Primary angiitis of the central nervous system

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ABSTRACT

Primary angiitis of the central nervous system (PACNS) was first identified half a century ago, but it remains a rare and challenging disease. However, important advances have been made in the field of PACNS, mainly through recently published retrospective analyses of large groups of PAC-NS patients, and the consideration of reversible cerebral vasoconstriction syndrome as a distinct entity. Clinical manifestations of PACNS are variable and non-specific. Even though neuroimaging can be suggestive of vasculitis, only a leptomeningeal biopsy can definitively confirm vasculitis. However, a brain sample is taken in less than half the patients and cannot further help to distinguish between PACNS and secondary vasculitis of the central nervous system. Hence, physicians should be aware of all alternative diagnoses and PACNS mimickers, which are now well-known. Whereas prognosis now appears to be much better than for the first reported cases, probably attributable to the use of corticosteroids and immunosuppressants, mainly cyclophosphamide, the optimal therapeutic regimen, potentially based on each patient's characteristics, and its duration remain to be determined. Only multicenter studies and prospective therapeutic trials will be able to clarify these issues on therapy and eventually provide some data on PAC-NS physiopathogenesis, which remains a poorly explored domain.

Introduction

Fifty years after its first description by Cravioto and Feigin in 1959 (1), primary angiitis of the central nervous system (PACNS) remains one of the most challenging diseases to deal with. This difficulty results from its rarity, its protean and non-specific clinical presentation, the limited performance of available diagnostic tests, the absence of unequivocal diagnostic criteria, and the lack of prospective trials to date to determine the most effective therapeutic strategy and provide consensual recommendations for the management of affected subjects.

However, analysis of several retrospective studies on PACNS (2-6), including the recent publication on a large monocenter group of patients (7), and the individualization of reversible cerebral vasoconstriction syndrome as a distinct and differential diagnosis (8, 9), have improved our current knowledge of PACNS in terms of diagnosis, prognosis and, but to a limited extent, treatment. Herein, we review these recent advances and information on PACNS, but also the limitations of available scientific data that stress the urgent need for prospective multicenter studies.

I. Historical perspective

The first cases of what is now considered PACNS were probably reported by Harbitz in 1922 (10), but it was only considered a new clinicopathological entity in 1959 by Cravioto and Feigin (1). They described 2 patients, who suffered from fatal isolated and unexplained progressive encephalopathy or hemiparesis, and whose autopsies revealed a "noninfectious granulomatous angiitis with a predilection for the nervous system". They also reviewed 6 other possibly similar cases (11, 12). Additional cases were reported later (13, 14) and the term "granulomatous angiitis of the central nervous system" was proposed to name this entity. However, because subsequent reports showed that some patients' lesions had non-granulomatous histology (15), the name "isolated angiitis of the central nervous system" was suggested instead (16). Finally, because some minor extra-neurological manifestations had been noted in some patients and other cases were demonstrated to be associated with varicella-zoster virus (VZV) infection (17) or Hodgkin's lymphoma (18, 19), "primary angiitis of the central nervous system" eventually appeared to be the more appropriate term (2, 15), emphasizing the need for a thorough investigation to exclude other diagnoses or causes.

Because antemortem histological proof of the diagnosis based on brain biopsy was rarely obtained, Moore (16), then Calabrese and Mallek (2), proposed different sets of diagnostic criteria for PACNS, which stated that cerebral angiographic findings suggestive of vasculitis could circumvent the absence of histological diagnosis confirmation, provided that all alternative diagnoses had been excluded.

Although PACNS is extremely rare, the number of reported cases has gradually increased since the late 1970s and after those diagnostic criteria had been devised. Since then, several case reports showed that aggressive regimens combining corticosteroids and cyclophosphamide could improve patients' outcomes (2, 20), contrasting with the almost constantly fatal outcomes of the earliest reported cases, within a few days to a couple of years (16). Most of these additional patients were indeed diagnosed on the sole basis of clinical manifestations and angiographic findings, without histological documentation. The alleged poor prognosis of the disease was therefore questioned by some authors, who even reported a favourable outcome with corticosteroids alone (21).

Calabrese et al. (22) pointed out that some of those angiography-diagnosed cases, which tended to have better outcomes, unlike histology-diagnosed cases, had some distinct clinical characteristics. "Benign angiopathy of the central nervous system" was therefore suggested to distinguish these patients from those with 'classical' PACNS, especially those histologically proven. Moreover, it was subsequently shown that multifocal arterial narrowing suggestive of vasculitis could also be seen in several other conditions, including acute hypertension (23) or vasoactive drug intake (24), raising the possibility that some of the reported patients with PACNS had suffered from cerebral artery vasospasms of unknown etiology rather than vasculitis. Concomitantly, numerous patients with acute headaches (25) and/or focal deficits with serial angiography-demonstrated segmental cerebral artery vasoconstriction that regressed spontaneously were reported. These cases closely resembled "benign angiopathy of the central nervous system", but were given different and eventually confusing names like Call-Fleming syndrome (26), benign acute cerebral angiopathy (27), postpartum angiopathy (28), migrainous vasospasm or 'crash migraine' (29), thunderclap headache with reversible vasospasm (30), or drug-induced arteritis (8, 31). Finally, the concept of a "reversible cerebral vasoconstriction syndrome" emerged that encompasses all these latter entities and is now accepted as a separate and non-vasculitic disease, as opposed to PACNS (8). However, in practice, making the distinction between these 2 different entities, with distinct underlying mechanisms, treatments and outcomes, is not always that easy, especially at disease onset.

II. Disease description

Because some of the oldest case reports and populations included patients diagnosed with PACNS but who might indeed have had reversible cerebral vasoconstriction syndrome or secondary cerebral vasculitis, we mainly focus herein on the largest and best documented studies on PACNS in adults (2, 7, 15, 32). In those studies, detailed data on patients with biopsy-proven cerebral vasculitis or those diagnosed based only on suggestive angiographic features of cerebral artery vasculitis are available. The Mayo Clinic (Rochester, MN) study (7) yielded an estimated annual PACNS incidence rate of 2.4 cases per 1,000,000 inhabitants (95% confidence interval, 0.3-4.4) for the period ranging from 1983 to 2003, further emphasizing its rarity.

II. 1. Clinical manifestations

PACNS can occur at any age but is predominant between the 4th and 6th decades of life, with no clear gender predilection. Clinical manifestations are non-specific and variable from one patient to another and over time, in accordance with the affected site and the progressive brain-damage pattern. The most frequent neurological findings include headaches (50-69% of the patients), cognitive impairments (30-71%), and persistent focal neurological deficit or stroke (13-50%) (2, 7). Transient ischemic attacks (16-33%), paraparesis (3-13%), seizure(s) (7-29%) can also occur, but more rarely, like intracranial hemorrhage (7-11%) or cranial nerve involvement.

The disease is progressive and worsens over weeks to months in half of the patients, with a mean first-symptomto-diagnosis interval about 5 months; however, it can sometimes have a more acute onset or even be fulminant (33). In Lie's article (15) on 12 PACNS patients, disease duration prior to diagnosis ranged from 3 days to 3 years. Notably, a remitting-relapsing disease pattern has been described, with no new event or progression of the disease for several months to years (16). Pertinently, one neurological manifestation, like stroke, seizure or headaches, does not remains isolated, as the only manifestation of the disease throughout its entire course (32, 34).

By definition, no constitutional or extra-neurological symptoms should be present. Some extra-neurological manifestations or findings were described in several reported cases, sometimes found at autopsy. Minor and non-specific symptoms, such as asthenia, mild fever and/or nausea and vomiting, possibly due to cerebral lesions, have also been reported occasionally, but also arthralgias, and it may be difficult, for these cases, to decide whether these non-specific findings plead in favour of secondary vasculitis, rather than PACNS. Also, the presence of peripheral neuropathy has sometimes been mentioned (6), which should, in our opinion, strongly suggest a diagnosis other than PACNS, possibly systemic vasculitis with cerebral involvement, unless peripheral nerve involvement is a symptom of another fortuitous and associated disease, such diabetes mellitus.



Fig. 1. (Left) Multiple bilateral hyperintense parenchymal lesions on axial brain MRI (FLAIR sequence) in a 38-year-old woman with PACNS. Note that such small vascular lesions, not enhanced after gadolinium injection, might be considered normal in an older healthy subject.

Fig. 2. (Below) Diffuse, multiple, cortical and white-matter lesions in a 37-year-old man PACNS. Note the left parietal pseudo-cystic cavities that are the sequelae of past parenchymal hemorrhagic infarctions (axial brain MRI; top left, T1-weighted sequence; top right, T2weighted sequence; bottom, FLAIR sequences; courtesy of Prof. Luc Mouthon and Dr Philippe Guilpain).



II. 2. Imaging Magnetic resonance imaging

(MRI) of the CNS

Brain MRI should, at best, include T1, post-gadolinium contrast-enhanced T1-, T2-, fluid-attenuated inversion recovery (FLAIR)-, and gradient-echo T2*-weighted sequences, as well as diffusion-weighted images. Complementary

imaging of the spinal cord should be obtained as a function of the clinical findings, because its involvement is rare in PACNS (cf. below). MRI is highly sensitive (97%) but its findings are nonspecific (35).

The most frequent findings reflect parenchymal brain damage induced by the vasculitis and consist of multiple bilateral infarctions (85%), involving both the cortex and the white matter (63%), as illustrated in Fig. 1, with recent infarctions being easily identified on diffusion-weighted images (7, 32, 36). Notably, such features, especially small hyperintense lesions on T2-weighted sequences, must be interpreted with respect to age and conventional cardiovascular risk factors (36), and can also be seen in patients with multifocal thromboses or emboli arising from other causes. More diffuse cortical and/or white matter alterations may also occur (Fig. 2). Intracerebral and/or subarachnoid hemorrhage are occasionally seen and the former events can later appear, after scarring, as microbleeds on T2*weighted, i.e. hemosiderin deposits. Contrast-enhanced intracranial or meningeal lesions are seen in one-third of the patients and are supposedly consequences of inflammation and/or a bloodbrain barrier rupture following ischemia but have no specificity.

Sometimes, inflammation and/or thickening of medium- and the larger of the small-sized cerebral artery walls, can be seen directly, but almost exclusively on high-resolution MRI with contrast-medium enhancement (36, 37). Perivascular enhancement of cerebral arteries can also be seen in some patients (38). On FLAIR sequences, hyperintense vessels can be found relatively more frequently, corresponding to intracranial artery stenoses or spasms, which may therefore be present in patients with PACNS but also those with reversible cerebral vasoconstriction syndrome (39).

Magnetic resonance angiography (MRA)

MRA with time-of-flight (TOF and 3D-TOF) sequences can reveal segmental stenoses in proximal cerebral arteries, including the circle of Willis, and some small arteries around 1 mm in diameter (Fig. 3). Hence, its being normal definitely does not preclude the diagnosis of cerebral vasculitis (or other vasculopathy) of smaller sized vessels that can only be visualized on conventional angiograms. However, the advent and dissemination of new 3-Tesla MRI scanners will probably enable examination of these smaller intracranial arteries in a near future.

REVIEW

Angiography

Conventional angiography remains the most sensitive neurovascular imaging technique at present and therefore is nearly always warranted when PACNS is suspected (40) and when MRA is non-informative. Angiography is indeed able to visualize small vessels as small as 500 µm in diameter. However, it still lacks sensitivity for PACNS, because it was reported to be normal in 40-60% of biopsy-proven cases (7, 34, 41) and necessitates a certain degree of invasiveness. Notably, the complication rate of cerebral angiography is reported to be about 1% in patients suspected of having cerebral vasculitis, including transient (up to 11% of the procedures) or permanent (less than 1%) neurological deficits, despite the use of digital subtraction to lower the amount of contrast-medium injected (42-44).

The most classical and typical findings of cerebral vasculitis are multifocal, alternating and segmental stenoses and/or irregularities of several intracranial arteries (36, 45), as shown in Figure 4. True microaneurysms are rarely observed, but fusiform arterial dilations are frequently seen. Multifocal vascular occlusions, development of collateral circulation, and/or delayed contrast-medium enhancement and washout time can also be seen (36, 46, 47).

However, all these suggestive vascular images on conventional angiography or MRA are non-specific and can be seen in reversible cerebral vasoconstriction syndrome and some other PACNS mimickers (see Table I) (32, 48-55). Our impression is that patients with the most striking and diffusely distributed images of multifocal artery stenoses and/or fusiform dilations, i.e. the 'best looking, most demonstrative and textbook quality' angiograms, more often suffer from reversible cerebral vasoconstriction syndrome than PACNS, in which abnormalities might be less demonstrative and more heterogeneously distributed (9, 56, 57).

II. 3. Laboratory findings

Cerebrospinal fluid (CSF) analysis is essential for both positive and differential diagnosis. Its major objective is indeed to rule out several infections (cf.

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Fig. 3. MR angiogram showing multifocal and segmental cerebral artery stenoses in a 47-year-old man with PACNS. Note the constriction of the proximal middle cerebral arteries (arrows), with dilation of the left anterior cerebral artery (asterisk) and occlusion of the left posterior communicating artery (ellipse). Also note the delayed and contrast-mepoor dium vessel enhancement of the whole right cerebral artery territory.



Fig. 4. Conventional angiogram showing segmental left posterior cerebral artery stenosis (arrow) in a 33-year-old male PACNS patient.

IV. Differential diagnoses and Table I) and malignancy, especially lymphoproliferative diseases. CSF is abnormal in 80-90% of patients with histologically proven PACNS (7, 32). However, observed abnormalities are usually mild: the white blood cell count ranges between 0 and 575 cells/ml, with the median below 20 cells/ml, and protein levels range from 15 to 1,034 mg/dl, with the median below 120 mg/dl (2, 7). Importantly, while a normal MRI or normal CSF examination does not exclude the diagnosis of PACNS when interpreted alone, one can probably rule out this diagnosis in patients in whom both tests are normal (58).

Whereas the initial evaluation of patients suspected of having PACNS requires several systematic blood analyses to exclude alternative diagnoses, their sera manifest no significant inflammatory syndrome or specific immunological abnormalities (at least not identified at present). However, some patients were reported to have slightly elevated erythrocyte sedimentation rates (>20 mm/hour in up to 70% of Table I. Differential diagnoses of PACNS, with graded rating of the most frequent or important to remind (+++ downwards).

Vasculitis mimickers (Reversible cerebra	no inflammatory vasculitis) Il vasoconstriction syndrome +++			
Acute hypertensio associated posterio	n with cerebral vasospasms (with or without or leukoencephalopathy syndrome)			
Intracranial athero	sclerosis			
Intracranial dissec	tion(s)			
Thrombotic disorc Antip Sned Dego	lers (with or without associated vasculopathy) hospholipid syndrome don syndrome s disease	Disseminated intravascular coagulation Thrombotic microangiopathy		
Arterial embolism Cathe Cardi Cardi Cardi	s eterization (traumatic plaque removal) iac shunt iac myxoma	Aortic arch atherosclerosis Infectious or non-infectious endocarditis		
Miscellaneous	5			
Demy Acuto Susac Moya CAD with Cerel Cerel Fabry MEL acido	yelinating disorders (Multiple Sclerosis, e Disseminated Encephalomyelitis) s's syndrome a-moya disease ASIL (cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy) proretinal vasculopathies pral radiotherapy s's disease AS (mitochondrial encephalomyopathy, lactic sis, and stroke-like episodes) syndrome	Sickle-cell anemia, thalassemia Neurofibromatosis Cerebral amyloid angiopathy Fibromuscular dysplasia Pseudoxanthoma elasticum Homocystinuria		
Secondary CNS vascul	litides			
Systemic vasculiti Gianı Taka Polya Kawa Chur, Wege Micro	des ++ -cell arteritis yasu's arteritis urteritis nodosa asaki disease g-Strauss syndrome ener's granulomatosis pscopic polyarteritis	Cryoglobulinemia Buerger disease Cogan's syndrome Behçet's disease Henoch-Schönlein purpura Goodpasture's syndrome		
Other systemic dis	seases			
Systemic lupus erythematosus Gougerot Sjögren's syndrome Antiphospholipid syndrome Systemic scleroderma Mixed connective tissue disease		Rheumatoid arthritis Inflammatory myopathies (dermatomyositis, polymyositis) Sarcoidosis Inflammatory bowel diseases (Crohn's disease, ulcerative colitis) Celiac disease		
Infections ++				
Bacte Ricka Tube Brucc Neiss Bartc Syph Endo Tropl	rra ettsiosis and Lyme disease + rculosis ellosis seira meningitis and other purulent meningitides nellosis ilis carditis neryma Whipplei (Whipple disease)	Viruses Human immunodeficiency virus ++ Varicella Zoster Virus + Herpes simplex virus + Cytomegalovirus Hepatitis C virus	Fungi, parasites Echinoccocosis Amibiasis Cryptococcosis Cysticercosis Schistosomiasis Aspergillosis Coccidioidomycosis Paracoccidioidomycosis Mucormycosis	
Hematological ma Hodg Myel Angi Hairy Liebo	lignancies ++ and other cancers kin and non-Hodgkin lymphomas odysplastic syndromes ocentric lymphoma /-cell leukemia w's lymphomatoid granulomatosis	Paraneoplastic (solid cancers) vasculitis	-	
Toxic vasculitis*				
Amp Coca Marij Contr	hetamine derivatives ine juana raceptives	Sympathomimetic agents Alkaloidal "Crack" Ectasy		
Miscellaneous	Miscellaneous			
Histie Graft	ocytosis -versus-host disease	ramilial hemophagocytic lymphohistiocytosis (perforin d	ieпciency)	

* All these compounds usually cause reversible cerebral vasoconstriction syndrome but they can also induce true vasculitis, which can evolve independently, even once the use is stopped.

the patients), but usually with normal C-reactive protein concentration, and/ or minor thrombocytosis (2). The few patients diagnosed with PACNS who tested positive for rheumatoid factor, antinuclear antibodies and/or anticardiolipin antibody (7) are more intriguing. Such immunological findings, particularly antinuclear antibodies-positivity, can be non-significant, especially in the elderly, but should signal the possibility of an underlying systemic autoimmune disease (which may become more clinically overt only later) (59).

II. 4. Biopsy

CNS vasculitis can only be confirmed by histological examination of a meningeal and brain (or spinal cord, when involved) biopsy. Even though, in trained hands, brain-biopsy morbidity has been shown to be relatively low, it remains a somewhat aggressive and dangerous procedure for most physicians and even neurosurgeons. Frame-based or frameless stereotactic brain biopsy is associated with a mortality rate of 0.3-1.5% and up to 12% can be complicated e.g. by haemorrhage in 1.7-7% of the cases, but half of them remain asymptomatic with no clinical impact (60-63). In their recent report, Burns et al. studied 42 free-hand non-stereotactic brain biopsies; only 3 (7%) patients experienced minor transient complications of the procedure and none suffered permanent deficits or death (64). Notably, PACNS is not a risk factor for brain-biopsy complications (65).

Because PACNS is often focal and scattered, small brain-biopsy samples, especially those obtained by needle biopsy, are non-diagnostic in 26-50% of the cases (34, 66). Hence, most authors recommend performing an open-wedge biopsy directed towards a lesion or the temporal tip of the non-dominant hemisphere, including parenchymal tissue and leptomeninges, especially if the latter are enhanced on MRI (5, 15, 16, 32, 41). Among the 101 patients studied by Salvarani et al. (7), 48.5% had biopsies, which yielded definite diagnoses of vasculitis for 63%. Notably, a higher percentage of male cases were histologically proven, whereas women were more often diagnosed based only on angiography.

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Fig. 5. Solitary left putaminal tumor- and/or abscess-like lesion in a 31-year-old PACNS patient (axial brain MRI; top left, axial brain MR image on T1-weighted sequence; top right, axial brain MR image after gadolinium contrast-medium injection on T1-weighted sequence; bottom, parasagittal brain MR image after gadolinium contrast-medium injection on T1-weighted sequence; courtesy of Dr Achille Aouba).

Biopsy samples must systematically be subjected to microbiological analyses to exclude infections, including tissue-specific staining, cultures in dedicated media for conventional but also mycobacterial and fungal agents, and virological tests (polymerase chain reaction for *Herpesviridae*). Staining of β -amyloid protein deposits should also be done, because its positivity might identify a specific PACNS subset (67). Ideally, but depending on each local technological environment, tissue samples should also be frozen for additional immunohistochemical analyses, molecular biology typing and/or electron microscope examination, even though the last two are more for research purposes than for diagnosis at present.

In a retrospective study on 61 patients with suspected PACNS, Alrawi *et al.* (41) found that brain biopsy could confirm vasculitis for 36% of them, led to an alternative diagnosis for 39%, and was non-diagnostic for the others. In another series of 30 suspected PACNS cases, Chu *et al.* (61) found that half the biopsies indicated an alternative

diagnosis, 30% showed vasculitis and only 16% were normal.

Angiography is not predictive of biopsy results. Indeed, only 25% of PACNS patients with positive angiograms had biopsies showing vasculitis, whereas 50-60% of those biopsy-proven PACNS had normal cerebral angiograms (7, 42), suggesting the existence of different patient subgroups, as discussed below.

PACNS mainly involves leptomeningeal and parenchymal small-sized vessels with multifocal and segmental distributions. Importantly, retaining the diagnosis of vasculitis mandates the demonstration of transmural inflammation with vessel-wall damage. Mild perivascular mononuclear infiltrates are non-specific and should not be overinterpreted as vasculitis, in our opinion. Three morphological vasculitis patterns have been described in PACNS, i.e. granulomatous inflammatory, purely lymphocytic and acute necrotizing vasculitis (5, 15). The first of these patterns is the most frequently observed (58%) and is characterized by angiocentric inflammation associated with granulomas and multinucleated giant cells, which can be located in any of the artery-wall layers. Patients with β-amyloid protein deposits are usually part of the latter granulomatous PACNS group (68). The lymphocytic and necrotizing subtypes account for 28% and 14% of the cases, respectively. No correlation between histology and clinical presentation or outcome has been identified yet (5). Notably, even when vasculitis is seen, histology cannot really help determine whether it is primary or secondary vasculitis. Although it seems unusual to observe more than one of those three different histological patterns in the same biopsy specimen, unlike secondary cerebral vasculitides (like in Wegener's granulomatosis), they can be seen in different parts of the brain of a given PACNS patient at autopsy (15).

II. 5. Are there any other potentially useful explorations?

In addition to all investigations required to exclude alternative diagnoses, especially infections, no other diagnostic test is available for PACNS. Electroencephalograms can be abnormal for 74% of the patients, but they are totally non-specific. Visual, auditory or somatesthetic and brainstem evoked potentials are hardly ever evaluated for PACNS. New functional imaging techniques, like dynamic perfusion scintigraphy or single photon emission computed tomography scan of the brain might yield some relevant findings and help to assess patients and their treatment responses.

Notably, no large study has explored eye fundus examination in PACNS, and its results are rarely mentioned in published PACNS case reports (69). In our opinion, it should be performed systematically to look for atherosclerosis and to exclude some cerebral vasculopathies, such as Susac's syndrome (retinocochleocerebral vasculopathy), and those infections with possible retinal and cerebral tropism (*e.g.*, toxoplasmosis, cytomegalovirus infection or candidiasis).

III. PACNS subgroups

PACNS can have uncommon clinical manifestations or neuroradiological findings, which might initially evoke other diagnoses, like lymphoma or malignancy, or represent patient subgroups with different prognoses. Whether childhood PACNS should really be considered a subgroup can be debated; the study by Benseler *et al.* (3) on 62 children with PACNS is also one of the largest on PACNS in general.

III. 1. Spinal cord involvement

Fewer than 30 patients with spinal cord involvement occurring before, concurrently or after cerebral involvement have been reported to date (2, 70-72). However, based on the rarity of PACNS itself, they represent 10-14% of all PACNS cases (71, 73). Definitely isolated and histologically proven spinal cord angiitis is very rare. Every level of the spinal cord can be affected (74), but most cases involved the thoracic level or terminal conus, sometimes with inflammation of the caudus equine nerve roots on MRI. Pertinently, associated spinal cord involvement in PACNS patients does not seem to worsen their outcomes.

In practice, spinal cord involvement might be difficult to distinguish from acute transverse myelitis, which can be encountered in systemic lupus erythematosus or neurosarcoidosis, unless a biopsy is performed. It must also be underlined that spinal cord angiitis has been reported in association with lymphoma, particularly Hodgkin lymphoma, which should be remembered as a major differential diagnosis.

III. 2. Tumor-like lesions

PACNS can manifest as a solitary pseudotumoral lesion in 5.6% (75) to 15% (32) of the cases (Fig. 5). Multiple tumor-like lesions are extremely rare. For many of the published cases of PACNS with tumor-like lesion(s) at onset, the diagnosis yielded by histology was unexpected. Indeed, a primary or secondary malignant brain lesion, a lymphoproliferative disorder or an infection, like mycobacterial or fungal infection, or nocardiosis, was naturally suspected first. Clinical manifestations depend on le-

sion site, but are somehow similar to those of other and classical PACNS. However, PACNS may progress more rapidly, as suggested by the reportedly first-symptoms-to-diagnosis shorter interval (75). Cerebral angiography, when performed, may reveal a mass effect but rarely shows features suggestive of vasculitis. Histologically, vasculitis is more often granulomatous than lymphocytic and it was recently reported that β-amyloid protein deposits were present in up to one-third of these biopsies, especially in lesions with a granulomatous pattern.

Notably, outcomes of these patients with tumor-like lesions seem favorable for most of them under adequate treatment with combined corticosteroids and immunosuppressant, mostly cyclophosphamide, but the presence of β -amyloid protein deposits indicates a poorer prognosis (75). The usefulness and benefit of surgical excision of the pseudo-tumor remain to be determined. When performed, it should, in our opinion and to date, not obviate for the need for concomitant immunosuppressive therapy.

III. 3 β -amyloid protein deposits and related angiitis

At present, it remains uncertain whether patients with β -amyloid protein depos-

its and vasculitis, more often with a histological granulomatous pattern, should be considered a subgroup of PACNS patients, whose characteristics and outcomes may differ slightly, or a distinct entity differing from PACNS. Another issue is whether β -amyloid protein deposits can induce vasculitis, or, conversely, are just bystander proteins of immune-mediated clearance of β -amyloid protein following vasculitis-related cerebral parenchymal injury (68).

Indeed, cerebral amyloid angiopathy is a relatively common disorder, whose frequency increases in parallel with aging, and the association might be fortuitous. However, PACNS patients are usually younger than those with common cerebral amyloid angiopathy (68), and the frequency of β -amyloid protein deposits seen in PACNS patients was reportedly higher than that in an agematched general population with other cerebral disorders requiring biopsy (21% versus 5-9%, respectively) (67). Furthermore, in PACNS patients, βamyloid protein deposits usually colocalize with inflammatory infiltrating cells, sometimes including multinucleated giant cells, which supposedly phagocytose these β-amyloid protein deposits (68, 76, 77).

PACNS patients with β-amyloid protein deposits accounted for one-quarter of the patients with biopsy specimens stained for amyloid deposits reported by Salvarani et al. (67). They tended to be older than those with classical PACNS, had more acute disease onsets, higher frequencies of cognitive dysfunction, and hallucinations, and gadolinium-enhanced leptomeningeal lesions on MRI. Conversely, by contrast with common cerebral amyloid angiopathy, hemorrhage was a rare manifestation. Lastly, their outcomes were variable and did not appear to differ strikingly from that of PACNS without β -amyloid protein deposits (67, 68).

III. 4. PACNS with prominent leptomeningeal enhancement

Salvarani *et al.* recently reported that among their 101 PACNS patients, the 8 patients (78) who had prominent leptomeningeal enhancement on MRI had more rapid early progression of the disease, more pronounced cognitive impairments, more frequent CSF abnormalities, always vasculitis findings on cerebral biopsies, and possibly better outcomes, but normal angiography for 6 of them. It should be noted that 4 were among the 8 patients from the same cohort who had histologically documented β -amyloid protein deposits (67).

III. 5. Angiogram-negative PACNS: large- or medium- versus small-sized vessel disease

It has been suggested that PACNS patients could be divided into two categories according to the size of the arteries (predominantly) affected (6), with different clinical presentations and outcomes. However, the precise definitions of these 2 categories and the delineation between large- or medium-, as the first group, and small-sized arteries, as the second group, are not consensual. Patients with large- (7) or medium-sized (6) vessel involvement usually have positive angiograms but negative biopsies, whereas those with small-sized vessel disease more often have biopsy-proven vasculitis but negative angiograms. For Salvarani et al. (7), large arteries referred to intracranial internal carotid arteries and proximal anterior, middle and posterior cerebral arteries, and small arteries to intracranial arteries, second division branches and smaller rami. For MacLarren et al. (6), the distinction between mediumand small-sized vessel PACNS relied on the combination of conventional or MR angiography and MRI findings, with only 1 of the 12 reported cases being biopsy-proven.

Patients with angiogram-negative biopsy-proven PACNS, *i.e.* small-sized vessel PACNS, had more pronounced cognitive disorders due to diffuse encephalopathy, as attested by the constantly abnormal MRI, mainly with parenchymal and/or meningeal gadolinium-enhanced lesions, and frequent CSF abnormalities, especially elevated protein levels. They usually have a better initial response to treatment than their counterparts with large- or medium-sized vessel involvement (79). Information on relapses is somewhat more puzzling. All 6 patients with small-sized vessel

PACNS reported by MacLarren et al. suffered at least one relapse, within the 2 years following initial diagnosis for one-third of them, whereas none of the patients with medium-sized vessel PACNS relapsed (6). Salvarani et al. also found that 4 (50%) of the 8 patients with angiogram-negative biopsyproven PACNS relapsed, compared to 23.7% of their 76 angiogram-positive counterparts, 6 of whom had biopsyproven disease (79). However, in their entire cohort of 101 patients, Salvarani et al. observed that those PACNS patients classified as having large- or combined large- and small-sized vessel involvement relapsed more often than those with only small-sized vessel involvement (30% versus 9%) (7).

Thus, because of the somewhat tortuous delineation of these 2 patient groups, with only a few diagnoses being biopsy-proven, it remains difficult to confidently conclude as to their respective characteristics and prognoses. Moreover, because of some overlapping between patient subsets described to date, *i.e.* those with angiogram-negative biopsy-proven PACNS, β-amyloid protein deposits, tumor-like lesions and/or prominent leptomeningeal enhancement on MRI, it remains to be determined which of these subgroups' characteristics have the most clinical impact and prognostic value.

III. 6. PACNS in children

Benseler et al. (3) from the Hospital for Sick Children, in Toronto (ON, Canada), reported the largest cohort to date of 62 children with PACNS, all diagnosed based on MR and/or conventional angiography. Only 5 children with PACNS have been earlier reported by Gallagher et al. (80). Indeed, children's brains are rarely biopsied, even though the morbidity rate is not higher than for adults. Median age at diagnosis was 7 years, with a male:female ratio of 1.6. Focal neurological deficits were the most frequent symptoms, including acute hemiparesis (80%), hemisensory deficits (79%), and fine motor deficits (73%). Diffuse neurological impairments included concentration difficulties for 29% of the children, cognitive dysfunction for 37%, and mood or

personality changes for 26%; 56% had headaches and 15% seizures. In ancillary studies on neuroimaging, the same group reported that arterial lesions were more often multifocal (76%) and proximal (86%) with a trend towards unilaterality and anterior circulation involvement (81, 82).

Notably, 32% of these children had progressive PACNS. The risk factors predictive of progression were neurocognitive dysfunction, multifocal parenchymal lesions and grey matter lesions on MRI, and bilateral or distal vessel stenoses on the initial angiogram.

Benseler et al. reported on 4 other children, all girls, with angiogram-negative biopsy-proven PACNS (83), whose diagnoses were initially suspected based on diffuse or focal neurological deficits progressing over weeks, including headaches and cognitive impairments, and MRI abnormalities. Erythrocyte sedimentation rates were elevated in 2, including 1 who was also tested positive for anticardiolipin antibodies. CSF examination revealed elevated protein levels in 3, and the brain biopsies of all 4 showed lymphocytic parenchymal and leptomeningeal vasculitis. They had good outcomes on corticosteroids, combined with an immunosuppressant for 3, and aspirin, with no relapse within their mean follow-up of 33 months.

IV. Differential diagnosis

One of the most challenging aspects of PACNS resides in the numerous diagnostic alternatives listed in Table I. Close monitoring of these patients is mandatory and can sometimes lead to reconsideration of the diagnosis after several weeks or months. Indeed, the first symptoms of an underlying systemic disease can be a cerebral manifestation. Conversely, the complete and rapid disappearance of all clinical and neuroradiological abnormalities within a few days or weeks should evoke reversible cerebral vasoconstriction syndrome rather than PACNS and might require changing therapy or even immunosuppressant withdrawal if it had been started.

Extensive description of reversible cerebral vasoconstriction syndrome is beyond the scope of this paper, and several recent reference papers are now available on this topic (8, 9). An early denomination of this entity, *i.e.* benign angiitis (or more appropriately, angiopathy) of the CNS, was confusing and it was only recently individualized and clearly distinguished from PACNS. The clinical presentation of reversible cerebral vasoconstriction syndrome is highly suggestive and stereotyped, with thunderclap headaches, possibly suggesting rupture or dissection of an intracranial aneurysm. It most usually occurs in a young woman and/or in a specific setting, like pregnancy, postpartum or simply physical exertion and/or after taking some triggering drugs (amphetamine derivatives, pseudoephedrine, ergotamine tartrate, selective serotonin reuptake inhibitors, cocaine, marijuana...). Notably, severe and/or prolonged artery spasms can lead to stroke, with a transient deficit occurring in 16-54% of the patients, and being definitive in 7% (9, 84). Small cortical or convexity subarachnoid hemorrhages can also be seen on MRI and may be suggestive of the diagnosis (9, 85). MRA or conventional angiography frequently reveals multifocal segmental cerebral artery vasoconstriction, which should reverse within 12 weeks after symptom onset. Angiograms are often impressive, with widely distributed arterial stenoses throughout the entire cerebral artery tree, by contrast with PACNS, in which vessel narrowing is often restricted to some arteries, as in Figures 3 and 4. However, in practice, it might be difficult or even dangerous to exclude PACNS in a young patient with such clinical and radiological findings and a rapidly deteriorating clinical course. Hence, in addition to vasodilators, corticosteroids, at least, are often prescribed. Even though corticosteroids do not seem to improve the prognosis of reversible cerebral vasoconstriction syndrome, they exert some vasodilatory effects and do not seem to be deleterious, unless continued after PACNS has been eventually excluded. Notably, some of the triggering agents, e.g. cocaine, can also induce cerebral artery inflammation and authentic vasculitis, which requires immunosuppressive therapy.

Other conditions or diseases can also mimic vasculitis, especially intracra-

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nial atherosclerosis. The radiological characteristics of arterial stenoses, the presence of vessel calcifications on CT scans (that were not mentioned above because they have no other input during the diagnostic work-up for PACNS), and sometimes echo-Doppler detection of atherosclerosis in extracranial arteries, especially the carotids, and/or retinal fundus examination can provide some clues to this alternative diagnosis. The first-line alternative diagnoses to be considered are infections, but also cancer and lymphoproliferative diseases. Several infections, mainly viral, can cause cerebral vasculitis, especially human immunodeficiency virus (HIV), Herpes simplex or VZV encephalitis, but also mycobacterial, parasitic, fungal or some bacterial infections, like syphilis, Lyme, Whipple disease (86, 87), and bacteria responsible for purulent meningitides. Notably, angiograms can show suggestive features, e.g. large aneurysms and multiple fusiform dilations alternating with stenoses of medium-sized cerebral arteries in HIV-related vasculitis (88), or predominant or exclusive involvement of arteries at the base of the brain in tuberculosis (58, 89).

CNS involvement is less common than that of peripheral nerves in systemic vasculitides and usually occurs later during the course of the disease. It can occur in 3-38% of patients with poly-arteritis nodosa, 6-44% of those with Wegener's granulomatosis, 6-25% of those with Churg-Strauss syndrome and 12-18% of those with microscopic polyangiitis (90). It can result from cerebral artery vasculitis, with encephalopathy, stroke, infarctions and/or cognitive impairment, but also from the local extension of ear, nose and throat or intraorbital granulomatous lesions of Wegener's granulomatosis. In Behçet's disease, cerebral parenchymal or spinal cord involvement, due to low-grade inflammation, demyelination and/or degenerative changes, meningoencephalitis and intracranial vein involvement, causing dural sinus thromboses, are more frequent than arterial emboli and/or thrombosis and true arteritis (91). CNS manifestations can occur in systemic lupus erythematosus, Gougerot-Sjögren syndrome or systemic scleroderma, but true vasculitis is rare. Notably, cerebral vasculitis should probably be considered for patients with these latter systemic diseases as a rare and exclusion diagnosis, especially after having ruled out opportunistic infections, lymphoproliferative diseases and/or associated thrombotic disorders, mainly antiphospholipid syndrome (92, 93).

V. Etiology and physiopathogenesis

Because of its rarity and the limited material retrieved from brain biopsy, no indepth immunohistological investigations on PACNS physiopathogenesis have been undertaken. Observation of isolated angiitis of the CNS resembling PACNS in patients with lymphomas and/or viral infections raised the possibility of an infectious etiology of PAC-NS, especially in immunocompromised patients. Notably, trigeminal VZV infection can be followed by arteritis of the ipsilateral middle cerebral artery through a retrograde viral invasion. In the immunocompromised setting, this vasculitis may spread to the whole brain, with histological changes similar to those of PACNS (94, 95). Two cases of PACNS associated with mycoplasma-like inclusions on electron microscopy of the brain-tissue specimen, but negative cultures, were reported (96). However, the only other rare attempts to identify pathogens in brain-tissue samples of PACNS patients were unsuccessful (97).

The presence of brain β -amyloid protein deposits in some patients is intriguing but its significance remains unknown or purely speculative at this time. It might be the consequence of chronic parenchymal inflammation due to PACNS itself, but data on Alzheimer's disease suggested that β -amyloid protein deposition could also induce inflammatory reactions (68).

VI. Outcome and treatment

At present, information on outcome and treatment of PACNS is available only from literature reviews and retrospective studies. In earlier reports, the prognosis was poor in almost every case, with death occurring within a maximum of a couple of years after diagnosis. Without treatment, as for the 8 patients described by Cravioto and Feigin (1), one patient died 3 days after the first symptoms appeared, three others died after 5-6 weeks, after 9.5 months for another, and after more than 2 years for the remaining three. Corticosteroids, alone or combined with cyclophosphamide since late 1980s, were subsequently reported to be effective and greatly improved patients overall and neurological outcomes. In the study by Salvarani et al. (7) on patients diagnosed between 1983 and 2001, mortality and relapse rates after a mean follow-up of 13 months were 17% and 26%, respectively, and only 3 patients had a Rankin score ≥ 4 , *i.e.*, moderately severe or severe disability, at their last

follow-up visit. In that study, 43% of the patients were treated with corticosteroids alone and 81% of them had good outcomes. In a retrospective study by Alreshaid and Powers (98) on 25 patients with suspected PACNS but negative biopsies, 6 of the 10 who received a combined regimen of corticosteroids and cyclophosphamide had good outcomes, compared to 8 of the 15 (53%) patients who received supportive care only but no immunosuppressant. However, since the earlier 1990s, the adjunction of an immunosuppressant, mainly cyclophosphamide, is considered by many physicians to be the gold standard regimen for PACNS patients, at least those with severe disability or manifestations at diagnosis. Indeed, 54% of the patients reported by Salvarani et al. (7) received corticosteroids and cyclophosphamide, and 81% of them had good outcomes, the same percentage as for those treated with corticosteroids alone.

Identification of patient subgroups and predictors of mortality or neurological damage might help in determining the best adapted treatment and its intensity for each patient individually. Salvarani *et al.* identified several PACNS subgroups with better outcomes, as mentioned above. They also found that patients with focal neurological deficits, cognitive impairments, cerebral infarctions and/or large-vessel involvements had a higher risk of death. In the pediatric study by Benseler *et al.* (3), none of the 62 patients was reported

to have died within the 20 months of mean follow-up, but only 34% of them recovered without any neurological sequelae. Predictors of these poorer neurological outcomes were neurocognitive dysfunctions, but also headaches, multifocal and bilateral parenchymal lesions on MRI, and multiple, bilateral and/or distal stenoses on angiography. Another conundrum is to determine on which parameters treatment response should be based; that decision would also enable consensual analysis of patients' outcomes in clinical studies. At present, whether patients should be followed based on serial cognitive evaluations, CSF analyses, MRI, MR and/or conventional angiographies, when initially abnormal, and at which intervals remain to be determined.

In current practice, we would recommend treating PACNS patients, at least those with biopsy-proven disease, similarly to those patients with severe forms of systemic vasculitides, like Wegener's granulomatosis or polyarteritis nodosa with CNS involvement, i.e. corticosteroids combined with pulse intravenous cyclophosphamide (99). The decision to add cyclophosphamide might be more delicate for patients without histological confirmation. Corticosteroids should be started at high dose, *i.e.* 1 mg/kg/d prednisone-equivalent, possibly preceded by 1-3 methylprednisolone pulses (7.5 to 15 mg/kg/day). The corticosteroid dose should subsequently be tapered, by approximately 10%, every 3 weeks. Cyclophosphamide infusions should be administered every two weeks for one month, then every three to four weeks, until remission or at least stabilization of disease manifestations is obtained. Maintenance therapy, using azathioprine, methotrexate or, probably mycophenolate mofetil as well, should probably be prescribed thereafter for at least one or two years, as for systemic vasculitides (99, 100). The decision to stop treatment thereafter can be very difficult, and despite a gradual dose deescalation without any untoward event, many physicians prefer maintaining low-dose immunosuppressant for many years or continuously. Adjunctive and prophylactic measures must be prescribed to limit the toxicity

of these treatments (*e.g.* cotrimoxazole to prevent pneumocystosis, calcium and vitamin D supplementation, prescription of mesna in conjunction with cyclophosphamide to prevent hemorrhagic cystitis...) (101). The exact and optimal duration of therapy is unknown. The concomitant use of antiplatelet drugs, or even anticoagulant for patients with ischemic stroke, should probably also be considered, and seems wise in our opinion, unless there is a contraindication, *e.g.* a recent cerebral hemorrhage, which indeed is not that common in PACNS.

Azathioprine, methotrexate or mycophenolate mofetil, all less toxic than cyclophosphamide, have also been given as first-line therapy, in combination with corticosteroids, to a few patients with newly-diagnosed or refractory or relapsing PACNS and yielded good results (7). However, to date, absolutely no data exist concerning their efficacy, as compared to cyclophosphamide, which should remain the treatment of first choice for the most severely affected patients. Their prescription should be restricted to patients with minor and not rapidly progressing disease in whom the balance between cyclophosphamideassociated toxicity and benefit goes against its use. Recently, tumor necrosis factor-alpha blockers were reported to be effective in 2 refractory patients: infliximab (5 mg/kg) as a single perfusion for one, and etanercept (25 mg) given twice weekly for 5 months, then once a week for 3 additional months (102) for the other. Intravenous immunoglobulins and an anti-CD20 monoclonal antibody (rituximab) were administered to some patients with systemic lupus erythematosus (103, 104) or Wegener's granulomatosis (105-107) and CNS manifestations, but no reliable published data are available on their use in PACNS at present. Notably, the absence of identified PACNS-associated autoantibodies tends not to support their hypothetical efficacy. Better understanding of the physiopathogenesis of PACNS may help identify other therapies.

VII. Conclusion

Advances have been made in the field of PACNS since its identification 50 years ago, mainly through retrospective analyses of larger cohorts of suspected or biopsy-proven PACNS, enabling the identification of some disease subsets with different prognoses. However, the diagnosis of PACNS remains difficult and many questions remain unanswered, particularly concerning its physiopathogenesis and treatment. Rheumatologists, neurologists, internists, pathologists and neuroradiologists should now work together to mount international initiatives to further improve diagnostic criteria and to conduct multicenter prospective clincial trials to determine the most effective therapeutic strategies and regimens.

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