Central Nervous System Vasculitis in Children

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Central nervous system (CNS) vasculitis is an increasingly recognized, often devastating inflammatory brain disease of children and adults. In primary or isolated CNS vasculitis/angiitis of childhood (cPACNS), the vascular inflammation is limited to the brain and spinal cord. Secondary CNS vasculitis occurs in a variety of conditions including infections, collagen vascular diseases, systemic vasculidities, and malignancies. Mimics of CNS vasculitis in children include dissections and noninflammatory vasculopathies. Diagnosis of primary CNS vasculitis in both adults and children is based on the Calabrese criteria. This review summarizes recent data on CNS vasculitis in children; reviews the clinical spectrum at presentation and the role of laboratory tests, neuroimaging, and brain biopsy; and discusses treatment strategies, outcome data, and overlapping conditions of cPACNS.

Introduction

Central nervous system (CNS) vasculitis of childhood is a newly recognized inflammatory brain and spine disease, which presents the clinician with significant diagnostic and therapeutic challenges. In the past, primary CNS vasculitis of childhood (cPACNS) was thought to be a rare disease [1–3]. More commonly, CNS vessel inflammation had been described in association with an identifiable systemic condition (secondary CNS vasculitis) such as an infectious process [4,5], a systemic inflammatory disease [6], systemic vasculitis [7–10], a collagen-vascular disease [11–13], or a malignancy [14,15] (Table 1). CNS vasculopathies, defined as noninflammatory vascular diseases such as Moyamoya disease [16] and fibromuscular dysplasia [17], as well as mimics of CNS vasculitis such as dissections and vasospasm, add another layer of complexity to the diagnosis of childhood CNS vasculitis. Intravascular stimuli such as drugs [18] and mechanical or radiation injuries [19] can trigger CNS vessel wall alteration. Hemoglobin disorders including sickle cell disease and thromboembolic conditions [20] trigger CNS vessel remodeling and can mimic an inflammatory brain disease (Table 1).

In 1959, Cravioto and Feigin [21] reported the first case of primary CNS vasculitis in an adult, a "noninfectious granulomatous angiitis with predilection for the nervous system." Since then, primary CNS vasculitis has been reported under a variety of descriptive terms including isolated CNS angiitis, idiopathic granulomatous angiitis of the CNS, and primary angiitis or vasculitis of the CNS. Leonard Calabrese [22], the pioneer of CNS vasculitis, coined the term "primary angiitis of the CNS (PACNS)" in 1987. Calabrese proposed and validated diagnostic criteria for PACNS in adults [23,24], which have since been adopted for primary angiitis of the CNS of childhood (cPACNS) [25••]. Diagnostic approach, disease course, and outcome in adult PACNS have subsequently been described by Calabrese's group [26–28].

In this review, we refer to primary CNS vasculitis in children as cPACNS. Despite similar terminology, it is important to recognize that there are striking differences between cPACNS in children and PACNS in adults, which this review discusses. The body of literature in cPACNS is growing, including case reports [29,30], smaller case series [1,2,31,32,33••], and a recent cohort study [25••]. This review focuses on clinical spectrum and diagnostic and therapeutic approach to cPACNS and disease outcome. It also describes two Varicella zoster virus (VZV)–associated CNS vasculidities in children, postvaricella angiopathy (PVA) [34,35] and transient cerebral arteriopathy (TCA) [36], discusses important similarities of these entities and cPACNS, and addresses the potential implications for the treatment.

Epidemiology

In 2001, Lanthier [2] reported two cases of biopsy-positive cPACNS and summarized the literature of all reported cases over 35 years, including 10 children. The same year, Gallagher [1] reported five children with angiography-positive primary CNS vasculitis. Since 2001, the recognition of childhood CNS vasculitis appears to have increased, as

Table 1. Differential diagnosis of primary CNS vasculitis in children

Systemic diseases associated with secondary CNS vasculitis
Infections
Viral: Varicella zoster, HIV, Hepatitis C, Parvovirus B19
Bacterial: *Borrelia*, tuberculosis
Fungal: *Aspergillus*
Systemic vasculitis
Polyarteritis nodosa
Microscopic polyarteritis nodosa
Wegener's granulomatosis
Takayasu's arteritis
Collagen vascular diseases
Systemic lupus erythematosus
Behçet's syndrome
Dermatomyositis
Sjögren's syndrome
Inflammatory diseases
Inflammatory bowel disease
Post-strep glomerulonephritis
Malignancy
Neoplasm
Graft versus host disease
Noninflammatory vasculopathies and mimics of CNS vasculitis
Primary vasculopathies
Migraine/vasospasm
Moyamoya disease
Fibromuscular dysplasia
Secondary vasculopathies
Hemoglobin disorders (sickle cell disease, thalassemia)
Thrombi/emboli
Metabolic diseases: MELAS
Antiphospholipid antibody syndrome
Vascular injury
Dissection
Radiation
Drugs
Amphetamines
Contraceptives

CNS—central nervous system; MELAS—mitochondrial myopathy, encephalopathy, lactacidosis, stroke.

reflected in an increasing number of publications. However, the true incidence this disease remains unknown. Within the North American Pediatric Vasculitis Network the number of new cPACNS cases is estimated to be 150 to 200 new cases/year (unpublished data).

Primary CNS Vasculitis

Diagnostic criteria

In 1987, Calabrese [24] proposed diagnostic criteria for PACNS in adults: an acquired neurological deficit plus angiographic or histopathologic features of angiitis within the CNS, in the absence of a systemic vasculitis or any other condition to which the angiographic or pathologic features could be secondary. The Calabrese criteria have since been validated in adults [24] and more recently have been adopted by pediatric neurologists and rheumatologists for cPACNS [25••].

Pathogenesis

The pathogenesis of cPACNS and PACNS remains unclear. cPACNS is an inflammatory brain and spine disease. As in many inflammatory diseases, research is focusing on two major areas: trigger mechanisms and host susceptibility. Infections are potent triggers of inflammatory responses. Cumulative evidence suggests that reactivation of latent VZV from the trigeminal ganglion can trigger an inflammatory response in the wall of the adjacent the CNS arteries, leading to focal, proximal vessel stenosis and ultimately causing stroke [34,37]. In immunocompetent patients, VZV is predominantly associated with the development of a CNS vasculitis. This underlying pathology is suggested for the two widely overlapping disease entities of childhood PVA [35] and transient cerebral arteriopathy (TCA) [36]. It is intriguing to hypothesize that reactivated VZV and other neurotropic viruses can induce a postinfectious, focal large-vessel CNS vasculitis in cPACNS. Therefore, in all cPACNS patients, viral studies including cultures and polymerase chain reaction (PCR) plus the search for intrathecal immunoglobulin production against viral antigen is suggested. For immunosuppressed pediatric patients, viral infections such as Parvovirus B19 have been reported to trigger CNS vasculitis [38].

Host susceptibility research in cPACNS is urgently needed. Animal models such as the p75TNFR transgenic mouse model document that expression of the human TNF-α p75 receptor on astrocytes can trigger endothelial cell activation, meningeal inflammation, and ultimately vessel fibrosis. Case reports imply that treatment of suspected multiple sclerosis with interferon-β is associated with the development of CNS vasculitis and stroke, suggesting the activation of a distinct inflammatory pathway in CNS vasculitis [39].

Classification

The spectrum of cPACNS includes three distinct disease entities: angiography-positive, progressive cPACNS (P-cPACNS); angiography-positive nonprogressive cPACNS (NP-cPACNS); and angiography-negative, small-vessel cPACNS (SV-cPACNS). In previous studies, the hallmarks of each disease entity were recognized [25,33]. Children with angiography-positive, P-cPACNS frequently present with both focal and diffuse neurologic deficits, may have raised inflammatory markers in the cerebrospinal fluid (CSF), and often show multifocal MRI lesions and evidence of both proximal and distal vessel stenosis on angiography. Untreated P-cPACNS patients progress beyond 3 months, acquiring new

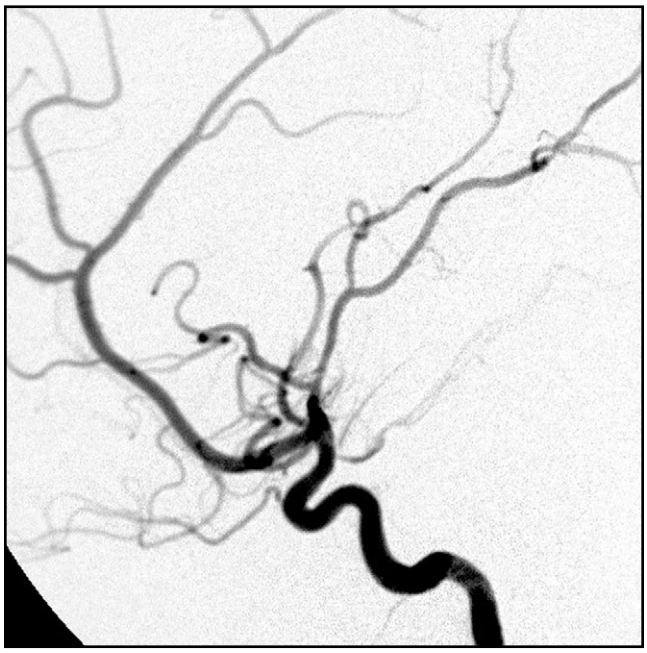

Figure 1. Conventional angiography diagnosis of nonprogressive primary central nervous system vasculitis of childhood (NP-cPACNS). Unilateral large-vessel stenosis of the distal internal carotid artery and proximal middle and anterior cerebral arteries on MR angiography in a 9-year-old boy with NP-cPACNS.

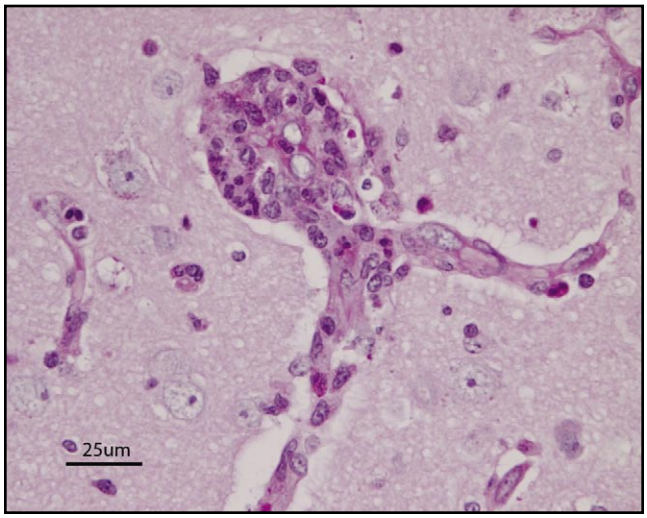

Figure 2. Primary small-vessel central nervous system (CNS) vasculitis of childhood. A brain biopsy of an 8-year-old girl revealing intramural infiltrates in the wall of a small muscular artery. Representative brain histology of primary, angiography-negative, small vessel CNS vasculitis of childhood showing intramural mononuclear infiltrates in a small muscular brain artery. Stained with Movat's pentachrome; original magnification x 400.

neurologic deficits and new angiographically confirmed areas of vessel inflammation.

In contrast, NP-cPACNS patients often present with predominantly focal deficits, negative inflammatory markers, unilateral MRI lesions, and proximal vessel stenosis on angiography. These patients have a monophasic inflammatory large-vessel disease, which does not progress beyond 3 months (Fig. 1).

Children with SV-cPACNS are the fastest growing group of patients in most centers. SV-cPACNS patients present with predominantly diffuse deficits, mild to moderately elevated inflammatory markers in the CSF, and multifocal MRI lesions. Angiography including conventional angiography remains normal; lesional brain biopsies confirm the diagnosis of SV-cPACNS (Fig. 2).

The terminology of cPACNS reflects the size of CNS vessel involvement, the disease progression, and the diagnostic modalities required to confirm the diagnosis. However, since CNS vasculitis in childhood is increasingly recognized, the spectrum may further expand and the terminology may need to be readdressed in the future.

Clinical features

Children with cPACNS present with a newly acquired focal and/or diffuse neurologic deficit. This deficit varies between patients depending on the size of affected CNS vessels, the degrees and numbers of stenoses, and the distribution of the inflamed CNS vessels. In general, patients with proximal, large CNS vessel stenoses present with clinical features of decreased perfusion in the area of the stenotic vessel and ischemia of the depending brain territory. Stroke features including hemiparesis, hemifacial weakness, or hemisensory loss are often resulting. Proximal, large-vessel inflammation with subsequent focal stenosis is the hallmark of NP-cPACNS. The majority of NP-cPACNS patients present with strokes (Table 2).

In contrast, distal CNS vessel inflammation is frequently associated with features of adjacent parenchymal inflammation. cPACNS patients with distal vessel stenoses often present with significant diffuse neurologic deficits including cognitive decline, behavior changes, school difficulties, and mood/personality changes. Distal vessel inflammation is commonly seen in P-cPACNS and SV-cPACNS. Notably, P-cPACNS patients have both large- and small-vessel inflammation and will therefore present with overlapping clinical features (Table 2). SV-cPACNS is increasingly recognized in children, who may present with an unexplained, severe cognitive decline, headaches, and/or seizures.

Overall, the most common presenting features of cPACNS are acute severe headaches and stroke features [1,2,25••,31,33••]. Neurocognitive dysfunction including concentration difficulties and mood and behavioral changes are to be sought, because they reflect an acquired diffuse neurologic deficit frequently associated with progressive inflammation. Movement abnormalities and constitutional symptoms are less frequently seen [1,2,25••,31,33••]. Dramatic presentations including acute loss of consciousness, status epilepticus, features of increased intracranial pressure, or refractory meningoencephalitis can be caused by intracerebral or subarachnoidal hemorrhage, a CNS mass lesion, or most commonly extensive meningeal and adjacent cortical inflammation, as seen in SV-cPACNS. The tempo of

disease progression in cPACNS is highly variable. Some patients present with rapidly progressive neurologic deficits, whereas others have diffuse or focal features slowly evolving over weeks or months.

Laboratory tests

Systemic inflammatory markers are frequently normal in children with cPACNS. A normal erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell count (WBC), C3 complement, or immunoglobulin G level by no means exclude an active vasculitic process in the CNS. However, as the inflammation progresses, some children may develop mildly elevated systemic inflammatory markers. There is no specific autoantibody profile associated with cPACNS [25,33]. Some children may have positive antinuclear antibodies (ANA) [1,31]; antineutrophil cytoplasmic antibodies (ANCA) are usually not detected. Low titer anticardiolipin antibodies may be found in up to 50% of patients [25••].

Cerebrospinal fluid

CSF analysis is an essential part of the diagnostic evaluation of cPACNS patients, not only to determine cell counts and protein levels, but also to exclude active CNS infections. In addition, presumed reactivations of latent virus infections such as VZV should be thoroughly investigated including VZV immunoglobulin M (IgM) ratio CSF/serum plus PCR as suggested by Gilden et al. [40].

Abnormal CSF analyses were reported in 90% of adults with biopsy-confirmed PACNS, whereas the sensitivity of CSF inflammatory markers was much lower in angiography-positive patients [41]. In children with cPACNS, positive CSF inflammatory markers are more commonly found in patients with distal-vessel involvement (P-cPACNS) and/or small-vessel disease (SV-cPACNS).

Gallagher et al. [1] reported 60% positive CSF inflammatory markers in angiography-positive c-PACNS cases (3 of 5 patients). The angiography-positive Toronto Cohort Study detected abnormal CSF analyses in only 39% of patients (9 of 23 tested). In contrast, a series of biopsy-positive SV-cPACNS patients reported a sensitivity of abnormal CSF markers between 50% (1 of 2) [2] and 100% (6 of 6) [31,33••]. Documented CSF inflammatory markers were either pleocytosis and/or raised CSF protein. Even though initial CSF analysis may be normal, mild to moderately elevated cell counts and protein levels may be seen in repeat CSF analyses as the disease progresses. CSF opening pressure is raised in the vast majority of P-cPACNS and SV-cPACNS patients and should be determined with all lumbar punctures.

Neuroimaging

CT and MRI

CT lacks sensitivity to detect inflammatory lesions in cPACNS patients. Even with contrast enhancement, this modality misses the majority of inflammatory brain and spine lesions [33••,42••].

Table 2. Features of 62 children with angiography-positive, primary central nervous system vasculitis

Clinical features at presentation	Progressive cPACNS, *n = 20*	Nonprogressive cPACNS, *n = 42*
Headaches	19 (95%)	16 (38%)
Focal neurologic deficit		
Hemiparesis	12 (60%)	37 (88%)
Hemifacial weakness	12 (60%)	24 (57%)
Hemisensory loss	19 (95%)	30 (71%)
Fine motor skills	15 (75%)	30 (71%)
Seizures	6 (30%)	3 (7%)
Diffuse neurologic deficit		
Concentration difficulties	15 (75%)	3 (7%)
Cognitive dysfunction	15 (75%)	8 (19%)
Mood/personality changes	12 (60%)	4 (10%)
Fever/fatigue	5 (25%)	1 (2%)

cPACNS—primary angiitis of the central nervous system of childhood. (*Data from* Benseler et al. [25••].)

However, MRI is crucial in the diagnostic process of cPACNS. All patients reported so far had abnormal MRI testing at diagnosis [42••]. Advanced MRI techniques including fluid attenuated inversion recovery (FLAIR), diffusion-weighted images (DWI) and gadolinium (GAD)-enhanced sequences may be required to detect the inflammatory lesions and allow for better characterization. Characteristic MRI patterns were recently described for cPACNS [42••]. Utilizing sensitive MRI techniques, the distribution of MRI lesions correlates closely with angiographic findings [42••]. To date, the negative predictive value of a combination of a normal CSF analysis and a normal brain MRI for cPACNS appears to be very high.

MRI lesions in cPACNS may be unifocal or multifocal and unilateral or bilateral. Characteristic MRI lesions in the angiography-positive cPACNS Toronto Cohort were multifocal and unilateral (93%) involving both grey and white matter. The vast majority of MRI lesions were supratentorial (98%); none of the cPACNS patients had isolated infratentorial lesions. The lateral lenticulostriate arteries territory was affected in 56% of cases, with involvement of a supratentorial deep grey matter structure in 91%. When comparing sequences, MRI lesions were seen on 98% of T2-weighted and 95% of FLAIR images. Lesions were only detected in 60% of DWI sequences [42••]. The predictive value of MRI patterns and the specific roles of FLAIR, DWI, and GAD-enhanced sequences in the initial assessment and monitoring in follow-up of cPACNS need further evaluation.

Angiography

Conventional angiography (CA) demonstrating cerebral arterial vessel stenoses is considered a diagnostic crite-

rion for PACNS [24] and cPACNS [25••]. CA is a safe procedure in adults [43] and apparently in children as well. In most pediatric series, CA is considered the gold standard for suspected medium- to large-vessel cPACNS [1,25••]. Aviv et al. [44] showed that the predominant angiographic feature in cPACNS was arterial vessel stenosis. Stenoses were most commonly unilateral (90%) and multifocal (76%). Proximal lesions were found in 86% of children. The anterior circulation was frequently involved (86%). The majority of lesions occurred within the middle cerebral artery (41%) with proximal predominance (62%). Anterior cerebral artery, internal carotid artery, and posterior circulation involvement occurred in 27%, 17.5%, and 14% of cases, respectively [44]. The majority of cPACNS patients had involvement of more than one vascular bed, consistent with angiographic findings in adults [45].

MR angiography (MRA) is an attractive diagnostic and monitoring tool, because it is noninvasive and does not utilize radiation. This technique is limited by lower spatial resolution and loss of selective dynamic information such as flow rate estimates compared with CA. In the cPACNS Toronto Cohort Study, CNS vessel stenosis was documented on MRA in 83% of patients with predominantly proximal involvement. Multifocal, unilateral lesions were seen in 63%. Considering CA as the gold standard, MRA failed to detect a number of distal vessel stenoses in this cohort. The sensitivity and specificity of MRA for a CA-confirmed vascular lesion was 70.3% (95% CI 70.2%–70.4%) and 97.5% (95% CI 93.6%–100%), respectively. There was a fair correlation between CA and MRA ($\kappa = 0.4$) limited by the presence of additional lesions on CA undetected on MRA [44].

Overall, the ability of CA to detect and characterize lesions in cPACNS is superior to MRA. A normal MRA in the context of a high clinical suspicion for cPACNS and lesions on MRI should lead to performing CA. Both underestimation and overestimation of vascular abnormalities on MRA have been observed when compared with CA. However, if good correlation exists between both techniques in an individual patient, MRA may be the preferred tool for follow-up assessments.

Other imaging techniques

Single photon emission CT and positron emission tomography have been shown to demonstrate perfusion abnormalities in patients with CNS vasculitis [46], but they have not been adequately evaluated for this disease.

Transcranial Doppler (TCD) ultrasound is a promising follow-up tool, which has recently been studied in adults and children with CNS vasculitis [47]. TCD is a noninvasive, inexpensive, easily accessible technique, but it has limited utility for small-vessel disease. TCD findings correlate better with CT and MR angiographic studies of large CNS vessels and may be useful for monitoring improvement or progression of an individual large-vessel abnormality.

Brain biopsy

Biopsy of the brain and leptomeninges is considered the gold standard for the diagnosis of PACNS in adults [48], most importantly in order to exclude mimicking conditions. In a series of 61 biopsies for suspected adult PACNS, the diagnosis was confirmed in only 36% of patients, with the majority of patients suffering from infectious, degenerative, or malignant CNS diseases [49]. The classical histology of adult PACNS reported in 80% of cases is a segmental necrotizing, frequently granulomatous vasculitis with evidence of intramural giant cells.

Elective brain biopsies in children are increasingly performed in many centers due to the increasing recognition of inflammatory brain diseases such as SV-cPACNS. Historically, necrotizing granulomatous large-vessel vasculitis had been reported in a number of fatal cases. All the recent biopsies performed at our center revealed nongranulomatous, lymphocytic vasculitis of small vessels as shown in Figure 2 [33••,50]. Similar to adults, brain biopsies in children with suspected SV-cPACNS serve two important purposes: confirmation of the diagnosis and exclusion of other conditions mimicking CNS vasculitis, including tuberculosis [51] and malignancies [52].

Brain biopsies should strongly be considered in children with clinical features of a newly acquired, progressive neurologic deficit; abnormal CSF analysis; and multifocal MRI lesions but a normal angiography. Lesional brain biopsies are recommended. Children with angiography-positive, proximal vessel inflammation may have inconclusive brain biopsies due to predominantly ischemic changes of the brain tissue accessible for biopsy.

A pragmatic approach

In the daily pediatric neurology and/or rheumatology practice, the diagnosis of cPACNS is a stepwise approach. A previously healthy child presents with a newly acquired focal and/or diffuse neurologic deficit, which can not be attributed to an infection, trauma, metabolic disease, or any other systemic condition. The differential diagnosis of an inflammatory brain disease is introduced. Laboratory markers, in particular CSF inflammatory markers including cell count, protein, and opening pressure, are determined. Parenchymal CNS inflammation is confirmed by MRI. Subsequently, vascular inflammation leading to vessel stenoses is determined by angiography [42••]. Angiography-negative cases with high suspicion for cPACNS require a lesional brain and leptomeninges biopsy to confirm the diagnosis of SV-cPACNS [33••].

Therapy

No controlled trials have been performed in adult or pediatric patients with CNS vasculitis. Daily oral cyclophosphamide and corticosteroid are frequently used in adults with PACNS [28]. In children, the current treatment approach depends on the cPACNS classification.

Patients with P-cPACNS and SV-cPACNS are commonly treated with intravenous (IV) monthly cyclophosphamide plus high-dose corticosteroids [25••,33••,53]. Physicians often follow the "induction/maintenance concept" used in other systemic autoimmune diseases such as systemic lupus erythematosus [54]. Induction therapy consists of seven IV cyclophosphamide pulses (500–1000 mg/m^2/month) plus corticosteroids (2 mg/kg/day, slow taper over 9 months). Maintenance therapy includes oral azathioprine or mycophenolate mofetil plus a tapering low dose of corticosteroids for 2 years. Relapses after many years of remission off all medication have so far been observed in a small number of children with SV-cPACNS. Partial response or refractory disease has been noted in a limited number of patients, who achieved sustained remission with experimental therapy (unpublished data).

Children with NP-cPACNS have a monophasic, focal inflammation of the proximal large CNS vessels causing stenosis. Some may argue that these patients, similar to children diagnosed by neurologists as "post-varicella angiopathy" or "transient cerebral arteriopathy," need no immunosuppressive treatment [32,36]. However, therapeutic recommendations for a suspected VZV virus-associated CNS vasculitis in adults include a short course of oral acyclovir plus corticosteroids [55].

The role of antithrombotic therapy and prophylaxis is controversial. Potential risks and benefits of anticoagulation with low molecular weight heparin or coumadin must be determined for each individual patient. Thromboembolic phenomena, prothrombotic conditions, and post-stenotic low-flow conditions may require prophylactic anticoagulation. Low dose ASA (3–5 mg/kg/d) should to be considered in all patients. cPACNS monitoring should include regular clinical visits, review of inflammatory markers, and sequential brain imaging.

Outcome

Only limited information exists on long-term outcome of children with cPACNS. Early reports suggested a poor prognosis and even described fatal cases. In a cohort study of 41 adult PACNS patients with a mean follow-up of 4 years, the relapse rate was 29%. In addition, 80% had an overall favorable neurologic outcome, but the mortality rate was 10% [27]. In children, the Toronto cPACNS cohort, which included 62 children with angiography-positive disease, documented a complete neurologic recovery in only 34% of patients at a mean follow-up of 20 months. Significant neurologic deficits were found in 45% of NP-cPACNS patients and 31% of P-cPACNS patients [25••]. The recovery of SV-cPACNS patients appears to be more encouraging [33••]. Validated follow-up tools such as the modified Pediatric Stroke Outcome Measure (PSOM) are suggested to determine neurologic deficits [56]. Long-term neurocognitive and behavioral outcomes in cPACNS patients must be evaluated.

Benign Angiopathy of the CNS

Benign angiopathy of the CNS (BACNS) refers to a subgroup of adult patients, who present at younger age, have a monophasic disease course, and do not have inflammatory CSF changes. The underlying pathomechanism is thought to be a cerebral vasospasm rather than a true vasculitis [57]. BACNS appears to be unique to adults; a comparable disease has not been described in children.

Transient Cerebral Arteriopathy

The term "TCA" was introduced by Chabrier et al. [32], reporting on nine children of a cohort of 34 consecutive patients with ischemic stroke. Sebire [36] defined TCA as a noninflammatory cerebral vessel vasculopathy with a nonprogressive course. The hallmarks of TCA are unilateral, proximal cerebral vessel stenoses causing arterial ischemic stroke [36]. About 50% of TCA cases also meet the diagnostic criteria for PVA [32], suggesting a wide overlap of TCA, PVA, and perhaps even NP-cPACNS, the latter defined as VZV workup negative.

Of note, the classification "transient" does not necessarily imply a favorable neurological outcome, since TCA patients may have severe, permanent neurologic sequelae [32].

Postvaricella Angiopathy

In 1999, Sebire et al. [58] implicated preceding VZV infection in the pathogenesis of arterial ischemic stroke in children. In a large prospective study, Askalan et al. [34] confirmed that VZV infections within 12 months are in fact a risk factor for childhood stroke. The group estimated an absolute risk of VZV-associated stroke of 1:15,000. The angiographic pattern of PVA of proximal, large-vessel stenoses widely overlaps with TCA [59]. It has been suggested that the diagnosis of PVA should be made based on 1) preceding VZV infection within 12 months; 2) evidence of unilateral, proximal large-vessel stenosis; and 3) PCR positivity for VZV and/or VZV IgG in the CSF [55]. The neurologic outcome of post-VZV CNS vasculitis was thought to be good [32]. However Askalan et al. [34] reported recurrent strokes in 45% of patients and residual neurologic deficits in 68%. All children were treated with anticoagulation only. More recently, Lanthier et al. [35] published the long-term outcomes of the same PVA cohort at a median follow-up time of 75 months. The group reported hemiparesis in 13 of 23 (57%) children, hemidystonia in 6 (26%), hemisensory deficit in 3 (13%), speech problems in 3 (13%), symptomatic epilepsy in 1 (4%), and no neurologic deficit or epilepsy in 9 (31%) [35].

Conclusions

Primary CNS vasculitis of childhood was thought to be a rare condition; however, an increasing number of children are diagnosed with an inflammatory brain disease often

primarily affecting the brain vessels. These children commonly present with headaches and an acquired neurologic deficit. The first step toward diagnosis, clinical recognition, should be followed by the search for inflammatory markers, both systemically and more importantly in the CSF. The suspected diagnosis of cPACNS is strongly supported by multifocal brain parenchymal lesions on MRI plus typical angiographic findings of vessel stenoses. However, small-vessel vasculitis may not be evident on CA, and this diagnosis is best made by a lesional brain and leptomeningeal biopsy.

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