Recurrence of Acute Disseminated Encephalomyelitis at the Previously Affected Brain Site

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Background: Acute disseminated encephalomyelitis (ADEM) is a usually monophasic demyelinating disorder of the central nervous system. Recurrences pose a diagnostic challenge because they can be overlooked or suggest an alternative diagnosis.

Objective: To examine the frequency, nature, and outcome of recurrent ADEM.

Design: Review of the medical records of patients diagnosed in our institution as having ADEM between January 1, 1983, and May 31, 1998. Recurrences were defined as appearance of new symptoms and signs at least 1 month after the previous episode.

Results: Five (24%) of 21 patients with ADEM developed recurrent disease episodes. In all, diagnosis was confirmed by brain biopsy. One patient had 4 disease episodes, 2 had 3, and the other 2 each had 2. Recurrence appeared 1.5 to 32 months after initial presentation and involved the same brain territory in 6 of 9 recurrences in 3 of 5 patients. In 2 patients, recurrences included neuropsychiatric signs. A good response to corticosteroid therapy was observed in 10 of 13 of treated ADEM attacks: in 3 of the 4 treated initial events and in 7 of 9 recurrences.

Conclusions: Recurrent ADEM may be more prevalent than previously recognized. Patients who relapse tend to have more than 1 recurrence that usually involves, clinically and radiologically, a brain territory that was affected before and can simulate a space-occupying lesion that requires histologic diagnosis. Neuropsychiatric features may be the main presentation of a relapse. Since recurrent ADEM is a corticosteroid-responsive condition, awareness and early diagnosis are mandatory.

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ACUTE disseminated encephalomyelitis (ADEM) is a demyelinating disorder of the central nervous system that is usually monophasic. Relapses are rare, and patients with recurrent episodes are eventually diagnosed as having multiple sclerosis (MS). Features of ADEM are quite well delineated. The disease can appear after infection or vaccination; is associated with fever, convulsions, drowsiness, meningeal findings, and multifocal signs; and may take a fulminant or even a fatal course. Unlike MS, in which magnetic resonance (MR) imaging usually demonstrates multiple white matter lesions with predilection for periventricular and pericallosal areas without mass effect, the ADEM lesions tend to be large, confluent, and asymmetric; can involve gray matter areas such as the cortex, basal ganglia, and thalamus; may have a mass effect; and usually enhance massively with gadolinium. Pleocytosis and elevated protein levels are characteristic of the cerebrospinal fluid (CSF) in ADEM. However, it is often difficult, both at presentation and in retrospect, to differentiate between hyperacute and/or malignant forms of MS and other fulminating central nervous system demyelinating diseases such as ADEM.

Recurrent or relapsing ADEM may present such a difficulty in definition and is a much less well-characterized entity. We were faced with this reality when we recently encountered 2 patients with ADEM who had multiple relapses and presented a diagnostic and therapeutic challenge. This prompted us to examine the frequency, nature, and outcome of the recurrent disease in patients diagnosed in our institution as having ADEM.

RESULTS

CHARACTERISTICS OF PATIENTS WITH ADEM

During the study period, 21 patients with ADEM (14 females and 7 males, aged 5-77 years; mean age, 37 years) were hospitalized at the Hadassah University Hospital. A history of previous febrile illness (8 patients) or vaccination (1 patient) was evident in 9 (43%) of the 21 patients.

Presenting symptoms were nausea and vomiting (6 patients), headache (5 patients), fatigue (4 patients), limb weakness (5 patients), gait disturbance (4 pa-
PATIENTS AND METHODS

Between January 1, 1983, and May 31, 1998, ADEM was diagnosed in 21 patients at Hadassah University Hospital, Jerusalem, Israel. The diagnosis was based on the clinical context, the clinical signs and course of the disease, and imaging and laboratory findings. In 7 patients, brain biopsy specimens showed demyelination, mononuclear perivascular infiltration, loosening of the white matter, and macrophages containing myelin debris, establishing the diagnosis of ADEM. In all patients, a possible infectious cause (such as syphilis and Lyme disease) was ruled out and an immunogram was negative for a systemic immune-mediated condition. Three patients with ADEM (1 with recurrent disease) underwent brain angiography, and cerebral vasculitis was excluded.

The medical files of all patients with ADEM were reviewed for symptoms; clinical, laboratory, and imaging findings; response to treatment; and disease relapses. In accord with the diagnostic criteria, recurrence was defined as the development of new symptoms and signs, lasting more than 24 hours and separated by a minimum of 1 month from the previous episode.

Characteristics of Patients with Recurrent ADEM

The patients with recurrent ADEM were 2 men and 3 women with an age range of 30 to 77 years (mean, 51 years). One patient had 4 episodes of neurologic disorder, 2 had 3, and 2 had 2 episodes each. None of the patients with recurrent ADEM had a history of infection or immunization.

An illustrative case was that of a 30-year-old man who was admitted after 1 week of headache, fever, and drowsiness. His medical history included trauma to the right eye 8 years before his admission, with resultant ophthalmoplegia, blindness, and sympathetic ophthalmia, treated with prednisone. Results of general examination on admission were unremarkable except for temperature of 40°C. On neurologic examination, he was alert and conscious. He had right-eye blindness and right medial rectus palsy. Left-sided hemiparesis and hyperreflexia were noted. Plantar responses were flexor, and results of sensory and cerebellar tests were normal. Erythrocyte sedimentation rate, complete blood cell count, results of blood biochemistry studies, and electroencephalogram were normal. Lumbar puncture showed an elevated protein level (1.02 g/L) with normal glucose level and no oligoclonal bands. The MR image demonstrated a large hyperintense T2 lesion involving the right basal ganglia and thalamus, causing moderate pressure on the lateral ventricle (Figure 1A). Biopsy of the lesion showed nonspecific inflammatory changes.

Treatment with intravenous methylprednisolone sodium succinate was associated with marked improvement of the hemiparesis and the drowsiness. An MR image obtained 2 months later demonstrated a significant decrease in lesion size (Figure 1B), but after an additional 4 months he again developed headache, fever, and left-sided weakness. On examination, mild left hemiparesis was found and a computed tomographic scan showed enlargement of the lesion in the right thalamus and basal ganglia. Lumbar puncture was traumatic and therefore inconclusive. A second brain biopsy was performed and disclosed inflammatory and demyelinating changes. Treatment with intravenous methylprednisolone was initiated, with marked improvement of the patient's symptoms and signs.

Seven months after the first episode, and during a gradual decrease of the corticosteroid dosage, the patient again developed marked (3+/5 on the Medical Research Council scale) left hemiparesis. An MR image showed postbiopsy changes and an increase in the right hemispheric lesion, with extension into the pons and midbrain. A third biopsy specimen and review of the second biopsy specimen showed loosening of the white matter, marked demyelination, foamy macrophages, and perivascular mononuclear infiltration, compatible with ADEM (Figure 2). The patient was again treated with high-dose intravenous corticosteroids, which were tapered down because of depression and suicidal thoughts and were maintained at a very low dose for about 1.5 years. However, about 30 months after the first episode, he developed fever, drowsiness, and gait disturbance, and on examination he was somnolent with mild left hemiparesis with hyperreflexia and right cerebellar syndrome. An MR image showed, in addition to the right hemispheric lesion, new lesions at the left thalamus and internal capsule and in the mesencephalon and upper pons (Figure 1C). The patient was again treated with corticosteroids, with a good response.
Initial Episode

Two patients had fever and 2 complained of headache (Table 1). Drowsiness or acute confusion was evident in 3 and hemiparesis was also present in 3 patients. In 4 patients, MR images or computed tomographic scans showed a large solitary lesion, and in 1 patient, multiple hyperintense T2 foci were seen. Cerebrospinal fluid was obtained from 4 patients and showed elevated protein level in 1 (patient 1) and oligoclonal bands in another (patient 3). In 1 patient (patient 5), initial diagnosis was a possible cerebrovascular event, and therefore correct diagnosis and therapy were delayed until the second disease episode 5 months later. Brain biopsy eventually established the diagnosis of ADEM in all 5 patients. Four of the 5 patients were treated with corticosteroids, and 3 of them markedly improved. In 2, this was accompanied by radiologic improvement.

Table 1. Clinical and Laboratory Features of the First Episode in 5 Patients With Recurrent Acute Disseminated Encephalomyelitis

<table>
<thead>
<tr>
<th>Patient No./Sex/Age, y</th>
<th>No. of Episodes</th>
<th>Clinical Presentation</th>
<th>Brain Biopsy</th>
<th>Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/30</td>
<td>4</td>
<td>Headache, fever, left hemiparesis</td>
<td>Demyelination and perivascular inflammation</td>
<td>Very good</td>
</tr>
<tr>
<td>2/M/34</td>
<td>2</td>
<td>Fever, acute confusion</td>
<td>Multifocal demyelination</td>
<td>Moderate</td>
</tr>
<tr>
<td>3/F/77</td>
<td>2</td>
<td>Acute confusion</td>
<td>Active inflammatory demyelination</td>
<td>Very good</td>
</tr>
<tr>
<td>4/F/53</td>
<td>3</td>
<td>Headache, aphasia, right hemiparesis</td>
<td>Inflammation and demyelination</td>
<td>Very good</td>
</tr>
<tr>
<td>5/F/61</td>
<td>3</td>
<td>Right hand monoparesis, aphasia</td>
<td>Not done</td>
<td>Not treated</td>
</tr>
</tbody>
</table>

Figure 1. Magnetic resonance imaging studies. A. At presentation, there is a large confluent lesion of the right basal ganglia and thalamus. B. After corticosteroid treatment, there is a decrease in lesion size and postbiopsy changes. C. At the fourth recurrence, in addition to the old lesion and postbiopsy changes in the right hemisphere, there are new lesions at the left thalamus and internal capsule.

Figure 2. Brain biopsy specimens showing a mononuclear perivascular infiltration, demyelination, loosening of the white matter, and foamy macrophage compatible with acute disseminated encephalomyelitis (hematoxylin-eosin, original magnification x 200).
Recurrents

The time range to recurrence was 1.5 to 32 months (mean, 13 months) (Table 2). The clinical presentation at recurrence involved, at least in part, the same central nervous system territory that was affected during the initial episode in 6 of 9 recurrences. In the remaining 3, the new symptoms and signs were attributed to a different brain territory. Two patients had neuropsychiatric symptoms at recurrence, which were attributed to parenchymatous brain involvement. Three patients had new radiologic abnormalities at recurrence. Brain biopsy was performed again in 4 of the 9 recurrences. In all, the histologic findings were compatible with ADEM. All patients were treated with corticosteroids. Four patients had good clinical improvement, while 1 had only a mild response. A good response to corticosteroids was evident in 7 of 9 recurrences. The 3 patients with more than 1 recurrence, who had responded to treatment at the first relapse, also responded in subsequent relapses.

COMPARISON BETWEEN PATIENTS WITH AND WITHOUT RECURRENTS

Comparison between the 16 patients with ADEM who had no disease relapse and the 5 patients with recurrent ADEM is summarized in Table 3. The only difference between patients with a single ADEM episode and those who relapsed was the presence of a previous febrile illness, a finding that was not statistically significant.

Table 3. Comparison Between Patients With and Without Recurrences

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Time to Relapse, mo</th>
<th>Presentation at Relapse</th>
<th>Laboratory and Imaging</th>
<th>Biopsy</th>
<th>Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>Fever, left hemiparesis</td>
<td>CSF: elevated protein MRI +</td>
<td>Active demyelination</td>
<td>Good</td>
</tr>
<tr>
<td>7</td>
<td>25</td>
<td>Right cerebellar syndrome</td>
<td>MRI +</td>
<td>Demyelination</td>
<td>Good</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>Paraplegia, psychosis</td>
<td>ND</td>
<td>ND</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>Right hemiparesis, ataxia</td>
<td>MRI +</td>
<td>Demyelination and inflammation</td>
<td>Very good</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>Headache, right hypesthesia</td>
<td>MR +, CSF: normal</td>
<td>ND</td>
<td>Good</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>Right hemiparesis, motor aphasia</td>
<td>MRI +</td>
<td>ND</td>
<td>Good</td>
</tr>
<tr>
<td>1.5</td>
<td>2</td>
<td>Right hemiparesis, motor aphasia</td>
<td>MRI +</td>
<td>Demyelination</td>
<td>Good</td>
</tr>
</tbody>
</table>

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A good response was also noticed in other series, and a very good response was observed in 7 of 9 recurrences. Patients were treated with intravenous methylprednisolone acetate (1000, 500, and 250, 200, and 100 mg for 2 days each), and a good or complete clinical and radiologic remission, there is still either a “locus of minor resistance” vulnerable to further disease relapse, even a long time after the first episode, or a residual area of subclinical disease activity that gives rise to a new relapse.

The occurrence of large focal tumorlike demyelinating brain lesions has been documented before. However, these cases, borderline or intermediate between ADEM and MS, were monophasic. The occurrence of such a relapse, clinically and radiologically simulating a brain tumor in 3 of our 5 patients with histologically confirmed ADEM, implies that not only MS, but also ADEM, may have a tumorlike form.

Our experience suggests that recurrent ADEM is a corticosteroid-responsive condition. Patients were treated with intravenous methylprednisolone acetate (1000, 500, 250, 200, and 100 mg for 2 days each), and a good or very good response was observed in 7 of 9 recurrences. A good response was also noticed in other series, and a long-term corticosteroid-dependent course was also reported. It is important to emphasize, however, that some of the patients with recurrent ADEM in the series by Miller and Evans improved or recovered spontaneously, although the relatively high rate of recurrences in their series can be attributed to the lack of treatment. These data justify a therapeutic protocol with corticosteroids in patients with recurrent ADEM.

In conclusion, recurrent ADEM is more common than previously regarded and may occur in a significant proportion of patients with ADEM. It tends to affect the same brain territory and thus may be overlooked or challenge the initial diagnosis. Correct diagnosis is mandatory, as this condition seems to be amenable to therapy in most patients.

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Table 4. Clinical Features of Patients With Recurrent ADEM*

<table>
<thead>
<tr>
<th>Present Study</th>
<th>Durston and Milnes</th>
<th>Miller and Evans†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, % (No.)</td>
<td>24 (5/21)</td>
<td>ND</td>
</tr>
<tr>
<td>Age range, y</td>
<td>30-77</td>
<td>40-50</td>
</tr>
<tr>
<td>Sex, No. M/F</td>
<td>2:3</td>
<td>0:3</td>
</tr>
<tr>
<td>Biopsy-proved cases, No.</td>
<td>5/5</td>
<td>0/3</td>
</tr>
<tr>
<td>History of previous infection/febrile disease, No.</td>
<td>0/5 at presentation</td>
<td>1/3 at presentation, 2/5 at recurrence</td>
</tr>
<tr>
<td>No. of recurrences</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>Recurrence at same territory as first episode, No.</td>
<td>6/9</td>
<td>1/5</td>
</tr>
<tr>
<td>Neuropsychiatric features during recurrence, No.</td>
<td>2/9</td>
<td>0/3</td>
</tr>
<tr>
<td>Beneficial response to corticosteroids, No.</td>
<td>3/4 at initial episode; 7/9 at recurrence</td>
<td>Good in all 3 patients (in all episodes)</td>
</tr>
</tbody>
</table>

* ADEM indicates acute disseminated encephalomyelitis; ND, no data.
† Data available only for 3 patients with myelopathy.

(3) The mechanism responsible for such a recurrence is intriguing. It may be speculated that, even after a complete clinical and radiologic remission, there is still either a “locus of minor resistance” vulnerable to further disease relapse, even a long time after the first episode, or a residual area of subclinical disease activity that gives rise to a new relapse.

In conclusion, recurrent ADEM is more common than previously regarded and may occur in a significant proportion of patients with ADEM. It tends to affect the same brain territory and thus may be overlooked or challenge the initial diagnosis. Correct diagnosis is mandatory, as this condition seems to be amenable to therapy in most patients.

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REFERENCES