The spectrum of CNS vasculitis in children and adults

Marinka Twilt and Susanne M. Benseler

Abstract | Children and adults who present with severe, newly acquired neurological or psychiatric deficits should be evaluated for an underlying inflammatory brain disease—the inflammation could be reversible, if diagnosed and treated rapidly. In our experience, primary angiitis of the central nervous system (PACNS) is the most common inflammatory brain disease and is increasingly recognized across patients of all ages. Distinct disease subtypes have been reported with characteristic disease courses, neuroimaging features and histopathological findings. In this Review, we provide a comprehensive comparison of childhood and adult PACNS, revealing distinct gender distributions, characteristic presenting clinical phenotypes and tailored differential diagnosis evaluations in the different subtypes of PACNS. Novel and traditional laboratory markers can help to define disease subtype and activity, whilst MRI and angiography can aid diagnosis in both children and adults. Characteristic patterns of parenchymal lesions and vessel involvement have been identified in PACNS and differ markedly between subtypes. Brain histopathology has also revealed distinct inflammatory pathways at different ages. Immunosuppressive treatment protocols have been shown to be effective and safe across the age spectrum; overall, in the past few years, the mortality of PACNS has decreased dramatically.

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Introduction

Primary angiitis of the central nervous system (PACNS) is an increasingly recognized condition in the expanding spectrum of inflammatory brain diseases in both children and adults.[1–3] PACNS was first described in adults in 1959.[4] Most historical cases are characterized by granulomatous inflammation of the cerebral arteries with fatal outcomes.[4–6] Calabrese and Mallek[7] first reviewed the adult literature and proposed diagnostic criteria for PACNS in 1988. Since then, numerous pediatric and adult case series and cohorts have been reported. However, these cases can represent the most severe end of the spectrum with regard to PACNS, suffer from potential publication bias and, thus, can underestimate the true incidence of pediatric and adult PACNS as only the worst cases are often published.

In clinical practice, the cut-off point of 18 years of age is arbitrary; this age definition is used to differentiate adult from childhood PACNS and can influence both diagnostic evaluation and treatment choices. In fact, no studies have ever compared the two age groups to explore if differences occur in the clinical presentation, histopathology, treatment response and disease course in adults and children. Disease phenotypes can occur independent of age grouping. This Review compares presenting features of adult and pediatric patients with PACNS, provides a diagnostic approach and summarizes the evidence-based treatment recommendations. The wide differential diagnosis of PACNS in both children and adults will also be discussed.

Competing interests
The authors declare no competing interests.

Diagnosis

Primary CNS vasculitis subtypes

The diagnosis of PACNS is based on the diagnostic criteria proposed by Calabrese and Mallek:[7] these include a newly acquired neurological deficit; specific angiographic and/or histopathological features of angiitis within the CNS; and no evidence of an underlying systemic disorder that explains the features.[7] These criteria were adopted for childhood PACNS with the addition of a newly developed psychiatric deficit and the age limit of ≤18 years of age at diagnosis.[8]

Childhood PACNS

In children, three distinct disease entities in the spectrum of childhood PACNS are currently recognized. These include the two large-vessel diseases—namely angiography-positive nonprogressive childhood PACNS and progressive childhood PACNS, and the small-vessel entity, angiography-negative small-vessel childhood PACNS.[1] In general in CNS vasculitis, the description 'large vessel' or 'medium-to-large' refers to all vascular segments visible on angiography, whereas 'small vessel' refers to those vessel diameters solely detectable on brain histology. All children with PACNS have so far been assigned to one category (large-vessel [angiography-positive] or small-vessel [angiography-negative] vasculitis) exclusively; a girl, described in 2001 by Lanthier and colleagues,[9] with angiographic evidence of a single stenosis of the middle cerebral artery plus evidence of vasculitis on brain biopsy is the only published exception to this categorization. Of importance to note is that the use of the terminology of 'large vessel' for all cerebral vessels is

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Key points

- Inflammatory brain diseases can affect males and females of all ages; in our experience, primary angiitis of the central nervous system (PACNS) is the most common type
- Distinct disease subtypes have been identified in children and adults with PACNS and found to be associated with typical demographic characteristics
- Newly acquired neurological or psychiatric deficits in children and adults mandate an evaluation for an underlying inflammatory brain disease
- Diagnosis of inflammatory brain diseases should include a thorough clinical evaluation, targeted laboratory investigations and specific parenchymal and vascular neuroimaging techniques, including vessel wall imaging and, if required, an elective brain biopsy
- The comparison of PACNS in children and adults has revealed major differences in classification strategies, clinical phenotypes, inflammatory markers, neuroimaging characteristics and inflammatory pathways
- Evaluated treatment regimens are available for childhood PACNS and treatment recommendations are now available for adult PACNS

discordant from the Chapel Hill classifications for vasculitis, in which only the aorta and its major branches are considered large vessels.[10]

Adult PACNS

In the literature pertaining to adult patients, PACNS classifications differ between studies. The US Cleveland Clinic cohort and initial literature review by Calabrese and Mallek[7] defined PACNS categories by evidence of characteristic findings of vasculitis on angiography and/or brain biopsy. The authors of this study recognized the limited specificity of angiographic findings in adults, given potential confounding by arteriosclerosis or other vascular processes. Calabrese and Mallek[7] reported angiography descriptors and proposed associated test probabilities. Patients with a high clinical suspicion and negative or 'low probability' angiographic findings frequently had additional brain biopsies performed. This process led to identification of a group of patients who had both findings from angiography and brain biopsy samples supporting the diagnosis of PACNS. Overall, Calabrese and Mallek[7] reported patients with PACNS in categories of classic, abnormal, or normal on angiography, in addition to biopsy diagnosis positive or negative. In the US Mayo Clinic cohort from 2007, Salvarani *et al.*[3] reported defined categories of large-vessel and small-vessel CNS vasculitis. The authors considered large-vessel disease as involvement of the intracranial segment of the internal carotid artery, proximal anterior cerebral artery, middle cerebral artery and/or the posterior cerebral artery.[3] Small-vessel disease according to this definition includes all vascular segments beyond the second branching. This definition merges distal segment, angiography-positive vasculitis with angiography-negative, brain-biopsy-confirmed disease. By contrast, MacLaren *et al.*[11] defined categories of small-sized and middle-sized vessel disease in PACNS. Small-vessel vasculitis, by their proposed definition, included all angiography-negative patients; those with angiography-positive vasculitis were defined as middle-sized vessel disease. Kraemer and colleagues[2] categorized patients by diagnostic modality, angiography or biopsy results. The researchers did not report any patients who had evidence of vasculitis on both modalities and therefore overlapped diagnostic categories. All adult series include substantial numbers of patients who did not have a confirmatory test (angiography or brain biopsy) according to the Calabrese criteria.[5]

Some clinicians distinguish spinal cord involvement, tumor-like lesions, or amyloid protein deposit angiitis as subgroups of PACNS.[12–17] In the past, 'benign angiopathy of the central nervous system' described by Hajj-Ali *et al.*[18] was considered a separate PACNS subgroup. In 2011, this entity was re-classified as 'reversible cerebral vasoconstriction syndrome' (RCVS) and is now considered a noninflammatory vasospastic disease.[19] Singhal *et al.*[19] described 139 RCVS cases, reporting a female predominance and presentation with thunderclap headache in 85% of patients. Cerebral angiographic abnormalities normalized within 2 months of diagnosis. A good clinical outcome was reported in 90% of patients.[19] As symptoms are overlapping and RCVS can mimic PACNS on angiography, distinguishing these disease entities early in the disease course is important as the outcome and treatment differ markedly. Early repeat of neuroimaging with a possible role for vessel wall enhancement should be considered in a patient with high suspicion of RCVS.

Demographic characteristics

PACNS can develop at any age and can affect both men and women. In adults, PACNS predominantly occurs between the fourth and sixth decades of life.[14] In children, no specific age distribution has been reported for PACNS—disease onset can be at any age until, by definition, 18 years of age.[1] Interestingly, a male predominance exists in angiography-positive childhood PACNS, which corresponds to the male predominance in childhood stroke.[20] By contrast, angiography-negative, biopsy-positive small-vessel childhood PACNS has an overwhelming female predominance.[21,22] In adults, more females are reported to develop angiography-positive PACNS, although, in angiography-negative disease, the genders are affected equally.[3,11] No ethnic predominance has yet been reported.

Clinical presentation

CNS vasculitis can present with a wide variety of neurological deficits and psychiatric symptoms. The mode of onset varies widely, ranging from acute stroke symptoms to slowly progressing cognitive decline or features of regression. Presenting clinical features in different cohorts are summarized in Tables 1 and 2.[1–3,9,11–13,15,18,21–32]

In childhood CNS vasculitis, angiography-positive and angiography-negative patients are usually reported separately.[21,22,26] In the adult literature, the majority of PACNS cases are presented as summary data including all disease subtypes. The only separate description of patients with angiography-negative PACNS comes from the Mayo Clinic in the USA.[29] Overall, pediatric patients with small-vessel PACNS present more frequently with seizures (50–100%), focal deficits (37–75%) and diffuse deficits (17–100%) when compared with adult patients (0%, 13%, 67%, respectively).[21,22,26,29] Comparison of

Table 1 | Presenting clinical features, treatment protocols and outcome of children with PACNS

Study	No. of patients (sex)	Age (years)	Presenting features	Diagnosis	Treatment	Outcome or disease course
Gallagher *et al.* (2001)[24]	5 (2M, 3F)	5–11	Headaches: 80% Focal deficits: 40% Diffuse deficits: 20% Seizures: 40% Psychiatric symptoms: NA	Childhood PACNS: angiography abnormal 60%; MRA abnormal 40%; no biopsy: CSF normal 100%	Prednisone plus cyclophosphamide: 100% (1 had only 1 dose)	1 lost to follow-up 1 normal after 2 yrs 3 improving with mild deficits at >1 year follow-up
Lanthier *et al.* (2001)[9]	2 (both F)	10–16	Headaches: 100% Focal deficits: 50% Diffuse deficits: NA Seizures: 50% Psychiatric symptoms: NA	Small-vessel childhood PACNS: biopsy positive 100%	Prednisone: 100% Cyclophosphamide: 50%	1 mild left hemiparesis after 6 years
Yaari *et al.* (2004)[25]	2 (1M, 1F)	3–12	Headaches: 50% Focal deficits: 50% Diffuse deficits: 50% Seizures: 0% Psychiatric symptoms: 0%	Small-vessel childhood PACNS: biopsy positive 100%	Prednisone: 100% Cyclophosphamide: 50% Methotrexate: 50%	Relapse in both patients
Benseler *et al.* (2005)[21]	4 (all F)	5–16	Headaches: 50% Focal deficits: 75% Diffuse deficits: 75% Seizures: 50% Psychiatric symptoms: NA	Small-vessel childhood PACNS: biopsy positive 100%	Prednisone: 100% Aspirin: 100% Cyclophosphamide: 50% Azathioprine: 25%	No relapse, complete neurological recovery
Benseler *et al.* (2006)[1]	62 (38M, 24F)	0.5–17.5	Headaches: 56% Focal deficits: 81% Diffuse deficits: 37% Seizures: 15% Psychiatric symptoms: NA	Childhood PACNS: angiography abnormal 100%	Aspirin: 100% Immunosuppressants: 34%	30% had progressive childhood PACNS
De Tiege *et al.* (2011)[26]	3 (2M, 1F)	9–15	Headaches: 67% Focal deficits: 67% Diffuse deficits: NA Seizures: 100% Psychiatric symptoms: NA	Small-vessel childhood PACNS: biopsy positive	Prednisone: 100% Cyclophosphamide: 100%	1 long-term relapse 8 yrs later All no deficit
Bitter *et al.* (2006)[27]	2 (both F)	5–7	Headaches: 50% Focal deficits: 100% Diffuse deficits: 0% Seizures: 0% Psychiatric symptoms: 0%	Childhood PACNS: 1 MRA abnormal; 1 biopsy abnormal	Prednisone: 100% Cyclophosphamide: 100%	1 relapse Both had remission
Sen *et al.* (2010)[23]	3 (1M, 2F; from 3 centers)	5–9	Headaches: 67% Focal deficits: 33% Diffuse deficits: 0% Seizures: 33% Psychiatric symptoms: 0%	Childhood PACNS: 1 MRA abnormal; 1 biopsy abnormal; 1 MRI abnormal	Prednisone: 100% Cyclophosphamide: 67% Methotrexate: 33%	2 relapses in 1 patient
Hutchinson *et al.* (2010)[22]	19 (4M, 15F)	5–17.5	Headaches: 89% Focal deficits: 37% Diffuse deficits: 100% Seizures: 84% Psychiatric symptoms: 32%	Small-vessel childhood PACNS	Prednisone: 100% Cyclophosphamide: 100% Azathioprine: 9% Mycophenolate mofetil: 5%	42% had disease flare 21% had remission of medication

Abbreviations: CSF, cerebrospinal fluid; F, female; M, male; MRA, magnetic resonance angiography; NA, not applicable; PACNS, primary angiitis of the central nervous system.

childhood and adult PACNS cohorts demonstrates more focal deficits in the pediatric cohorts than the adults (33–81% versus 42–46%, respectively); conversely, more diffuse deficits occurred in the adult cohorts than the pediatric ones (38–73% versus 0–37%, respectively).[1–3,11–13,24,30,31,33] No marked difference was observed between the rates of headaches, seizures or psychiatric deficits between childhood and adult disease (Tables 1 and 2).[1–3,11,21,24] Psychiatric symptoms are rarely reported as a separate category in either childhood or adult PACNS publications; these symptoms seem to be more frequently present in angiography-negative patients of all ages.[3,21] Diagnosing psychiatric deficits in very young patients and in the elderly could be challenging.

Laboratory findings

Systemic inflammatory markers are neither sensitive nor specific in PACNS in adults or children. However, laboratory testing is essential to support the diagnosis and/or to rule out other causes. Testing includes hemoglobin levels, white blood count, C-reactive protein levels and erythrocyte sedimentation rate. Overall, inflammatory markers are frequently normal or only mildly elevated in both adults and children.[1,3] Raised markers are more commonly seen in angiography-negative patients. Hutchinson *et al.*[22] described at least one abnormal inflammatory markers in 76% of children with small-vessel childhood PACNS. By contrast, Salvarani *et al.*[29] reported abnormal erythrocyte sedimentation rates in only 13% of adults

Table 2 | Presenting clinical features, treatment protocols and outcome of adults with PACNS

Reference	No. of patients (sex)	Age (years)	Presenting features	Diagnosis	Treatment	Outcome or disease course
Maclaren *et al.* (2005)[11]	105 in total (5M, 7F had PACNS)	16–55*	Headaches: 42% (5/12) Focal deficit: 42% (5/12) Diffuse deficit: NA Seizures: 33% (4/12) Psychiatric symptoms: NA	12 had PACNS: angiography abnormal 66%; MRI abnormal 75%; biopsy positive 8%; CSF normal 66%	Prednisone: 100% Cyclophosphamide 100%	More relapse in small-vessel PACNS
Volcy *et al.* (2004)[28]	5 (4M, 1F)	16–36*	Headaches: 80% (4/5) Focal deficits: 80% (4/5) Diffuse deficit: 40% (2/5) Seizures: 60% (3/5) Psychiatric symptoms: NA	All had PACNS	Prednisone: 100%	All had good outcome, no relapses 1 had residual seizures
Salvarani *et al.* (2007; 2008)[3,12,15,29,31]	101 (43M, 58F)	17–84*	Headaches: 63% (64/101) Focal deficit: 44% (44/101) Diffuse deficit: 50% (50/101) Seizures: 16% (16/101) Psychiatric symptoms: NA	PACNS: angiography abnormal 69%; biopsy positive 31%; amlyoid biopsy 7.6%; spinal cord involvement 4.8%	Prednisone: 97% Cyclophosphamide: 45%	Relapse: 26% Death: 16%
Molloy *et al.* (2008)[13]	38 adults (19M, 19F; 30 from literature)	6–74	Headaches: 74% (28/38) Focal deficit: 64% (24/38) Diffuse deficit: 50% (18/38) Seizures: 47% (16/38) Psychiatric symptoms: NA	PACNS: 100% biopsy positive	Prednisone: 60% Cyclophosphamide: 26%	Remission: 68% Death: 16% Residual deficits: 76%
Kraemer *et al.* (2011)[2]	21 (8M, 13F)	11–65*	Headaches: 43% (9/21) Focal deficit: 62% (14/21) Diffuse deficit: 38% (8/21) Seizures: 10% (2/21) Psychiatric symptoms: NA	PACNS: angiography abnormal 62%; biopsy positive 28%	Aspirin: 57% Prednisone intravenous: 50% Prednisone oral: 78% Cyclophosphamide intravenous: 39%	Good treatment response: 72% Death: 14%
Salvarani, *et al.* (2011)[30]	131 adults (11 with rapidly progressive disease; of whom, 5M, 6F)	38–74	Headaches: 46% (5/11) Focal deficit: 64% (7/11) Diffuse deficit: 73% (8/11) Seizures: NA Psychiatric symptoms: NA	Progressive PACNS	Prednisone: 100% Cyclophosphamide: 55% Azathioprine: 18%	Death: 100%
Chevenier *et al.* (2009)[32]	1 (M)	29	Headaches: 100% Focal deficit: 0% Diffuse deficit: 0% Seizures: 0% Psychiatric symptoms: 0%	PACNS: angiography abnormal; biopsy positive	Prednisone Mycophenolate mofetil	Relapse with hemiparesis after 2 months
Hajj-ali *et al.* (2002)[18]	16 (3M, 13F)	10–66*	Headaches: 88% (14/16) Focal deficit: 63% (10/16) Diffuse deficit: 44% (7/16) Seizures: 20% (3/16) Psychiatric symptoms: NA	BACNS: angiography abnormal 100%; MRI abnormal 77%; CSF normal 94%	Probably reversible cerebral vasoconstriction syndrome, no treatment	Recovery: 94%

*Data from mixed population of adults and children. Abbreviations: BACNS; benign angiopathy of the central nervous system; CSF, cerberospinal fluid; F, female; M, male; NA, not applicable; PACNS, primary angiitis of the central nervous system.

with brain-biopsy-positive PACNS. In 2010, Cellucci *et al.*[34] suggested that Von Willebrand factor antigen is a potential biomarker for childhood PACNS, and is closely correlated with disease activity.[34]

Cerebrospinal fluid (CSF) analysis is essential for both diagnosis and differential diagnosis. Most infections can be excluded after thorough microbiological testing of the CSF.[14,35,36] Neuronal antibody testing such as anti-NMDAR (*N*-methyl D-aspartate receptor) antibody is increasingly performed.[37–40] CSF samples should be analyzed for cell count (including white blood count and blood differential), protein level and glucose level. CSF analysis is abnormal in 80–90% of adults with biopsy-confirmed PACNS and 90% of children with small-vessel childhood PACNS.[3,22,35] CSF abnormalities can be mild and reflect aseptic meningitis, including modest pleocytosis and elevated protein levels.[3,35] Unfortunately, angiography-positive PACNS patients (both adult and pediatric) infrequently demonstrate CSF abnormalities; consequently, a normal CSF analysis does not rule out a diagnosis of CNS vasculitis in children and adults.[1,3] The role of opening pressure of CSF remains to be determined.

Autoantibodies (such as antinuclear, antineutrophil cytoplasmic and anticardiolipin antibodies) other than neuronal autoantibodies are rarely positive in all patients with PACNS.[3,14,22,35] Low titer levels of anticardiolipin antibodies were found in both children and adults with PACNS; although, their role remains unclear.[1,3] Autoantibodies should be interpreted in the context of clinical and laboratory findings.

Neuroimaging

A CT scan is frequently the first imaging modality used to assess patients with a newly acquired neurological deficit. However, parenchymal lesions of CNS vasculitis are only detected in 30% of CT scans.[41] Lesions can be either inflammatory or ischemic, cerebral hemorrhage can be found in adults.[3,42] The preferred modality for

parenchymal imaging is MRI and for vascular imaging, conventional angiography and/or magnetic resonance angiography (MRA).[3,41]

MRI studies should include T1 and T2 sequences, fluid-attenuated inversion recovery (FLAIR), gradient-echo T2-weighted sequences, diffusion-weighted images and postgadolinium contrast-enhanced T1–T2.[14] MRI studies were abnormal in 97% of adults with PACNS and 98% of children with PACNS.[3,41] Salvarani *et al.*[3] reported that multiple and bilateral infarctions in PACNS (87%), involving both cortex and subcortex (63%), are the characteristic findings in adults. Aviv *et al.*[38] found that multifocal parenchymal lesions within the lenticulostriate distribution occur more frequently in children.[41] In the past few years, studies towards the use of the apparent diffusion coefficient (ADC)—which measures the integrity of structures in the brain[42]—and vessel wall contrast enhancement in PACNS have been reported in adults and are currently also used in childhood PACNS.[43,44] White *et al.*[43] described an increase in the ADC in adults with PACNS who had normal MRI scans. Adding the ADC sequence to the roster of neuroimaging could help monitoring treated patients with PACNS, as it detects lesions earlier than standard MRI.[45] Kuker and co-workers[44] demonstrated that vessel wall contrast enhancement was present in 82% and wall thickening in 92% of adults with PACNS (Figure 1). Future studies will need to determine the specificity of these findings in adults and children.

Vascular imaging should be performed in every patient with a suspected inflammatory brain disease. Conventional angiography has long been considered the gold standard; however, this modality is invasive. The major complication of conventional angiography is stroke and the prevalence of stroke after conventional angiography in adults has been estimated at 0.25%.[46] Studies in both adults and children with PACNS compared MRA and conventional angiography and showed that MRA is a good initial imaging modality in disease diagnosis.[3,47–49] Aviv *et al.*[49] showed no major difference in the ability of MRA to detect and characterize vascular abnormalities when compared to conventional angiography (Figures 1 and 2). As some studies demonstrated that MRA failed to identify all lesions detected by conventional angiography, a conventional angiography should be performed in all suspected cases with negative MRA.[47,48]

In adult PACNS, angiography was positive in 90% of patients, with multiple bilateral vessel abnormalities in 71% of patients.[3] Intracranial hemorrhages are uncommon in adults (8%) and have not been reported in children.[3,41] Interestingly, in childhood PACNS the most common large-vessel involvement was unilateral, affecting the proximal, anterior circulation.[41] Comparing angiography studies of children and adults is challenging, as study authors commonly present summary data of vessel involvement, rather than reporting the exact anatomical distribution.

Brain biopsy characteristics

In the early days of CNS vasculitis coverage, most pathology reports were based on autopsy results instead of findings from biopsy samples.[50] Nowadays, in an increasing number of centers, elective brain biopsies are included in the algorithm for diagnosing inflammatory brain diseases; the use of brain biopsy is well established in the field of neoplastic lesions.[51] Few studies on brain biopsies in adults with neurological decline or suspected neurodegenerative disease are reported.[52] Alrawi *et al.*[53] only confirmed PACNS on biopsy in 36% of 61 adults with suspected PACNS. This finding led to the conclusion that the diagnostic yield of PACNS on brain biopsies is low. However, in the Alrawi *et al.*[53] series, brain biopsy determined an alternative diagnosis in an additional 39% of patients; hence, the overall diagnostic yield should be considered 75% in adults. In the past, there was a strong reluctance to perform elective brain biopsies in children with suspected PACNS. A 2008 single-center study of children presenting with devastating neurological deficits who underwent brain biopsy demonstrated an overall diagnostic yield (confirming different diagnoses, including PACNS) of 48.5% and even 68.8% between 1996 and 2003.[54] Brain biopsies are important to not only confirm the diagnosis of childhood PACNS, but also to exclude other causes, such as Rasmussen encephalitis, rare infections, demyelination and malignancies.[53,54]

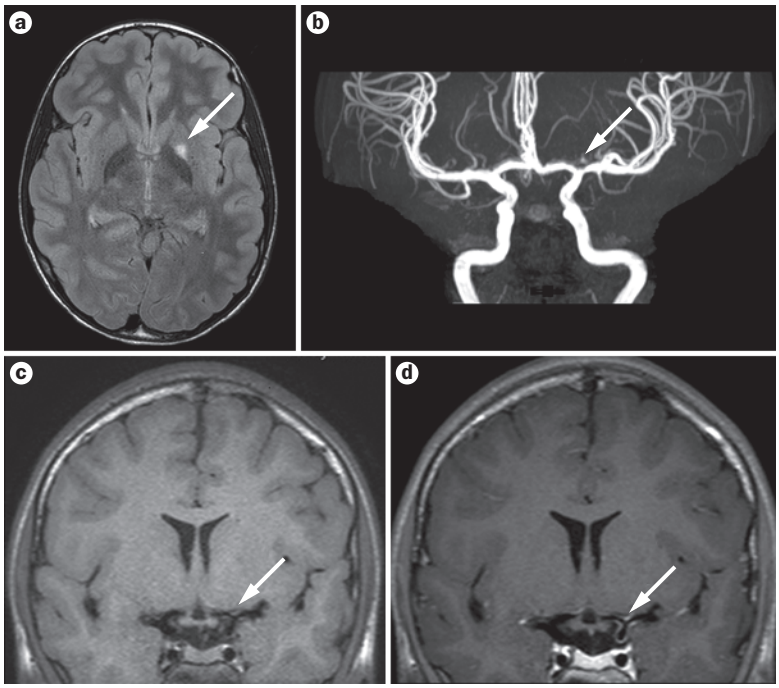

Figure 1 | Neuroimaging of nonprogressive primary CNS vasculitis and stroke. Findings from a 10-year-old child with nonprogressive primary CNS vasculitis and stroke. **a** | MRI FLAIR sequences demonstrate lesions in the posterior limb of the left internal capsule and the left globus pallidus (arrow). Diffusion-weighted imaging confirmed diffusion restriction suggestive of ischemic stroke (images not shown). **b** | MRA demonstrates focal narrowing of the terminal left internal carotid artery (arrow). **c** | Pre-gadolinium contrast high-resolution coronal T1 FLAIR sequences of the terminal internal carotid artery demonstrate focal vessel narrowing and wall thickening (arrow). **d** | Postgadolinium contrast high-resolution coronal T1 FLAIR sequences of the terminal internal carotid artery reveal contrast vessel wall enhancement (arrow) of the stenotic internal carotid artery confirming inflammatory vessel wall disease (vasculitis) Abbreviations: CNS, central nervous system; FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography.

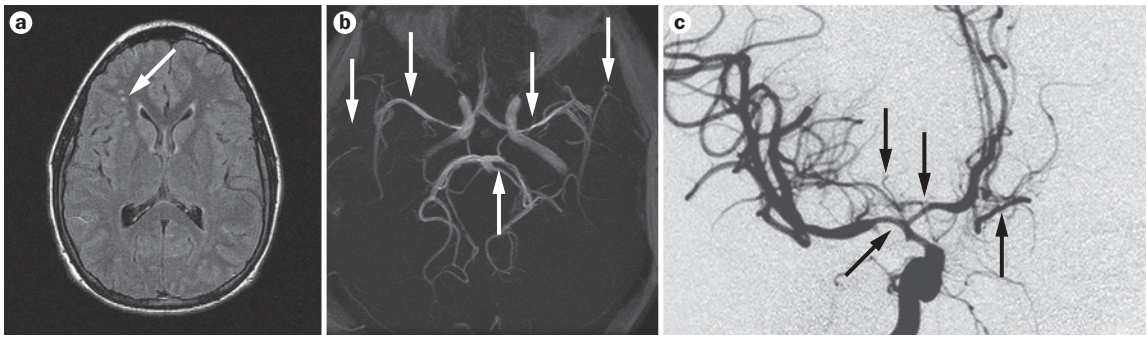

Figure 2 | Neuroimaging of progressive primary CNS vasculitis. Findings from a 16-year-old young man with progressive primary CNS vasculitis and severe cognitive decline. **a** | MRI FLAIR sequences demonstrate small lesions in the right frontal white matter (arrow). An increased signal on T2-weighted imaging was observed in the posterior left thalamus (images not shown). No diffusion restriction was seen in any of the lesions. **b** | MRA demonstrates marked irregular narrowing (arrows) in multiple segments of distal internal carotid arteries, middle cerebral arteries and anterior cerebral arteries with **c** | conventional angiography reveals corresponding vessel stenoses (arrows) involving multiple segments of of the same arteries bilaterally. Abbreviations: CNS, central nervous system; FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography.

Table 3 | Biopsy characteristics of children and adults with PACNS

Author	No. of patients	Brain biopsy findings	Diagnosis	Biopsy site
Childhood				
Lanthier *et al.* (2001)[9]	2 children	Lymphocytic infiltrate	Childhood PACNS	Right temporal lobe biopsy: 1 Suboccipital craniotomy for decompression and cerebellar biopsy: 1
Yaari *et al.* (2004)[25]	2 children	Lymphocytic infiltrate	Childhood PACNS	Unknown: 1 Right frontal biopsy: 1
Elbers *et al.* (2010)[56]	13 children	11 biopsy samples had lymphocytic infiltrate 2 biopsy samples had nonspecific perivascular infiltrate (lesional biopsy)	Childhood PACNS	Lesional biopsy: 7 Nonlesional biopsy (nondominant frontal lobe): 6
Adulthood				
Alrawi *et al.* (1999)[53]	61 adults	All had lymphocytic infiltration in PACNS	Definite PACNS: 17 patients Probable PACNS: 5 patients Other diagnosis: 24 patients Nondiagnosis: 15 patients	Lesional biopsy: 39 Nondominant frontal lobe biopsy (nonlesional): 22 Developed small intraparenhcymal hematoma: 3
Nogueras *et al.* (2002)[58]	1 adult	Lymphocytic infiltrate	PACNS (pre-existing HIV)	Autopsy finding
Volcy *et al.* (2004)[28]	5 adults	5 biopsy samples had lymphocytic infiltrate plus necrotizing infiltrate in 2	PACNS	Lesional biopsy: 5
Miller *et al.* (2009)[55]	46 adults (53 biopsies)	19 biopsy samples (from 17 patients) had granulomatous infiltrate 10 biopsy samples (from 8 patients) had lymphocytic infiltrate 4 biopsy samples (4 patients) had necrotizing infiltrate	PACNS: 33 patients	Lesional biopsy: 41 Nonlesional biopsy: 4
Myung *et al.* (2010)[33]	4 adults	4 biopsy samples had B-cell dominant lymphocytic infiltrate	PACNS	Lesional biopsy: 4
Wong *et al.* (2006)[61]	1 adult	Lymphocytic infiltrate with amyloid	Cerebral amyloid angiopathy	Lesional biopsy
Tamargo *et al.* (2003)[57]	1 adult	Granulomatous infiltrate with amyloid	PACNS with cerebral amyloid angiopathy	Lesional biopsy
Scolding *et al.* (2007)[45]	15 adults (plus literature review*)	9 biopsy samples had amyloid infiltrate 6 biopsy samples had granulomatous infiltrate	ABRA: 9 patients PACNS: 6 patients	Unknown
Schwab *et al.* (2003)[16]	2 adults (plus literature review*)	1 biopsy sample had macrophages plus amyloid deposits 1 biopsy sample had eosinophylic plus amyloid	PACNS with cerebral amyloid angiopathy	Lesional biopsy: 2
Panda *et al.* (2000)[60]	3 adults	2 biopsy samples had granulomatous infiltrate 1 lymphocytic infiltrate and sporadic granulomatous infiltrate	PACNS	Autopsy findings: 3

*Patients from literature review not included in the table. Abbreviations: ABRA, amyloid B peptide-related angiitis; PACNS, primary angiitis of the central nervous system.

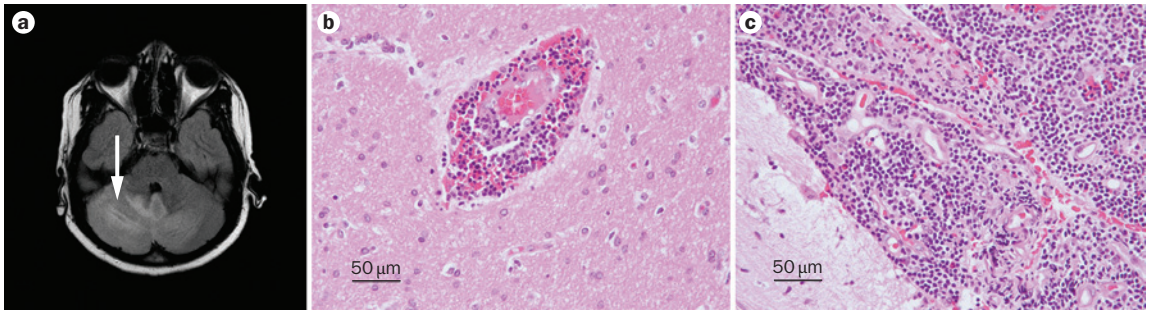

Figure 3 | Neuroimaging and brain histopathology of small-vessel primary CNS vasculitis. Findings from a 10-year-old girl with small-vessel primary CNS vasculitis with ataxia, headache and vomiting. **a** | MRI FLAIR sequences demonstrates an ill-defined lesion (arrow) in the right cerebellar hemisphere that extends into the left cerebellar hemisphere. Leptomeningeal contrast enhancement was present (images not shown) and no evidence of ischemia was observed in diffusion-weighted imaging (images not shown). MRA and conventional angiography were normal (images not shown). **b** | Lesional brain biopsy of the cerebellar lesion identified on MRI demonstrating the classic mononuclear intramural and perivascular infiltrate of small-vessel primary CNS vasculitis. The infiltrate predominantly consists of lymphocytes and monocytes. **c** | Histopathology of the lesional brain biopsy displays marked leptomeningeal infiltrate corresponding to the gadolinium enhancement of the leptomeninges on MRA. The infiltrate consists of mononuclear cells. Parts b and c stained with hematoxylin and eosin; magnification ×200 and kindly provided by C. Hawkins, Hospital for Sick Children, Toronto, Canada. Abbreviations: CNS, central nervous system; FLAIR, fluid attenuated inversion recovery; MRA, magnetic resonance angiography.

Brain biopsy characteristics of children and adults with PACNS are summarized in Table 3.[53,55,56] Interestingly, the histopathology seen in adult and childhood PACNS differed markedly. Although the brain pathology of adults with PACNS included granulomatous, necrotizing or lymphocytic infiltration, children exclusively demonstrated lymphocytic infiltrates (Table 3; Figure 3).[9,16,17,25,28,33,53,55–61] Beyond the difference in infiltrates, adult biopsies also demonstrated amyloid deposits, these deposits were not reported in children.[16,17]

Diagnostic algorithm

Noninvasive tests have a somewhat low sensitivity and specificity for suspected PACNS.[1,3] Nevertheless, laboratory tests are mandatory to exclude other causes, such as infection and malignancy.[14] Neuroimaging is required to identify parenchymal lesions and their characteristics. Vascular imaging can confirm the diagnosis in children and adult with large-vessel disease, in particular when supported by vessel wall imaging. Negative angiography in the context of high clinical suspicion mandates an elective brain biopsy after the differential diagnoses are excluded.[35] The proposed diagnostic algorithm for children with suspected inflammatory brain diseases is shown in Figure 4.

Treatment and outcome

Adults

An early report on adult PACNS in the 1980s documented a dismal prognosis with a mortality rate of 61% in the collective series of Calabrese and Mallek.[7] More recent experience indicates that early diagnosis and aggressive treatment have substantially reduced the PACNS mortality in adults.[1–3,11,13,22,24]

No standardized treatment protocols are available for PACNS and no controlled clinical trials have been performed. According to treatment recommendations summarized by Hajj-Ali and colleagues,[62] high-dose corticosteroids (such as methylprednisolone pulses 30 mg/kg per day with a maximum of 1,000 mg or oral prednisone 2 mg/kg per day with a maximum of 60 mg) are required to achieve disease control in adult PACNS.[62] The researchers also suggested that granulomatous PACNS mandates additional cyclophosphamide.[62] The duration of cyclophosphamide therapy (dose 500 mg/m^2) commonly ranges between 3–6 months.[3,62] Alternative immunosuppressant agents include azathioprine and mycophenolate mofetil.[2,3,32]

In the Mayo Clinic adult PACNS cohort, most patients (97%) received corticosteroids. A total of 46% of patients of all subtypes were treated with additional cyclophosphamide, of whom 81% had a favorable response.[3] However, 44% had a residual moderate-to-severe disability (Rankin score ≥3). Overall, relapses were documented in 26 of 101 patients and 17% died within the study interval. Kraemer *et al.*[2] reported corticosteroid use in 78% of adults with PACNS and additional cyclophosphamide use in 39%. In this series from Essen, Germany, the diagnosis was based on positive angiography in 62% and on brain biopsy in only 29%. Cyclophosphamide was used in all subtypes. A treatment response was documented in 72% of adults independent of the subtype; 14% of PACNS patients died.[2]

Children

For children with PACNS, a standardized treatment approach for small-vessel disease has been developed and evaluated. Hutchinson *et al.*[22] reported a single-center open-label cohort study of 19 patients with small-vessel-childhood PACNS. The treatment protocol consisted of induction therapy with corticosteroids and seven pulses of intravenous cyclophosphamide. Postinduction maintenance treatment with azathioprine or mycophenolate mofetil was initiated in all children. Overall, 90% had a

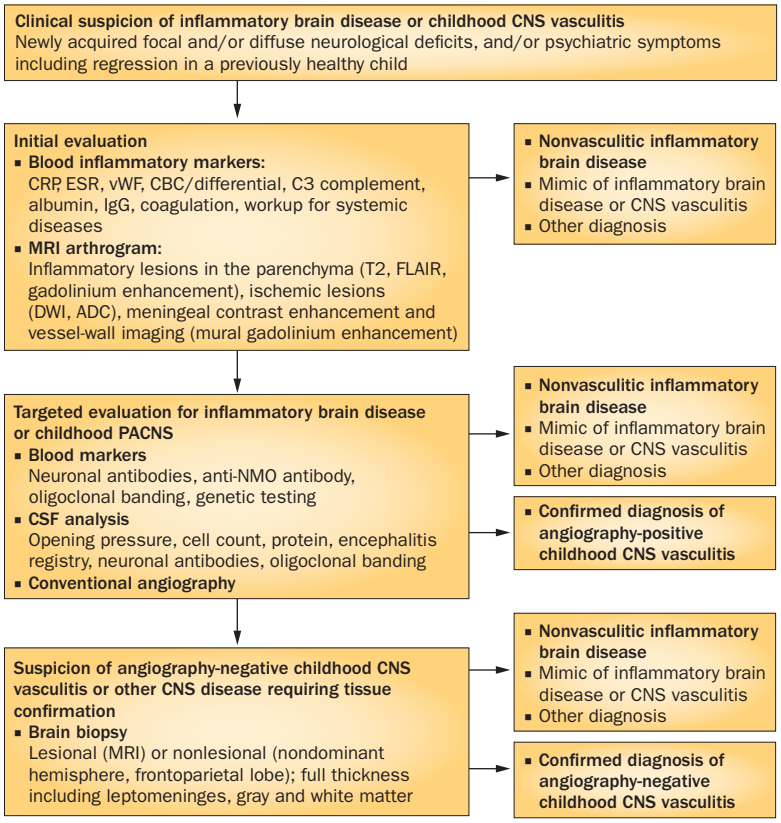

Figure 4 | Diagnostic algorithm for suspected inflammatory brain diseases in children. All patients need an initial evaluation, including laboratory tests and MRI or angiography. If initial evaluation does not reveal a definitive diagnosis, a targeted evaluation should be performed. Patients not diagnosed after the targeted evaluations require a brain biopsy to confirm diagnosis. Abbreviations: ADC, apparent diffusion coefficients; CBC, complete blood count; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; DWI, diffision-weighted imaging; ESR, erythrocyte sedimentation rate; FLAIR, fluid-attenuarted inversion recovery; NMO, neuromyelitis optica; vWF, von Willebrand factor.

favorable response to treatment; however, 47% experienced a disease flare, the majority of which occurred while receiving azathioprine maintenance treatment. Disease control was achieved when switching to mycofenolate mofetil, which is now considered the preferred maintenance drug.[22] At 24 months, 70% of children had a good neurological outcome, defined as no functional neurological deficit. No child died. Treatment protocols have been proposed for angiography-positive childhood PACNS, including addition of corticosteroids to antithrombotic treatment for nonprogressive childhood PACNS and combination of corticosteroids and cyclophosphamide in progressive angiography-positive disease.[1] Early rehabilitation efforts might improve the long-term outcome of children with all subtypes of PACNS.

Spectrum of disease and mimics

PACNS has a wide differential diagnosis including secondary CNS vasculitis, nonvasculitic inflammatory brain diseases and noninflammatory vasculopathies of the CNS. Boxes 1 and 2 provide the differential diagnosis for children and adults and list the different diseases that mimic CNS vasculitis.

Secondary CNS vasculitis

The most common etiology for inflammatory brain disease is infection.[36] Many infections can cause symptoms that mimic CNS vasculitis. Cultures and PCR of serum and CSF can identify most infections. Varicella-Zoster virus (VZV) can infect a wide variety of cell types in the central and peripheral nervous system.[63] Reactivation of VZV was found to cause inflammatory stenoses of the proximal large vessels, commonly referred to as post-Varicella angiopathy.[64] HIV-infected patients can present with CNS vasculitis, with evidence of HIV on brain histopathology.[58] Secondary CNS vasculitis can develop during or even be the presenting symptom in rheumatic diseases such as systemic lupus erythematosus, and systemic vasculitides, including granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiits, polyarteritis nodosa, and Takayasu arteritis.[65–69] CNS vasculitis can also be present in patients with inflammatory conditions such as Kawasaki syndrome, hemophagocytic lymphohistiocytosis and inflammatory bowel disease.[70,71]

Mimics of CNS vasculitis

Inflammatory disease including Rasmussen encephalitis and demyelinating diseases such as acute disseminated encephalomyelitis and multiple sclerosis are important mimics of CNS vasculitis.[72,73] Antibody-mediated inflammatory brain diseases are a newly recognized disease entity. CNS-specific antibodies are described in both adults and children. These lead to inflammatory brain diseases such as anti-NMDAR encephalitis, antibody-mediated limbic encephalitis and neuromyelitis optica.[38,39,74] Systemic antibodies can cross the blood–brain barrier and cause Hashimoto encephalitis, celiac-disease-associated encephalitis and PANDAS (pediatric autoinflammatory neuropsychiatric disease associated with streptococcal infections).[75,76]

In both adults and children, noninflammatory vasculopathies can mimic CNS vasculitis. In adults, arteriosclerosis is the most important mimic to exclude. Vasospastic conditions such as RVCS, migraines, drugs and pregnancy can lead to transient stenoses of the cerebral blood vessels;[19]of note, RVCS is rare in childhood.[77] Drugs (such as cocaine and amphetamine) can additionally cause a secondary vasculitis as well as be a mimic. Susac syndrome, Cogan syndrome and Sneddon syndrome are rare conditions in adults that can present with CNS involvement.[78–80]

In children, noninflammatory mimics include Moyamoya disease, dissection of the internal carotid artery, thrombembolic disorders, fibromuscular dysplasia and hemoglobin disorders.[81,82] Graft-versus-host disease and radiation-induced arteritis can also mimic PACNS.[83] CNS involvement can also occur in multiple metabolic and genetic disorders, including homocysteinuria, polymerase gamma deficiency and Fabry disease.[84,85] Overall, the differential diagnosis is wide and diverse and should be addressed with every patient with suspected PACNS. Some of the diagnosis can be excluded based on thorough clinical examination or

Box 1 | CNS vasculitis: spectrum & differential diagnosis

Primary CNS vasculitis
- Evidence of vasculitis exclusively on angiography: children, progressive angiography-positive childhood PACNS and nonprogressive angiography-positive childhood PACNS subtypes; adults, PACNS (51% in Mayo clinic cohort[3])
- Evidence of vasculitis exclusively on brain biopsy: children, small-vessel childhood PACNS; adults, PACNS (25% in Mayo clinic cohort[3])
- Evidence of vasculitis on angiography and brain biopsy: children, single cases of childhood PACNS;[9] adults, PACNS (24% in Mayo clinic cohort[3])

Childhood secondary CNS vasculitis[86]
- Active infections or postinfectious states: viral (VZV, HIV, EBV, CMV); bacterial (*Mycobacterium tuberculosis*, *Mycoplasma pneumonia*, *Streptococcus pneumoniae*); fungal (*Aspergillus* spp., *Candida albicans*, *Actinomyces* spp.)
- Systemic rheumatic diseases: SLE, systemic vasculitis, scleroderma, dermatomyositis, plus others
- Systemic inflammatory diseases: inflammatory bowel disease; hemophagocytic lymphohistiocytosis; Kawasaki syndrome
- Other systemic diseases or exposures: graft-versus-host disease, radiation, malignancies

Adult secondary CNS Vasculitis[87–89]
- Active Infections or post-infectious states:[63,88] viral (VZV, HIV, CMV, HBV, HCV, HSV); bacterial (*Borrelia burgdorferi* [Lyme disease], *Treponema pallidum* [syphilis], *Mycobacterium tuberculosis*, *Salmonella Typhi*, *Streptococcus pneumoniae*); fungal (*Aspergillus*, *Coccidoides*, *Mycomycoses*, *Histoplasma capsulatum*, *Toxoplasma*); protozoa (*Toxoplasma*, *Plasmodium* [malaria])
- Systemic rheumatic diseases[87–89]: Behçet syndrome; systemic vasculitis (giant cell arteritis, Takayasu arteritis, polyarteritis nodosa and ANCA-associated vasculitis); SLE; sarcoidosis or neurosarcoid, RA, Sjögren syndrome, scleroderma
- Systemic inflammatory diseases: inflammatory bowel disease; hemophagocytic lymphohistiocytosis; cryoglobulinemia
- Other systemic diseases or exposures: graft-versus-host diseases, radiation, drugs (cocaine, amphetamines, among others), malignancies (Hodgkin and non-Hodgkin lymphoma, among others)

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; CMV, cytomegalovirus; CNS, central nervous system; EBV, Epstein–Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HSV, herpes simplex virus; PACNS, primary angiitis of the CNS; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; VZV, Varicella-Zoster virus.

Box 2 | Mimics of CNS vasculitis in adults and children

Mimics of angiography-positive CNS vasculitis in children
- Noninflammatory CNS vasculopathies: dissection; thrombembolic disease; hemoglobin disorders; aPL syndrome; fibromuscular dyplasia; collagen vascular disorders; focal cerebral angiopathy (Marfan Syndrome, Ehlers–Danlos Syndrome, among others);[82,90] Moyamoya disease (idiopathic)
- Conditions associated with cerebral vasospasms: channelopathies including familiar hemiplegic migraine and calcium channelopathy; reversible vasoconstrictive syndrome[77]
- Genetic syndromes with associated vasculopathy: neurofibromatosis type 1; Down's syndrome; PHACES; CADASIL; Fabry disease; homocysteinuria
- Other syndromes with associated cerebral vasculopathy: Cogan syndrome (vasculopathy plus inflammatory eye disease [interstitial keratitis] and vestibulaurditory dysfunction);[78] Susac syndrome (noninflammatory vasculopathy resulting in retinopathy, hearing loss and encephalopathy)

Mimics of angiography-negative CNS vasculitis in children
- Nonvasculitic inflammatory brain diseases: demyelinating diseases (acute demyelinating encephalomyelitis, MS, optic neuritis);[72] Antibody-mediated inflammatory brain diseases[38] (anti-NMDAR encephalitis, antibody-mediated limbic encephalitis, neuromyelitis optica, Hashimoto encephalitis, postmycoplasma encephalitis, celiac-disease-associated encephalitis, PANDAS); T-cell-mediated inflammatory brain diseases (Rasmussen encephalitis);[73] granulomatous inflammatory brain diseases (neurosarcoidosis, ANCA-associated vasculitis)[66]
- Infections: tuberculosis; JC Virus
- Metabolic diseases with associated inflammatory or ischemic brain lesions: MELAS; ROME; polymerase gamma deficiency[84,85]
- Malignancies: angiocentric lymphoma

Mimics of angiography-positive CNS vasculitis in adults
- Arteriosclerosis
- Vasospastic diseases: reversible vasoconstriction syndrome; migraines; vasospasms secondary to hypertension, drug exposure, subarachnoid hemorrhage, eclapsia, pheochromocytoma
- Thrombembolic disease, bacterial endocarditis[91]
- Hemoglobin disorders
- Antiphospholipid antibody syndrome
- Fibromuscular dyplasia
- Genetic diseases associated with obliterating cerebral vasulopathies: Degos disease, retinocerebral vasculopathy with cerebral leucodystrophy[92]
- Other Syndromes with associated cerebral vasculopathy: Cogan syndrome; Susac syndrome; Sneddon syndrome (progressive noninflammatory cerebral arteriopathy and livedo)[80]

Mimics of angiography-negative CNS vasculitis in adults
- Demyelinating diseases (MS, optic neuritis)
- Antibody-mediated inflammatory brain diseases: anti-NMDAR encephalitis; antibody-mediated limbic encephalitis; neuromyelitis optica; Hashimoto encephalitis; postmycoplasma encephalitis; celiac-disease-associated encephalitis[75,76]
- T-cell-mediated inflammatory brain diseases: Rasmussen encephalitis
- Granulomatous inflammatory brain diseases: neurosarcoidosis; ANCA-associated vasculitis
- Infections: tuberculosis; JC virus; syphilis
- Autoinflammatory syndromes: FMF[93]
- Malignancies

Abbreviations: ANCA, antineutrophil cytoplasmic antibody; aPL, antiphospholipid antibody; CADASIL, Cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy; CNS, central nervous system; FMF, familial Mediterranean fever; MELAS, mitochondrial encephalopathy lactic acidosis and stroke-like episodes; MS, multiple sclerosis; NMDAR, *N*-methyl D-aspartate receptor; PANDAS, pediatric autoinflammatory neuropsychiatric disorder associated with streptococcal infections; PHACES, posterior fossa malformations-hemangiomas-arterial anomalies-cardiac defects-eye abnormalities-sternal cleft and supraumbilical raph syndrome; ROME, rolandic mitochondrial encephalomyopathy.

with simple noninvasive test; however, frequently more invasive testing is needed.

Future directions

Clinical care of children and adults with CNS vasculitis and inflammatory brain diseases mandates an interdisciplinary team. Publications have increased the recognition of this novel group of diseases. Standardized algorithms are required to facilitate rapid diagnostic evaluation and standardized treatment protocols will hopefully lead to decreasing variation in care and increased survival of children and adults with PACNS. International collaborations provide the framework to increase our understanding of how to best diagnose, treat and monitor patients of all ages. Translational studies are mandatory to comprehend the underlying pathogenesis, facilitate the discovery of noninvasive biomarkers and

novel treatment approaches for children and adults with CNS vasculitis and inflammatory brain diseases.

Conclusions

CNS vasculitis and inflammatory brain diseases in children and adults are an increasingly recognized cause of newly acquired severe neurological and psychiatric deficits. In patients with a high clinical suspicion of an inflammatory brain disease a thorough work-up including laboratory testing of blood and CSF and specific neuroimaging is necessary. New diagnoses such as neuronal-antibody-mediated inflammatory brain diseases, metabolic syndromes with secondary brain inflammation and complex genetic disorders such as inherited channelopathies should be considered in children. In adults, reversible vasoconstrictive syndromes and arteriosclerosis are key mimics of PACNS. Often, invasive tests (such as conventional angiography or elective brain biopsy) are mandatory to confirm a definitive diagnosis.

Standardized treatment protocols are established for children with confirmed PACNS. No evaluated protocols are currently available for adults with the disease, but treatment recommendations have now been proposed. Historically, mortality rates in adults were as high as 61%, but have now decreased to 15–20% with aggressive immunosuppressive treatment. In children, historical cases of PACNS were exclusively diagnosed on autopsy. Increasing recognition and rapid diagnostic evaluation followed by protocolized immunosuppression have improved the prognosis of these patients substantially. In fact, no deaths in childhood PACNS have been reported in the past 5 years. In adults with PACNS, persistent neurological deficits are reported in 50% of patients. By contrast, only 20–30% of children with PACNS have persistent deficits. We suggest that children and adults with PACNS should be rapidly evaluated and treated. Monitoring of disease activity and outcome should follow a structured protocol, including repeated neuroimaging and functional outcome assessments.

Review criteria

Original articles on PACNS were identified in the PubMed database using the search terms: "primary angiitis of the central nervous system", "CNS-vasculitis", "central nervous system vasculitis" and "children", in various combinations. Only English-language, full-text papers were selected, with a focus on studies published after 2008. In addition, relevant publications were selected from the reference lists of other reviews on similar topics and from the authors' own bibliographical files.

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