Primary angiitis of the CNS

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Meaningful progress in our understanding and clinical approach to primary angiitis of the CNS (PACNS) has been made in the past three decades. Increased recognition of PACNS and general advances in diagnosis of neurological disorders have led to an aggressive diagnostic approach and a proliferation of case reports providing enriched clinical and pathological descriptions. We have witnessed major advances not only in the diagnosis of PACNS but in the recognition of its mimics. Epidemiological, clinical, neuroradiagnostic, and laboratory findings have enhanced our diagnostic accuracy and recognition of PACNS mimics, however, many challenges to our understanding and management of the disease in children and adults remain.

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Introduction

Primary angiitis of the CNS (PACNS) is a rare disorder resulting in inflammation and destruction of CNS vessels without evidence of vasculitis outside the CNS. This disorder was first considered a distinct clinical entity in 1959 by Cravioto and Feigin.[1] PACNS remained rare, with only 46 cases reported in peer-reviewed English-language publications by 1986.[2] Since then, with increased awareness and recognition of the disease and the widespread application of diagnostic criteria proposed by Calabrese and Mallek[2] in 1988, the number of reported cases has risen substantially, with over 450 cases described by 2007.[3] In the same year, the largest single-centre series (101 cases from the Mayo Clinic, Rochester, MN, USA) brought the total to well over 500 cases worldwide.[4] Despite these additional cases, few reports have included patient series in excess of ten cases. We do not yet have an integrated view of the clinical picture of PACNS for various reasons, including a scarcity of prospective multicentre registries with meaningful data. Additionally, in view of the many single-case and small series reports, a bias towards new or unusual features is probable.

PACNS is poorly understood, and formidable challenges to our understanding and management of the disease remain: few clinicians are highly experienced with the disease, the clinical presentations are non-specific, we lack highly efficient non-invasive modalities for diagnosis, no useful animal models exist to aid our understanding of the disease, and no randomised trials of treatments have been done. Despite such limitations, substantial progress has been made including growing recognition of a specific constellation of epidemiological, clinical, neuroradiograhic, and laboratory findings that could enhance diagnostic accuracy.[5] A clear view of multiple clinical and pathological disease subtypes with prognostic implications within the spectrum of PACNS is now accepted.[6] Our ability to recognise and diagnose diseases that mimic PACNS has improved, especially with the general acceptance of reversible cerebral vasoconstrictive syndrome (RCVS),[7] a confounder of many early case series of PACNS and the most common diagnostic mimic. Advances in diagnostic neuroimaging, especially indirect angiography, seem promising.[8] The specialty of childhood PACNS has rapidly matured.[9] We review the main advancements in the clinical, diagnostic, and therapeutic approaches to adult and childhood PACNS. Moreover, we discuss the main diseases that mimic PACNS and review the substantial progress made in our clinical approach to PACNS, despite vast limitations. In view of several excellent reviews of PACNS,[5,6] we will attempt to review this topic with an emphasis on those areas that have the greatest effect on clinical management.

Diagnostic criteria and clinical features

Diagnostic criteria for PACNS were proposed over 20 years ago (panel 1),[2] and recently adopted for childhood PACNS.[10] Although unvalidated, these criteria have been used widely for clinical reporting and investigation.[11] Birnbaum and Hellman[5] have suggested incorporation of definite and probable diagnostic subcategories. Implicit and explicit changes in the application of these criteria have occurred with advances in diagnostic testing, the elucidation of PACNS mimics, both new and old, and the changing approach to unexplained neurological disease; these changes have been described in detail elsewhere.[12]

PACNS affects patients of all ages but peaks at around 50 years of age and is most common in males. The clinical signs and symptoms are non-specific and reflect the diffuse and often patchy nature of the pathological process. The course of the illness is also variable with presentations ranging from hyperacute to chronic and insidious. In patients with the disease variant granulomatous angiitis of the CNS (GACNS), characterised by a presentation of chronic meningitis and a small-vessel distribution, signs or symptoms might precede diagnosis by 3 years or more.[4,11,13]

***Panel 1*: Criteria for primary angiitis of the CNS (PACNS) and childhood PACNS**

- The presence of an acquired otherwise unexplained neurological or psychiatric deficit
- The presence of either classic angiographic or histopathological features of angiitis within the CNS
- No evidence of systemic vasculitis or any disorder that could cause or mimic the angiographic or pathological features of the disease

Patients should meet all three criteria to be diagnosed with PACNS.[2] Childhood PACNS mandates a patient age of ≤18 years at diagnosis and excludes neonates (1 month of age)

Reproduced from Calabrese and Mallek,[2] by permission of Lippincott Williams & Wilkins.

Headache is the most common symptom and might vary in description, intensity, and pattern. In our experience, thunderclap headache is almost never reported by patients with PACNS and should indicate a diagnosis of RCVS.[7] Cognitive impairment is also common and can be insidious.

Stroke and transient ischaemic attacks are common, occurring in 30–50% of patients with PACNS.[4,11,13] Stroke usually affects many different vessels; presentation of PACNS as a single stroke is uncommon. Cranial nerve involvment including ocular nerves, in addition to myelopathy, seizures, and ataxia have been described.[4,11,13,14] Importantly, signs and symptoms of systemic vasculitis including marked constitutional symptoms, weight loss, or visceral target-organ disease are all rare and should raise the likelihood of systemic illnesses. Although PACNS can present in many ways, this diagnosis should be considered in patients with the following presentations: (1) cerebral ischaemia that affects different vascular territories and that is distributed over time, in association with inflammatory changes in the CSF; (2) subacute or chronic headache with cognitive impairment or chronic aseptic meningitis; (3) chronic meningitis after infectious and neoplastic disorders have been ruled out. Regardless of the degree of pretest probability, all disorders producing similar angiographic abnormalities or pathological changes of an angiocentric inflammatory process must be ruled out before diagnosis can be confirmed.

Disease subtypes

Initial attempts at subclassification of PACNS described three broad subtypes: GACNS, benign angiopathy of the CNS (BACNS), and atypical PACNS.[11] The most clinically significant advance in our understanding of BACNS is its recognition as a vasospastic disorder rather than as a subtype of PACNS, and BACNS is now subsumed by the umbrella term of RCVS. Atypical PACNS has previously been used to refer to patients who did not clearly meet criteria for either GACNS or RCVS. This terminology remains unsatisfactory for several reasons. First, since RCVS is no longer considered a subtype of PACNS, these atypical cases represent most patients with PACNS. Second, substantial heterogeneity exists within this group, which needs further delineation. Consequently, the term atypical PACNS is best avoided and patients who do not meet criteria for GACNS should instead be categorised, where possible, as one of the four additional PACNS subtypes proposed below.

This proposed classification has several axes and is based on available clinical and neuroimaging, angiographic, pathological, and age data. This classification is based on available evidence and our clinical experience and is accepted among specialists.[3,15,16] A prospective multicentre study is needed to better characterise and validate these disease subtypes in terms of clinical presentation and optimum treatment and outcomes in an independent sample of patients with PACNS.

Granulomatous angiitis of the CNS

GACNS refers to patients with the classic PACNS presentation of insidious onset of headache and diffuse and focal neurological deficits.[1,2] MRI is abnormal and CSF examination reveals evidence for aseptic meningitis in over 90% of patients.[5] MRI typically shows multiple bilateral ischaemic foci. The combination of a normal MRI and normal CSF examination is judged to have a high negative predictive value for the diagnosis of GACNS. Brain biopsy is required to confirm the diagnosis and exclude other causes, especially when treatment with cyclophosphamide is considered. The finding of small-vessel granulomatous angiitis on brain biopsy categorises this entity; even when definite vasculitis is present, secondary causes such as infection and malignancy must be considered. False-negative biopsy rates of 25–50% have been reported;[17] strategies to increase tissue yield include targeting the biopsy to a radiographically abnormal area, and combined parenchymal and leptomeningeal biopsy. Most studies show that open biopsies have a higher tissue yield than do stereotactic biopsies.[18] Cerebral angiography is typically normal in these patients, reflecting the size of the vessels affected.

Lymphocytic PACNS

Patients with this disorder might have clinical, radiological, and CSF findings that resemble those of patients with GACNS, but can be distinguished by the presence of lymphocytic rather than granulomatous angiitis on CNS biopsy.

Angiographically defined PACNS

This group is characterised by abnormal cerebral angiography and CSF examination but usually a normal CNS biopsy. This constellation of findings suggests that medium-sized vessels are affected, rather than the small vessels typically affected in patients with GACNS. Angiography has poor specificity for the diagnosis of PACNS, so when the possibility of PACNS is suggested by this technique, a diligent workup should be done to rule out other vasculopathies. Moreover, other indirect signs of inflammatory brain disease should be present such as abnormal CSF findings (with no evidence of infectious or malignant causes) or enhancement of the arterial vessel wall (in the absence of other causes of arterial-wall enhancement). RCVS is a major disorder that should also be ruled out; it is differentiated from angiographically diagnosed PACNS by normal CSF findings and reversibility of the angiographic abnormalities, shown by follow-up vascular imaging. The absence of histological documentation of vasculitis in such cases mandates continued vigilance for an alternative diagnosis, even when no such alternative diagnosis is identifiable at initial presentation.