen can be considered. In the rare cases refractory to cyclophosphamide or rituximab, the diagnosis should be reconsidered. In isolated case reports, PACNS responded to TNF-alpha inhibitors or tocilizumab (anti-IL6 receptor monoclonal antibody).<sup>102-104</sup>

The benefit of aspirin in PACNS has not been demonstrated.<sup>6</sup> Aspirin should probably be avoided in patients with hemorrhagic manifestations and may be considered in the presence of medium vessel disease. All patients treated with glucocorticoids should receive adequate prophylaxes for osteoporosis (calcium, vitamin D ± biphosphonates) and gastric ulcers (proton pump inhibitors). Cotrimoxazole is frequently prescribed for *Pneumocystis jiroveci* prophylaxis in patients initially treated with cyclophosphamide or rituximab. This treatment should be avoided in patients who receive maintenance therapy with methotrexate, due to the risk of drug interaction and methotrexate toxicity.

In the largest PACNS cohorts, induction therapy is associated with remission in 68-95% of patients.<sup>4-6</sup> Absence of remission should encourage clinicians to re-examine the diagnosis of PACNS and increases the justification for a CNS biopsy. In unremitting patients, a second biopsy may also be considered, as CNS lymphoma can initially present with a vasculitic pattern on histopathology.<sup>81</sup>

## **Section 7 : How should I follow PACNS?**

During the induction and maintenance phases, patients are closely monitored for signs of persistent disease activity or treatment-related complications. In absence of clear recommendations, we suggest controlling the brain MRI in the 3-4 months after introducing induction therapy, to document the presence of new lesions and establish a new baseline prior to initiating maintenance therapy. Afterwards, a brain MRI can be repeated every 6-12 months, or earlier if a relapse is suspected. Vascular imaging should be included in the follow-up of all patients. If medium vessel disease was demonstrated on non-invasive vascular imaging, a CTA or an MRA are sufficient for routine follow-up. Lumbar puncture can be discussed for patients with a potential relapse. Vessel wall enhancement can persist on MRI after remission, and is hypothesized to result from subclinical vasculitis, vascular remodeling, or post-inflammatory mural neovascularization.<sup>105</sup> Persistent vessel wall enhancement without other signs of active CNS vasculitis probably does not justify intensifying immunosuppressive therapy. In these patients, closer clinical and radiological follow-up is reasonable.

During follow-up visits, patients should be screened for complications of CNS vasculitis, such as cognitive decline, epilepsy, or neuropsychiatric symptoms. Clinical evaluation and imaging can reveal signs of a PACNS relapse, which is more likely to occur in patients with isolated SVV, gadolinium enhancement at presentation, and absence of maintenance therapy.<sup>6, 16</sup> Increasing age and cerebral infarcts at diagnosis are associated with higher odds of disability or death during follow-up.<sup>4</sup> Overall mortality was 8% in the French PACNS cohort.<sup>6</sup> However, mortality after CNS vasculitis is likely underestimated, as patients with catastrophic presentation are more likely to die prior to diagnosis and not be included in retrospective cohort studies.

## **Conclusion**

The diagnostic approach to PACNS is complex, due to the rarity of the disease, its multiple potential presentations and its numerous differential diagnoses. The distinction between medium and small vessel vasculitis is useful to guide the clinical approach. Cerebral vasculitis is more often suspected than confirmed, and alternative diagnoses should always be considered prior to exposing patients to the potential toxicity of immunosuppressants. Multidisciplinary collaboration (neurology, internal medicine, rheumatology, neuroradiology) is essential during the workup and the follow-up of the disease. Further studies are needed to identify and validate new diagnostic tests (biomarkers, advanced imaging), better define patient subgroups (monophasic versus recurrent PACNS), and allow the design of prospective therapeutic trials.

**Table 1. Selected non-vasculitic mimics of central nervous system medium vessel vasculitis**

<b>Reversible cerebral vasoconstriction syndrome</b>	Thunderclap headaches Triggers (e.g. vasoconstrictive drugs, postpartum, sexual activity) Convexity subarachnoid hemorrhage or vasogenic edema Resolution of arterial stenoses at three months
<b>Intracranial atherosclerosis</b>	Vascular risk factors Arterial calcifications on CT Extracranial atherosclerosis Lipid core or intraplaque hemorrhage on vessel wall imaging
<b>Intracranial dissection</b>	Intramural hematoma (hyperintensity on T1 fat-saturated MRI) Double lumen or intimal flap Subarachnoid hemorrhage Pseudoaneurysm
<b>Moya-moya disease or syndrome</b>	Stenosis of the intracranial internal carotid artery and its proximal branches Dilated collaterals (puff of smoke pattern) Ivy sign on MRI
<b>Intracranial fibromuscular dysplasia</b>	String of beads pattern Extracranial fibromuscular dysplasia Cerebral aneurysms
<b>Cerebral embolism</b>	Partially recanalized cerebral emboli (e.g. atrial myxoma or other cardiac tumors, non-bacterial thrombotic endocarditis, aortic atherosclerosis ...)
<b>Post-subarachnoid hemorrhage vasospasm</b>	History of recent thunderclap headache Cerebrospinal fluid xanthochromia
<b>Lymphoma</b>	Intravascular lymphoma (elevated lactate dehydrogenase, skin lesions, small > medium vessel disease)
<b>Prothrombotic state</b>	Antiphospholipid syndrome Sneddon syndrome (livedo racemosa) Malignancy-associated hypercoagulability
<b>Drug-induced vasospasm</b>	Amphetamines, cannabis, cocaine
<b>Radiation induced vasculopathy</b>	History and other complications of cranial radiotherapy (e.g. small vessel disease, cavernoma, telangiectasia, meningioma)

<b>Hereditary disorders with intracranial medium vessel disease</b>	ACTA2 mutation (abnormally straight course of intracranial arteries, periventricular white matter hyperintensities, patent ductus arteriosus) Divry-van-Bogaert syndrome (juvenile ischemic stroke and dementia, arterial occlusions, cerebromeningeal angiomas, livedo racemosa) Hereditary moyo-moya disease
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**Table 2. Selected non-vasculitic mimics of central nervous system small vessel vasculitis**

<b>Sporadic small vessel disease</b>	Deep perforator arteriopathy Cerebral amyloid angiopathy
<b>Hereditary disorders with small vessel disease</b>	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL) COL4A1 small-vessel disease Retinal vasculopathy with cerebral leukodystrophy ( <i>TREX1</i> mutation) Fabry disease Homocystinuria Hereditary cerebral amyloid angiopathy
<b>Other causes of small vessel disease</b>	Drugs (amphetamines, cocaine) Radiation induced small vessel disease
<b>Neoplastic vasculopathy</b>	Intravascular lymphoma Primary central nervous system lymphoma Vascular infiltration by leptomeningeal neoplastic cells
<b>Immune-mediated endotheliopathy</b>	Susac syndrome
<b>Prothrombotic state</b>	Antiphospholipid syndrome Sneddon syndrome Myeloproliferative disorders (polycythemia vera, essential thrombocythemia) Thrombotic thrombocytopenic purpura Disseminated intravascular coagulation Malignancy-associated hypercoagulability
<b>Cerebral embolism</b>	Cholesterol embolization syndrome
<b>Non-vascular disorders</b>	Autoimmune encephalitis (primary or secondary to systemic disorder) Acute demyelinating encephalomyelitis Metabolic disease (ex: mitochondrial encephalopathy with lactic acidosis and stroke)

**Table 3. Etiologies of central nervous system vasculitis**

<b>Infectious</b>	Infectious endocarditis Bacterial ( <i>Streptococcus Pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Neisseria Meningitidis</i> , syphilis, brucellosis, leptospirosis, Lyme disease, rickettsia) Mycobacterial (tuberculosis) Viral (varicella-zoster, cytomegalovirus, dengue, Epstein-Barr, hepatitis B and C, herpes simplex, West Nile) Fungal (aspergillosis, candidiasis, coccidiomycosis, cryptococcus, histoplasmosis, mucormycosis, paracoccidiomycosis) Parasitic (neurocysticercosis, malaria, schistosomiasis, toxoplasmosis)
<b>Systemic vasculitides</b>	Large vessel vasculitis (giant cell arteritis, Takayasu) Medium vessel vasculitis (Kawasaki, polyarteritis nodosa) Small vessel vasculitis (ANCA-associated vasculitis, cryoglobulinemic vasculitis, Goodpasture's syndrome, IgA vasculitis) Behcet's disease Buerger's disease Degos disease
<b>Vasculitis associated with systemic disease</b>	Connective tissue disorder (systemic lupus erythematosus, Sjogren, dermatomyositis, mixed connective tissue disease, systemic sclerosis) Graft versus host disease Inflammatory bowel disorder (Crohn, ulcerative colitis) Relapsing polychondritis Rheumatoid vasculitis Sarcoidosis Sweet syndrome
<b>Vasculitis with ear, nose and throat involvement</b>	Acute posterior multifocal placoid pigment epitheliopathy Cogan syndrome
<b>Cancer</b>	Paraneoplastic cerebral vasculitis (Hodgkin's lymphoma, non-Hodgkin's lymphoma, leukemia, solid cancers)
<b>Drugs</b>	Amphetamine, cannabis, cocaine

	Immune checkpoint inhibitors Propylthiouracil
<b>Hereditary disorders</b>	Adenosine deaminase 2 deficiency Common variable immunodeficiency
<b>CNS-isolated vasculitis</b>	Amyloid-beta related angiitis Primary angiitis of the CNS

Abbreviations: CNS - Central Nervous System

**Table 4. Workup of central nervous system vasculitis**

<b>Blood and urine</b>	<p><i>Suggested</i></p> <p>Complete blood count, routine coagulation testing (prothrombin time, partial thromboplastin time) Creatinine, urine protein test, liver function tests C-reactive protein Anti-nuclear antibodies, anti-dsDNA antibodies, antineutrophil cytoplasmic antibodies, complement levels, rheumatoid factor Anti-cardiolipin antibodies, anti-B2GP1 antibodies, lupus anticoagulant Serum protein electrophoresis Lactate dehydrogenase Syphilis, HIV, hepatitis B, hepatitis C, Lyme, hemocultures, Quantiferon or tuberculin skin test</p> <p><i>Optional</i></p> <p>Cryoglobulins Street or urine drug test Genetic workup</p>
<b>CSF</b>	<p><i>Suggested</i></p> <p>Oligoclonal bands and IgG index Cytopathology Varicella Zoster PCR Bacterial and mycobacterial cultures</p> <p><i>Optional</i></p> <p>Flow cytometry, T-cell receptor clonality assay, immunoglobulin heavy chain gene rearrangement studies CSF/serum quantitative anti-VZV IgG/IgM ratio PCRs for Herpes Simplex, Cytomegalovirus, Epstein-Barr, Mycobacterium Tuberculosis Fungal cultures Cytokine panel Metagenomics next generation sequencing</p>
<b>Imaging</b>	<i>Suggested</i>

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Brain MRI (including T1, T2, FLAIR, diffusion, MR-angiography, gadolinium injected sequences)  
Head and neck CT-angiography  
Transthoracic or transesophageal echocardiogram  
Fundus examination  
Whole body imaging (CT or PET)  
**Optional**  
High resolution MR vessel-wall imaging  
Digital subtraction angiography  
Spinal cord MRI  
Fluorescein angiography  
Audiogram

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### Figure legends

#### Figure 1 – Imaging findings in cerebral vasculitis

A-D: Medium vessel vasculitis findings in different patients. A: Large and multiterritorial acute infarcts. B: Arterial stenoses in the proximal left anterior and middle cerebral arteries. C: Arterial stenoses (black arrows) with post-stenotic dilatation (white arrow) in the left anterior cerebral artery. D: Concentric enhancement of the second segment of the left middle cerebral artery on MRI vessel wall imaging.

E-H: Small vessel vasculitis findings in different patients. E: Multiple areas of punctiform non-ischemic parenchymal enhancement. F: Numerous cortical microbleeds. The arrow shows the biopsy site. G: Cerebral and spinal parenchymal enhancement. H: Pseudotumoral cerebral vasculitis.

#### Figure 2 – Imaging and histopathological findings in amyloid-beta related angiitis (small vessel vasculitis)

A: MRI diffusion weighted-imaging shows multiple punctiform acute and predominantly cortical infarcts. B: FLAIR sequence demonstrates predominantly posterior white-matter hyperintensities (circled), which can occur in cerebral amyloid angiopathy. C: Susceptibility-weighted imaging reveals multiple and exclusively cortical cerebral microbleeds (arrows). D: Hematoxylin and eosin stain shows eosinophilic vessel walls, with mononucleate (arrow) and giant cell (triangle) infiltration of the vessel wall. E: Congo red staining is positive for amyloid (arrow). Giant cells are also seen in the perivascular space (triangle). Inflammatory changes colocalize with vascular amyloid deposits. F: Anti-amyloid  $\beta$  immunostaining reveals amyloid fibrils in the cortical and leptomeningeal vessel walls (arrows). Case courtesy of Dr Émile Lemoine (Centre Hospitalier de l'Université de Montréal).

#### Figure 3 – Varicella Zoster medium vessel vasculitis in a patient with multiple sclerosis on fingolimod

A: MRI diffusion-weighted imaging reveals acute infarction of the right parieto-occipital region. B: FLAIR sequence shows periventricular multiple sclerosis-related white matter lesions and infarction of the right parieto-occipital region. C: MRI vessel wall imaging demonstrates concentric enhancement of the right supraclinoid carotid artery (white arrow). D: MR-angiography with gadolinium reveals multifocal intracranial arterial stenoses (black arrows). Reproduced with permission from Elsevier (Muccilli et al. Varicella-zoster virus vasculopathy in a multiple sclerosis patient on fingolimod, J Neurol Sci 2019;403:119-21).

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