Treatment of CNS Vasculitis in Children

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Opinion statement

Inflammatory brain diseases, including childhood primary CNS vasculitis, are increasingly recognized disease entities. Mortality and morbidity have improved markedly due to rapid recognition and initiation of treatment. Treatment regimens are mostly derived from the adult literature. In this review, we summarize the most important adult and pediatric literature on therapy of primary CNS vasculitis. Evidence is all based on prospective or retrospective studies, as no trials have been performed in CNS vasculitis. Future new biomarker discoveries and increased knowledge on the pathophysiology are key for developing targeted treatment regimens.

Introduction

Primary angiitis of the central nervous system (PACNS) is an inflammatory disease of the cerebral blood vessels resulting in devastating neurological and psychiatric symptoms in previously healthy children [1–3]. First reported in 1959 in adults, the diagnosis was almost exclusively made on autopsy describing a granulomatous inflammation of the cerebral arteries [4]. In 1988, Calabrese [1] proposed diagnostic criteria for adults with PACNS including the following: newly acquired focal or diffuse neurological deficits plus angiographic or histological evidence of CNS vasculitis in the absence of a systemic condition that could explain or mimic these findings [1]. Over the past decade, these were modified and adopted for childhood PACNS (cPACNS) [5, 6].

Undoubtedly, the Calabrese criteria resulted in increased recognition and improved outcome of children and adults with primary CNS vasculitis. In addition, CNS vasculitis is increasingly recognized in the context of other illnesses such as infections, inflammatory or rheumatic diseases, immune dysregulations, malignancies, metabolic diseases, and other illnesses, commonly classifying it as secondary CNS vasculitis [7].

Cerebral vessel wall inflammation is the central, complex pathology in cPACNS. It is characterized by intramural and perivascular infiltration of immune cells, resulting in wall edema, vessel stenoses, endothelial activation and pro-thrombotic effects, perivascular brain tissue inflammation and irritation causing parenchymal

dysfunction such as seizures and neuronal injury, critically decreased blood flow through the narrowed vessel, and the risk of ischemic injury to the vascular territory [8]. Treatment of CNS vasculitis aims to reverse the inflammation, the pro-thrombotic state, and acquired

brain and/or spinal cord dysfunction. This review will provide an update of the current treatment approaches to primary and secondary CNS vasculitis in children. Treatment approaches differ between different disease subtypes and associated conditions.

Childhood primary CNS vasculitis

Inflammation of the CNS blood vessels and the perivascular space is the hallmark of childhood PACNS (cPACNS) [8]. Distinct subtypes have been identified based on the vessel size involved and course of inflammatory illness [5, 6]. Large-medium vessel cPACNS or angiography-positive cPACNS is an inflammatory vascular disease that can affect the intracranial internal carotid arteries (ICA), the circle of Willis and its branches, the posterior cerebral circulation, and the spinal vessels up to the resolution of 3-T magnetic resonance angiography and/or conventional angiography [5, 9]. This definition excludes small muscular arteries, arterioles, capillaries and venules, which are considered “small vessels of the brain.” Therefore, by definition, small vessel cPACNS is an angiography-negative inflammatory brain disease [6]. Within a cerebral vessel, the distinction of proximal segments—defined as the first- and second-order branches—and distal segments—defined as any segments beyond second branching—is commonly made. Currently, four distinct subtypes of cPACNS are recognized, two affecting the large-medium vessels and two the small cerebral vessels [5, 6]. Nonprogressive cPACNS and progressive cPACNS are subtypes of angiography positive, large-medium cPACNS. Angiography-negative, biopsy-positive cPACNS consists of a subtype affecting the arterials and capillaries, which is commonly named “small vessel cPACNS” and an isolated cerebral venulitis. Each subtype has distinct presenting clinical features, laboratory findings, neuroimaging appearances, disease course, and prognosis. Each subtype has a distinct treatment approach. All treatment regimens are based on observational cohorts or case reports; no clinical trials have been conducted in primary CNS vasculitis [10, 11].

Nonprogressive childhood primary angiitis of the central nervous system

Nonprogressive cPACNS (NP-cPACNS) is the most common CNS vasculitis in children. It is a monophasic, strictly unilateral inflammatory disease affecting the proximal vessel segments of the anterior and/or middle cerebral artery and/or the intracranial segment of the ICA. NP-cPACNS is largely overlapping with conditions including “transient cerebral arteriopathy (TCA)” [12], “post-varicella angiopathy (PVA)” [13], and “focal cerebral arteriopathy (FCA)” [14]. Children with NP-cPACNS present with an acute onset of focal neurological deficits and arterial ischemic stroke [3]. This subtype is more commonly seen in boys. Presenting focal abnormalities may include hemiparesis, hemifacial weakness, aphasia, hemisensory loss, and unilateral deficits in fine motor skills [3, 5]. Headaches are commonly reported, while diffuse deficits such as memory, behavior, or cognitive deficits are uncommon. Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)

are frequently normal [15]. Autoantibody testing is commonly negative; a small subgroup may have detectable anti-phospholipid antibodies. Importantly, von Willebrand factor antigen levels are commonly raised [16]. Cerebrospinal fluid (CSF) analysis is commonly normal with $\ll 50\%$ of the children having a mildly raised white cell count (lymphocytes), mildly elevated protein level, or opening pressure. Bacterial and viral cultures remain negative. Polymerase chain reaction (PCR) and CSF: serum ratios for varicella zoster virus (VZV) antibody should be tested to identify an active infection [5]. MRI reveals diffusion-restricted lesions in a characteristic unilateral, anterior vascular distribution. Most commonly unilateral basal ganglia lesions are seen; however, any area of the anterior and/or middle cerebral artery territory may be affected [3] (Fig. 1). Angiography confirms unilateral inflammatory vessel wall disease of the proximal anterior and/or middle cerebral arteries and/or distal ICA with evidence of contrast wall enhancement [17]. Distal vessel segments are spared,

Fig. 1. Childhood primary nonprogressive CNS vasculitis in a 4-year-old boy presenting with vascular stroke and hemiparesis. Legend: The parenchymal imaging revealed lesions in the left middle cerebral artery (MCA) territory on T2/fluid attenuated inversion recovery (FLAIR) images (axial sequences, **a**). The corresponding diffusion-weighted images demonstrated decrease diffusion within the lesion representing a fresh stroke (axial sequences, **b**). Vascular imaging revealed the vascular nature of the stroke: MRA time-of-flight identifies mildly narrowed, irregular proximal MCA segments (**c**).

posterior circulation involvement is atypical, and spinal cord disease has not been reported in NP-PACNS [9]. The disease is a monophasic inflammatory disease and does not spread to other, previously unaffected, vascular territories; however, recurrent ischemic event can occur in the affected vascular territories when vessel wall inflammation persists. By definition, in NP-cPACNS, the suggested follow-up imaging at 3 months post-diagnosis does not reveal any new inflammatory vessel wall changes [3, 5].

Treatment of nonprogressive childhood primary angiitis of the central nervous system

Children with NP-cPACNS require anti-thrombotic therapy (see Tables 1 and 2) [35]. The optimal choice of anti-thrombotic medication may vary between patients depending on their vessel disease. The treatment aim is the prevention of recurrent ischemic event in the face of vessel stenosis, flow alteration, and endothelial cell activation [3]. Commonly, heparin, either conventional or low-molecular-weight (LMW), is primarily started. Anti-platelet agents are often introduced after 2 weeks and heparin is stopped. Some centers use anti-platelet agents up front in children with mild to moderate vessel stenosis. High-risk patients including those with moderate-to-severe vessel stenosis, rapid progression of vascular narrowing, preexisting thrombi, or recurrent artery-to-artery emboli may require ongoing LMW heparin, Coumadin, or even combination anti-thrombotic therapy. These approaches carry a higher risk of bleeding. In many centers, the monophasic inflammatory vessel wall disease in NP-cPACNS is treated with a 3-month course of corticosteroids [11]. Typically, children receive IV methylprednisolone pulses for 3–7 days followed by oral prednisone at a dose of 2 mg/kg, max 60 mg/day as a single dose for a month with a taper over the subsequent 2 months (50, 40 mg). Vessel and parenchymal MRI imaging re-evaluation is recommended at the 3-month mark before discontinuing prednisone. Supplementary therapies should include vitamin D, calcium, and stomach protection, if required. Early, structured rehabilitation strategies appear to result in improved outcomes. The pediatric stroke outcome measure (PSOM) is a useful instrument to capture the functional status [36].

Progressive childhood primary angiitis of the central nervous system

Progressive cPACNS is a chronic inflammatory disease of the large-medium size vessels characteristically affecting both proximal and distal vessel segments [3]. The latter being the key differentiating factor from NP-cPACNS. Progressive cPACNS (P-cPACNS) can affect vessel in one or both hemispheres, involve the anterior and/or posterior circulation, the brainstem, cerebellum, and spinal cord vasculature [3]. Children presenting with angiographic evidence of distal vessel segment vasculitis have a progressive disease course and therefore require combination immunosuppression [5]. Similar to NP-cPACNS, P-cPACNS more commonly affects boys than girls. Children with progressive P-cPACNS typically present with both focal and diffuse neurological deficits [3, 18]. Headaches are present in 95 % of P-cPACNS patients. Any sensorimotor deficits can be seen, commonly hemisensory loss and fine or gross motor deficits; however, also movement abnormalities, seizures, speech, or vision problems can be seen. Difficulty in concentration, cognitive dysfunction, and mood and personality changes are frequently observed diffuse neurological deficits. The onset is often insidious [5]. Inflammatory markers in blood and CSF analysis are commonly abnormal, yet only mildly

raised compared to levels in systemic vasculitides. Von Willebrand factor antigen is commonly raised [16]. Complement levels and immunoglobulin G levels may be elevated; specific antibodies are commonly negative. Characteristic MRI findings include both—ischemic and inflammatory lesions. Any pattern and distribution is possible; no “typical MRI appearance” of P-cPACNS exists [3]. Angiography reveals either unilateral or bilateral multifocal involvement of the proximal and distal segments of the cerebral arteries [9]. Thrombi and artery-to-artery embolism can be seen. Isolated vessel disease in the posterior circulation, brainstem, cerebellum, or spinal cord has been described. Hemorrhages are rare in childhood. Gadolinium contrast wall enhancement is seen in newly affected vascular segments [17, 37].

Table 1. Treatment of childhood primary CNS vasculitis

Author	Nr patients	Age M/F	Diagnoses	Treatment	Outcome/course
Gallagher et al. [18]	5 children	5–11 years, 2 M, 3 F	PACNS angio abnormal 60 %, MRA abnormal 40 %, no biopsy CSF nl 100 %	5 Prednisone, 4 cyclophosphamide, 1 cyclophosphamide, one dose	1 = lost-up 1 = nl 2 years 3 = improving mild deficits >1 year follow-up
Lanthier et al. [19]	2 children	10–16 years, 2 F	cPACNS small vessel, biopsy positive	2 Prednisone, 1 cyclophosphamide	One mild left hemiparesis after 6 years
Yaari et al. [20]	2 children	3–12 years, 1 M, 1 F	cPACNS small vessel, biopsy positive	2 Prednisone, 1 cyclophosphamide, 1 methotrexate	Relapse in both patients
Benseler et al. [6]	4 children	5–16 years, 4 F	SV-PACNS biopsy + 100 %	4 Prednisone, 4 ASA, 2 cyclophosphamide, 1 azathioprine	No relapse, complete neurologic recovery
Benseler et al. [5]	62 children	0.5–17.5, 38 M, 24 F	cPACNS angio abnormal 100 %	62 ASA, 21 immunosuppressants	30 % Progressive cPACNS
De Tiege et al. [21]	3 children	9–15 years, 2 M, 1 F	SV PACNS, biopsy positive	3 Prednisone, 3 cyclophosphamide	1 long-term relapse 8 years later; all no deficits 1 relapse both remission
Bitter et al. [22]	2 children	5–7 years, 2 F	PACNS, 1 MRA abnormal, 1 biopsy abnormal	2 Prednisone, 2 cyclophosphamide	2 relapses in one patient
Sen et al. [23]	3 children (three centers)	5–9 years, 1 M, 2 F	PACNS, 1 MRA abnormal, 1 biopsy abnormal, 1 MRI abnormal	3 Prednisone, 2 cyclophosphamide, 1 methotrexate	8/19 relapse 4/19 remission of medication
Hutchinson et al. [10]	19 children	5–17.5 years, 4 M, 15 F	SV-cPACNS	19 Prednisone, 19 cyclophosphamide Maintenance: 9 azathioprine, 5 MMF	

Table 2. Treatment of adult primary CNS vasculitis

Author	Nr patients	Age M/F	Diagnoses	Treatment	Outcome/course
Maclaren et al. [24]	105 adults	16–55 years, 5 M, 7 F	12 PACNS 8 angio abnormal, 9 MRI abnormal, 1 biopsy positive, 8 CSF normal 5 PACNS	12 prednisone, 12 cyclophosphamide	More relapse in SVPACNS
Volcy et al. [25]	5 adults	16–36 years, 4 M, 1 F		5 Prednisone	All good outcome, no relapses, 1 residual seizure
Salvarani et al. [2, 26–28]	101 adults	17–84, 43 M, 58 F	PACNS 70 angio abnormal, 31 biopsy positive 8 amyloid + biopsy positive, 5 spinal cord involvement PACNS 38 biopsy positive	98 Prednisone, 45 cyclophosphamide	26 relapses, 16 deaths
Molloy et al. [29]	38 adults (30 from lit)	6–74 years, 19 M, 19 F		23 prednisone, 10 cyclophosphamide	26 remissions, 6 died, 29 residual deficits
Kraemer et al. [30]	21 adults	11–65 years, 8 M, 13 F	PACNS 13 angio abnormal, 8 biopsy positive	12 ASA, 10 IV prednisone, 18 prednisone, 8 cyclophosphamide IV/PO	15 good treatment response 3 deaths
Salvarani et al. [31]	11 rapid progressive (131 adults) 1 adult	38–74 years, 5 M, 6 F	11 Progressive PACNS	11 Prednisone, 6 cyclophosphamide, 2 azathioprine Prednisone MMF	10 deaths
Chevenier et al. [32]	29 years, 1 M		PACNS angio abnormal Biopsy positive		Relapse with hemiparesis after 2 months
Salvarani et al. [33]	163 adults	17–85 years, 74 M, 89 F	PACNS 104 angio abnormal, 59 biopsy positive PACNS 12	156 prednisone, 72 cyclophosphamide	24 died, 44 Rankin 4–6
Vera-Lastra et al. [34]	12 adults	32±13.19 years, 1 M, 11 F		12 Prednisone, 12cyclophosphamide	1 Relapse

Follow-up imaging in untreated children commonly documents the spread of the disease with new inflammatory vessel wall changes.

Treatment of progressive childhood primary angiitis of the central nervous system

Similar to NP-cPACNS, children with P-cPACNS require anti-thrombotic therapy (see Tables 1 and 2). In many centers, heparin is the preferred first-line medication followed by anti-platelet drugs. Some primarily start antiplatelet agents to prevent recurrent ischemic event secondary to endothelial cell activation resulting from vessel wall inflammation. All children with P-cPACNS require immunosuppression, most commonly after 3–7 days of IV methylprednisolone pulses (30 mg/kg, max 1 g); high-dose oral prednisone (2 mg/kg, max 60 mg/day) is combined with monthly IV cyclophosphamide [5, 18, 22, 35]. Commonly, cyclophosphamide induction therapy is given over 6 months (seven doses, 500 mg/m² plus Mesna) and is followed by oral maintenance treatment with either mycophenolate mofetil (MMF, 800–1200 mg/m²/day) or azathioprine (2 mg/kg/day) for 18 months [5, 18]. Supplementary therapies should include pneumocystis prophylaxis while receiving cyclophosphamide, vitamin D, calcium, and stomach protection, if required. Early rehabilitation strategies may improve outcomes; however, residual focal neurological deficit is more often seen in this subtype. Monitoring of treatment effectiveness commonly includes serial functional clinical testing (PSOM), von Willebrand factor antigen (vWF) levels, cognitive testing yearly, and six monthly MRI/A studies. Follow-up is best provided in an interdisciplinary team. Children with refractory P-cPACNS may benefit from anti-TNF alpha therapy with monthly infliximab for 24 months [38].

Small vessel childhood primary angiitis of the central nervous system

Angiography-negative, small vessel cPACNS is the most challenging subtype due to its clinical heterogeneity, the exponential risk of severe brain injury due to frequently disease-associated seizures, the lack of specific biomarkers, and the need for invasive brain biopsies to confirm the diagnosis [6, 10]. Disease and treatment result in a very high burden for patients and families. Small vessel cPACNS has a female predominance. Children often present with an insidious onset of cognitive deficits, headaches, and seizures. Constitutional symptoms may be present; leading clinical features of meningitis, optic neuritis, or transverse myelitis can be seen [39]. Eight of ten children with small vessel vasculitis present with seizures—most commonly generalized. Refractory seizure status is a well-recognized presentation of small vessel vasculitis and mandates a rapid evaluation. Blood inflammatory markers are commonly raised in children with small vessel cPACNS; the elevation may be modest though [10]. vWF antigen strongly supports a vasculitic etiology as opposed to demyelinating or other conditions; 90 % of children have abnormal CSF studies at diagnosis including increased protein level and/or leukocytosis [16]. The MRI is a sensitive, yet nonspecific test for small vessel cPACNS. The vast majority has T2/FLAIR-positive, not diffusion-restricted MRI abnormality lesions in variable distributions [6]. Lesions can affect all matters, may be unifocal or multifocal, symmetrical, or asymmetrical, and may enhance contrast. Atypical appearances including ring enhancement, mass lesions, and hemorrhages have been documented [40]. Focal or diffuse meningeal enhancement is characteristic for small

vessel vasculitis, when untreated. Repeatedly normal MRIs have been documented in children presenting with status epilepticus. By definition, MRA and conventional angiography studies are normal in children with small vessel cPACNS. Lesional brain biopsy should target new, accessible areas [8]. Distinctly different from experience in adult CNS vasculitis, nonlesional approaches have similar diagnostic yields due to the diffuse, nonpatchy nature of the disease in children [4, 8, 41]. Intramural and perivascular lymphocytic infiltrates predominantly consisting of CD8-positive T cells are the hallmark of childhood small vessel vasculitis [8]. Distinctly different from adult PACNS brain biopsies, granulomatous inflammation or neutrophilic infiltrates with fibrinoid necrosis are absent in children with cPACNS [2, 7]. Small vessel cPACNS is a chronic disease with highly variable speed of progression and fluctuation in disease activity even when untreated that remain unexplained. Prolonged time to diagnosis and the presence of seizures were found to impair recovery dramatically and result in severe cognitive deficits [10].

Treatment of small vessel childhood primary angiitis of the central nervous system

Combination immunosuppressive therapy should be initiated rapidly; delay to therapy may result in a higher risk for irreversible brain injury. Similar to the P-cPACNS regimen, a 6-month induction treatment with intravenously cyclophosphamide (500 mg/m²) plus corticosteroids (methylprednisolone pulses 30 mg/kg, max 1000 mg for 3–7 days followed by daily oral prednisone 2 mg/kg, max 60 mg/day) is followed by 18 months of maintenance treatment; MMF was found to be superior to azathioprine (see Tables 1 and 2) [10]. Recent series report the effective primary use of MMF [32, 33]. Supplementary therapies including pneumocystis prophylaxis while on cyclophosphamide, vitamin D, calcium, and stomach protection should be considered. At 24 months, 70 % of the children were found to have a good functional neurological outcome by PSOM [10]. The key concern remains the cognitive outcome of children with small vessel cPACNS, in particular when initially presenting with prolonged seizures. Most children receive antiepileptic drugs for years [10].

Secondary CNS vasculitis

Secondary CNS vasculitis associated with infection

The most common etiology for secondary vasculitis is infection [42]. CNS vasculitis can be mimicked by many infections; therefore, it is necessary to include a complete infectious workup. PCR of serum and CSF can identify most infections [42]. Varicella zoster virus (VZV) is a notorious mimic of CNS vasculitis and is known as post-varicella angiopathy (PVA) [13, 43]. A wide variety of cell types in the central and peripheral nervous system can be infected by VZV [44]. PVA is a reactivation of VZV that causes inflammatory stenoses of the proximal large vessels [44–46]. Signs of CNS vasculitis have been noted to be present in adult patients with human immunodeficiency virus (HIV), with on brain biopsy only evidence of HIV [47]. Many other viruses, bacteria, and fungal infections can cause secondary CNS vasculitis. Patients with HIV can also develop secondary CNS vasculitis based on infections due to immune reconstitution syndrome (IRIS) [48]. IRIS develops usually in the first 2 months after start of antiretroviral therapy. IRIS has been linked with several types of

infections or inflammation including the following: cytomegalovirus (CMV), cryptococcal meningitis, hepatitis B and C, herpes zoster and herpes simplex, *Mycobacterium avium* complex (MAC), and viral brain infections causing progressive multifocal leukoencephalopathy (PML) [48]. IRIS can be treated by prednisone while continuing antiretroviral therapy, allowing the immune system to recover while treating the inflammation [48].

Secondary CNS vasculitis in rheumatic diseases

In rheumatic diseases, secondary CNS vasculitis may develop during or may even be the presenting symptom [49]. Involvement of the CNS is more commonly seen in adults with rheumatic diseases but can be seen in children with ANCA-associated vasculitis, such as granulomatosis with polyangiitis (GPA, previously known as Wegener granulomatosis) and microscopic polyangiitis (MPA), polyarteritis nodosa (PAN), Takayasu arteritis, and systemic lupus erythematosus (SLE) [49–53] (Fig. 2). Treatment of CNS manifestations in rheumatic diseases is mostly done with corticosteroids and cyclophosphamide, in agreement with the treatment for primary CNS vasculitis [54].

Secondary CNS vasculitis in systemic inflammatory diseases

Secondary CNS vasculitis is increasingly recognized in systemic diseases; it may be the primary symptom or complication of hemophagocytic lymphohistiocytosis (HLH), Kawasaki disease, inflammatory bowel disease, or systemic immunedysregulations [55, 56].

HLH is a rare but potentially fatal disease of nonmalignant but overactive histiocytes and lymphocytes commonly triggered by an infection. The clinical picture of HLH includes fever, hepatosplenomegaly, pancytopenia, hyperferritinemia, raised liver enzymes, and hypertriglyceridemia [57, 58]. CNS vasculitis is well described in children with HLH [56, 59] (Fig. 3). An increasing

Fig. 2. Secondary CNS vasculitis in a 14-year-old girl with systemic lupus erythematosus complicated by macrophage activation syndrome. Legend: The parenchymal imaging revealed thickening of the meninges in the absence of significant parenchymal lesions on T2/fluid attenuated inversion recovery (FLAIR) images (axial sequences, **a**). With progression of the inflammatory process and the HLH-associated cytopenia lesions extended into the parenchyma causing hemorrhages and mass effect and requiring a craniectomy (**b**).

Fig. 3. Secondary CNS vasculitis in a 17-year-old teenager with Griscelli syndrome and hemophagocytic lymphohistiocytosis (HLH). Legend: The parenchymal imaging revealed ill-defined lesions in the cerebellum (Fig. 3a) and in the white matter of both hemispheres (Fig. 3b) on T2/fluid attenuated inversion recovery (FLAIR) images (axial sequences). Vascular imaging including MRA and conventional angiography was normal. The brain biopsy revealed a small vessel CNS vasculitis with a predominant macrophage infiltrate (not shown); genetic testing confirmed a RAB 27A gene mutation characteristic for Griscelli syndrome type 2.

list of immune dysregulations is reported to carry a potential higher risk of CNS vasculitis and HLH including X-linked lymphoproliferative disease type 1 (XLP1) with mutations in SH2 domain protein 1A (SH2D1A), X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN), Hermansky-Pudlak syndrome, chronic granulomatous disease (CGD), and idiopathic hypereosinophilic syndrome (IHES). Secondary HLH typically occurs in children with severe infections, malignancies, or rheumatologic diseases most commonly in those with systemic juvenile idiopathic arthritis or lupus. The treatment of CNS vasculitis in primary or secondary HLH follows the Histocyte Society treatment protocol (HLH-94) including dexamethasone in combination with cyclosporine and VP-16[60]. Intrathecal MTX is added in selected patients. Kawasaki disease is a systemic inflammatory disease accompanied by vasculitis, mainly involving the coronary arteries. Inflammation of the cerebral blood vessels has been reported in Kawasaki; post-mortem brain examinations may reveal leptomenigeal thickening, endarteritis, and periarteritis [61]. Children with organ-specific inflammatory disease such as inflammatory bowel disease can present with CNS vasculitis [62]. Granulomatous vessel wall inflammation resulting in strokes and hemorrhages has been reported [63, 64].

Secondary CNS vasculitis in other systemic diseases/exposures

Secondary CNS vasculitis can also be caused by drugs, such as cocaine and amphetamines; however, these are also capable of mimicking CNS vasculitis without an inflammatory component but a vasoconstrictive component [65]. Secondary CNS vasculitis in form of radiation-induced arteritis has been described in patients after radiation therapy [66]. In children, who were treated for malignancies, CNS vasculitis has been seen in graft versus host disease [67, 68].

CNS vasculitis in new monogenic disease

Newly recognized diseases such as early-onset stroke and vasculopathy associated with mutations in adenosine deaminase 2 (ADA2) and activated stimulator of interferon genes (STING)-associated vasculopathy with onset in infancy (SAVI) are both mimics of CNS vasculitis [69–71]. ADA2 mutations have also been described in children with a polyarteritis nodosa [70]. Treatment with etanercept has been successful in patients with ADA2 mutations [69]. JAK inhibitors have been shown to be effective in vitro in SAVI [71].

Aicardi-Goutieres syndrome (AGS) can also mimic secondary CNS vasculitis. In a significant minority of AGS patients, problems start in utero and this form is associated with mutations in *TREX1*, *RNASEH2A*, and *RNASEH2C* [72]. More frequently, a late-onset presentation of AGS is seen. This form is associated with mutations in *RNASEH2B*, *SAMHD1*, and *ADAR1* [72]. The clinical phenotype of the late-onset presentation may be associated with a lesser degree of neurological dysfunction. AGS can be difficult to distinct due to the fact that neurological dysfunction is not always severe, microcephaly is not invariable, onset is not always in the first year of life, white matter changes and calcifications are not inevitable, and CSF lymphocytosis can be absent [72, 73]. AGS is associated with increased levels of interferon alpha in the CSF and serum. Treatment of AGS has been empirical and has included many of the immunomodulatory treatments [72].

Approach to treatment secondary CNS vasculitis

The identification and rapid management of the underlying condition are crucial in controlling secondary CNS vasculitis. This includes anti-microbial therapy and targeted approaches toward systemic inflammation and immune dysregulation. Immunosuppressive therapies for cerebral vessel inflammation are commonly either started, modified, or their dose adjusted.

Corticosteroids

Steroids are the first-line therapeutic option children with secondary CNS vasculitis. They have an acute onset of action in the CNS diseases, which may be partially explained by their ability to close the blood-brain barrier and thus reducing inflammation [74]. The typical treatment dose of IV methylprednisolone for acute CNS inflammation is 15 to 30 mg/kg of body weight given intravenously [10]. Dexamethasone is an alternative treatment option and may have better CNS penetration [60]. After 3–5 days of high-dose intravenous therapy, often, patients are then switched to high-dose oral corticosteroids with a slow taper over weeks. Abrupt withdrawal is avoided after long dosing schedules because of the suppression of endogenous cortisol production.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIG) is frequently used in secondary CNS vasculitis, in particular when associated with infection [75]. IVIGs can be used acutely not only because of their rapid onset of action, but also as part of chronic therapy. Effects can last weeks or months; however, they may lose effectiveness in some cases with chronic use. The typical acute treatment dose is a total of 2 g/kg of body weight divided over 2 to 5 days. Chronic recurrent

treatments usually consist of a 1 g/kg dose given over 1 day. Alternate-week dosing with IVIG is reasonable since the elimination half-life of human immunoglobulins is approximately 2–3 weeks.

Plasmapheresis/exchange

Plasmapheresis is frequently used in catastrophic, life-threatening inflammation including involvement of the brainstem and spinal cord. PE requires large-bore intravenous access and special procedural center expertise. There is limited published evidence for its efficacy [76]. A typical treatment course is 5 to 7 exchanges spaced out over 5–10 days [54].

Rituximab

Rituximab is a chimeric monoclonal antibody that targets the CD20 surface antigen and causes a rapid loss of CD20-positive B cells from the circulation. The circulating B cell population reconstitutes from memory B cell pools and nascent B cells. The typical dose is 375 mg/m² intravenously every 2 weeks for two doses. Follow-up cycles are prescribed depending on the response. Side effects of RTX may include those typically seen with infusions such as hypotension, flushing, headache, pruritus, fever, nausea, and fatigue [77]. Rare cases of associated progressive multifocal leukoencephalopathy (PML) have been reported [78].

Cyclosporin A

Cyclosporin A (CSA), a cyclic nonribosomal peptide, and FK506, a macrolide immune suppressor, act through similar mechanisms by calcineurin inhibition, which prevent T lymphocyte activation. They are often considered interchangeable, but patients with side effects on one can often be switched to the other with good effect. The oral dose can be titrated up to 5 mg/kg/day divided twice daily [79]. Levels are checked exactly 12 h after the last dose because of erratic absorption. Side effects may include hypertension, renal/hepatic toxicity, tremor, and gastrointestinal complaints.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is a reversible inhibitor of inosine monophosphate dehydrogenase, in the purine metabolism. It reduces B and T lymphocyte proliferation. The dose is titrated up to 600 mg/m² given orally twice a day with a maximum daily dose of 2 g [10]. Side effects may include diarrhea, headache, elevated liver transaminases, and bone marrow suppression. Rare cases of PML have been reported with this medication in adults and children after renal transplant [80].

Cyclophosphamide

Cyclophosphamide (CP) is an alkylating agent that causes DNA interstrand crosslinkage and reduces lymphocyte proliferation. It is generally reserved for refractory diseases because of its long-term concerns for secondary malignancies and sterility. This medication is most commonly used in severe vasculitis

conditions. The dose is generally monthly 750–1000 mg/mg² intravenous pulse given for 6–12 months [10, 54]. The dose is titrated to cause a white blood cell count nadir of approximately 1500–2000. Mesna and prehydration can be given to decrease side effects.

Objective improvements which translate into meaningful gains in functional abilities, such as a return to school or resumption of independent daily living, should prompt consideration of a long-term plan for immunotherapy for that patient, since most patients will have a relapse of their symptoms on withdrawal of acute therapies. General guiding principles include maintenance of remission and a reduction in corticosteroid or IVIG dependence whenever possible. Some patients remain corticosteroid or IVIG dependent, despite optimization of oral immunosuppressant therapy.

Supportive therapy

Adjunctive therapy is frequently required to manage concomitant seizure disorders and psychotic symptoms. Additional treatment with *Pneumocystis jirovecii* prophylaxis while on CP or rituximab and vitamin D and calcium plus gastric protection while on high-dose steroids is required.

Beyond the medical treatment, early rehabilitation, including physiotherapy, occupational therapy, and cognitive therapy, is required to optimize the long-term outcome.

Overall, diagnosing primary CNS vasculitis remains difficult and the spectrum of secondary CNS vasculitis and mimics is rapidly expanding. Physicians should be aware of new disease entities, and an extensive workup is mandatory. Increased recognition and prompt accurate treatment of CNS vasculitis have led to a significant decreased mortality and improved morbidity.

Compliance with Ethics Guidelines

Conflict of Interest

Marinka Twilt and Susanne M. Benseler declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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