

## Review

## Childhood inflammatory brain diseases: pathogenesis, diagnosis and therapy

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## Abstract

Inflammatory brain diseases (IBrainDs) are a leading cause of devastating neurological deficits or neuropsychiatric syndromes in previously healthy children. The spectrum is expanding rapidly and new disease entities have been discovered in the last decade. IBrainD can occur as a primary disease or may occur secondary to an underlying cause. This review focuses on the clinical presentation, diagnostic features, pathology and histology characteristics and treatment of the primary childhood IBrainDs.

**Key words:** inflammatory brain disease, childhood primary angiitis of the central nervous system, Rasmussen encephalitis, NMDA receptor encephalitis, neuromyelitis optica, multiple sclerosis, neurosarcoidosis.

## Introduction

Inflammation is an increasingly recognized underlying pathology in children with severe acquired neurological deficits. Components of the central and peripheral nervous system can be targets of dysregulation of the innate and adaptive immune system [1, 2].

Childhood inflammatory brain disease (IBrainD) is an umbrella term that is increasingly used to describe primary and secondary inflammation of the CNS. Primary IBrainDs solely affect the brain and/or spinal cord and encompass vasculitic and non-vasculitic IBrainDs such as demyelinating disease, antibody-mediated IBrainDs, T cell-mediated parenchymal IBrainDs such as Rasmussen's encephalitis and granulomatous IBrainDs such as neurosarcoid and more rare forms of IBrainD such as acute necrotizing encephalitis and acute haemorrhagic leucoencephalitis [3]. Secondary causes of IBrainD correspond to brain inflammation in the context of a systemic disease and include infections, underlying systemic inflammatory diseases, and non-inflammatory causes, among others, and are not covered in this review [4].

Knowledge has increased over the years, new entities have been recognized, specific inflammatory pathways have been identified and treatment protocols have been initiated [5]. All children with small-vessel (SV) CNS vasculitis described in the literature before 2000 were based on autopsy reports, suggesting that the mortality and morbidity of this disease was very high. Recent studies have shown that implementation of tools to diagnose disease entities early, such as MRI, MR angiogram, conventional angiography and brain biopsy, have led to earlier initiation of immunosuppressive treatment and decreased mortality [6]. The morbidity and cognitive burden of these diseases are still unknown and future long-term studies should be designed to answer these pressing patient-related questions.

## Vasculitic IBrainD

## Childhood primary CNS vasculitis

CNS vasculitis is also known as primary angiitis of the CNS (PACNS). In our tertiary centre, childhood PACNS (cPACNS) is the most common cause for severe, acquired neurological deficits in previously healthy children. In 1959 Cravioto and Feigin [7] described this disease as non-infectious granulomatous angiitis with a predilection for the nervous system. In 1988 Calabrese [8] proposed criteria for PACNS in adults, including (i) a newly acquired otherwise unexplained neurological symptom, (ii) angiographic and/or histopathological features of CNS angiitis and (iii) no systemic associated disease. These criteria were slightly modified for the paediatric population, adding a newly diagnosed neurological and/or psychiatric symptom and the age limit of 18 years [9]. The current classification for cPACNS is based on affected cerebral

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vessel size and disease course. Three subtypes are currently recognized: (i) non-progressive (NP) medium-large vessel cPACNS (angiography positive), (ii) progressive (P) medium-large vessel cPACNS (angiography positive) and (iii) SV cPACNS (angiography negative, biopsy positive) [9, 10]. The three subtypes are associated with distinct presenting symptoms, pathogenesis, disease course and treatment outcome. Demographic characteristics, clinical presentation and brain histopathology differ between adults and children [5]. In cPACNS a distinct difference is seen between angiography-positive and angiography-negative disease. Different from adults, where major diagnostic confounders such as arteriosclerosis are frequently present, the diagnosis of childhood large-vessel CNS vasculitis is based on characteristic angiographic features and does not require a confirmatory brain biopsy. Reversible vasoconstriction syndrome (RVCS) is rarely seen in children, but is one of the major mimics in the adult population. MRI with vessel wall enhancement has been shown to be able to differentiate between RVCS and CNS vasculitis in adults. Reports of vessel wall enhancement in cPACNS are confirmative of this finding; however, a control group such as RVCS is not available, due to its rarity. In contrast, suspected SV vasculitis in children warrants an elective, confirmatory brain biopsy.

#### NP angiography-positive large-vessel vasculitis

NP angiography-positive large-vessel vasculitis (NP-cPACNS) is a monophasic inflammatory disease causing childhood arterial stroke [9]. Transient cerebral arteriopathy (TCA) and post-varicella angiopathy (PVA) are also terms used to describe a monophasic condition characterized by unilateral arteriopathy with stenosis of the most typically the distal internal carotid artery or proximal middle cerebral or anterior cerebral vessels [11–13]. When associated with reactivation of varicella zoster viruses from the trigeminal ganglion the term PVA is commonly used to characterize the associated vessel wall inflammation [12]. In a recent classification approach, the unifying, yet descriptive term focal cerebral arteriopathy (FCA) was proposed [14].

Recent studies support an inflammatory aetiology of the vascular stenoses in TCA and PVA, suggesting that these vasculopathies may represent the same disease as NP-cPACNS [15, 16]. Children with NP-cPACNS usually present with an unilateral stroke, both clinically and radiologically. CSF analysis and serum inflammatory markers are commonly normal [9, 13]. MRI typically shows unilateral, proximal and anterior circulation vascular changes with corresponding multifocal parenchymal lesions. MR or conventional angiography show stenotic changes in the affected cerebral vessels [17, 18]. The role of vessel wall contrast enhancement as a sign of vascular inflammation remains controversial. Sensitivity and specificity have not yet been established [19, 20]. Recent studies in adults suggest that vessel wall contrast enhancement can differentiate PACNS from non-inflammatory RVCS [21].

#### Progressive angiography-positive large-vessel vasculitis

In contrast to NP-cPACNS, children with progressive CNS vasculitis commonly have focal and diffuse deficits on presentation. They also present with unilateral stroke with hemiparesis or hemisensory loss, however, diffuse symptoms such as headaches, behavioural changes, seizures and cognitive dysfunction may precede the stroke symptoms within days to weeks [9]. CSF analysis frequently shows mild pleocytosis, increased protein levels and increased opening pressure. Inflammatory markers may be within normal limits or slightly increased. Depending on the calibre of the cerebral vessels involved, both inflammatory and ischaemic lesions can be seen on MRI [17]. The hallmark of progressive angiography-positive large-vessel vasculitis (P-cPACNS) is evidence of cerebral vessel abnormality affecting proximal and distal segments on initial angiography with evidence of neuroradiological progression at 3 months when left untreated [9]. Both NP- and P-cPACNS show a male predominance, in accordance with the findings in the stroke literature, where more boys are affected than girls [22].

The pathogenesis of both large-vessel CNS vasculitis subtypes remains uncertain, but recent studies have shown novel inflammatory biomarkers in the CSF of children with large-vessel involvement [15, 16]. In children, the diagnosis is a purely based on angiography and biopsies are not indicated. Research on biomarkers in large-vessel disease is ongoing and will hopefully lend support to the inflammatory nature of cerebral large vessel involvement and to commercially available tests to identify patients at higher risk for progressive disease and the need for more aggressive treatment.

#### Angiography-negative, brain biopsy-positive SV vasculitis

This subtype of cPACNS shows a female predominance [10]. Symptoms of angiography-negative, brain biopsy-positive SV vasculitis (SV-cPACNS) differ from the angiography-positive subtypes and the most common symptoms include seizures and constitutional symptoms [6, 10]. In SV-cPACNS, inflammatory markers such as ESR and CRP are mildly to moderately increased [6]. The von Willebrand factor antigen has been suggested as a clinical marker of disease activity in cPACNS [23]. CSF analysis is an important diagnostic modality in SV-cPACNS and frequently shows an increased opening pressure, increased protein level, pleocytosis and, in 20% of patients, positive oligoclonal bands [6, 10]. MRI studies are abnormal in the majority of children, demonstrating white and/or grey matter involvement not restricted to a particular vascular territory (see Fig. 1A and B) [10]. Leptomeningeal gadolinium enhancement is present in one-third of patients and is important for differentiating SV-cPACNS from demyelinating diseases [10, 17]. A normal MRI does not rule out the diagnosis of SV-cPACNS, as a very small group of children have repeatedly normal MRIs [24]. Clinical, neuroimaging and

**Fig. 1** Neuroimaging and brain histology of a 5-year-old child with angiography-negative SV primary CNS vasculitis (SV-cPACNS)



T2/Flair-positive MRI lesions of (A) the brainstem and cerebellum and (B) bilateral periventricular and subcortical white matter. (C) Lesional brain biopsy demonstrates intramural lymphocytic infiltrates (haematoxylin and eosin stain, magnification  $\times 400$ ).

laboratory tests lack specificity, therefore a brain biopsy is necessary to confirm the diagnosis.

The utility of brain biopsy in PACNS has been controversial due to low yield in a study in adults [25]. In a large paediatric study evaluating elective brain biopsies in children with progressive neurological decline, diagnostic yields of 48.5% and 68.8% in the last 8 years were reported [26]. The most commonly made diagnosis was CNS vasculitis. The yield of brain biopsy is dependent on a variety of factors. The quality of the brain biopsy is very important; preferably all three layers are present [26]. For instance, if only the leptomeninges are biopsied, the diagnostic yield will decrease to  $\sim 20\%$  [24]. Although lesional biopsies are preferred, the diagnostic yields from non-lesional biopsies are comparable to lesional biopsies in our centre. The information on inflammation from a brain biopsy is influenced by treatment before and at the time of biopsy. If immunosuppressive treatment has been initiated  $>7$  days before the biopsy is performed, the intramural inflammation might have resolved, leaving an inconclusive biopsy to review. To date, brain biopsies are crucial not only to confirm the diagnosis, but to exclude other mimics, and inherently belong in the diagnostic algorithm.

The aetiology of SV-cPACNS remains unclear. In contrast, certain distinct pathological hallmarks of SV-cPACNS have been described [24, 27]. The infiltrate is located perivascularly and can extend through the vessel wall, without signs of granulomas, necrosis or  $\beta$ -amyloid depositions (see Fig. 1C). An intramural distribution of inflammation and reactive endothelial changes are considered histological hallmarks of CNS vasculitis [24, 25]. The absence of significant parenchymal inflammation is crucial. Associated findings include reaction of glial cells and perivascular demyelination. An exclusive lymphocytic infiltrate has been reported in cPACNS

[24]. In adult PACNS, three distinct histological phenotypes are recognized: predominantly granulomatous, lymphocytic and necrotizing [28]. The granulomatous pattern with multinucleated giant cells is the most frequent, followed by lymphocytic and necrotizing inflammation. The lymphocytic pattern resembles the childhood lymphocytic infiltrate. In adults,  $\beta$ -amyloid deposits can accompany inflammation, but only in a minority of patients ( $\sim 10\%$ ) [29].

### Demyelinating IBrainDs

The term demyelinating diseases encompasses a broad spectrum of disease entities characterized by presumed primary demyelination. The most common demyelinating diseases in childhood are acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS).

#### Acute disseminated encephalomyelitis

ADEM is a monophasic, acute, immune-mediated demyelinating disorder. A correlation with a recent vaccination or viral infection as a trigger in otherwise healthy children has been suggested [30–34].

Clinical manifestations, laboratory results and neuroimaging can resemble MS [33]. ADEM usually presents with multiple symptoms, including prodromal constitutional features, which can occur shortly before neurological deterioration begins. The clinical neurological course is progressive over hours and lasts from weeks to months. The most common neurological abnormalities include ataxia, cranial nerve palsy, hemiparesis, seizures and impaired consciousness [30, 33, 34]. Laboratory analysis reveals slightly elevated blood inflammatory markers, moderately elevated CSF cell counts and protein. Oligoclonal bands are usually absent compared with MS [32, 33, 35]. MRI scans typically show large, widespread



and asymmetric lesions, predominantly in the subcortical and central white matter. Deep grey nuclei can be affected. In contrast, children with MS have a higher rate of periventricular lesions [32]. A lack of dissemination in time and complete or partial resolution in neuroimaging differentiates ADEM from MS [33, 34].

The pathological hallmark of ADEM is presumed primary demyelination. Histology reveals cuffs of tightly arranged lymphocytes mixed with phagocytes between necked axons and around venous vessels [36]. CD3<sup>+</sup> and CD8<sup>+</sup> T cells are present perivascularly (venular) and parenchymally [36, 37]. Foamy macrophages contain degraded myelin debris and lipid droplets [30, 33, 36–38]. There are no features of necrosis present [36].

### Multiple sclerosis

MS is a chronic demyelinating disease of the CNS. The typical MS course is relapsing and remitting. Fewer than 1% of MS patients present before the age of 10 years [39, 40]. In childhood, the onset of MS symptoms is commonly around the age of 12–14 years. Childhood-onset MS is characterized by isolated long tract dysfunction, optic neuritis and brain stem dysfunction. Diffuse deficits and constitutional symptoms such as abnormalities in the level of consciousness, seizures, fever and nausea are more commonly seen in childhood MS [39, 41, 42]. In paediatric MS, laboratory analysis reveals increased inflammatory markers (ESR and CRP) during the acute phase of MS, with normalization between attacks. CSF analysis may reveal mild increased protein, pleocytosis and positive oligoclonal bands [33, 40, 43].

Neuroimaging is the key modality in the diagnostic evaluation. The McDonald criteria are utilized to confirm the diagnosis of childhood and adult MS. MRI T2-weighted imaging frequently detects hyperintense lesions, predominantly in the parietal and frontal subcortical

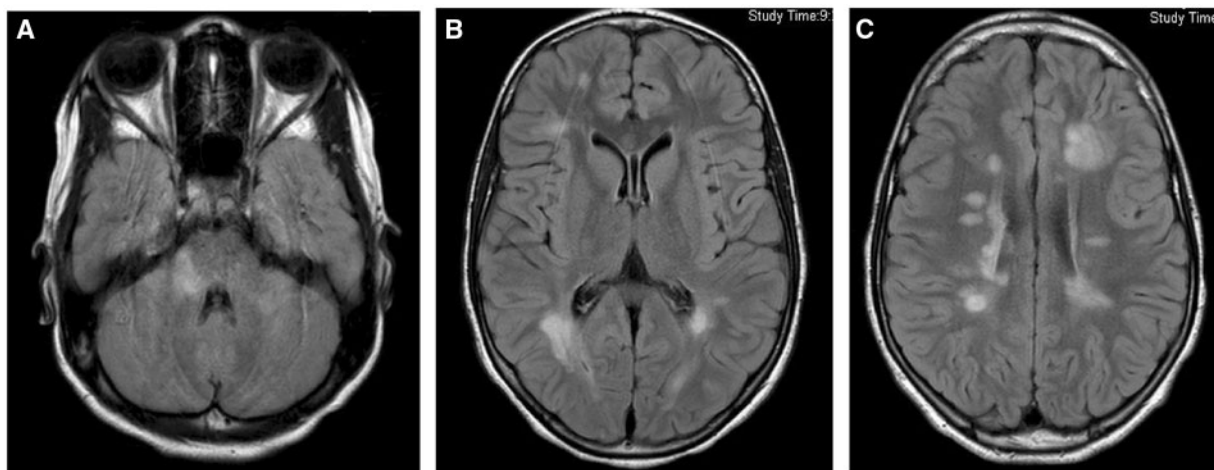
white matter, periventricular white matter, optic nerves, brain stem and cervical spinal cord (see Fig. 2) [33]. Unfortunately these MRI features lack specificity and can be present in other IBrainDs, such as SV CNS vasculitis [44]. Due to overlapping clinical, laboratory and neuroimaging features, it is frequently difficult to differentiate MS from other IBrainDs without a brain biopsy.

The pathogenesis of MS remains unclear. Elective brain biopsies are rarely performed. Histology knowledge is mostly based on autopsy findings. MS is considered to be a white matter disease, however, involvement of grey matter (cortical demyelination) has been described [45]. Specific histology findings are lipid-laden macrophages and variable T cell inflammation [46–48]. T lymphocytes are located perivascularly (venular) and intraparenchymally. Significant axonal injury is not restricted to the demyelinated lesions but can also be present in adjacent normal-appearing periplaque white matter [48, 49]. Signs of remyelination can be present.

### Antibody-mediated IBrainDs

Antibody-mediated encephalopathies encompass a wide spectrum of newly recognized diseases. Neuronal antibody-mediated encephalopathies often present with neuropsychiatric syndromes. In the past, neuronal antibodies were commonly identified as a part of paraneoplastic syndrome in adults. In contrast, in children, an association with malignancies is rare; children present with primary neuronal antibody-mediated IBrainDs [50]. Antibodies can target extra- or intracellular epitopes or soluble antigens. Antibodies against *N*-methyl-D-aspartate receptor (NMDAR), voltage-gated potassium channel-complex proteins, glutamic acid decarboxylase acid, gamma-aminobutyric acid (GABA) B and other neuronal antibodies are increasingly recognized and diagnosed and new antibodies are being discovered [50]. Neuromyelitis optica

**Fig. 2** Neuroimaging in a 12-year-old child with MS at diagnosis



T2/FLAIR-positive MRI lesions of (A) the brainstem and cerebellum and bilateral periventricular (B) deep and (C) subcortical white matter.

(NMO) is caused by aquaporin-4 antibodies and is restricted to the brain and spinal cord. Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection and Hashimoto encephalitis are also thought to be antibody-mediated IBrainDs.

Anti-NMDAR encephalitis is an increasingly recognized antibody-mediated disease and has a very distinct clinical disease course [51–53]. Children develop behavioural changes, memory loss, psychosis, orofacial dyskinesia, movement disorders, seizures, alteration of speech leading to mutism and autonomic dysfunction and hypoventilation if not treated [52, 53].

The diagnosis of antibody-mediated encephalopathies is made by testing for specific antibodies in CSF and/or serum. CSF analysis is more sensitive than serum [52]. Clinical course and improvement correlates with antibody titres in serum and CSF [53]. Associated CSF findings are increased protein, pleocytosis and positive oligoclonal bands. MRI is frequently normal [51]. The pathogenesis is characterized by internalization of the NMDAR with no distinct histology changes, minimal inflammation, no clear features of neuroaxonal injury and no complement activation [51, 54].

### Neuromyelitis optica

NMO is an aggressive inflammatory antibody-mediated disorder targeting aquaporin-4 protein (IgG NMO antibodies) with a predilection for the optic nerves and longitudinal extensive spinal cord lesions [55–57]. Typically the course of the disease is relapsing, with a high likelihood of visual loss [58]. The typical first manifestation in previously healthy patients includes visual impairment caused by optic neuritis and transverse myelitis sequentially or simultaneously [58]. In the paediatric population, NMO can present with diverse clinical features such as encephalopathy, hiccup, vomiting or seizures [55]. CSF analysis usually shows increased cell counts and protein levels.

Oligoclonal bands are frequently negative [58]. Aquaporin-4 is the most common water channel in the brain, occurring in high concentration in the hypothalamus and fourth ventricle [59]. Neuroimaging of NMO can be specific, with inflammatory lesions in a prominent perivascular distribution (see Fig. 3), but may overlap with MS. NMO was first thought to be a disease in the spectrum of demyelinating diseases, until antibodies against aquaporin-4 were discovered [57, 59]. Atrophy and cavitations can be seen in the late stage of NMO [56].

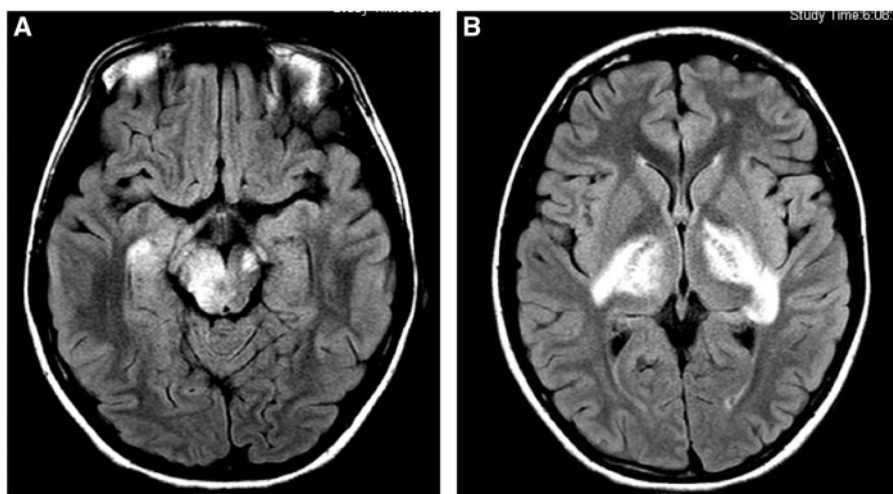
The pathogenesis of NMO is based on acute perivascular inflammation of predominantly neutrophils, eosinophils and extensive macrophage infiltration, with immunoglobulin (mainly IgM) and complement C9neo antigen deposition, a marker for the activated lytic complement complex [60]. Vascular fibrosis and hyalinization without any signs of fibrinoid necrosis of the vessel wall are present [60]. Secondary demyelination may occur [57].

### T cell-mediated parenchymal IBrainDs

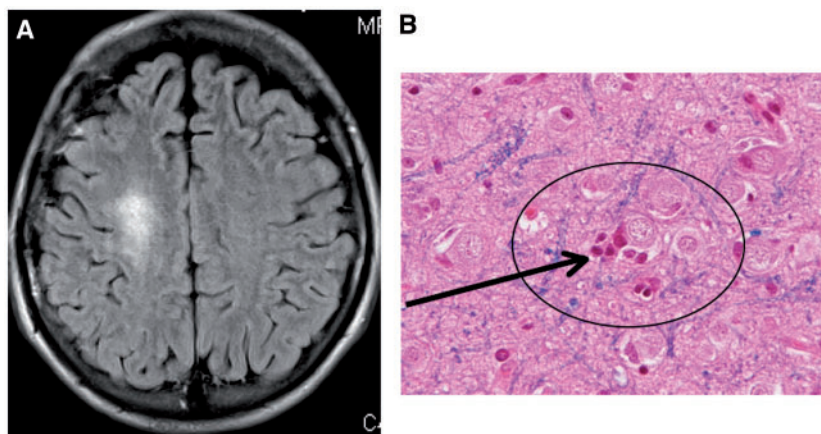
Rasmussen's encephalitis is a T cell-mediated parenchymal IBrainD mainly presenting in childhood as a rare, devastating epileptic disorder [61, 62]. Rasmussen *et al.* [63] first described this condition as a chronic localized encephalitis accompanied by focal seizures.

Two distinct patterns relative to age are distinguished: childhood onset with more severe and rapid progression and atrophy of brain parenchyma, and adolescent or adult onset with a protracted prodromal phase and milder consequences [64]. Onset is characterized by focal intractable epilepsy: *epilepsia partialis continua*. Three stages in the disease course are recognized, with an increasing severity of hemiparesis and stabilization of seizure activity [64]. Typically only one brain hemisphere is involved (see Fig. 4A). Inflammatory markers are usually not present. CSF analysis inconsistently shows oligoclonal bands, protein levels and pleocytosis [65].

**Fig. 3** Neuroimaging of a 16-year-old teenager with neuromyelitis optica



T2/FLAIR-positive MRI lesions of (A) the brainstem and (B) bilateral basal ganglia.

**Fig. 4** Neuroimaging and brain histology of a 17-year-old teenager with Rasmussen's encephalitis

**(A)** T2/FLAIR-positive MRI lesion in the right hemisphere including the cortex (not shown). **(B)** Lesional brain biopsy specimen demonstrates parenchymal lymphocytic infiltrates targeting neurons with evidence of neuronophagia (haematoxylin and eosin stain, magnification  $\times 400$ ).

Chronological MRI may capture the different stages corresponding with the clinical course of Rasmussen encephalitis. Onset imaging is characterized by cortical swelling and hyperintense T2 signal, followed by ostensible MRI normalization and initiation of brain volume loss and finally progressive atrophy [66, 67].

The aetiology of Rasmussen encephalitis remains unknown, but histology is characterized by the presence of a predominantly T lymphocytic infiltrate in the parenchyma and around neurons with microglia nodular activation, and a perivascular B lymphocytic infiltrate (see Fig. 4B). Bien *et al.* [68] showed the role of cytotoxic CD8<sup>+</sup> lymphocytes, which contain granzyme B in a polar orientation against neurons. Neuronophagia is a classic indication of neuronal destruction [69]. The differential diagnosis of T lymphocytic infiltrates and microglial nodules includes viral encephalitis, paraneoplastic encephalitis and non-paraneoplastic limbic encephalitis [70–72].

### Granulomatous IBrainDs

Sarcoidosis is characterized by the presence of granulomas. The onset of sarcoidosis is most commonly in the fourth decade of life and is seen more often in African Americans [73, 74]. Childhood-onset sarcoidosis is rare and can occur as a part of systemic sarcoidosis or as a solitary presentation regardless of age of onset [75–77]. If present as part of systemic sarcoidosis, neurosarcoidosis usually develops within the first 2 years of the disease [74, 78, 79]. Up to 17% of neurosarcoidosis has been reported as isolated neurosarcoidosis [80, 81].

Sarcoid granulomas can occur in any tissue, but the respiratory and lymphatic systems are typically affected. In childhood, seizures, hypothalamic dysfunction as diabetes insipidus, lack of growth or sexual development and mental problems are the most frequent neurological disease features [73, 74, 77, 82]. CSF findings are non-specific, with mild elevated protein and pleocytosis. Oligoclonal bands,

hypoglycorachia and increased levels of angiotensin-converting enzyme can be present, but are often negative. MRI findings can be mistaken for a tumour or demyelinating disease. Solitary or multiple enhanced intraparenchymal masses, often periventricular, are present (see Fig. 5). Leptomeningeal enhancement and hydrocephalus can be present on MRI [83–85].

Histology is characterized by non-caseating granulomas and lymphocyte cuffs around vessels [81]. CD4<sup>+</sup> lymphocytes predominate in inflammatory infiltrates more than CD8<sup>+</sup> lymphocytes [86]. Inflammation might be localized or widespread and can occur anywhere in the brain, from the meninges to the deeper periventricular locations, and is frequently situated perivascularly [78].

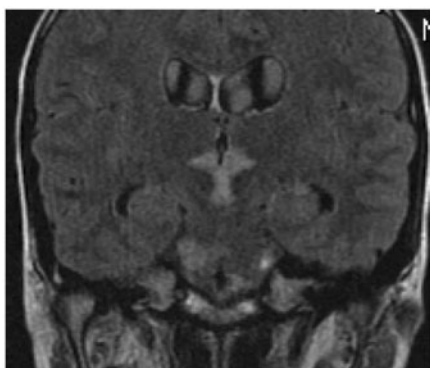
### Treatment of IBrainDs

The treatment of IBrainDs aims to rapidly control the inflammatory response. After stabilization, the choice of the immunosuppressive treatment is directed by the inflammatory pathways involved in the primary disease process, as far as it is known at that moment. Most IBrainDs are T cell driven, thus T cell-targeted treatment is indicated. B cell-targeted therapy is used in autoantibody-/antibody-driven diseases.

The treatment concept for primary CNS vasculitis is different for the different disease subtypes. NP-cPACNS is a monophasic cerebral vasculitis. It requires a limited course of corticosteroids aimed at halting the progression of vessel wall inflammation, improving vascular stenosis, reducing the risk of secondary clot formation and thus recurrent ischaemic events in the affected vascular territory and potentially improving vascular remodelling. Typically children receive 3 months of oral prednisone (2 mg/kg, maximum 60 mg/day  $\times$  1 month, then 1.5 mg/kg/day  $\times$  1 month and finally 1 mg/kg/day  $\times$  1 month, often with initial pulse i.v. methylprednisolone) in addition to antithrombotic therapy, calcium, vitamin D and acyclovir (10–14 days) in varicella zoster virus-positive disease.



**Fig. 5** Neuroimaging of a 15-year-old teenager with granulomatous IBrainD (neurosarcoid)



T2/FLAIR-positive MRI lesions of the brainstem with basal enhancing nodules (arrow).

In contrast, children with both progressive angiography-positive cPACNS and SV-cPACNS are commonly treated with long-term combination immunosuppression. An induction-maintenance regime is frequently used: induction therapy consists of seven pulses of monthly i.v. CYC plus high-dose oral corticosteroids tapered monthly in addition to antiplatelet therapy, calcium, vitamin D and pneumocystis prophylaxis. Maintenance treatment is commonly given for 18 months in both subtypes. Daily oral MMF is the first-choice maintenance drug for SV-cPACNS, while both MMF and AZA have been used successfully for P-cPACNS. During maintenance therapy, children are slowly tapered off prednisone while being kept on antiplatelet therapy, calcium and vitamin D.

Corticosteroids are a first-line, cost-effective treatment for many of the IBrainDs. Typically, initially pulse treatment is started for acute severe CNS inflammation with a dose of 30 mg/kg/day (maximum 1000 mg) given once daily i.v. for a duration of 3–5 days [6, 87]. Subsequently children are commonly switched to prednisone at a dose of 1–2 mg/kg/day either i.v. or orally. The tapering regimen depends on the exact underlying disease and its severity. Administration of corticosteroids is complicated by many side-effects besides suppression of the endogenous cortisol production. Side-effects include hypertension, impaired glucose tolerance, bradycardia, gastrointestinal upset, increased irritability, sleep disturbance, psychosis, weight gain, osteopenia, bone fragility, avascular necrosis and cataract.

IVIg is frequently used as an immunosuppressive treatment, specifically in antibody-mediated IBrainDs. IVIg has been shown to be efficacious in several autoimmune disorders of the central and peripheral nervous systems [88]. IVIg can be used in the acute phase of the disease, but also as a part of long-term treatment. The typical acute treatment dose is 2 g/kg/day (maximum 70 g) either as a single dose or divided over 2–5 days.

#### B cell-targeted treatment

Rituximab is at this time the only B cell-targeted treatment available. Long-term immunological memory is commonly maintained. The typical dose is either 375 mg/m<sup>2</sup> weekly

for four consecutive weeks or 500 mg/m<sup>2</sup> weekly for 2 weeks [87]. The most common side-effects are infusion reactions, including flushing, hypotension, rigor, headaches, pruritus, fever and fatigue. Rare cases of multifocal leukoencephalopathy have been reported in adults.

Plasma exchange or plasmapheresis has been used in life- or organ-threatening inflammatory diseases, especially when an autoantibody disease is suspected [89, 90]. This treatment requires specific expertise, as many electrolytes, soluble factors, coagulation and complement proteins and cytokines are trafficking during this treatment. A typical treatment course is 5–10 cycles over 5–14 days.

#### T cell-targeted treatment

The most frequently used T lymphocyte-targeted treatment for severe IBrainDs is CYC. It has been shown to be highly effective in CNS vasculitis and refractory demyelinating IBrainDs [6]. The dose is 500–750 mg/m<sup>2</sup> for seven monthly i.v. pulses. Mesna and hyperhydration are mandatory to prevent side effects. CYC is used for induction treatment, after which maintenance treatment is started. AZA interferes with lymphocyte activation and is used with a starting dose of 1 mg/kg/day and a target dose of 2–3 mg/kg/day. MMF reduces B and T lymphocyte proliferation and has been shown to be more efficacious for SV-cPACNS for maintenance than AZA [6]. The dose is titrated up to 800–1200 mg/m<sup>2</sup>/day, with a maximum of 2000 mg.

#### Other biologic treatments

TNF- $\alpha$ -blocking agents such as infliximab have been successfully used in refractory SV-cPACNS [93]. Orencia (CTLA-4 fusion protein of IgG4) has been anecdotally used in SV-cPACNS. Supportive and/or symptomatic therapy can include anti-seizure medication, anti-psychotic medication, calcium and vitamin D, among others, and should be considered in all children with IBrainD.

### Summary

In children, IBrainDs are increasingly being recognized. Clinical, neuroimaging and laboratory features are overlapping and an exact diagnosis can be significantly delayed. Novel antibodies have been discovered and should be included in the diagnostic evaluation. Specific neuroradiological tests such as conventional angiography or vessel wall enhancement can assist in supporting the diagnosis. Brain biopsy should be considered in children with IBrainD with unclear pathology. Treatment should be tailored to the underlying pathogenesis.

#### Rheumatology key messages

- Childhood inflammatory brain diseases (IBrainDs) are a leading cause for new-onset devastating neurological deficits in children.
- IBrainDs are some of the most rapidly expanding disorders in childhood.
- Further determination of involved cell types could lead to tailored treatment for childhood IBrainDs.

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