Primary Angiitis of the Central Nervous System – Clinical Approaches, Challenges and Controversies

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Abstract

Primary angiitis of the central nervous system (PACNS) is a rare and life-threatening form of vasculitis confined to the CNS. A timely diagnosis is a real challenge because clinical manifestations of PACNS are diverse and nonspecific. Headaches, cerebrospinal fluid inflammation and abnormal brain magnetic resonance imaging are prevalent. When PACNS is suspected, a thorough investigation is mandatory to rule out several potential simulators and confirm the diagnosis. Treatment of PACNS is also a challenge involving competing forces, which include the threat of serious adverse effects of potent immunosuppressive agents and the risk of neurological deteriorations due to insufficient immunosuppressant therapy. Efforts are ongoing to delineate subtypes requiring different therapeutic approaches and having distinct prognoses. Despite recent progress, PACNS is still fatal in as much as one-sixth of cases. Long-term follow-up is mandatory in patients with PACNS.

Keywords

Angiitis, vasculitis, central nervous system, brain, headache, stroke, magnetic resonance, cerebrospinal fluid, angiography, immunosuppressive therapy

Disclosure: Sylvain Lanthier has received funding from the Fondation des Gouverneurs de l'Espoir for the creation and implementation of the INTERSPACE, an international database on primary angiitis of the central nervous system. Alexandre Y Poppe and Sylvain Lanthier are principal investigators of this database. The authors have no other conflicts of interest to declare.

Acknowledgements: This article was prepared with the assistance of the Research Support Office at Centre Hospitalier de l'Université de Montréal. The authors thank the Fondation des Gouverneurs de l'Espoir for supporting research on cerebral vasculitis.

Received: 9 May 2011 **Accepted:** 2 August 2011 **Citation:** *European Neurological Review*, 2011;6(3):181–6 *DOI:10.17925/ENR.2011.06.03.181*

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Primary angiitis of the central nervous system (PACNS) fascinates by the multiplicity of its clinical manifestations, the complexity of its investigation, and the extensiveness of its differential diagnosis (see *Table 1*). Immunosuppressive therapy is central in the management of PACNS, but the optimal approach remains the subject of debate. Efforts are ongoing to identify subtypes with different treatment requirements and outcomes. This article aims to summarise the literature on PACNS, and to highlight its diagnostic and therapeutic challenges and controversies.

Histopathology

PACNS affects small vessels and medium-sized arteries of the brain, spinal cord, and leptomeninges. The multifocal and multisegmental infiltration of the vessel wall by polyclonal T-lymphocytes is variably associated with granulomas or fibrinoid necrosis, defining the lymphocytic, granulomatous, and necrotising histopathological patterns that may coexist in individual patients.[1–3] The vessel wall may also contain eosinophils, giant cells,[1] B-lymphocytes,[4] or beta-amyloid deposits.[5,6] Other changes include endoluminal thrombi and vascular occlusion.

Pathophysiology

The pathogenesis of PACNS and its predilection for central nervous system (CNS) vessels remains poorly understood. Systemic infections may trigger CNS vasculitis in a host with defective defence mechanisms.[2,7] Evidence supporting this hypothesis can be found in the secondary CNS vasculitides resembling PACNS seen in association with myelo- or lymphoproliferative diseases, other immunosuppressive states,[8] and infection by a variety of agents, including human immunodeficiency virus (HIV)[9] and varicella zoster virus.[10] Following the undetermined causative agent, lymphocytic infiltration occurs at the vessel wall, followed by fibrinoid change in the vessel wall, histiocyte accumulation, necrosis, fragmentation of internal elastic lamina, with further transmural infiltration.[11] Consequently, vascular obstruction produces cerebral ischaemia, and vascular rupture causes intracranial haemorrhages. PACNS does not involve immune complexes or autoantibodies.

Clinical Manifestations

The clinical manifestations of PACNS are diverse and non-specific. PACNS affects both genders with a slight male predominance, and frequently occurs in the fourth to sixth decade, although PACNS is reported in all age groups.[12–14] Prodromal periods of several weeks or months are common. Initial manifestations include headaches, behavioural changes, seizures and focal or multifocal neurological deficits (indicating brain, cranial nerve, spinal cord, or nerve root lesions). Ischaemic stroke is common at onset and often recurs.[14]

Table 1: Differential Diagnosis of Primary Angiitis of the Central Nervous System

Secondary Vasculitides
Systemic vasculitides affecting the central nervous system (e.g. temporal arteritis, Takayasu arteritis, polyarteritis nodosa, Wegener granulomatosis, Churg–Strauss syndrome, Kawasaki disease, Cogan syndrome, Henoch-Schönlein purpura, acute posterior multifocal placoid pigment epitheliopathy, microscopic polyangiitis)
Vasculitides associated with connective tissue disorders or other systemic diseases (e.g. systemic lupus erythematosus, Sjögren syndrome, Behçet disease, inflammatory bowel diseases, coeliac disease, graft versus host diseases, Buerger's disease, rheumatoid arthritis, dermatomyositis, relapsing polychondritis, Susac syndrome, sarcoidosis)
Cancer-associated vasculitides (e.g. lymphoproliferative diseases, leukemia, lung cancer, lymphomatoid granulomatosis and intravascular/angiocentric lymphoma)
Infectious vasculitides (e.g. neurosyphilis, human immunodeficiency virus, varicella zoster virus, hepatitis C virus, Lyme disease, mycobacterium tuberculosis)
Drug-induced and other hypersensitivity vasculitides
Non-vasculitic Vasculopathies
Atheromatosis
Arterial dissection
Fibromuscular dysplasia
Radiation vasculopathy
Post-varicella arteriopathy
CADASIL syndrome
CARASIL syndrome
Fabry disease
Moyamoya
Malignant hypertension
Reversible cerebral vasoconstriction syndrome
Conditions Other Than Vasculopathies
Emboligenic cardiopathies (e.g. infectious endocarditis, atrial myxoma)
Prothrombotic conditions (e.g. antiphospholipid syndrome, sickle cell disease)
Mitochondriopathies (e.g. MELAS)
Cerebral venous thrombosis
CNS infections (e.g. encephalitides, brain abscess, meningitides)
Inflammatory disorders of the CNS (e.g. chronic aseptic meningitides, multiple sclerosis, transverse myelitis, acute demyelinating encephalomyelopathy, cerebral amyloid angiopathy with lobar hyperintensities)
Malignancies affecting the CNS (e.g. CNS lymphoma, metastases, glioblastoma, carcinomatous meningitis)

CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CARASIL = cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy; CNS = central nervous system; MELAS = mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes.

Conversely, intracranial haemorrhage is infrequent.[14] Myelopathy occurs in 5–14 % of cases,[2,15] and is more frequently associated with other neurological symptoms than isolated.[16,17] Globally, five clinical patterns describe most patients: chronic aseptic meningitis, sub-acute or chronic encephalopathy, recurrent focal neurological deficits or seizures, intracranial tumour-like lesion, and progressive myelopathy. A combination of multiple patterns in an individual raises the likelihood of PACNS. Fever is reported in 19 % and weight loss in 12 % of patients.[8] Systemic manifestations of vasculitis such as skin rash and arthritis are typically absent in PACNS, and suggest a systemic inflammatory disease with secondary CNS involvement. However, there are occasional reports of PACNS with symptomatic uveitis,[18–20] as well as histopathological evidence of sub-clinical involvement of the lungs, heart, kidneys[21] and sural nerve.[22]

A tumour-like presentation accounts for 5–15 % of PACNS. Patients present with focal neurological deficits, headache, or seizures. Magnetic resonance imaging (MRI) shows a non-specific tumour-like lesion, indistinguishable from other causes such as malignancy.[23] A confirmatory biopsy is needed for proper diagnosis and management. Granulomatous and lymphocytic histopathological patterns are reported. Intravascular beta-amyloid deposits are prevalent and associated with poor outcomes (mortality in 38 %).[24] Tumour-like lesions without amyloid deposits respond well to immunosuppressive therapy, but radiological relapses occur.[23]

A rapidly-progressive subtype of PACNS presents with significantly more acute para- or quadriparesis, multiple bilateral infarctions of the cortical and subcortical regions on MRI, as well as angiographic evidence of bilateral, large-vessel vasculitis.[25] Blood markers of inflammation may also be present. Biopsies performed on three patients with rapidly progressive PACNS showed a granulomatous and/or necrotising pattern. Most patients fail to respond to usual immunosuppressive therapies and rapidly progress towards death.

Another subtype with prominent leptomeningeal enhancement on brain MRI is considered to be a mild variant of PACNS.[26] Such patients show significant evidence of cerebrospinal fluid (CSF) inflammation on lumbar puncture with few anomalies on cerebral angiography compared with patients without meningeal enhancement. A granulomatous vasculitis and intravascular beta-amyloid deposits are common. Although relapses are possible, these patients have a prompt response to immunosuppressive therapy and favourable outcomes on follow-up.

Patients with PACNS associated with beta-amyloid deposits are significantly older, predominantly male, and present with a more acute onset, greater cognitive decline, as well as fewer headaches and seizures compared with those without amyloid deposits.[5,6] Interestingly, the higher prevalence of cognitive decline in amyloid-related PACNS remains lower than what is seen in cerebral amyloid angiopathy.[5] Furthermore, amyloid-related PACNS shows a

faster response to immunosuppressive therapy and similar outcomes compared to PACNS without beta-amyloid deposits.[6]

PACNS selectively involving larger intracranial arteries or small vessels (angiography-negative) have diverging features.[14] The small vessel subtype is more likely to present with behavioural changes, headache, seizures and normal cerebral angiography, such that brain biopsy is central to the diagnostic process. Conversely, patients with large vessel involvement have more frequent stroke presentations with abnormal cerebral angiography. Similar findings are described in childhood PACNS.[12] Large vessel involvement may predict relapses and death,[14] although contradictory findings have been reported[27] that may be partially explained by differences in populations and definition of vessel sizes and relapses.

Diagnostic Investigations

The original diagnostic criteria for PACNS proposed by Calabrese and Mallek[28] in 1988 require that a patient has:

- a history of a neurological deficit that remains unexplained after a vigorous diagnostic workup, including lumbar puncture and neuroimaging studies;
- either classic angiographic evidence of vasculitis or histopathological evidence of vasculitis within the CNS; and
- no evidence of systemic vasculitis or any other condition to which the angiographic or pathological evidence can be attributed.

Description of the entity now known as reversible cerebral vasoconstriction syndrome, which will be detailed below, has provided clinicians with further evidence that a vasculitic appearance on angiography does not necessarily indicate the presence of an inflammatory vasculopathy. As such, tissue biopsy becomes essential to confirming a diagnosis and initiating disease-specific therapy. Given that angiography and histopathologic evidence of vasculitis are presented as interchangeable in the original PACNS diagnostic criteria, Birnbaum and Hellmann[29] proposed a modification to these criteria in 2009:

- patients receive a definite diagnosis of PACNS if there is confirmation of vasculitis on analysis of a tissue biopsy specimen; and
- patients have a probable diagnosis of PACNS, in the absence of tissue confirmation, if there are high probability findings on an angiogram with abnormal findings on MRI and a CSF profile consistent with PACNS.

The diagnosis of PACNS remains challenging, in large part due to its rarity and the impressive list of pathologies to consider in the differential diagnosis (see *Table 1*). Once there is sufficient clinical suspicion for PACNS, investigations require exclusion of other diagnoses in addition to confirmation of PACNS using blood tests, parenchymal brain imaging, neurovascular imaging, CSF analysis, and parenchymal and meningeal biopsy.

Blood Tests

Blood markers of inflammation such as leukocyte count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are rarely elevated in PACNS, primarily owing to the blood–brain barrier. However, some authors reported an elevated ESR (30–40 mm/hr) in 30–60 % of cases of PACNS.[30,31] In addition, markers of systemic vasculitis and connective tissue disease (antinuclear antibodies, antineutrophil cytoplasmic antibodies, complement levels, rheumatoid factor), and infectious serologies (including Lyme, syphilis, HIV, hepatitis B and C) should generally be normal in order to confidently exclude secondary causes of CNS vasculitis.

Parenchymal Brain Imaging

Brain imaging is abnormal in the majority of cases of PACNS, although the sensitivity of computed tomography (CT) is only about 30 %.[32] MRI, however, is abnormal in 80–100 % of cases,[14,18,32] and is the brain imaging modality of choice in PACNS. The most common abnormalities are non-specific multifocal hyperintensities in the subcortical white matter on T2-weighted sequences suggestive of leucoaraiosis. Other affected regions include the basal ganglia and cerebral cortex. Actual ischemic infarcts can also be seen in up to 50 % of patients, often in multiple vascular territories, of varying ages and involving cortical and subcortical structures.[14] Intraparenchymal hemorrhage, either from rupture of necrotic vessel wall or transformation of ischemic infarction, may be seen in a minority of cases, as may subarachnoid hemorrhage.[33] In the appropriate clinical context, spinal cord MRI may also reveal medullary infarction.[15,34]

Other less common radiological findings include tumor-like lesions, confluent white matter hyperintensities resembling multiple sclerosis, unilateral lesions mimicking Rasmussen's encephalitis, and multifocal punctate lesions.[27,30,35–38]

Imaging should always include gadolinium-injected sequences since enhancement may be present in 30–60 % of patients.[14,32,39] Such enhancement may be seemingly parenchymal, along affected perforating vessels, or leptomeningeal, and in the latter case, may represent a favorable target for biopsy. In fact, leptomeningeal enhancement may be more sensitive for PACNS than parenchymal abnormalities.[32,40] Some authors have also proposed using brain L-[methyl-11C] methionine positron emission tomography as an adjunct to MRI in order to identify metabolically active brain lesions and thereby guide biopsy towards affected regions so as to possibly improve diagnostic yield.[41]

Vascular Imaging

Despite significant advances in non-invasive imaging of the cerebral vasculature using MRI- and CT-angiography (MRA and CTA), the gold standard for vascular imaging in suspected PACNS remains digital subtraction angiography (DSA). CTA and MRA remain too insensitive to changes in small calibre vessels to obviate the necessity of DSA.[42] The classical findings of PACNS on DSA are multifocal stenoses with interposed regions of normal vessel calibre or sausage-like dilatation, creating the typical 'beading' appearance. Affected arteries tend to be more distal branches of the anterior or posterior circulation and changes tend to occur bilaterally.[43] Other angiographic findings include multiple vessel occlusions and vessel lumen irregularity, however when pathology only involves vessels with diameters less than 500 μm, angiography may be entirely normal. In addition, multiples micronaneurysms, as may be seen in peripheral vasculitides like polyarteritisnodosa, are conspicuously absent in PACNS.[32,43]

While it is generally safe, angiography suffers from both a lack of specificity and sensitivity in the diagnosis of PACNS. Specificity is

limited because of multiple potential mimics which may cause beading on angiography, including noninflammatory vasculopathies like fibromuscular dysplasia, intracranial atherosclerosis, reversible multifocal vasospasm, intravascular malignancy, and systemic or infectious vasculitides. Sensitivity has been estimated at only 60 % in biopsy-proven cases, primarily owing to the lack of spatial resolution for small vessels which are commonly affected in PACNS.[8,14,40,44] Some authors have suggested that fluorescein retinal angiography may be of use in some cases with normal cerebral angiography.[45]

Recent research has explored the use of MRI with gadolinium to identify markers of inflammation and active vasculitis within vessels, such as wall-enhancement and thickening, which could suggest an active vasculitis. Such vessel wall imaging shows promise in differentiating vessel inflammation from atherosclerosis and dissection[46] and has been shown to be abnormal in most patients with large-vessel PACNS.[47]

Cerebrospinal Fluid Analysis

Lumbar puncture is essential in the investigation of suspected PACNS, both to help support the diagnosis and more importantly, to exclude other diagnoses. CSF is abnormal in about 90 % of biopsy-proven PACNS cases, usually demonstrating non-specific inflammatory changes.[14,28,48] Moderate pleocytosis, generally lymphocytic, with mild to moderate proteinorachia and normal glucose are the most common findings. More marked elevations in white blood cell count (>250 cells/μl), non-lymphocytic predominance and highly abnormal protein should alert the clinician to other diagnoses, included infection and neoplasm.[29] Cultures, stains or polymerase chain reaction studies (PCR), as appropriate, should be obtained to exclude fungal, mycobacterial, and herpes virus infections. Finally, cytology with flow cytometry and oligoclonal bands should all be included in the CSF analysis.

Tissue Biopsy

Brain and leptomeningeal biopsy remains the gold standard for diagnosing PACNS and should be performed in the vast majority of suspected cases prior to initiation of long-term immunosuppressive therapy. Biopsy is generally open and should include a 1 cm wedge of cortex and white matter as well as leptomeningeal tissue and vessels in order to maximise diagnostic yield.[49] Targeting regions of leptomeningeal enhancement on MRI may improve the yield of biopsy, although the validity of this approach remains to be proven.[32] In the absence of an accessible lesion, the non-dominant temporal tip can be sampled. Stereotactic needle biopsy can be used for deep-seated lesions but the risk of sampling error increases with this technique.[40,41]

False-negative biopsy is not uncommon, owing to the patchy nature of vasculitic changes and sensitivity of biopsy ranges from 53–74 % in studies that used post-mortem tissue as a gold standard for diagnosis.[1,8] Rates of false-negative biopsy increase when disease is limited to large- and medium-sized arteries not sampled by this procedure, and if obtained tissue is restricted to the brain,[31] leptomeninges,[50,51] or evacuated necrotic tissue from cerebral infarctions.[52]

As is true of all investigations performed in patients with suspected PACNS, the essential role of biopsy is to exclude other pathologies which may mimic PACNS. In a study of 61 individuals with suspected PACNS, CNS biopsy disclosed alternative diagnoses in 24 (39 %) and no diagnosis in 15 (25 %).[50] Among alternative diagnoses, infection (including abscess) and neoplasm (including CNS lymphoma) were the most common. For this reason, biopsy specimens should be extensively cultured and stained to exclude diagnoses for which treatment differs (or may be diametrically opposed) to that used for PACNS. The neurological morbidity of brain biopsy ranges from 0.3–2 %, which is comparable to that of DSA but which should be weighed against the risks of unwarranted chronic immunosuppressive therapy.[30,32,50]

The decision to pursue brain biopsy should be predicated on the clinical suspicion raised by patient symptoms and the results of ancillary tests, particularly CSF examination and MRI. In fact, the combination of normal MRI and normal CSF has a high negative predictive value for the diagnosis of PACNS.[2] Given the high prevalence of headache in PACNS (being sensitive but not specific for this disorder), we use this symptom in an algorithm intended to select patients for biopsy. Our approach is to obtain tissue diagnosis in the presence of two or more of the following in patients with suspected PACNS: headache, abnormal CSF, and MRI consistent with PACNS. If only one element is present, the diagnosis of PACNS is highly unlikely and biopsy may be deferred.

Reversible Cerebral Vasoconstriction Syndrome

This entity, first described by Call and Fleming in 1988, deserves mention because it is a common diagnostic consideration in the initial work-up of patients with suspected PACNS and its likely presence in older case series of PACNS may have contaminated their conclusions.[53] This syndrome is in fact a group of disorders which generally affect younger women and all produce prolonged, reversible vasoconstriction of intracranial arteries leading most commonly to severe, recurrent thunderclap-type headaches over a period of days to weeks and occasionally to focal neurological deficits on the basis of ischaemic infarction, intraparenchymal and subarachnoid haemorrhage.[54–56] Aetiologic mechanisms include pregnancy and the puerperium, vasoactive drugs (including nasal decongestants and selective serotonin reuptake inhibitors) and illicit drugs (cannabis, cocaine), although a third of cases are idiopathic.[55]

Diagnosis is made based on the clinical presentation and the documentation of segmental, multifocal narrowing of medium and large-sized intracranial arteries on initial CTA, MRA, or DSA with normalisation of vessel calibre on follow-up angiographic studies. CSF is generally normal or shows evidence of subarachnoidal haemorrhage. MRI may be normal or show areas of haemorrhage or infarction. Differentiation of this condition from PACNS is essential since treatment usually involves calcium-channel blockers and not long-term immunosuppressive drugs.[54] However, by definition, the diagnosis can only be confirmed retrospectively once normalisation of vessel abnormalities has been demonstrated.

Treatment

Untreated, PACNS follows a progressive and relapsing course that leads to severe disability or death, with exceptional spontaneous remissions.[21] In 1983, the combination of prednisone and cyclophosphamide was recognized as therapy for PACNS.[57] Nowadays, corticosteroids are often used as first-line monotherapy, cyclophosphamide or other cytotoxics being used if corticosteroids fail to control the disease or cause unacceptable side effects.[14,58] Evidence supporting this approach is limited to retrospective and possibly biased comparisons between corticosteroids alone versus

corticosteroids plus cytotoxic agents (mainly cyclophosphamide), which showed similar short-term outcomes in 28 unmatched literature cases of biopsy-proven PACNS[21] and similar response rates (81 %) in a series of 101 patients (biopsy-proven in 31 %).[14] However, relapses are frequent (26 %),[14] regardless of the response to initial therapy, and reported to be prompt in three overlapping subsets: PACNS with negative angiography (50 %),[59] with prominent leptomeningeal involvement (38 %),[26] and with cerebral amyloid angiopathy (13 %).[6] Conversely, relapse risks that vary with the intensity and duration of immunosuppressive therapy are described: >90 % with prednisone alone, 30 % with combined cyclophosphamide and low-dose prednisone continued for six months after remission, and <10 % with the same regimen for 12 months.[60]

Like others,[2,29,61] we favor the combined regimen for patients with definite PACNS. We initiate high-dose oral prednisone 1 mg/kg/d, preceded in severe presentations by intravenous methylprednisolone 1 g/d for at least three days to rapidly control vasculitis. We concurrently start oral cyclophosphamide 2 mg/kg/d or intravenous pulses 15 mg/kg every two to three weeks, with doses adjusted for age, renal function, and other variables.[62] Based on systemic vasculitis trials, the pulsed cyclophosphamide approach would be as effective to induce remission, with lower total dose, less leukopenia, but possibly more relapses.[63] A prolonged course of intravenous corticosteroids combined with tumour necrotising factor alpha (TNF-α) blockers[64] was proposed as first-line therapy in a rapidly progressive variant affecting larger intracranial arteries bilaterally, which is refractory to the usual inductive approach.[25]

If there is no residual evidence of active vasculitis after 10 weeks of inductive therapy, we slowly taper corticosteroids over 12 months. After three to six months of remission, we replace cyclophosphamide with a non-alkylating agent such as azathioprine or mycophenolate mofetil for maintenance therapy. During treatment with cyclophosphamide, complete blood counts are recommended at least bi-weekly to detect myelosuppression.[29] Throughout corticotherapy, calcium, vitamin D, and bisphosphonate are prescribed to prevent osteoporosis, and proton pump inhibitors for enteric protection. Prophylaxis against Pneumocystis jiroveci infection is encouraged during cyclophosphamide treatment.[62]

The optimal duration of immunosuppressive therapy is unknown. Some authors recommend treating most cases for 12–18 months.[14] Others prolong treatment to two to three years following remission.[29] MacLaren et al. studied 12 patients (with PACNS proven by biopsy in one case) and recommend treating small-vessel PACNS for at least five years and a milder non-relapsing variant affecting larger arteries for two years or less.[27]

Response to immunosuppressive therapy is monitored by serial clinical evaluations and investigations. At 10 weeks, before tapering corticotherapy, we repeat brain MRI to exclude new silent lesions,[65] and blood tests if initially abnormal as well as CSF analysis in selected cases to confirm improvement of inflammation markers.[66] We also re-image brain vessels in individuals with angiographic changes at presentation, to ascertain stabilisation or reversibility of the vascular lesions.[43] During immunosuppressive therapy, it is recommended to repeat MRI at 3–4 month intervals.[61] Persistent or recurrent headaches, new neurological or systemic manifestations, persistent inflammation evidenced from blood and CSF analysis, and new CNS lesions shown by MRI or vascular imaging may reflect lack of disease control or complications of immunosuppressive therapy (e.g., CNS infections) and should prompt re-investigation and adjustment of treatment. In refractory or relapsing PACNS, new attempts to induce remission often combine high-dose corticosteroids with one or more of cytotoxic agents, plasmapheresis, intravenous immunoglobulins,[67] anti-CD20 monoclonal antibodies (rituximab),[68] and TNF-α blockers (infliximab, ethanercept).[64]

Prognosis

Despite therapy, which sometimes can be aggressive and multimodal,[25,68] PACNS remains fatal in approximately one-sixth of patients.[14] In survivors, neurological status tends to improve over time, more than 90 % being left with no-to-moderate disability.[14]

Long-term follow-up remains essential after discontinuation of immunosuppressive therapy to identify rare adverse effects of immunosuppressive drugs such as cyclophosphamide-related bladder cancer, delayed manifestations of a systemic vasculitis, and PACNS recurrence that sometimes occur several years after remission.[27,41]

Future Directions

Many authors have stressed advantages of multicentre prospective studies on PACNS.[58,69] The International study on primary angiitis of the central nervous system (INTERSPACE), which commenced this year, promises to provide valuable insight into manifestations, diagnosis, treatment, and outcome of PACNS, and may identify relevant patient subgroups. Advances in arterial wall imaging with 3-tesla contrast-enhanced high-resolution MRI may help to differentiate active vasculitis from non-vasculitic diseases of larger intracranial arteries and monitor response to immunosuppressive therapy.[46,47] Current research aims at identifying CSF markers of vasculitis that could complement or even replace other investigations. Such advances may facilitate setting up in the near future the first therapeutic trials in PACNS. ■

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