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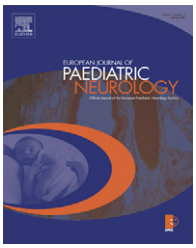

Original article

Acute disseminated encephalomyelitis cohort study: Prognostic factors for relapse

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ABSTRACT

To date, there is no available epidemiological study about prognostic factors of acute disseminated encephalomyelitis (ADEM) in children, using a cohort of patients with homogenous inclusion criteria. We aimed to evaluate prognostic factors for relapse after ADEM in children. A total of 132 children from the French National KIDSEP Neuropediatric Cohort (mean age at onset: 6±3.3 years; mean follow-up: 5.4±3.3 years; lost to follow-up: 10%). ADEM diagnosis was considered in a previously healthy patient acutely presenting more than one neurological deficit, change in mental state and MRI alterations including white matter changes. We used multivariate survival analysis (Cox model) evaluating the prognostic value of baseline clinical, biological and MRI covariates, for the occurrence of a second attack. Twenty-four (18%) of included patients had a second attack. An increased risk of relapse was associated with optic neuritis (hazard ratio, 5.23; 95% CI, 2–13.65), familial history of central nervous system inflammatory demyelination (7.79; 1.54–39.5), Barkhof multiple sclerosis (MS) criteria on MRI (2.52; 1.04–6.12) and no neurological sequelae after first attack (3.79; 1.12–12.85). Clinical and MRI prognostic factors for relapse in ADEM may contribute to an early distinction between monophasic and relapsing disease, which may be related to MS.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is a disseminated inflammation of the central nervous system (CNS) that occurs more frequently in children than in adults. It is usually associated with various neurological deficits, changes in mental state and white matter abnormalities seen on MRI that mostly consist of fuzzy, poorly defined lesions over large area.[1–5] Although recognised by paediatric or adult neurologists as a specific entity in CNS inflammatory demyelination, no consensus definition of ADEM has been reached in recent publications. Most definitions were based on initial clinical

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Abbreviations: A1, first attack; A2, second attack; A3, third attack; ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; DSS, disability status scale; MS, multiple sclerosis
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and MRI characteristics, with no reference to follow-up despite further demyelinating episodes being described in 10–30% of patients and despite there being some debate about the relationship between ADEM and multiple sclerosis (MS).[1–9] Patients who suffer relapse are frequently classified as "recurrent", "*multiphasic*" or "relapsing" ADEM but might as well be diagnosed with MS according to international classifications.[7,10–14]

We used a large cohort study and survival analysis methods to define the prognostic factors for relapse occurrence after ADEM in children, according on the clinical, biological and MRI characteristics at onset. The recognition of such factors has practical implications for the care of individual patients.

2. Methods

2.1. *Patients and inclusion criteria*

The studied cohort consisted of 132 children who had an episode of ADEM before the age of 16 between January 1990 and December 2003. This subcohort was derived from a larger cohort of children suffering a first episode of acute CNS inflammatory demyelination during the same period of time.[4,5] Patients were followed up during routine clinical visits from the onset of their condition until June 2005. For 14 of the 132 patients (10%), the follow-up is currently interrupted, with the more recently available information being from more than 2 years ago. However, we have included and used in our study the available data obtained before interruption.

We chose to define ADEM as the occurrence in a previously healthy child of acute symptoms associating the following at onset: more than one neurological deficit ("polysymptomatic" onset); change in mental state; and any combination of alterations seen on MRI, providing that these included white matter lesions. We chose a restrictive definition to obtain homogenous inclusion criteria, which will be discussed later, and thus excluded children with a similar acute polysymptomatic onset but with no change in mental state and children with inflammation occurring at an isolated CNS site (transverse myelitis, optic neuritis, brainstem dysfunction). Conversely, the MRI inclusion criteria were very comprehensive for two reasons. One was to avoid any prior assumptions that could bias the analysis and the other was that reported MRI criteria aiming to differentiate ADEM and MS are trends and not absolute.[2,4,6,8,11] We also excluded children with previous destructive white matter processes or neurological abnormalities as well as children suffering from diagnosed infectious, metabolic or immuno-genetic disorders.

2.2. *Data collection*

Baseline data were date of birth; sex; antecedent of CNS inflammatory demyelination (MS, ADEM, transverse myelitis, optic neuritis or brainstem dysfunction) in the family (father, mother, grand-parents and siblings); infection during the month before onset; calendar date of onset; detailed clinical; biological and MRI characteristics at onset; and use of intravenous high-dose steroids. Sequelae after an acute episode were assessed at routine clinical visits by the referring paediatric neurologist, using the Kurtzke Disability Status Scale.[15] Disability was noted if irreversible, that is, confirmed for a minimum of 12 months. Brain MRI scans was carried out in all patients within one week of onset and were reviewed for the purpose of this study as previously described and blind to information on the subsequent evolution.[5] Evolution data were the subsequent observation of a second attack (A2) or third attack (A3) and the date of their occurring. Data were obtained directly from the medical records of the paediatric neurologist in charge of the patient and from an annual telephone questionnaire used to obtain additional data. Information was entered into a computerised system that had received approval from the French freedom of information committee—"Comité National Informatique et Liberté". Families were provided with written information and gave verbal consent to the referring physician to participate in this observational study without intervention.

The clinical and MRI definitions were identical to those of previously published studies.[4,5] Optic neuritis was diagnosed on the basis of visual loss and defects in colour vision (if evaluation was possible depending on the age of the patient), with or without optic nerve swelling seen on *fundoscopic* examination.[16] Brain MRI characteristics were classified as previously described.[5] The MRI "child-MS criteria" uses the presence of corpus callosum long axis perpendicular lesions and/or the presence of well-defined lesions (i.e., only lesions with well-defined limits on brain MRI). The "Barkhof adult MS criteria" are the association of three of four criteria: at least one gadolinium-enhancing T1 lesion or $\geqslant$nine T2 lesions; at least one infratentorial T2 lesion; at least one juxtacortical T2 lesion; and $\geqslant$three periventricular lesions.[17]

2.3. *Outcome*

The outcome was the occurrence of a second attack (A2), defined as a new occurrence of neurological symptoms lasting more than 24 h, which stabilised or resolved either partially or completely.[14] Fatigue alone or the transient fever-related worsening of symptoms was not considered as an attack. We did not consider patients with steroid-dependence—relapse associated with a decrease in steroid dose or the cessation of steroid treatment—as having a true relapse. New symptoms occurring within a month of clinical onset were considered to be part of the same episode, as previously described.[4,5] We also carried out an analysis in which we considered new symptoms occurring within 3 months of clinical onset to be part of the first attack.

2.4. *Statistical analyses*

Descriptive data were compared using the χ^2 test or Fisher's exact test for proportions and Student's *t*-test or the Wilcoxon test for continuous data. The date of onset of symptoms was considered as the date of entry into the cohort and taken as time zero for the survival analysis. The end-point was the date when the outcome (A2) occurred. For event-free subjects, the follow-up period ended on the date of the last known visit. We used the Cox proportional hazards model to evaluate the prognostic value of each covariate measured at the first