Acute Disseminated Encephalomyelitis followed by Optic Neuritis: A Rare Syndrome of Uncertain Treatment and Prognosis

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Neuropediatrics 2020;51:286–291.

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Abstract

Aim Acute Disseminated Encephalomyelitis followed by optic neuritis (ADEM-ON), first described in 2013, is a rare demyelinating syndrome, typical of the pediatric age. We conducted a mini review of the existing literature, focusing on clinical, laboratory, radiological, therapeutic, and prognostic aspects in order to improve the identification of new cases.

Methods We searched PubMed and Cochrane Library for studies on ADEM-ON between 2013 and 2018.

Results Examination of the reported cases (three case reports and eight observational studies) established the following features. Time between ADEM and ON is highly variable. Almost all patients show antimyelin oligodendrocyte glycoprotein antibody (MOG-abs) seropositivity. High-dose intravenous steroid and plasmapheresis efficacy is reported for the acute phase; oral prednisone and other maintenance drugs may be useful in avoiding relapses. The clinical history may lead to a complete recovery but also to residual deficits.

Conclusion MOG-abs detection strongly supports ADEM-ON diagnosis, confirming this entity as part of MOG-abs spectrum disorder. Owing to the very small number of cases so far reported, predicting clinical evolution is very difficult.

Keywords

- acute disseminated encephalomyelitis
- optic neuritis
- antimyelin oligodendrocyte glycoprotein antibodies
- pediatric demyelinating syndromes

Introduction

Acquired demyelinating syndromes (ADS) are disorders of the central nervous system (CNS) with monophasic, chronic, or relapsing course, and differ from each other in their clinical course, magnetic resonance imaging (MRI) lesions, treatment and outcome. Increasing research and emerging technology have led to the identification of various ADS subtypes.[1] Diagnostic criteria for pediatric ADS were updated by the International Pediatric Multiple Sclerosis Study Group (IPMSSG) in 2013, with revised definitions for Acute Disseminated EncephaloMyelitis (ADEM), clinically isolated syndromes (CIS), neuromyelitis optica (NMO), and multiple sclerosis (MS) in the pediatric age.[1] ADEM is one of the more frequent types of ADS in children, characterized clinically by the acute onset of encephalopathy (alterations in consciousness or behavior that cannot be explained by fever, systemic illness, or postictal symptoms) with polyfocal neurologic deficits (pyramidal signs, ataxia, acute hemiparesis, optic neuritis or other cranial nerve involvement, seizures, spinal cord syndrome, and speech impairment), sometimes preceded by prodromes (fever, malaise, irritability, somnolence, headache, nausea, and vomiting).[1–3] Its course is mainly monophasic, but a small subset of patients will subsequently be diagnosed with relapsing disorders.[1–3] Optic neuritis (ON) is one of the more typical CIS, characterized

received
March 7, 2019
accepted after revision
October 31, 2019
published online
January 14, 2020

DOI https://doi.org/10.1055/s-0039-3402004.
ISSN 0174-304X.

by an inflammation of the optic nerve, with anterior or retrobulbar involvement, presenting acute or subacute visual loss, frequently associated with pain, dyschromatopsia, and central visual field loss.[4] In 2013, a new subgroup of relapsing demyelinating pediatric patients was identified, not falling into any of the existing diagnostic categories. The patients initially presented ADEM and relapsed with one or more episodes of ON.[5] They were all positive for antimyelin oligodendrocyte glycoprotein-antibodies (MOG-abs), a relatively new class of antibodies, strongly associated with some demyelinating relapsing syndromes.[6] This new clinical entity came to be known as ADEM-ON, given its typical clinical course.[5] Following this initial description, the very close association between ADEM-ON and MOG-abs seropositivity has since been confirmed. Moreover, MOG-abs have been more recently detected in pediatric patients with different forms of monophasic or relapsing ADS, all grouped under the umbrella-term "MOG-spectrum disorder" (MOG-SD), including ADEM-ON as a distinct entity within this spectrum.[6–8]

The goal of the current study is to review the literature on ADEM-ON, to analyze the demographic, clinical, laboratory, and radiological aspects of pediatric patients affected by this new subtype of ADS and to understand its clinical course and therapeutic features more completely.

Methods

We examined studies from the first description of ADEM-ON in 2013 till the present using the following keywords: "optic neuritis," "ON," "acute disseminated encephalomyelitis," "ADEM," "ADEM-ON," "pediatric; children," and "MOG-antibodies" for our literature search of the PubMed and Cochrane Library databases. From these studies, we extracted data about ADEM-ON including clinical features and course, laboratory findings (MOG-abs, aquaporin-4 antibodies [AQP4-abs], and cerebrospinal fluid [CSF]), radiological findings, treatment options, clinical evolution, and prognosis.

Results

The literature search identified three case reports[9–11] and eight observational studies,[2,5,12–17] whose main findings are summarized in ►**Table 1**.

ADEM-ON

ADEM-ON is a rare relapsing demyelinating syndrome, almost exclusively affecting the pediatric age, characterized clinically by ADEM or Multiphasic ADEM (MDEM), followed by one or more episodes of ON.[1,8,16] Demographic data (age of onset and gender distribution), collected from the revised study, is reported in ►**Table 1**. The sequence of the events characterizing the syndrome (ADEM followed by ON) seems to depend on the typical distribution of ADS during childhood, with encephalopathic syndromes concerning younger children, and monofocal or multifocal nonencephalopathic events more typically affecting the older ones.[7,18] It has been demonstrated that MOG-abs are common in younger patients with encephalopathy and that MOG-abs syndromes frequently affect the optic nerves.[14] The data in the literature indicates that ADEM-ON represents a common evolution of MOG-abs seropositive patients who initially presented ADEM.[16]

Clinical Features and Course

In ADEM-ON, clinical features of ADEM and ON events are typical for both disorders. The time between ADEM and ON is variable. The first report described it as ranging from 3 weeks to 2 years,[5] but in subsequent descriptions of ADEM-ON, ON relapses were reported from a few months to several years after the onset.[13,16] The number of episodes of ON is not constant; in fact, in the reviewed cases, after ADEM or MDEM, ON events ranged between one and nine.[5,11,13,16,17]

In ADEM-ON diagnosis, clinicians should also consider differential diagnosis with other ADS types such as MS and NMO-SD.[1,19]

Laboratory Findings

- *MOG-abs*:

The majority of reports highlight the very close association between ADEM-ON and MOG-abs seropositivity. Of the 63 ADEM-ON patients reported in this review, 59 were positive for MOG-abs, three were seronegative, while one was not tested,[9,14,16] confirming the widely shared view that ADEM-ON diagnosis is supported by MOG-abs detection.[8]

MOG is a glycoprotein exclusively expressed in the CNS. Its precise function is not known, but it is thought to play a role in myelin sheath structural integrity and maintenance.[18,19] Its location on the outer surface of myelin sheaths makes it available for antibody binding and a potential target for autoantibody mediated diseases.[20,21] MOG-abs, widely studied in recent years, are now considered a marker of demyelination, by transiently disrupting oligodendrocytic microtubule organization.[6,13,19] They are thought to be mainly peripherally synthesized, demonstrating their serum testing to be more sensitive than CSF.[6,20,22] MOG-abs have been described in literature in one-third of all children presenting ADS, with monophasic (i.e., ADEM, transverse myelitis, or ON) or multiphasic course (i.e., AQP4-abs seronegative NMO-SD, MDEM, relapsing ON, or ADEM-ON).[2,5,6,12,16,17,21–24] Seropositivity for MOG-abs generally pleads against a MS disease course, being detected in a small subset of MS patients with low-titer levels.[6,13,20,21,24,25] Very recent studies consider MOG-abs useful for diagnosing ADEM-ON and NMO-SD in AQP4 seronegative patients and chronic relapsing ON.[26] MOG-abs titers decline over the following months in children with a monophasic disease course, but not in multiphasic forms, confirming the reliable association between MOG-abs and pediatric relapsing demyelination.[6,20,24,25] Hence persisting high levels of MOG-abs could be considered as a potential biomarker for the risk of new events in ADEM-ON and MOG-abs syndromes in general.

- *AQP4-abs*:

AQP4-abs are a class of autoantibodies highly specific for NMO-SD diagnosis.[27] ADEM-ON patients who were tested

Table 1 Studies reporting clinical, laboratory, therapeutic and radiological aspects of ADEM-ON

Publication (y)	Number of ADEM-ON patients (M:F ratio)	Age at onset: mean (range of years) [if not otherwise specified]	Time between ADEM and ON	MOG-abs seropositivity (number of patients)	AQP4-abs seropositivity	CSF		Therapy		MRI features	
						OCBs (number of patients)	Pleocytosis (number of patients)	Steroids (number of patients)	Types of other treatments (number of patients)	During ADEM (number of patients)	During ON (number of patients)
Huppke et al (2013)[5]	7 (1:2.4)	5.8 (4–8)	3wk–2 y	Yes (7)	No	No	Yes (6)	Yes (7)	Interferon β, glatiramer acetate (2) Azathioprine (2)	Typical for ADEM (6)	No new T2 lesions
Ryu et al (2014)[9]	1 (0:1)	6	3 wk	NA	NA	NA	NA	Yes	No	NA	NA
Miyauchi et al (2014)[10]	1 (0:1)	5	10 wk	Yes	NA	NA	NA	NA	NA	NA	NA
Baumann et al (2015)[2]	3 (NA)	5.3 (5–6)	2mo–3 y	Yes (3)	No	No (3)	Yes (1)	Yes (3)	Intravenous Ig (1)	Typical for ADEM (3)	NA
Ketelslegers et al (2015)[12]	4 (1:1)	NA	NA	Yes (4)	NA	NA	NA	Na	NA	NA	NA
Fernandez-Carbonell et al (2016)[14]	3 (NA)	NA	NA	Yes (1)	NA	NA	NA	NA	NA	NA	NA
Baumann et al (2016)[13]	2 (0:2)	4 (2–6)	NA	Yes (2)	No	No	Yes (2)	Yes (2)	Intravenous Ig (2) Plasmapheresis (1)	Typical for ADEM (2)	Only the enhancing optic nerve lesion (1)
Ramanathan et al (2018)[15]	4 (NA)	NA	NA	Yes (4)	NA	NA	NA	NA	NA	NA	NA
Wong et al (2018)[16]	17 (1:0.9)	Median (IQR): 6.1 (5,1–9.2)	NA	Yes (16)	No	NA	NA	Yes (12)	Azathioprine, mycophenolate, intravenous Ig, cyclophosphamide (10)	Typical for ADEM (15)	NA
Hacohen et al (2018)[17]	20 (1:1.2)	6.9 (3.9–15)	NA	Yes (20)	No	Yes (1)	Yes (13)	NA	Disease modifying drugs (10)	NA	NA
Nagashima et al (2018)[11]	1 (0:1)	4.7	3–33 mo	Yes	No	No	NA	Yes	Rituximab, azathioprine	Typical for ADEM	Typical for ON

Abbreviations: ADEM, acute disseminated encephalomyelitis; ADEM-ON, acute disseminated encephalomyelitis followed by optic neuritis; AQP4-abs: aquaporin-4 IgG antibodies; CSF, cerebrospinal fluid; F, female; Ig, immunoglobulin; IQR, interquartile range; M, male; MOG-abs, antimyelin oligodendrocyte glycoprotein antibodies; MRI, magnetic resonance imaging; N/A, not available; OCBs, oligoclonal bands.

for AQP4-abs were demonstrated to be seronegative.[2,5,13,16,17]

- *Cerebrospinal fluid*:

Where performed, CSF analysis showed no specific ADEM-ON pattern. In some cases, pleocytosis was observed, typically described during ADEM.[5,13,17] An increase in the number of CSF white blood cells was also observed in a group of MOG-abs seropositive ADS patients compared with seronegative ones.[14] The detection of oligoclonal bands (OCBs), considered as a typical immunopathic pattern during MS, appears only rarely in children with ADEM-ON.[5,13,17]

Radiological Findings

MRI findings are typical for ADEM and ON, in the different stages of the disease.

In ADEM, typical MRI pattern is fluid attenuation inversion recovery (FLAIR) and T2 hyperintense large lesions (>1–2 cm), with poorly defined borders, affecting the white matter of the brain, and spinal cord, with possible deep gray matter involvement, detectable during the acute phase (3 months).[1–3,23] Gadolinium enhancement is reported in less than one third of patients.[1,3]

In ON, the acute inflammatory lesion of the optic nerve is commonly detectable on MRI with gadolinium enhancement or with changing of T2-weighted optic nerve signal.[27,28] A large-scale review, published in 2017, illustrates the state of the art regarding pattern recognition of ON in MS (MS-ON) and in other neuroinflammatory conditions associated with MOG-abs (MOG-ON) or AQP4-abs (AQP4-ON).[19] MOG-ON seems to be longitudinally extended, with anterior predominance, severe swelling, and twisting. AQP4-ON is longitudinally extended, but with posterior predominant involvement, milder swelling, and rare twisting. Both are often bilateral, unlike MS-ON which is more typically unilateral and short-extended.[19]

Among the studies reviewed, only a few reported radiological data. Five studies report ADEM typical lesions in almost all the patients,[2,5,11,13,16] while one report describes unspecified abnormal lesions at onset.[17] Regarding ON relapses, three studies report the absence of new T2 or contrast-enhancing lesions typical for ADEM during subsequent ON attacks, with improvement or complete resolution of the previous lesions.[5,11,16] Two reports describe typical ON MRI lesions affecting the optic nerves.[11,13] In the last two cases, MRI data during ON is missing.[2,17] A notable finding is that only a few studies report a specific lesion of the optic nerve during ON attacks. We suggest some possible reasons for (1) the lack of MRI data specific to ON relapses in several of the reported studies; (2) the need for a specific orbit MRI study (contrast and fat suppressions methods), which is only rarely mentioned in the reported studies, to detect optic nerve lesions. Further data, provided by a routine use of MRI for the orbits in the diagnosis of ON, would provide more information about the radiological features of ON in course of ADEM-ON, which are expected to be similar to those described for MOG-ON, given ADEM-ON's status as a member of the MOG-SD group.

Optical Coherence Tomography

Optical coherence tomography (OCT) is a noninvasive technology creating high-resolution images of biological tissues microstructures, such as the retina and the optic nerve, by using reflection of near-infrared light.[28] It has become increasingly used in case of ON and other optic neuropathies. The most visible retinal layer is the inner one, called retinal nerve fiber layer (RNFL), consisting of unmyelinated axons of the ganglion cells. In acute ON, RNFL thickness may increase with the optic disc swelling. After the acute phase, a thinning of the RNFL and ganglion cell layer (GCL) may occur due to axonal loss correlating with visual dysfunction (visual acuity, visual field, and color vision).[4,28] OCT can easily detect even subtle axonal loss and is useful both in assessing the severity of an episode of ON and predicting possible persistent visual dysfunction.[4,28]

Treatment Options

What we know about ADEM-ON therapy is due to the few cases collected in this review and the emerging knowledge about treatment of MOG-abs syndromes, including ADEM-ON. Since the first descriptions of ADEM-ON, efficacy of high-dose steroids (20–30 mg/kg/die, for 3–5 days) or plasmapheresis during the acute phase was reported.[5,6,9,13,15,18] The main effect of high-dose steroid treatment seems to be hastening the recovery phase.[5] Maintenance oral prednisone has been recommended to reduce early relapses in ADEM-ON and, generally, in MOG-SD.[9,15,17,18] However, patients responsive to steroids showed relapse rate within the first 2 months of steroid cessation with a rapid taper.[15,16] Two studies on ADEM-ON children and MOG-SD pediatric/adult patients report oral prednisone efficacy, in terms of avoiding relapses, if given at a dosage higher than 10 mg/die.[15,16] Other maintenance drugs, such as azathioprine, mycophenolate mofetil, rituximab, and intravenous immunoglobulins (IVIg) have been associated with a reduction in relapse frequency in MOG-SD.[6,15,17,22] Nevertheless, several reports suggest a high propensity of relapse in ADEM-ON under maintenance immunotherapy.[8,16] A very recent case report suggests efficacy of rituximab in preventing ADEM-ON relapses when CD19 count is kept low, with the hypothesis of an insufficient effectiveness of azathioprine in MOG-abs seropositive ADEM-ON.[11] Other findings strongly discourage the use of MS drugs in MOG-SD, because of their inefficacy and, in some cases, dramatic effects (i.e., alemtuzumab).[6,17,22] Some neuroprotective agents (i.e., simvastatin, phenytoin, and eritropoietin) have shown promising results in preclinical and clinical studies by reducing RNFL and GCL thinning, suggesting potential efficacy in preventing residual visual disability due to ON relapses.[29,30] Hence OCT has been shown to be an ideal technology for evaluating neuroprotective agents in clinical trials.

Clinical Evolution and Prognosis

The very small number of ADEM-ON patients makes it difficult to predict the clinical evolution of this syndrome. Despite the need for confirmatory, longitudinal studies, the evidence so far acquired about this relapsing syndrome

suggests no risk of developing chronic neuroinflammatory diseases, such as MS or NMO-SD, in patients diagnosed with ADEM-ON.[5,6,8,16] In addition to cases where the outcome is complete recovery, some residual deficits have been described as possible, declining visual abilities (despite good response to steroids), cognitive impairment (attention, memory, and learning), behavioral problems, seizures, motor dysfunction, weakness, and bladder/bowel dysfunctions.[5,13,16,17]

The close association with MOG-abs seropositivity allows us to consider what literature reports about the clinical outcome in MOG-SD. MOG-abs syndromes outcomes compare favorably with AQP4-abs positive ones, with evidence of less disability at follow-up.[22] Outcomes differ between monophasic and multiphasic MOG-abs syndromes. Monophasic forms are reported as frequently having good clinical recovery, with declining MOG-abs titer and MRI lesions resolution; motor sequelae and seizures are possible but rare.[6] On the other hand, multiphasic conditions are more subject to accumulating functional impairment due to relapses.[6]

Conclusions

ADEM-ON has been described in recent years as a new type of ADS. Our knowledge about this disorder is still limited owing to the small number of patients. Some features have been frequently reported, supporting the need to classify it as a clinical entity distinct from other types of ADS. These include one or more ON events after an initial ADEM or MDEM, MOG-abs seropositivity and AQP4-abs seronegativity, CSF nonspecific pattern with frequent pleocytosis and rare OCBs, no new ADEM-like MRI lesions during ON attacks, good response to intravenous steroids during the acute phase, reliable efficacy of some maintenance drugs in avoiding relapses, and possible residual deficits. MOG-abs detection strongly supports ADEM-ON diagnosis, confirming that this entity is to be classified under MOG-SD.

Author Contributions

M.S. and A.N.P. equally contributed to this study; they conceived and collected the data and M.S. wrote the manuscript. M.F. contributed in the literature review. R.P., A.N.T.P., and M.M. helped in drafting the manuscript. L.M. supervised the research. All the authors reviewed and edited the manuscript.

Funding

No funding.

Competing Interests

The authors declare that they have no conflict of interest.

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