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Primary Angiitis of the Central Nervous System (PACNS): A Commentary on a Proposed Screening Algorithm and an Update on Diagnosis and Treatment

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Current Knowledge and State-of-the-art on PACNS Diagnosis

Primary angiitis of the central nervous system (PACNS) is a rare disorder difficult to suspect in clinical practice due to its rarity, not specific/protean clinical presentation and imaging findings. Also, diagnosis is hindered by the lack of noninvasive specific diagnostic tests. In our review of 24 case series of PACNS, amounting to a total of 585 patients, the following clinical (1) and neuroradiological (2) pictures emerged: 1- patients with PACNS tend to present more frequently with headache, mild to severe cognitive impairment, focal neurological deficits difficult to be otherwise classified, stroke or transient ischemic attack (TIA) 2- multiple cerebral lesions, parenchymal or meningeal contrast enhancement, vessel wall abnormalities. Other less frequent clinical and radiological presentations include seizures, confusion, impaired level of consciousness, psychiatric or mood disorders, single cerebral lesion with or without mass effect, parenchymal/subarachnoid hemorrhage [1]. This clinical picture was confirmed by the most recently published case series [2-4].

Non-invasive tests are mostly insufficient to achieve a conclusive diagnosis, as they often show unspecific or no abnormalities [5].

Specifically:

- Hematologic tests, including markers of inflammation, are usually normal

- Cerebrospinal fluid (CSF) can reveal mild lympho-/monocytic pleocytosis, protein elevation, and occasionally oligoclonal bands and elevated IgG synthesis. In up to 20% of cases CSF is unremarkable

- MRI can show ischemic infarctions, signs of microangiopathy, hemorrhage, contrast enhancement or tumor-like lesions, but there is no pathognomonic picture associated with PACNS. In recent years, techniques such as high-resolution contrast-enhanced MRI (such as 'black blood MRI') were developed. This MRI sequence is more sensitive to pathological changes like wall thickening and wall enhancement, and can aid in differentiating between inflammation, intracranial atherosclerosis and other wall abnormalities based on typical enhancement patterns reported [5,6]. In contrast-enhanced MRI, signal of the blood is suppressed (thus the name 'black blood' or 'dark blood' imaging) and discrimination of the vessel wall from the lumen is increased: in PACNS there is usually a smooth, concentric, and long-segment wall thickening with strong enhancement and perivascular edema, whereas intracranial arteriosclerosis exhibits a more eccentric, irregular, and short-segment wall thickening without perivascular edema and only mild enhancement, depending on composition and activity of the plaque [7]. Vessel wall imaging (VWI) appears to be safe and very promising in clinical practice, but some limitations need to be addressed: first of all, most VWI techniques require a 3T MRI, limiting their availability on a large scale. Secondly, there is a risk of false positives due to normal vasa vasorum of intracranial arteries appearing as concentric enhanced

wall thickening. Moreover, different pathological conditions may present with overlapping features on VWI, such as reversible cerebral vasoconstriction syndrome (RCVS), cocaine-induced vasculopathy, moyamoya disease, radiation-induced arteriopathy, aneurysms, and post-thrombectomy changes [8] thus the radiologist evaluating the images needs to be highly experienced in this kind of technique.

Thus, when clinical suspicion is high, there is an indication to proceed to more invasive tests, like digital subtraction angiography (DSA) or cerebral biopsy.

According to present literature, DSA, albeit more sensitive than MRA, has nonetheless limited sensitivity, especially when PACNS changes affect vessels <500 μm in diameter [9], thus a negative angiogram cannot be used to definitively exclude the disease. In two series of patients with biopsy proven PACNS, amounting to a total of over 100 patients, the sensitivity of angiography was only 60 percent [10,11]. Typical findings on DSA include multiple areas of narrowing and dilatation ('beading') or multilocular occlusions, fusiform arterial dilatations, or the presence of collateral circulation. Conversely, long segment stenoses, microaneurysms and complete occlusions are quite uncharacteristic for PACNS [12]. In clinical practice it is uncommon to repeat angiograms as a way of following response to treatment. Repeated angiography can have a rationale if the diagnosis remains uncertain days to weeks after the initial study: a rapid change in angiographic findings (such as a normalization of a positive exam within days or weeks) strongly argues in favor of a diagnosis of RCVS rather than PACNS [13].

The gold standard for diagnosis remains brain biopsy, which is mandatory when suspicion is high, and all other tests are inconclusive. Due to the focal and segmental nature of the disease though, it should be underlined that the sensitivity of brain biopsy is less than 75%, as a result of sampling errors [14,15], but it can increase to over 80% by targeting areas of imaging abnormalities [10]. When affected areas do not appear accessible for surgery, it is recommended to sample tissue from the nondominant frontal or temporal lobe with its overlaying leptomeninges [16,17]. Typical findings on biopsy are granulomatous segmental vasculitis with Langerhans or foreign body giant cells affecting the small and medium leptomeningeal and cortical arteries. This typical pattern is present in less than 50 percent of the biopsies. In other instances, findings can be less specific but still point to inflammation, for example showing only lymphocytic vasculitis. Biopsy is extremely valuable also in pointing to an etiology different from PACNS: stains, viral studies, and cultures should be performed on the biopsies, since the finding of vasculitis does not preclude the possibility of a vasculitis caused by an infection or a lymphoproliferative process [18].

Both DSA and brain biopsy carry a risk of complications. Specifically, there is a 0.14 to 1 percent risk of stroke, a 0.4 to 3 percent risk of TIA, and a very small risk of mortality associated with DSA [19-21]. Likewise, brain biopsy carries a risk of bleeding, brain swelling, seizures, stroke, infection, reactions to anesthesia and death [15].

Proposed Algorithm to Suspect PACNS

We developed a clinical/radiological screening algorithm to select patients with a high suspicion of the disease, for whom the benefit of undergoing invasive tests outweighs the risk of complications. From the literature review of case series of patients with definite diagnosis of PACNS, we divided clinical and neuroradiological features into 'major' or 'minor', based on the reported frequency. Specifically:

- Major clinical features: new onset or modified headache, cryptogenic recurrent stroke, subacute cognitive impairment, and focal neurological deficits.
- Minor clinical features: seizure(s), altered level of consciousness, and psychiatric disorders.
- Major neuroradiological features: multiple parenchymal lesions, parenchymal or meningeal contrast enhancement, vessel abnormalities (single or multiple stenoses/occlusion) and vessel wall contrast enhancement.
- Minor neuroradiological features: parenchymal or subarachnoid hemorrhage and single parenchymal lesion

We then screened published case reports of patients with definite PACNS to check which combinations of these features better identified them.

We concluded that all patients with PACNS could be identified as follows (Figure 1):

1- one clinical feature (major or minor) associated with one major neuroradiological feature or

2- two clinical features (at least one major) associated with one minor neuroradiological feature,

and no better explanation for the presenting complaint [1].

New Potential Diagnostic Tools

Our algorithm did not include, for scarcity of data available at the time, any other biomarkers of PACNS, which are still being researched to this day. Among the most promising we can cite: the presence of high Interleukin-17 or reduced Amyloid-beta A4 Protein (APP) in the CSF or the detection of Circulating Endothelial Cells (CECs) in the peripheral venous blood. When validated, these biomarkers will be a valid addition to the screening algorithm.

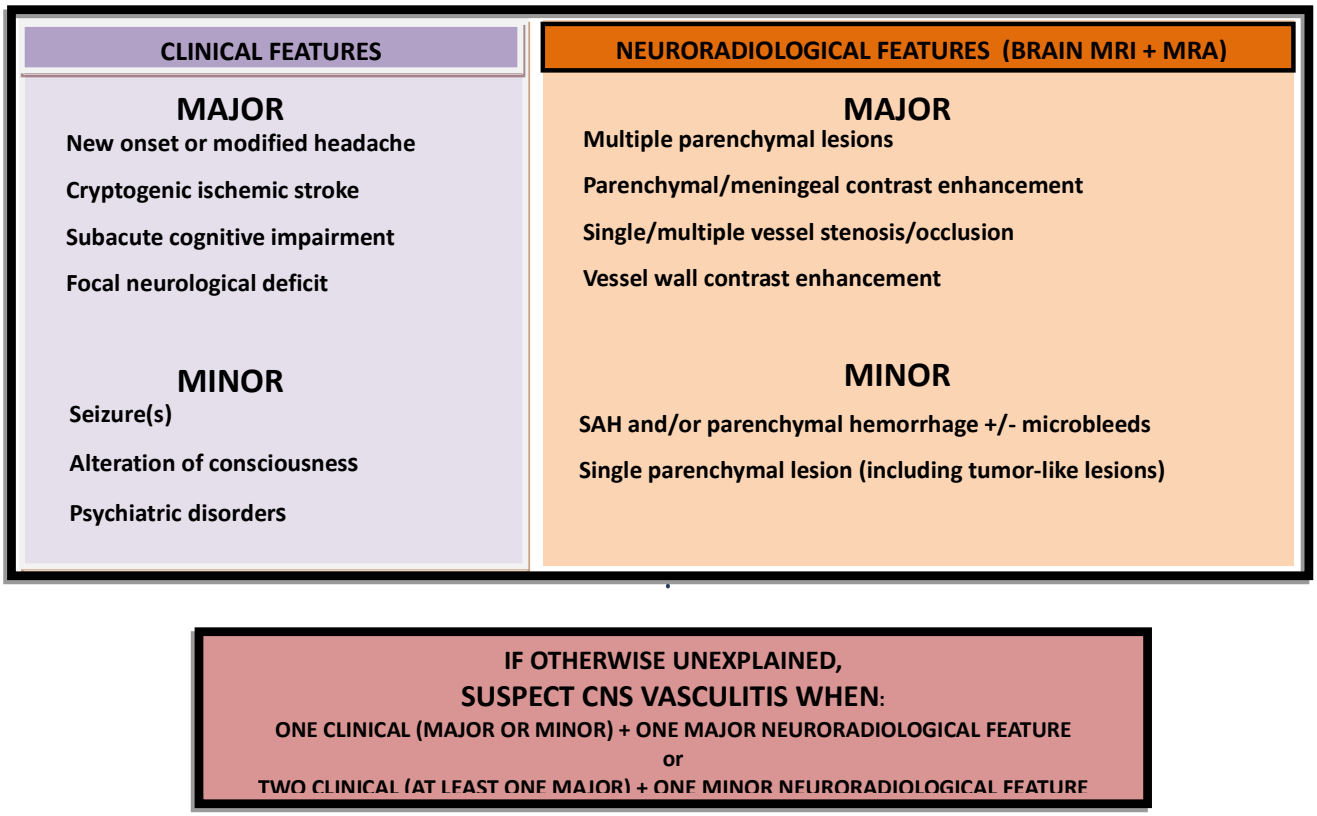

Figure 1: Clinic-radiological screening algorithm.

Fluoro-desoxy-glucose Positron Emission Tomography (FDG)-PET depicts brain metabolic activity and may potentially reveal vessel wall inflammation [1,22].

Update on Therapy

Regarding treatment, no prospective studies have been conducted, so current therapy of PACNS is based on retrospective studies and anecdotal evidence only. Treatment is usually initiated with glucocorticoids, either with high-dose administration of intravenous methylprednisolone (1000 mg daily for 3 to 5 days) or oral prednisone (1 mg/kg per day). In a retrospective study of 163 patients, glucocorticoids alone have shown to be as effective as combination therapy with glucocorticoids and cyclophosphamide, even though the latter showed a lower rate of relapses [23]. The typical regimen for intravenous cyclophosphamide is 600 to 750 mg/m^2, infused once a month, or as an oral dose of 2 mg/kg per day, generally for three to six months [23,24].

Nowadays, there is also increasing evidence that the use of biological agents like rituximab or tumor necrosis factor-alpha blockers can induce remission in PACNS. Rituximab can be administered either as two 1 gr infusions separated by 14 days or as 375 mg/m^2 weekly for 4 weeks; either as first-line therapy or following a failed course of glucocorticoids/cyclophosphamide [25-27].

The aim of initial treatment is to induce remission, afterward maintenance therapies can limit the risk of relapses and prevent long-term disability. Average time to initiation of maintenance therapy is 4 to 6 months, and the agents most often used are corticosteroid-sparing agents such as azathioprine (1-2 mg/kg/d), mycophenolate mofetil (1-2 g/d) or methotrexate (20-25 mg/week) [27].

Relapse rate, even with maintenance therapy, tends to be high (between 27 and 59%), thus treatment should be tailored to the individual patient [23,28,29]. Interestingly, one study found that only patients who relapsed within 30 months after the initiation of the first-line therapy relapsed beyond 30 months, while patients without relapses in the first 30 months remained relapse-free in the follow-up period of at least 60 months. However, cessation of immunotherapy after 30 months in patients without relapses is not recommended [29].

Conclusion and Commentary on the Proposed Algorithm

For such a rare but disabling condition, it is fundamental to maintain high suspicion in clinical practice and delineate a standardized path to guide diagnosis. Based on our review of literature, there is a somewhat peculiar, albeit non-specific, presentation of PACNS: it should always be suspected in patients presenting with recurrent cryptogenic stroke in the absence of typical risk factors, in patients with a new onset or modified headache and typical MRI/MRA findings, or in patients with subacute cognitive impairment and abnormal neuroimaging. These presentations can point to PACNS, but the disease is so protean that it should be suspected in other settings as well. That is the reason why we felt the need to develop a tool that could help clinicians decide which patients should be put at risk of undergoing more invasive tests to confirm this suspicion. Our algorithm needs to be validated in larger cohorts, but we believe it could make a useful addition to any neurologist's clinical practice, helpful in guiding both diagnosis and management [1].

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