PRIMARY CEREBRAL VASCULITIS

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ABSTRACT

Vasculitides are rare conditions affecting vessels of different type and caliber. They are characterized by inflammation of the blood vessel walls and vascular damage causing alterations in blood flow. The resulting clinical syndromes mostly result from tissue ischemia, vascular damage and inflammation affecting one or more organs or systems. Primary isolated vasculitic involvement of the central nervous system (primary CNS vasculitis) is a rare form characterized by inflammation of the blood vessels in the brain and medulla without evidence of vasculitis symptoms outside the CNS.

Keywords*: primary CNS vasculitis, PACNS, CNS primary angiitis, CNS vasculitides, vasculitis.*

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Introduction

Primary central nervous system vasculitis is a rare and little known inflammatory process affecting the brain and spinal cord. It was first classified as a disease in its own right in 1959 when Cravioto and Feigin[1] described several cases of non-infectious vasculitis of the nervous system[2]. Primary cerebral vasculitis has since been described as granulomatous angiitis of the central nervous system[3,4] or more specifically, non-infective[5] or idiopathic[6]. granulomatous angiitis, isolated vasculitis of the central nervous system[7] or primary vasculitis of the central nervous system (PACNS)[8].

Most vasculitic processes of the CNS are caused by pathological conditions in the blood vessels of various organs and tissues and therefore represent a continuation of the systemic pathological process to the nervous system. PACNS can occur at any age, though the most affected group is typically young adults aged between 30 and 60 years, with a peak around 50, without vascular risk factors. There seems to be no gender prevalence[9,10].

Etiology and pathogenesis

The causes and pathogenesis of PACNS remain unknown. Infectious agents have been implicated as possible triggers owing to the well-known association of cerebral vasculitis with certain infections, namely varicella zoster virus (VZV)1[11]. From a histopathological standpoint, PACNS is a vasculitis involving small and medium caliber leptomeningeal and parenchymal arteries[12,13]. Clinically, there are no specific signs or symptoms, reflecting the widespread and often irregular nature of the inflammation: presentation is highly variable, appearing as a process with chronic to hyperacute progression.

Symptomatology

Different types of headache are the commonest symptom of PACNS. Also reported are cognitive impairment, often with an insidious presentation, stroke and transient ischemic attacks, found in approximately 30-50% of patients[13-15]. Rarer manifestations may involve the cranial nerves (visual impairment and diplopia), myelopathy, and ataxia[13-16]. One case report described an unusual clinical presentation mimicking schizophrenia, associated with lesions involving the bilateral thalami[17].

Other studies report, in descending order, clinical symptoms such as headaches, focal or diffuse symptoms, and seizures, with the diagnosis established by cerebrospinal fluid (CSF), neuroradiological, angiographic and bioptic examinations. The most commonly used treatments were prednisolone, cyclophosphamide, and azathioprine, with improvement in 20 to 100% of cases[18]. At presentation, clinical manifestations were headache (63%), altered cognition (50%), hemiparesis (44%), any type of visual symptom (42%), persistent neurological deficit or stroke (40%), aphasia or dysarthria (28%), ataxia (19%), seizures (16%) and, to a lesser extent, other manifestations[19].

General symptoms such as weight loss, fever and visceral multiorgan involvement are rare and when present should raise the suspicion of other systemic diseases.

Diagnosis

Calabrese and Mallek[8] proposed three criteria for the diagnosis of PACNS: detection of an acquired neurological deficit of unknown origin after initial basic evaluation; cerebral angiography with typical characteristics of vasculitis or a brain biopsy sample showing vasculitis elements; no evidence of systemic vasculitis or other diseases in which angiographic or pathologic characteristics could be secondary. These criteria have been established for both adults and children, and though not entirely validated, are currently used in clinical practice[19]. There is no sufficiently sensitive and specific laboratory test to confirm or exclude the diagnosis.

Birnbaum and Hellmann[10] subsequently proposed two diagnostic criteria for PACNS: definite diagnosis with confirmation of vasculitis on analysis of a tissue biopsy specimen; probable diagnosis in the absence of tissue confirmation, if there are high probability findings on an angiogram with abnormal findings on magnetic resonance imaging (MRI) and a CSF profile consistent with PACNS.

Traditional inflammatory markers, the erythrocyte sedimentation rate, C-reactive protein test and typical autoantibodies of vasculitis, anti-nuclear antibodies, and antineutrophil cytoplasmic antibody (ANCA) are generally normal in PACNS patients, but should also be investigated to exclude any intercurrent systemic illness. CSF examination is also essential in evaluating patients with PACNS as it will exclude many clinically similar diseases, especially those of infectious origin. It is sometimes possible to observe moderate lymphocytic pleocytosis (an average of about 20 cells/ml), normal glycorrhachia, high protidorrachia (around 100-200 mg/dl), and occasionally oligoclonal bands with a high IgG synthesis rate. Neuroimaging features are not specific and may resemble other conditions such as demyelination or ischemic processes. MRI is the preferred examination for investigating parenchymal brain lesions as it shows both cortical and subcortical white matter alterations. Typical lesions include multiple infarcts involving both the cortex and subcortex. Hyperintensities on T2/FLAIR sequences are common but not specific for the diagnosis of PACNS[20]. A mass lesion has also been reported as an atypical presentation[21].

Cerebral angiography and magnetic resonance angiography are often used, though both techniques are poorly specific: stenotic or dilated areas commonly found in PACNS are also encountered in atherosclerosis, radiation-induced vasculopathy, infections and reversible cerebral vasoconstriction syndrome (RCVS). In addition, the sensitivity of angiography may be less than 30% when cerebral biopsy[22] is performed. Brain biopsy not only remains the gold standard for PACNS diagnosis, but is also important to identify radiologically and clinically similar pathologies, especially infections and neoplasia[23,24]. Nonetheless, even a negative biopsy cannot exclude the diagnosis of PACNS: some factors such as patchy spread or a poorly accessible position have led to false negatives in 25% of cases resulting positive at autopsy[25].

In terms of differential diagnosis, PACNS does not have a highly characteristic presentation either during onset or in the later stages, but some symptoms should elicit a degree of suspicion (e.g. patients with subacute or chronic headaches, or with minor ischemic multifocal strokes occurring over a long period).

A correct diagnostic work-up should include a diagnostic evaluation for acute cerebrovascular ischemic events including appropriate blood tests, screening for genetic thrombophilia, echocardiography, Holter monitoring (ECG) and cerebrovascular imaging to rule out embolism, carotid dissections and conditions associated with acute or subacute multiple ischemic events (as may occur in infective endocarditis) or hypercoagulable states. Diagnosis is facilitated when alterations in cerebral angiography are detected during a thorough neurological diagnostic process performed for other reasons. In this case too, premature atherosclerosis, the most common cause of pathological angiography, must be considered the prime cause and appropriately excluded. Other conditions responsible for similar changes to cerebral angiography are fibromuscular dysplasia and Moyamoya disease, but these illnesses have characteristic angiographic features, including involvement of the extracranial arteries or proximal intracranial arteries, seldom affected in PACNS[26].

RCVS is the condition most frequently mimicking PACNS. This syndrome comprises pathologies associated with cerebral vasoconstriction rather than vasculitis (such as Call-Fleming syndrome, postpartum angiopathy, migraine and cerebral vasospasm caused by drugs such as cocaine, amphetamines, triptans and other serotonergic and sympathomimetic agents)[27,28]. RCVS can trigger severe and sudden migraines with or without paroxysmal symptoms and focal neurological deficits; angiography shows a narrowing of the cerebral arteries which resolves spontaneously within one to three months. The disorder mainly affects women at an average age of 45 years. About 60% of female patients develop RCVS in the postpartum period or after exposure to vasospastic substances[27]. The poorly specific features of PACNS, such as ischemic strokes, diffuse white matter changes, and more rarely space-occupying lesions, make its characterization challenging since they may be found in numerous conditions including demyelinating disorders such as multiple sclerosis, cerebral lymphomas and cerebral gliomatosis. In addition, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy must also be considered, especially in a young patient with a telling family history who complains of headaches, depression, recurrent ischemic strokes and presents white matter alterations on MRI scans[29]. In some cases, prion diseases should also be excluded[30].

It is highly important to rule out any infectious vasculitis, in that immunosuppressive therapy may have dramatic consequences. VSV infections most frequently cause vascular inflammation, which may often occur even in the absence of obvious signs of viral infection[31]. Indeed, a herpes-associated small-vessel vasculitis can develop without any history of skin lesions. In suspected cases, it is good practice to search for anti-VZV antibodies in the CSF[32]. Other infections that should be excluded include: human immunodeficiency virus[33], hepatitis C[34], Parvovirus B19[35], cytomegalovirus[36], Mycoplasma pneumoni[37], Borrelia burgdorferi[38], and Mycobacterium tuberculosis[39] from Bartonella sp[40] and Rickettsia spp[41,42].

In some cases, a number of fungal infections (aspergillosis, mucormycosis, coccidioidomycosis and candidiasis) and cysticercosis have also been implicated[43,44]. Some authors claim that PACNS could result from systemic vasculitides such as (ANCA)-associated vasculitis, Behçet's disease, and less frequently polyarteritis nodosa, Schönlein-Henoch purpura, Kawasaki disease and Takayasu's arteritis[45-58]. Symptoms similar to those of PACNS have also been observed in 7-10% of patients with Wegener's granulomatosis[45,46] and in 1-8% of patients with Churg-Strauss syndrome[47,48]. PACNS-like symptoms are seldom observed in patients with neurolupus(49,50) (7% of cases) and even more rarely in patients with Sjǿgren's syndrome[59] (about 5% of cases). Some cases of cerebral vasculitis secondary to Crohn's disease have also been described as a rare phenomenon manifesting with headache, vomiting, and left-sided weakness[60]. Summarizing, the differential diagnosis of PACNS(61) must be made with:

- Multifocal cerebrovascular diseases or cerebral thrombo-embolism
- Demyelinating/ dysmyelinating diseases;
- Systemic vasculitides;
- Systemic inflammatory diseases;
- Viral, bacterial or fungal infections;
- Brain neoplasms;
- Posterior reversible encephalopathy syndrome;
- Progressive multifocal leukoencephalopathy.

Treatment

Numerous randomized studies on PACNS treatment deriving from the management of vasculitides in general show the efficacy of cyclophos-

phamide in combination with corticosteroids[7,62]. In a cohort study of 101 patients, glucocorticoids alone or in combination with cyclophosphamide had a satisfactory response in most patients[63].

Glucocorticoid therapy should be started as soon as PACNS is diagnosed. If the patient does not respond promptly, cyclophosphamide administration is recommended. Thereafter, to maintain remission, the introduction of a low-risk immunosuppressant such as azathioprine or methotrexate may be considered, though there is little direct evidence of the efficacy of these drugs. In general, a treatment cycle of about 12-18 months is adequate for most patients[63,64]. Two other therapeutic options, namely anti-TNFα and mycophenolate mofetil, may prove successful in patients with little response to corticosteroids and cyclophosphamide[64,65]. Treatment with the anti-CD20 antibody rituximab has been used successfully in refractory Wegener's granulomatosis with CNS involvement, suggesting a possible therapeutic role for this drug in PACNS[66]. Lastly, it is vital to monitor the disease during treatment by performing serial brain MRI examinations (4-6 weeks after the start of treatment, then every 3-4 months during the first year of treatment, or when new neurological symptoms arise). Sometimes, despite the stability of MRI, when clinical symptoms worsen it may be necessary to repeat CSF examination or cerebral angiography. For those patients who did not undergo a brain biopsy during initial diagnosis and who deteriorate despite immunosuppressive treatments, this procedure should be considered, bearing in mind the general clinical condition of the patient.

Conclusions

PACNS remains one of the major challenges in diagnostic neurology, rheumatology, immunology and possibly medicine in general. Diligent teamwork is essential to exclude similar pathologies and thus ensure the correct diagnosis.

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