Childhood CNS inflammatory demyelinating diseases

Michael Absoud

Evangeline Wassmer

Abstract

CNS inflammatory demyelinating diseases are rare disorders in childhood and at first presentation children are diagnosed with acute disseminated encephalomyelitis (ADEM), clinically isolated syndrome (CIS) such as transverse myelitis, or Neuromyelitis Optica. These diseases may culminate in physical and cognitive disability or ultimately be diagnosed as Multiple Sclerosis (MS). MS is a chronic inflammatory neurodegenerative demyelinating disease of the CNS that is usually relapsing remitting at onset. There has been significant recent interest and progress in these disorders culminating in the creation of consensus definitions by the International Paediatric Multiple Sclerosis Study Group (2007). Encephalopathy (behavioural change or altered consciousness) distinguishes ADEM from other demyelinating conditions. A high index of suspicion for CNS inflammatory demyelinating diseases is required in children presenting with neurological deficits, encephalopathy, and first onset status epilepticus. Several UK and international studies are underway to further our understanding of these diseases. In this review we describe current understanding of the epidemiology, pathogenesis, clinical features, outcome and management of childhood CNS inflammatory demyelinating diseases.

Keywords Acute disseminated encephalomyelitis (ADEM); clinically isolated CNS demyelinating syndrome; Multiple Sclerosis; Neuromyelitis Optica; optic neuritis; transverse myelitis

Definitions

The available literature on paediatric CNS inflammatory demyelinating disease (CIDD) and Multiple Sclerosis (MS), is primarily limited to smaller case series and larger retrospective reviews of established adult MS populations. The International Paediatric MS Study Group, have recently published consensus definitions (Table 1) of paediatric CNS inflammatory demyelinating disorders and MS to help facilitate uniformity in clinical practice and future research.

- The first acute demyelinating event can manifest with signs and symptoms caused by a single lesion (monofocal) or with polyfocal features, implicating multiple lesions.
- Encephalopathy (behavioural change or altered consciousness) distinguishes ADEM from CIS.
- CNS inflammatory demyelination may have a monophasic (Table 1) or relapsing course (Table 2).

Abbreviations: ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CIDD, CNS inflammatory demyelinating disease; CSF, cerebrospinal fluid; EDSS, expanded disability status scale; IPMSSG, International Paediatric Multiple Sclerosis Study Group; MRI, magnetic resonance imaging; MS, Multiple Sclerosis; ON, optic neuritis; TM, transverse myelitis.

Michael Absoud *MRCPCH Clinical Research Fellow at the Institute of Child Health, Birmingham Children's Hospital, Birmingham B4 6NH, UK. Conflict of interest: funded by the MS Society and Action Medical Research to carry out the UCID-SS and PUDDLS studies.*

Evangeline Wassmer *MRCPCH Consultant Paediatric Neurologist, Birmingham Children's Hospital, Birmingham B4 6NH, UK. Conflict of interest: funded by the MS Society and Action Medical Research to carry out the UCID-SS and PUDDLS studies.*

Epidemiology

- The incidence of childhood CIDD is unknown. A recent Canadian study reported an incidence of 0.9 per 100,000 children/year of CIDD with 22% classified as ADEM and 78% classified as CIS (23% optic neuritis, 22% transverse myelitis). However, the incidence of these disorders is likely to be geographically different and further studies are underway to determine this.
- Mean age of presentation of ADEM is 5–8 years, and the sex ratio is balanced.
- NMO is rare and comprises less than 5% of CNS inflammatory demyelination diseases.
- Approximately 3–10% of all patients with MS have had onset in childhood (female:male ratio 2:1).

Various new trends in adult MS have been reported, which include geographic rising rate of MS, and a rising female to male sex ratio by year of birth. There is evidence that Indian and Pakistani immigrants who entered England younger than 15 had a higher risk of developing MS than those that entered after this age. The vanguard of any change in trends in the epidemiology of MS is likely to be evident in a paediatric population.

Pathogenesis

The cause of CNS inflammatory demyelination (Figure 1) is still unknown, and no biomarker has been established for ADEM or MS diagnosis.

Pathologically, ADEM is characterized by perivenular infiltrates of lymphocytes, macrophages, and occasional plasma cells with oedematous and demyelinated adjacent white matter. Lesions are multifocal or diffuse and may be found in white and grey matter of brain, optic nerves, and spinal cord. Characteristically, and in contrast to MS, all lesions are of the same age, and axonal injury is minimal.

Multiple Sclerosis is a chronic inflammatory demyelinating disease of the CNS characterized by myelin loss, axonal degeneration and, often, progressive neurological dysfunction. Irregular immune activity in the CNS could occur both as a primary component of MS autoimmunity and as a response to tissue injury.

Gene/environment interactions

Genetic and environmental risk factors are likely to be operating in CIDD and MS immunopathology. Adult MS prevalence varies from very low rates in peri-equatorial regions, to over 100 per 100,000 population in temperate regions distant from the equator, hence prompting consideration of limited sunlight and vitamin D insufficiency as potential risk factors for MS. In a large study of MS patients living in temperate countries, significantly fewer were

Monophasic CNS inflammatory demyelinating disease definitions

Condition	Definition
Acute disseminated encephalomyelitis (ADEM)	(1) A polysymptomatic clinical event with acute/subacute onset that must include encephalopathy (behavioural change or altered consciousness). (2) *MRI* brain shows multifocal (usually diffuse bilateral lesions), predominantly involving white matter. New symptoms or signs within 3 months of initial onset of ADEM are considered part of the same event. IF a new event occurs ≥3 months later and ≥1 month after completing steroid treatment, it is defined as: • Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. • Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
Clinically isolated syndrome (CIS)	A first acute-clinical episode of CNS symptoms which may either be monofocal or polyfocal, but does not include encephalopathy (except in brainstem syndromes). The *MRI* will show area of white matter demyelination. These include: *Transverse myelitis*: weakness and/or numbness of both legs ± arms, usually with maximal deficits 1 week after symptom onset supported by demyelination on MRI spine. *Brainstem*, *cerebellar*, and/or *hemispheric* dysfunction, supported by demyelination on MRI.
Optic neuritis (ON)	Acute or subacute loss of vision and ≥1 of: relative afferent pupillary defect (unilateral cases), visual field deficit or scotoma, impaired colour vision, optic disc oedema, or abnormal visual evoked potentials. MRI is not necessary for diagnosis.
Neuromyelitis Optica (NMO)	Must have: i. optic neuritis ii. acute myelitis Must also have: iii. spinal MRI lesion extends over three or more segments *OR* iv. NMO antibody testing is positive. The brain MRI must not meet Multiple Sclerosis diagnosis criteria.

Table 1

born in November and significantly more in May, suggesting that seasonally-related environmental risk factors may be relevant in the perinatal period. Several retrospective case-control studies have shown that greater sun exposure during childhood and adolescence was associated with a reduced risk of adult-onset MS. These features are yet to be shown in childhood CIDDs.

Relapsing CNS inflammatory demyelinating diseases

Recurrent and multiphasic ADEM	IF a new event occurs ≥3 months later and ≥1 month after completing steroid treatment, it is defined as: • Recurrent ADEM: recurrence of initial symptoms without involvement of new clinical areas. • Multiphasic ADEM: New event, but involving new anatomical areas of the CNS.
NMO	Relapse of NMO as described in Table 1.
Multiple Sclerosis (MS)	• Two or more **CIS** episodes separated in time (4 weeks) and space. • New MRI lesions developing ≥3 months after initial event can be used to show dissemination in time. • Adult (McDonald) and other proposed childhood criteria are yet to be validated in children.

Table 2

Clinical features and outcome

The first attack of demyelination is characterized by a constellation of neurological deficits, occasionally accompanied by systemic features, with acute or subacute onset in a previously healthy child. A comprehensive history, system and neurologic examination with particular focus on the following symptoms and signs is recommended (Table 3):

- In one large cohort study of childhood CIDD, long-tract signs (motor, sensory, or sphincter dysfunction) was the most common finding (76%), followed by symptoms localized to the brainstem (41%), optic neuritis (22%), and transverse myelitis (14%). Monofocal presentation was more common in adolescents.
- A high index of suspicion for CIDD is required in children presenting with neurological deficits, encephalopathy, and first onset status epilepticus.

Acute disseminated encephalomyelitis (ADEM)

The recent International definitions (see Table 1) emphasize that encephalopathy must be present for the term 'ADEM' to be used in a child with acute demyelination accompanied by multifocal MRI lesions.

ADEM occurs more commonly in young children less than 10 years of age (equal male: female ratio). ADEM may be preceded by infectious symptoms, although a specific pathogen is rarely implicated. Meningism, fever, and seizures are more seen in ADEM. Outcome after ADEM is favourable with a complete recovery expected in approximately 70% within a few weeks. However, ADEM may result in varying levels of neurodisability (physical, cognitive, neuropsychiatric) or very rarely death.