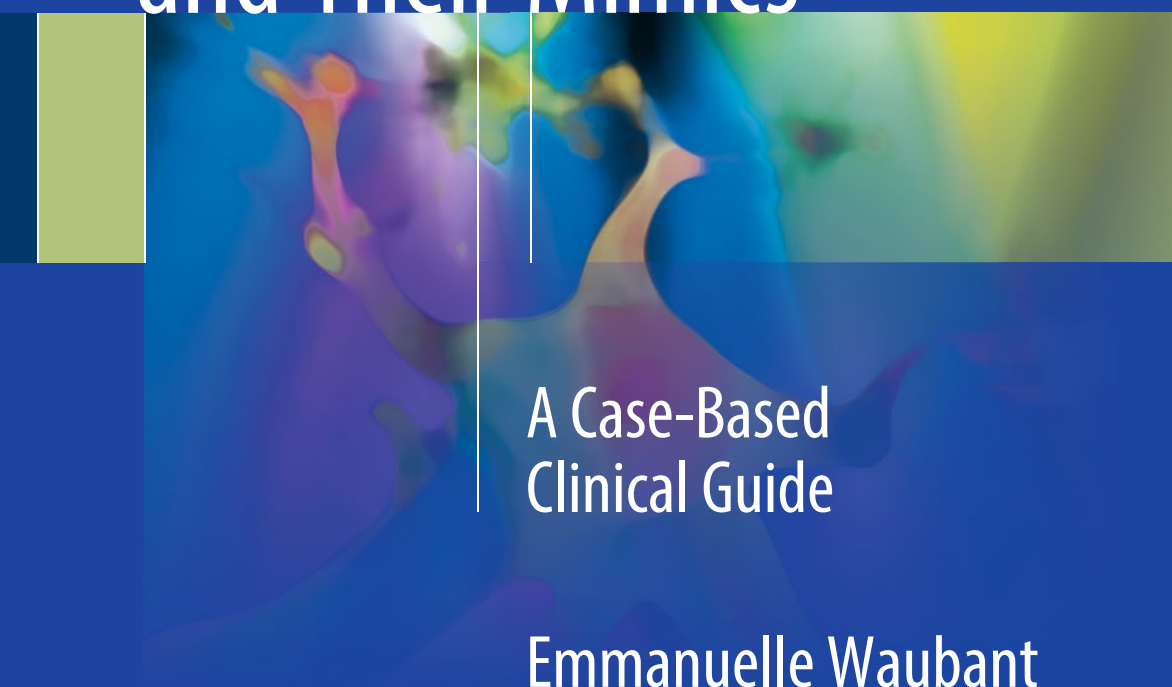
Pediatric Demyelinating Diseases of the Central Nervous System and Their Mimics



A Case-Based Clinical Guide

Emmanuelle Waubant
Timothy E. Lotze
Editors

Springer

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Preface

While multiple sclerosis was once considered to be strictly an adult disease, its occurrence in pediatric populations has been clearly demonstrated over the past two decades. Diagnostic criteria were initially developed in 2007 and subsequently revised in 2013 to aid clinicians in diagnosing the condition and initiating disease-modifying therapy. While many patients present with classic features of multiple sclerosis, clinicians can struggle to reach a diagnosis if they have not encountered a pediatric patient with the disease. In addition, a unique spectrum of diseases affecting the white matter of the central nervous system in pediatric populations to include acute disseminated encephalomyelitis, neuromyelitis optica, inborn errors of metabolism, leukodystrophies, and vasculopathies can further broaden the considered differential diagnosis leading to an expansive and expensive workup that can overwhelm patients, families, and clinicians.

In 2006, the National Multiple Sclerosis Society recognized the inconsistencies in the management of patients with onset of multiple sclerosis under the age of 18 and the need for improved diagnosis and care. As a result, a national pediatric MS Network was created with an initial emphasis on promoting clinical care of patients with the disease and mimics thereof. Rapidly, the network recognized the critical need for more broadly sharing difficult cases so as to improve physician education and care of such patients in light of the limitations in and access to the global knowledge of these diseases.

In 2010, under the auspices of the US Pediatric Multiple Sclerosis Network, a monthly teleconference was initiated to discuss challenging or informative cases and to help clinicians benefit from each other's experience and wisdom, as well as expose more junior physicians to the care of patients with CNS demyelinating disorders. These monthly calls would not exist without the tenacity of Dr. Jayne Ness and "our mother of all," Deborah Hertz, who worked at the National MS Society, who, from the very beginning, has been the strongest advocate for children with MS and related disorders (http://www.usnpmsc.org).

Based upon these teleconferences, this book is the product of a collection of passionate care providers who work tirelessly together to improve diagnosis and treatment of young patients with demyelinating disorders of the central nervous system.

The range of clinical cases presented herein reflects years of observations and sharing, illustrating the challenges in the diagnosis and management of these disorders. We have carefully chosen a series of representative clinical cases ranging from typical multiple sclerosis, neuromyelitis optica, and acute disseminated encephalomyelitis to mimics of these disorders with the hope to fill a major gap in the care of such patients as most of these disorders are reasonably rare and challenging to diagnose and treat. We are deeply indebted to the many authors who have volunteered their time to put these chapters together, often working in teams. We dedicate this book to the improved care of children with rare (but not that infrequent) inflammatory disorders of the central nervous system.

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Part I
Diseases That Affect the Brain

Chapter 1
Acute Disseminated Encephalomyelitis

Gulay Alper

Case Presentation

A 4-year-old boy with no past medical history presented to the emergency room with a 4-day history of progressive weakness and sleepiness. His parents initially noticed drooling followed by weakness and difficulty walking. On the day of admission, he was noted to have asymmetry of the face and left-sided arm and leg weakness. In addition, he had altered mental status alternating between lethargy and aggressive behaviors. There was no history of recent illness, immunization, or trauma. No family history of autoimmune disorders was reported.

Upon admission he was lethargic with intermittent irritability but responded to simple commands. There were no meningeal signs. His cranial nerve examination showed flattening of the nasolabial fold on the left side. There was no afferent pupillary defect. He demonstrated left-sided weakness of the upper and lower extremities with an ipsilateral extensor plantar response. Strength in the right arm and leg was normal. Due to the weakness, the patient had difficulty performing finger-to-nose testing on the left and was unable to walk. No sensory deficits were noted, and there was no truncal or appendicular ataxia.

An initial head CT showed parenchymal hypodensities in the thalamus and some gray and white matter involvement. An MRI brain was then performed and showed extensive T2 hyperintense white matter lesions extending from the subcortical white matter of bilateral peri-rolandic areas to the centrum semiovale. There was a large right hemispheric white matter lesion extending from the internal capsule to the brainstem involving the right cerebral peduncle as well as the ventral portion of the pons and tegmentum (Fig. 1.1). This lesion additionally extended across the splenium of the corpus callosum. There was expansion of the right cerebral peduncle

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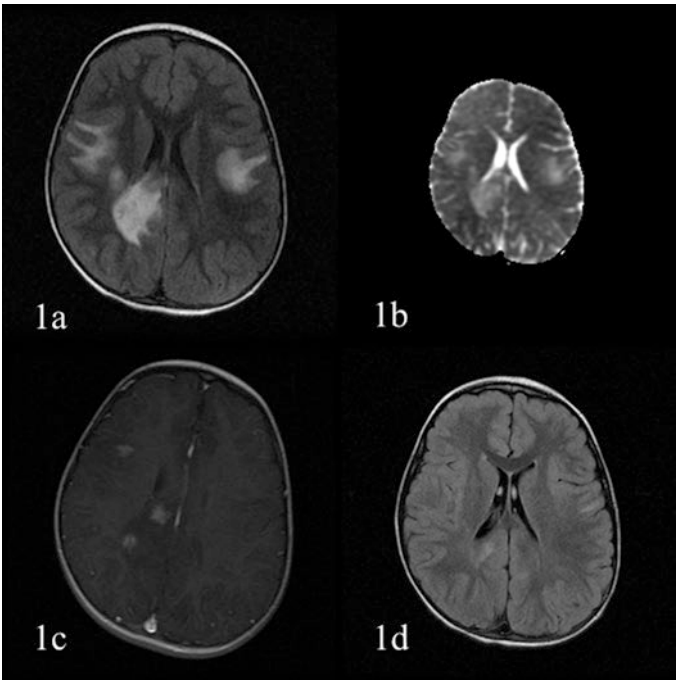

Fig. 1.1 (**a**) Axial T2-weighted FLAIR image reveals extensive white matter signal hyperintensity extending from the subcortical white matter of the peri-rolandic areas to the centrum semiovale, with T2 prolongation also seen across the corpus callosum. (**b**) Diffusion studies show increased diffusivity of the involved areas. (**c**) T1-weighted imaging demonstrates heterogeneous enhancement pattern. (**d**) Follow-up T2-weighted FLAIR image obtained 3 months after onset shows almost-complete resolution of lesions

and the right thalamus with some mass effect seen in the right centrum semiovale. However, there was no midline shift or effacement of the ventricles. There was no diffusion restriction to suggest ischemic injury. MRA of the circle of Willis and neck arteries did not show any evidence for vasculopathy or stenosis. After the administration of gadolinium, there were areas of ill-defined nonhomogeneous enhancement in the lesions affecting the right parietal juxtacortical and periventricular white matter, right cerebral peduncle, and left temporal region. Gadolinium-enhanced MRI of the entire spine was normal. An EEG demonstrated background slowing with no epileptiform discharges.

Cerebrospinal fluid (CSF) examination showed a white cell count of 11/mm^3 (with lymphocyte predominance), protein of 40 mg/dL, glucose of 47 mg/dL, normal IgG index (0.44), and no oligoclonal bands. CSF PCR for herpes simplex virus was negative.

Peripheral white cell count, comprehensive metabolic panel, erythrocyte sedimentation rate, and CRP were normal. Serology was negative for Lyme disease. Serum meningoencephalitis panel was unremarkable. NMO-IgG (aquaporin-4 antibody),

antinuclear antibody, thyroid antibodies, anticardiolipin antibodies, and autoimmune markers for systemic rheumatological disorders were negative. Serum levels of ACE, ferritin, LDH, lactate, and pyruvate were normal.

The patient was diagnosed with acute disseminated encephalomyelitis (ADEM) and was treated with IV methylprednisolone 30 mg/kg/day for 5 days followed by an oral corticosteroid taper over 5 weeks. Through the hospital course, his condition significantly improved. At discharge, 5 days after his presentation, his facial weakness had nearly completely resolved; he had regained the ability to perform fine motor tasks with his left hand, and he was able to ambulate independently without signs of left lower extremity weakness.

Follow-up MRI obtained 3 months later showed significant improvement (Fig. 1.1). The patient has been relapse-free for over 7 years, and serial MRIs obtained during the follow-up did not show any new lesions.

Clinical Questions

1. What are the current diagnostic criteria for ADEM?
2. How does the acuity of symptom development help to distinguish ADEM from other diseases of the central nervous system?
3. What are typical MRI features of ADEM, and how do these distinguish ADEM from other diseases of the central nervous system?
4. How does CSF examination help with the differential diagnosis?
5. What is the treatment for ADEM?
6. Why is it important to obtain serial follow-up MRIs to establish the diagnosis of ADEM?

Diagnostic Discussion

1. ADEM is better considered as a syndrome, rather than a specific disorder, as the presentation is heterogeneous. In 2013, the International Pediatric Multiple Sclerosis Study Group (IPMSSG) published revisions to the initial 2007 diagnostic criteria for various acquired demyelinating diseases of childhood to include ADEM [1]. The diagnostic criteria for ADEM are:

   - A first polyfocal, clinical CNS event with presumed inflammatory demyelinating cause.
   - Encephalopathy (persistent alteration in consciousness or behavior change) that cannot be explained by fever, systemic illness, or postictal symptoms.
   - No new clinical and MRI findings emerge 3 months or more after the onset.
   - Brain MRI is abnormal during the acute (within the first 3 months) phase.
   - Typical findings on brain MRI:

- Diffuse, poorly demarcated, large (>1–2 cm) lesions involving predominantly the cerebral white matter.
- T1 hypointense lesions in the white matter are rare.
- Deep gray matter lesions (e.g., thalamus or basal ganglia) can be present.

Rarely, children with ADEM have an isolated relapse of the syndrome, which occurs beyond the initial 3 months of the first presentation and must again meet the above diagnostic criteria to determine a multiphasic ADEM diagnosis. Further relapses are exceedingly rare and should prompt consideration for an alternate diagnosis.

2. This child presented with acute neurological symptoms, which continued to progress over 4–5 days. Onset was gradual over a period of days rather than abrupt and, therefore, not highly suggestive of acute ischemic stroke. Neoplasms of the central nervous system usually present with a subacute course, meaning that symptoms worsen gradually over a few weeks or months, rather than days. Leukodystrophies more often present over even longer periods with no acute exacerbations. Acute inflammatory demyelination should be considered in any child presenting with acute onset of focal or multifocal neurological findings.

   The time course of a first attack would not necessarily be able to distinguish ADEM from other forms of acquired demyelination, such as MS or NMO. In this regard, the clinical history, examination findings, and ancillary diagnostic studies can better discern between these various conditions. A principal and required diagnostic feature of ADEM is encephalopathy. While encephalopathy is less often encountered in the acute presentation of MS or NMO, pediatric MS patients under the age of 10 years may uncommonly present with an ADEM phenotype as their initial attack. Likewise, the expanding phenotypic spectrum of NMO can present with cerebral and/or brainstem symptoms causing altered mental status and mimicking ADEM. Therefore, initial investigation results of serum antibody studies and CSF as well as long-term follow-up are needed to best assure a final diagnosis of ADEM
3. In a child presenting with focal or multifocal neurological signs and symptoms, imaging studies should be obtained immediately. Magnetic resonance imaging is the best diagnostic tool for acquired demyelinating disorders. Although this patient presented with unilateral weakness, his encephalopathy suggested a more extensive involvement, and brain imaging demonstrated bilateral and multifocal abnormalities (Fig. 1.1a). Symptomatic and asymptomatic lesions are frequently seen on imaging studies in acute demyelination. Symptoms are determined mainly by the location and/or the size of the lesion(s). ADEM predominantly affects white matter tracts of the brain but, in contrast to MS, also commonly involves the deep gray matter of the thalami, and basal ganglia are also frequently involved [2]. The lesions in ADEM typically involve the cortex, juxtacortical, and central white matter as well as the cerebellum, brainstem, and spinal cord [2]. Although the lesions are bilateral, they are characteristically asymmetric. Lesions in ADEM tend to be larger than those seen in multiple