Acute Fulminant Demyelinating Disease

A Descriptive Study of 60 Patients

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Background: Acute demyelinating encephalomyelitis (ADEM) is characterized by a severe inflammatory attack, frequently secondary to infectious events or vaccinations. To date, no clear criteria exist for ADEM, and the risk of subsequent evolution to multiple sclerosis (MS) remains unknown.

Objective: To evaluate the risk of evolution to MS after a first episode of ADEM.

Design: Observational, retrospective case study.

Setting: Thirteen French MS centers.

Patients: We retrospectively studied 60 patients with ADEM who were older than 15 years with no history suggestive of an inflammatory event who presented to MS centers from January 1, 1995, through December 31, 2005. We excluded 6 patients with multiphasic ADEM because this is a rare condition and somewhat difficult to classify. After a mean follow-up of 3.1 years (range, 1-10 years), the remaining 54 patients were then classified into 2 groups: monophasic ADEM (ADEM group) (n=35) and clinically definite MS (MS group) (n=19).

Main Outcome Measures: Clinical, laboratory, magnetic resonance imaging, and follow-up data were evaluated for each group.

Results: Patients in the ADEM group more frequently had atypical symptoms of MS (26 of 35 [74%]) than patients with MS (8 of 19 [42%]) (P=.02). Oligoclonal bands were more frequently observed in the MS group (16 of 19 [84%]) than in the ADEM group (7 of 35 [20%]) (P<.001). Patients in the ADEM group more frequently had gray matter involvement (21 of 35 [60%]) than those in the MS group (2 of 19 [11%]) (P<.001). On the basis of these results, we consider that the presence of any 2 of the following 3 criteria could be used to differentiate patients with ADEM from those with MS in our cohort: atypical clinical symptoms for MS, absence of oligoclonal bands, and gray matter involvement. On this basis, 29 of the 35 patients in the ADEM group (83%) and 18 of the 19 patients in the MS group (95%) were classified in the appropriate category.

Conclusions: Our study found some differences concerning the risk of evolution to clinically definite MS after a first demyelinating episode suggestive of ADEM. These findings led us to propose criteria that should now be tested in a larger, prospective cohort study.

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defined as new brain lesions observed on magnetic resonance imaging (MRI) performed during the months after the first demyelinating episode. Furthermore, previous studies reported that new gadolinium-enhanced lesions could appear several months after a first episode of ADEM in adults without any new clinical relapse. This fact could be a limitation for the application of the new criteria for MS in cases of ADEM.

Only a few studies on ADEM have been performed, mostly involving children. To our knowledge, only 1 large study has focused on ADEM in adults. The results of that study were clearly different from those of pediatric series, especially in terms of clinical and MRI presentation and the possible evolution to MS. In pediatric series, the following were found to be risk factors for monophasic ADEM compared with MS: previous infection or vaccination, polysymptomatic manifestations, lack of periventricular lesions, and the absence of oligoclonal bands (OCB) in the cerebrospinal fluid (CSF). In contrast, in the adult cohort study, patients with ADEM were older, had more frequent brainstem involvement, and had similar periventricular lesions compared with those patients who subsequently developed MS. A finding of OCB in the CSF was also a risk factor for MS in this cohort. Currently, no clear criteria are available that predict the evolution after a first demyelinating episode corresponding to ADEM. The aim of our study was to define the spectrum of ADEM in a large, multicenter, adult cohort and look for possible predictive criteria for evolution to clinically definite MS.

In a large, collaborative, multicenter study, we retrospectively studied patients identified as having ADEM in a European database on MS. In this database, patients with a differential diagnosis of MS, such as neuromyelitis optica or ADEM, are specifically identified. In the database, ADEM is defined as a first acute fulminant demyelinating episode without any previous neurologic history. Patients who presented with acute neurologic symptoms and multiple supratentorial and/or infratentorial demyelinating lesions on MRI that were suggestive of a first and severe acute inflammatory process, as usually described in ADEM, were included in our study. The lesions included widespread, multifocal, or extensive white matter lesions. We excluded patients younger than 16 years (pediatric cases), patients with a history suggestive of an inflammatory event, and patients with transverse myelitis or optic neuritis as the only neurologic deficit. We also excluded patients with central nervous system infection, vasculitis, or other autoimmune diseases. From January 1, 1995, through December 31, 2005, a total of 60 patients from 13 French MS centers were identified as having presented with ADEM.

CLINICAL AND DEMOGRAPHIC DATA

We noted age, sex, date of onset, previous infectious diseases or vaccinations, and clinical presentation. Clinical presentation was considered atypical for MS in cases of consciousness alteration, hypersomnia, aphasia, hemiplegia, paraplegia, tetraplegia, seizure, vomiting, bilateral optic neuritis, or confusion. We also recorded the occurrence of new relapses and the number of relapses, treatments during the acute phase, and treatments during the follow-up. Finally, we noted the Expanded Disability Status Scale score at the final visit.

BRAIN AND SPINAL CORD MRI

All patients underwent brain MRI during the first clinical episode. The MRIs were performed on a 1.0- or 1.5-T unit with at least the following sequences: sagittal and axial T1-weighted images before and after gadolinium infusion and axial T2 or fluid attenuation inversion recovery sequences. Spinal cord MRI was performed in 38 of the 54 patients. All patients had a follow-up brain MRI with a mean ± SD delay of 5.7 ± 1.9 months (range, 3–8 months). The MRIs were reviewed by a neuroradiologist blinded to clinical diagnosis and were classified according to the following data: number of T2-weighted lesions, number of gadolinium-enhanced lesions, and presence of edema. Because the MRIs were not all performed with the same protocol and were analyzed retrospectively, an evaluation of the T2-lesion load was not possible. We also noted the localization of lesions that affected the brainstem, periventricular, corpus callosum, basal ganglia, or cortical regions. We included as gray matter involvement both basal ganglia and cortical lesions. For the spinal cord MRI, we noted the size of the lesions (<2 vertebral segments or ≥2 vertebral segments in the sagittal plane), gadolinium enhancement, and whether the spinal cord was swollen. For the follow-up brain MRI, we noted patients with an overall regression of lesions, patients with a brain MRI similar to that observed at baseline, and patients with new T2- and T1-weighted gadolinium-enhanced lesions.

BIOLOGICAL ANALYSIS

All patients underwent biological and immunological tests, including measurement of complete blood cell count, erythrocyte sedimentation rate, serum cryoglobulins, total serum gammaglobulins, serum protein immunoelectrophoresis, C-reactive protein, complement factors, antinuclear antibodies, antineutrophic DNA, anticardiolipin antibodies, rheumatoid factor, and anti-prothrombinase and serologic testing for human immunodeficiency virus, herpes simplex virus, varicella-zoster virus, hepatitis C and B, cytomegalovirus, and Epstein-Barr virus.

All patients underwent a CSF analysis with blood cell count, protein level, and OGB evaluation by isoelectrofocusing methods. They did not undergo a CSF follow-up analysis. Four patients had brain biopsies performed in stereotactic conditions. In all cases the result was nonspecific demyelinating lesions.

FINAL CLASSIFICATION

We first analyzed clinical, CSF, and MRI data for the entire study population. All patients were followed up at least 1 time per year by the same neurologist. After a mean follow-up of 3.1 years (range, 1–10 years), patients were classified into 3 groups: the MDEM group (n=6), when the patients had recurrent episodes similar to the first one; the ADEM group (monophasic ADEM) (n=33), when patients did not have any new neurologic manifestations; and the MS group (n=19), when a second relapse was observed with new symptoms in new clinical territories at least 1 month after the first episode to define clinical space and time dissemination. We subsequently excluded patients with MDEM from the comparative study because this was a rare condition and difficult to classify.

We analyzed the clinical, MRI, and CSF data for all groups. We then sought to identify clinical, MRI, and CSF data that could help to predict the evolution of the disease in an individual patient after a first episode of ADEM.
Where appropriate, results are presented as mean±SD. For the statistical comparison between the ADEM group and the MS group, we used χ² or Fisher exact tests for qualitative variables, depending on the number of patients, and an unpaired Mann-Whitney test for quantitative variables. The proposed criteria for ADEM were evaluated using sensitivity, specificity, positive-negative predictive value, and accuracy.

## RESULTS

### DEMOGRAPHIC AND CLINICAL DATA

We did not find many differences in terms of demographic data between the groups (Table 1). Patients in the ADEM group were older (P = .04). Infectious episodes or vaccinations before the neurologic episode were reported in 26 of the 35 patients in the ADEM group (74%) compared with 10 of the 19 patients in the MS group (53%), but the difference did not reach statistical significance. The proposed criteria for ADEM were evaluated using sensitivity, specificity, positive-negative predictive value, and accuracy.

### Table 1. Demographic and Initial Clinical Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N = 54)</th>
<th>ADEM (n = 35)</th>
<th>MS (n = 19)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female/male</td>
<td>34/20</td>
<td>20/15</td>
<td>14/5</td>
<td>.24</td>
</tr>
<tr>
<td>Age, mean ± SD, y</td>
<td>32.7 ± 13.2</td>
<td>35.9 ± 15.4</td>
<td>27.1 ± 8.2</td>
<td>.04</td>
</tr>
<tr>
<td>White race</td>
<td>47 (87)</td>
<td>29 (83)</td>
<td>18 (95)</td>
<td>.20</td>
</tr>
<tr>
<td>Infections or vaccinations</td>
<td>26/10 (67)</td>
<td>19/7 (74)</td>
<td>7/3 (53)</td>
<td>.12</td>
</tr>
<tr>
<td>Delay after infection or vaccination episode, mean ± SD, d</td>
<td>23.3 ± 6</td>
<td>26 ± 37</td>
<td>18 ± 15</td>
<td>.18</td>
</tr>
</tbody>
</table>

Symptoms

- Polysymptomatic
- Atypical for MS
- Sensory
- Motor
- Paralysis
- Paresis
- Optic neuritis
- Bilateral
- Unilateral
- Intracranial hypertension
- Brainstem
- Cerebellar
- Urinary
- Aphasia
- Seizure
- Hemianopia

| Abbreviations: ADEM, acute demyelinating encephalomyelitis; MS, multiple sclerosis. |
| a Patients could have 1 or more clinical symptoms. Data are presented as number (percentage) of patients unless otherwise indicated. |
| b Comparison between the ADEM and the MS groups. |

Statistical Analysis

Where appropriate, results are presented as mean±SD. For the statistical comparison between the ADEM group and the MS group, we used χ² or Fisher exact tests for qualitative variables, depending on the number of patients, and an unpaired Mann-Whitney test for quantitative variables. The proposed criteria for ADEM were evaluated using sensitivity, specificity, positive-negative predictive value, and accuracy.

Clinical symptoms were not different between the 2 groups when we considered each symptom separately. Furthermore, although patients in the MS group were more frequently polysymptomatic (17 of 19 [89%] compared with 21 of 35 [60%] in the ADEM group), the difference did not reach statistical significance. The only statistically significant difference we found concerning clinical symptoms was with regard to atypical features for MS (consciousness alteration, hypersomnia, aphasia, hemiplegia, paraplegia, tetraplegia, seizure, vomiting, bilateral optic neuritis, or confusion), which were more frequent in the ADEM group (26 of 35 [74%]) than in the MS group (8 of 19 [42%]) (P = .02).

### MRI FINDINGS

Gray matter involvement (basal ganglia or cortical lesions) was more frequent in the ADEM group (21 of 35 [60%]) than in the MS group (2 of 19 [11%]) (P < .001) (Table 2). In contrast, corpus callosum involvement was less frequent in the ADEM group (8 of 35 [23%]) than in the MS group (15 of 19 [79%]) (P < .001). We did not find any differences in terms of the number of T2 lesions, gadolinium enhancement, edema, or periventricular or brainstem lesions. The Barkhof criteria (included in the criteria of McDonald et al) were not discriminant between the 2 groups.
CSF AND BIOLOGICAL DATA

The inflammatory reaction in the CSF was more severe in the ADEM group (mean±SD white blood cell count, 49.2±134.1/µL; to convert white blood cell count to /H1003 /109 per liter, multiply by 0.001) than in the MS group (28.2±35.6/µL), but the difference was not statistically significant (Table 3). The protein level was not different between the 2 groups. Similarly, if we considered the frequency of atypical CSF features for MS (protein level higher than 1 g/dL [to convert protein to grams per liter, multiply by 10.0] or white blood cell count higher than 30/µL), we did not observe any difference between the 2 groups. In contrast, OCB were more frequently observed in the MS group (16 of 19 [84%]) than in the ADEM group (7 of 35 [20%]) (P < .001). We did not find any differences between the 2 groups in terms of biological data, including dose of autoantibodies (antinuclear, anticardiolipin antibodies).

CLINICAL AND MRI FOLLOW-UP

During a mean±SD follow-up of 3.4±2.9 years (range, 1-8 years), patients in the MS group had 2.3±1.3 relapses, corresponding to a mean of 0.68 relapse per year (Table 4). The last Expanded Disability Status Scale evaluation was higher in the MS group (2.9±1.3) than in the ADEM group (1.9±1.9), but the difference did not reach statistical significance (P = .08).

The control brain MRI showed a complete regression of lesions in 2 patients in the ADEM group. New gadolinium-enhanced lesions were observed in 3 patients in the ADEM group (9%) and in 9 patients in the MS group (47%) (P < .001). New T2-weighted lesions were observed in only 1 patient in the ADEM group (3%) and in 11 patients in the MS group (58%) (P < .001). In the ADEM group, 4 patients (11%) met the MRI criteria (ie, dissemination in time defined by MRI follow-up) for MS.10 In these 4 patients, follow-up brain MRIs were per-

Table 2. Baseline Brain and Spinal Cord MRI Dataa

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 54)</th>
<th>ADEM (n = 35)</th>
<th>MS (n = 19)</th>
<th>P Valueb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain MRI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of T2 lesions, mean ± SD</td>
<td>13.2 ± 7.8</td>
<td>12.2 ± 7.4</td>
<td>15.3 ± 8</td>
<td>.68</td>
</tr>
<tr>
<td>Barkhof criteriaa met</td>
<td>43 (80)</td>
<td>26 (74)</td>
<td>17 (89)</td>
<td>.20</td>
</tr>
<tr>
<td>Edema</td>
<td>26 (48)</td>
<td>17 (49)</td>
<td>9 (47)</td>
<td>.80</td>
</tr>
<tr>
<td>Gadolinium-enhanced lesions</td>
<td>41 (76)</td>
<td>23 (66)</td>
<td>18 (95)</td>
<td>.06</td>
</tr>
<tr>
<td>Periventricular lesions</td>
<td>49 (91)</td>
<td>30 (86)</td>
<td>19 (100)</td>
<td>.24</td>
</tr>
<tr>
<td>Corpus callosal lesions</td>
<td>23 (43)</td>
<td>8 (23)</td>
<td>15 (79)</td>
<td>.001</td>
</tr>
<tr>
<td>Cerebellar lesions</td>
<td>25 (46)</td>
<td>15 (43)</td>
<td>10 (53)</td>
<td>.52</td>
</tr>
<tr>
<td>Brainstem lesions</td>
<td>27 (50)</td>
<td>16 (48)</td>
<td>11 (58)</td>
<td>.52</td>
</tr>
<tr>
<td>Gray matter (basal ganglia or cortical)</td>
<td>23 (43)</td>
<td>21 (60)</td>
<td>2 (11)</td>
<td>.001</td>
</tr>
<tr>
<td>Basal ganglia lesions</td>
<td>17 (31)</td>
<td>15 (43)</td>
<td>1 (5)</td>
<td>.004</td>
</tr>
<tr>
<td>Cortical lesions</td>
<td>21 (39)</td>
<td>11 (31)</td>
<td>1 (5)</td>
<td>.003</td>
</tr>
<tr>
<td>Spinal cord MRIb</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spinal cord lesions</td>
<td>25 (66)</td>
<td>15 (68)</td>
<td>10 (63)</td>
<td>.49</td>
</tr>
<tr>
<td>Swollen spinal cord</td>
<td>2 (5)</td>
<td>2 (6)</td>
<td>0</td>
<td>.80</td>
</tr>
<tr>
<td>Gadolinium-enhanced lesions</td>
<td>8 (22)</td>
<td>5 (23)</td>
<td>3 (19)</td>
<td>.70</td>
</tr>
<tr>
<td>Large lesion (≥2 vertebral levels)</td>
<td>9 (24)</td>
<td>7 (32)</td>
<td>2 (13)</td>
<td>.37</td>
</tr>
</tbody>
</table>

Table 3. Biological Dataa

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N = 54)</th>
<th>ADEM (n = 35)</th>
<th>MS (n = 19)</th>
<th>P Valueb</th>
</tr>
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<tbody>
<tr>
<td>Cerebrospinal fluid</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>White blood cells/µL, mean ± SD</td>
<td>41.7 ± 102.5</td>
<td>49.2 ± 134.1</td>
<td>28.2 ± 35.6</td>
<td>.09</td>
</tr>
<tr>
<td>&gt;30/µL</td>
<td>13 (24)</td>
<td>8 (23)</td>
<td>5 (26)</td>
<td>.80</td>
</tr>
<tr>
<td>Proteins, mean ± SD, g/dL</td>
<td>0.58 ± 0.3</td>
<td>0.63 ± 0.3</td>
<td>0.5 ± 0.3</td>
<td>.70</td>
</tr>
<tr>
<td>&gt;1 g/dL</td>
<td>7 (13)</td>
<td>5 (14)</td>
<td>2 (11)</td>
<td>.80</td>
</tr>
<tr>
<td>Oligoclonal bands</td>
<td>34 (42)</td>
<td>7 (20)</td>
<td>16 (84)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>3 (6)</td>
<td>1 (3)</td>
<td>2 (11)</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: ADEM, acute demyelinating encephalomyelitis; MRI, magnetic resonance imaging; MS, multiple sclerosis.
a Data are presented as number (percentage) of patients unless otherwise indicated.
b Comparison between the ADEM and the MS groups.

c Included in the criteria of McDonald et al.10
d The sample sizes for these entries are 38 for all patients, 22 for the ADEM group, and 16 for the MS group.
formed between 3 and 6 months after the clinical event. These 4 patients did not differ from the other patients in the ADEM group in any other respect. Furthermore, if we omitted these 4 patients, the results were similar (data not shown).

TABLE 4. Clinical and MRI Follow-up Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (N = 54)</th>
<th>ADEM (n = 35)</th>
<th>MS (n = 19)</th>
<th>P Valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical data, mean ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follow-up, y</td>
<td>3.1 ± 3.4</td>
<td>2.9 ± 3.6</td>
<td>3.4 ± 2.9</td>
<td>.17</td>
</tr>
<tr>
<td>No. of relapses</td>
<td>0.87 ± 1.1</td>
<td>0</td>
<td>2.3 ± 1.3</td>
<td>NA</td>
</tr>
<tr>
<td>Last EDSS score</td>
<td>2.2 ± 1.7</td>
<td>1.9 ± 1.9</td>
<td>2.9 ± 1.3</td>
<td>.28</td>
</tr>
<tr>
<td>Control brain MRI, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized</td>
<td>2 (4)</td>
<td>2 (6)</td>
<td>0</td>
<td>.80</td>
</tr>
<tr>
<td>New gadolinium-enhanced lesions</td>
<td>12 (22)</td>
<td>3 (9)</td>
<td>9 (47)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New T2 lesions</td>
<td>12 (22)</td>
<td>1 (3)</td>
<td>11 (58)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>McDonald criteria met</td>
<td>23 (43)</td>
<td>4 (11)</td>
<td>19 (100)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
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<td>.17</td>
</tr>
<tr>
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</tr>
<tr>
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<td>2.9 ± 1.3</td>
<td>.28</td>
</tr>
</tbody>
</table>

Abbreviations: ADEM, acute demyelinating encephalomyelitis; EDSS, Expanded Disability Status Scale; MRI, magnetic resonance imaging; MS, multiple sclerosis; NA, not applicable.

Table 5. Proposed Criteria for Differentiation Between MS and ADEM

ADEM corresponds to patients with at least 2 of the following 3 criteria:
Clinical atypical symptoms of MS. One or more of the following:
- consciousness alteration, hypersomnia, seizures, cognitive impairment, hemiplegia, tetraplegia, aphasia, or bilateral optic neuritis;
- Absence of oligoclonal bands in the cerebrospinal fluid;
- Gray matter involvement (basal ganglia or cortical lesions).

Twenty-nine of the 35 patients with ADEM (82.9%) at the end of the follow-up had 2 or more of these criteria and would therefore have been correctly classified, and 18 of the 19 patients with MS (94.7%) had no criteria or only 1 criterion and would also have been correctly classified.

Statistical data concerning the criteria for ADEM:
- Sensitivity = 82.9%
- Specificity = 94.7%
- Positive predictive value = 96.7%
- Negative predictive value = 75.0%
- Accuracy = 87.0%

Approximately 15%. This difference might, however, be largely dependent on the length of follow-up. Patients

TREATMENT

All patients were treated with intravenous corticosteroids (3-10 g per patient). Oral substitution was performed in 14 cases at a dosage of 1 mg/d during 1 month. We did not observe any differences between patients with and without oral substitution, including with regard to the risk of relapse. Fourteen patients (9 [26%] in the ADEM group and 5 [26%] in the MS group) were treated with immunosuppressive drugs: 7 with mitoxantrone, 4 with cyclophosphamide, 2 with methotrexate, and 1 with azathioprine. Three patients (all in the ADEM group) were treated with intravenous immunoglobulin and 1 with plasma exchange. Nine patients (all in the MS group) were treated with immunomodulatory drugs (8 with interferon beta and 1 with glatiramer acetate). Because of the retrospective aspect of our study and the lack of randomization, we did not look for any correlation between treatment and clinical outcome.

PROPOSED CRITERIA FOR DIFFERENTIATION BETWEEN ADEM AND MS

On the basis of the results of clinical, MRI, and CSF data, we propose that ADEM could correspond to patients with at least 2 of the following 3 criteria: (1) clinical symptoms atypical for MS, including 1 or more of the following: consciousness alteration, hypersomnia, seizures, cognitive impairment, hemiplegia, tetraplegia, aphasia, or bilateral optic neuritis; (2) absence of OCB in CSF; and (3) gray matter involvement (basal ganglia or cortical lesions) (Table 5). We also observed marked differences concerning corpus callosum involvement, but we did not include this in our proposed differential diagnostic criteria because it did not increase the discrimination between the 2 groups.

According to these criteria, 29 of the 35 patients with ADEM at the end of the follow-up (83%) were classified in the correct category: 18 of the 19 patients with MS (95%) had none or only 1 of the criteria and were classified in the correct category. On the basis of these results, the criteria have a sensitivity of 83%, a specificity of 95%, a positive predictive value of 97%, a negative predictive value of 73%, and an accuracy of 87%. When we considered only those patients with a minimum follow-up of 3 years, the results were similar (data not shown).

COMMENT

Our study of 60 adults with an initial feature of ADEM showed a 32% rate of conversion to clinically definite MS after a mean follow-up of 37 months. This result confirms the first and only other study, to our knowledge, on ADEM in adults, which found a 35% rate of conversion to MS after a mean follow-up of 38 months. This rate in adults is higher than that reported in pediatric studies which found a rate of conversion to MS of approximately 15%. This difference might, however, be largely dependent on the length of follow-up. Patients

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with isolated events of demyelination often do not experience a second event until 10 to 20 years later. It seems likely, therefore, that a longer follow-up in our cohort would have increased the number of conversions to MS.

Adult and pediatric ADEM cohorts are also slightly different in terms of age risk for MS, MRI data, and outcome. However, the diagnostic criteria for ADEM proposed in the pediatric literature are similar to those we propose in the present study, including clinical presentation, OCB in CSF, and gray matter involvement.

Although no specific diagnostic criteria for ADEM are available in the literature, an analysis of the different profiles of the patients confirms a consistency between the various MS centers in the way that ADEM is diagnosed. The clinical presentation of ADEM described in our study is in accordance with the only previous large study in adults for most of the data, including age, sex ratio, and symptoms. The authors found a significant difference between ADEM and MS in terms of brainstem symptoms. In contrast, we did not find any differences between our 2 groups with regard to clinical symptoms, except for what we refer to as symptoms atypical for MS, which were more frequently found in the ADEM group than in the MS group. In our study, the ADEM definition is based on a clinicoradiologic pattern, which could explain the relatively low percentage of patients with atypical clinical presentation for MS.

With regard to MRI data, the most important finding for the differentiation between ADEM and MS was the gray matter involvement in patients in the ADEM group. This variable was not clearly evaluated in the previous study in adults for most of the data, including age, sex ratio, and symptoms. The authors found a significant difference between ADEM and MS in terms of brainstem symptoms. In contrast, we did not find any differences between our 2 groups with regard to clinical symptoms, except for what we refer to as symptoms atypical for MS, which were more frequently found in the ADEM group than in the MS group.

In our study, the ADEM definition is based on a clinicoradiologic pattern, which could explain the relatively low percentage of patients with atypical clinical presentation for MS.

One possible explanation for the differentiation between MS and ADEM may be that high-affinity autoantibodies could be present in a subset of patients with ADEM and not in those with MS. Unfortunately, because we evaluated antinuclear antibodies but not high-affinity antibodies in our study, we are not yet in a position to resolve this issue.

The CSF results remain important for the differentiation between MS and ADEM, especially the presence or absence of OCB, which is highly discriminatory. Surprisingly, the white blood cell count was not discriminatory. Twenty-five percent of our patients with MS had a white blood cell count of more than 30/μL, a finding considered to be a red flag for MS. This result could be related to the high level of inflammation observed in this particular subtype of patients. This finding raises the question of whether these patients represent a different biological process than that of patients with more classic MS.

Multiple sclerosis may have been underdiagnosed in patients without OCB in the CSF, since reports have been made of early MS cases in which OCB appeared with time. It would therefore be interesting to perform a CSF follow-up in all patients with ADEM; OCB tend to disappear in ADEM and other fulminant demyelinating diseases, such as neuromyelitis optica, but may appear subsequently in MS.

At the end of our study, we suggest criteria that could be highly predictive of conversion from ADEM to MS. The presence of at least 2 of the 3 criteria, namely, atypical clinical symptoms, absence of OCB in the CSF, and the existence of gray matter involvement on brain MRI (basal ganglia or cortical lesions), appears to be highly suggestive of ADEM because this was the case in 29 of 35 patients with ADEM (83%), whereas only 1 of the 19 patients diagnosed as having MS (5%) had the criteria for monophasic ADEM. This result could well be modified after a longer follow-up, which would likely reveal new relapses among the patients classified as having ADEM in this study. Furthermore, the validity of these criteria in terms of their sensitivity and specificity will need to be verified in a new, more robust prospective cohort.

Our patients were not randomized for the therapeutic approach, and the various treatments were chosen empirically. It is therefore not possible to draw any conclusions regarding efficacy. Many proposals have been put forward for the treatment of ADEM, including plasma exchange, intravenous immunoglobulin, a high dose of intravenous corticosteroids, and immunosuppression.

Multicenter randomized studies are necessary to determine the efficacy of these therapeutic strategies. Furthermore, to enable disease-modifying drugs to be used early in MS, it is absolutely essential to define the risk of developing MS.

In conclusion, our study confirms the wide spectrum of the disease currently referred to as ADEM, including patients with a monophasic disease (ADEM) and a few with similar, recurrent episodes (MDEM), and an overall risk of subsequently developing MS of approximately 30%. Our study found some differences concerning the risk of an evolution to clinically definite MS after a first demyelinating episode suggestive of ADEM. These
findings led us to propose criteria that should now be tested in a larger, prospective cohort.

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REFERENCES


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