Published in final edited form as:

Curr Infect Dis Rep. 2008 July ; 10(4): 307–314. doi:10.1007/s10072-008-0966-6.

Acute disseminated encephalomyelitis

Enrico Marchioni[✉], Eleonora Tavazzi, Lorenzo Minoli, Serena Del Bue, Pasquale Ferrante, Giovanni Piccolo, Stefano Bastianello, and Sabrina Ravaglia

E. Marchioni, E. Tavazzi, G. Piccolo, S. Bastianello, S. Ravaglia, Neurological Institute-Foundation IRCCS “C. Mondino” Pavia, L. Minoli, Clinic of Infectious Diseases-Foundation IRCCS “Policlinico S. Matteo”, Pavia, S. Del Bue, P. Ferrante, S. Giuseppe Hospital - University of Milano, Milano, Italy

Abstract

Acute disseminated encephalomyelitis (ADEM), which is classified as a demyelinating disease of the central nervous system (CNS), is a condition that may be regarded as a bridge linking neurology and the infectious diseases. According to the classic definition, ADEM is a monophasic disease that can arise spontaneously; in most cases, however, it is triggered by systemic viral infections or, more rarely, by vaccinations. As the most recent publications on this topic have shown, ADEM can present a relapsing course, being described as “recurrent” if the affected districts are always the same, or “multiphasic” if there is a dissemination in space and time of the lesions, together with a more or less marked association with polyradiculoneuritis. The clinical features and history of the disease create difficulties in differential diagnosis both with encephalomyelitis caused by infectious agents and with noninfectious inflammatory diseases (other demyelinating syndromes, vasculitis, nonvasculitic autoimmune encephalopathies). This paper describes the main features of ADEM, focusing in particular on the factors that influence its outcome and can guide the process of differential diagnosis.

Keywords

ADEM; Encephalomyelo-radicoloneuritis; Mini-review

Introduction

ADEM, classified among the monophasic demyelinating diseases of the CNS, is diagnosed only through a careful process of exclusion of other diseases. Onset of ADEM usually occurs following an infection or, more rarely, following a vaccination. Generally speaking, the different forms of ADEM can be classified on the basis of the involved districts and the course of the disease. Applying the first of these criteria, it is possible to identify classic forms, characterized by brain and spinal cord involvement, and “site-restricted” forms, such as pure encephalitis, myelitis, cerebellitis, and optic neuritis. In both cases, there can be involvement of the peripheral nervous system (PNS) [1]. As regards the second criterion, on the other hand, it is possible to distinguish between monophasic, recurrent, and multiphasic forms [2,3]. Authors often disagree over various fundamental aspects of the disease, namely the characteristics and frequency of occurrence of the “relapsing” variants, the criteria for differential diagnosis versus multiple sclerosis (MS), the role of PNS involvement, and the main factors conditioning outcome and response to treatment [2]. These “gray areas” are the focus of this study.

e-mail: enrico.marchioni@mondino.it.

Conflict of Interest statement The Authors declare that they have no conflict of interest related to the publication of this manuscript

Methods

This study was conducted following a manual and computerized literature search, conducted in order to identify important primary studies and quality reviews relating to ADEM. This search identified two prospective studies [1,4] and three reviews of the literature [2,3,5], all published in the period 2001–2007.

The disease course

ADEM usually has a monophasic course, but relapses can occur in between 5% and 25% of cases [1,4]. The wide range of these estimates can be attributed, in part, to the different levels of selectivity of the inclusion criteria used by different authors; indeed, some studies consider only the monophasic variants of the disease. The relapsing forms can be subdivided into two categories: “recurrent” (80%), if the disease recurs at least 2 months after its onset and the lesions affect the same district that was involved in the first episode, and “multiphasic” if the lesions present a dissemination in space and time (20%). In our experience [1] relapses are restricted to the spinal cord in 98% of cases, even when the disease involved the brain during the first episode. Relapses generally occur 6–18 months after the onset, and can be much more severe than the first episode.

Differential diagnosis

ADEM, with its protean clinical manifestations and lack of specific biological markers, raises serious problems of differential diagnosis both with some microbial infections (herpes simplex encephalitis, listeria meningoencephalitis), and with other inflammatory demyelinating and vasculitic diseases. Of all of these, Multiple Sclerosis (MS) is perhaps the condition that most closely resembles ADEM, particularly the multiphasic ADEM variants. Classic ADEM during the acute phase can easily be distinguished from MS by a series of findings, such as the frequent impairment of consciousness, the common occurrence of pleocytosis and blood-brain barrier damage in the CSF, the almost constant absence of oligoclonal bands (OBs) which, even when present (10% of cases), are in any case transitory [6], and the different cytokine-chemokine profile [7]. The multiphasic variants of ADEM are the ones that come closest to the concept of dissemination in space and time typical of MS, in relation to which they nevertheless present a series of differences: a much older mean age at onset (6th decade or after), the absence of OBs in relapses, an almost constant tendency to relapse only in form of myelitis, the disappearance of lesions at Magnetic Resonance Imaging (MR), neurophysiological (50% of cases) and clinical (30% of cases) evidence of PNS involvement [8].

Peripheral nervous system involvement

As regards this aspect of the disease, which is not considered in the classic definition, the estimates of frequency again range widely: from 5% to 43% [2]. The percentage varies, above all, according to the criterion used to define peripheral involvement. In the only study that has systematically investigated PNS involvement using neurophysiological techniques, the frequency of polyradiculoneuritis was reported to be 43%, clinically evident in 26% [1]. PNS involvement is also documented far away from the site of the spinal damage, demonstrating that, probably, central and peripheral myelin are affected at the same time.

Involvement of the PNS seems to be associated with a worse prognosis, both in terms of functional recovery after the first episode and as regards the likelihood of a relapse in the 12 months following it.

Prognostic factors

In our own series we have identified five variants of the disease, based on both clinical characteristics and lesion distribution on MR, at the first episode: pure encephalitis (E, 20%), pure myelitis (M, 23.3%), encephalomyelitis (EM, 13.3%), myeloradiculoneuritis (MRN, 16.7%), and encephalomyeloradiculoneuritis (EMRN, 26.7%). The last two forms are clearly characterized by combined CNS and PNS involvement. A multivariate model suggested that the following factors are associated with an increased risk of relapse: age over 55 years, elevated CSF albumin >100 mg/dl, female sex, spinal cord and PNS involvement. These findings, already published in a series of 60 subjects, were confirmed in a recent update of the cohort.

Response to treatment

The literature contains no controlled trials on treatment in ADEM. The therapeutic approach to the first episode is generally borrowed from the MS. Therefore, patients are administered 6-methylprednisolone (6-MP), a total dose of 6–8 grams over 6–8 days, followed by prednisone per os (tapering doses). Around 30% of the patients in our series were “nonresponders,” and half of these nonresponders benefited from treatment with intravenous immunoglobulin (IVIg). Nearly all of these patients were affected by MRN or EMRN. In patients with conditions predisposing them to relapse, an immunosuppressive treatment with cyclophosphamide (CPM) was started, either during the first episode or when the first relapse occurred. However, the results were largely disappointing.

Conclusions

According to our observations and the literature data, –contrary to the classic definitions that define it as a monophasic disease of the CNS—is a relapsing condition in 5%–25% of cases, and is associated with PNS involvement in 5%–26%. These two conditions seem to be associated. Other factors associated with poor prognosis, both as regards functional outcome and as regards the risk of relapse, are spinal cord involvement, older age, and raised inflammatory markers in the CSF. From a clinical point of view, MRN and EMRN are the subgroups most at risk of relapse. In our experience, the problem of differential diagnosis with MS, which many authors regard as the most difficult to resolve, can be approached effectively through an overall evaluation of the clinical, biological, and MR data available.

References

1. Marchioni E, Ravaglia S, Piccolo G, et al. Postinfectious inflammatory disorders: subgroups based on prospective follow-up. *Neurology* 2005;65:1057–1065. [PubMed: 16217059]
2. Young NP, Weinshenker BG, Lucchinetti CF. Acute disseminated encephalomyelitis: current understanding and controversies. *Semin Neurol* 2008;28:84–94. [PubMed: 18256989]
3. Poser CM, Brinar VV. Disseminated encephalomyelitis and multiple sclerosis: two different diseases—a critical review. *Acta Neurol Scand* 2007;116:201–206. [PubMed: 17824894]
4. Tenenbaum S, Chamoles N, Fejerman N. Acute disseminated encephalomyelitis: a long-term follow-up study of 84 pediatric patients. *Neurology* 2002;59:1224–1231. [PubMed: 12391351]
5. Tenenbaum S, Chitnis T, Ness J, Hahn JS. International Pediatric MS Study Group *Neurology*. Acute disseminated encephalomyelitis 2007;8(Suppl 2):S23–S36.
6. Tavazzi E, Ravaglia S, Franciotta D, Marchioni E. Differential diagnosis between ADEM and MS during the first episode. *Arch Neurol*. 2008in press
7. Franciotta D, Zardini E, Ravaglia S, et al. Cytokines and chemokines in cerebrospinal fluid and serum of adult patients with acute disseminated encephalomyelitis. *J Neurol Sci* 2006;247:202–207. [PubMed: 16784758]

8. Marchioni E, Tavazzi E, Franciotta D, Ravaglia S. Recurrent ADEM versus MS: differential diagnostic criteria. *Neurol Res* 2008;30:74. [PubMed: 17711619]