Recurrence of Acute Disseminated Encephalomyelitis after a 12-year Symptom-free Interval

Toshiyuki OHTAKE and Shunsaku HIRAI

Abstract

We report a patient with recurrent acute meningoencephalitis who had three episodes of headache, fever and unconsciousness; the first episode was at age 6 and the second, at age 7. After a 12-year symptom-free interval, she had a relapse, exhibiting the same symptoms as those in the previous two episodes. Head magnetic resonance imaging also revealed the recurrence of lesions in the basal ganglia and medial portion of the temporal lobe. The occurrences of stereotyped symptoms with meningoencephalitis and the same lesions in the basal ganglia observed in each episode favor the diagnosis of recurrent acute disseminated encephalomyelitis (ADEM) rather than multiple sclerosis or multiphasic disseminated encephalomyelitis. The occurrence of this rare case suggests that ADEM can relapse after a very long symptom-free interval.

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Key words: ADEM, MRI, recurrence

Introduction

Acute disseminated encephalomyelitis (ADEM), which is characterized by the acute demyelinating disorder of the central nervous system (CNS), has been considered to be a cell-mediated autoimmune disease. Although the clinical course of ADEM is usually monophasic, there have been several reports of the recurrent type (1–4). We report here a rare case of a patient with recurrent ADEM after a 12-year symptom-free interval.

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Case Report

A Japanese woman patient suffered from the first episode of headache, fever, unconsciousness and vomiting at age 6 in May 1987. There were no signs of a preceding clinical pharyngitis before this episode, and no cutaneous or orogenital lesions. Neurological examinations revealed only drowsiness. Cerebrospinal fluid (CSF) examinations showed an increased pressure of more than 200 mmH₂O and a predominantly lymphocytic pleocytosis of 26/mm³. Head magnetic resonance imaging (MRI) revealed high-intensity areas in the left basal ganglia and bilateral medial portion of the temporal lobe (Fig. 1A). The analysis of a brain biopsy from the left basal ganglia confirmed only the presence of perivascular cell infiltration, which suggested an inflammatory process, without any tumor cells and demyelination (Fig. 2). The symptoms gradually disappeared in a month.

The second episode occurred in July 1988. She presented with the same symptoms as those in May 1987. In addition, psychiatric symptoms, such as agitation and emotional disturbance, and hyperreflexia of the lower extremities were also observed. Findings of head MRI were the same as those in the first episode, and those of routine laboratory tests were also normal except for signs of inflammation such as an elevated erythrocyte sedimentation rate, an elevated leukocyte count and an elevated C-reactive protein level. The levels of immunological markers, including the anti-nuclear antibody, immune complex and angiotensin-converting enzyme, were all normal. The human leukocyte antigen B51 was absent and a pathergy test for needle pricks showed negative findings. CSF examination showed an increased pressure of more than 200 mmH₂O and a predominantly lymphocytic pleocytosis of 100/mm³, which were the same findings as those in May 1987. Oligoclonal IgG bands were absent and myelin basic protein levels were normal in the CSF. Electroencephalography (EEG) showed focal delta waves in the right frontal lobe where no abnormalities were detected by MRI. The symptoms gradually disappeared as in the first

From the Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo

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Reprint requests should be addressed to Dr. Toshiyuki Ohtake, the Department of Neurology, Tokyo Metropolitan Ebara Hospital, 4-5-10 Higashi-yukigaya, Ota-ku, Tokyo 145-0065

Figure 1. A: T₂-weighted MRI (0.5 Tesla, TR 2,000 ms/TE 80 ms) on June 29, 1987 shows abnormal high-intensity areas in the left basal ganglia and bilateral medial portion of the temporal lobe. B: Abnormal high-intensity areas completely disappeared in images obtained on November 18, 1988. C: T₂-weighted MRI (1.5 Tesla, TR 4,000 ms/TE 90 ms) on April 23, 2001 shows abnormal high-intensity areas in the same regions as those detected by MRI on June 29, 1987.

Figure 2. Analysis of brain biopsy from the left basal ganglia revealed the presence of perivascular cell infiltration, which suggested an inflammatory process. HE stain. Scale bar indicates 20 μ m.

episode and the lesions completely disappeared 4 months after the onset of the second episode (Fig. 1B). Her developmental course thereafter was normal and no clinical deficits such as cognitive impairment or behavioral problems were observed.

The third episode occurred in April 2001 when she was 19 years old. Severe headache and nausea as in the two previous episodes prevented her from eating. She was admitted to our hospital 4 days after the onset of headache. Physical examinations revealed a fever of 38.2°C and no significant findings in the chest or abdomen. Neurological examinations showed only minor neck stiffness and hyperreflexia of the lower extremities in addition to drowsiness. There was no motor deficit, sensory disturbance or cranial nerve involvement. Blood examinations revealed an elevated C-reactive protein level and an elevated leukocyte count. CSF examinations revealed an increased pressure of 400 mmH₂O, pleocytosis of 524/mm³ (48% polymorphonuclear cells, 52% lymphocytes), an increased protein concentration of 68 mg/dl, and a normal sugar level and cytology. CSF oligoclonal IgG bands were absent and myelin basic protein levels were normal, similar to those in July 1988. The MRI findings were the same as those in June 1987, indicating T2-weighted high-intensity areas in the left basal ganglia and left medial portion of the temporal lobe (Fig. 1C) with slight swelling and enhancement by gadolinium. Levels of immunological markers including anti-streptolysin O antibody, anti-neutrophil cytoplasmic antibody (ANCA), anti-cardiolipin antibody and lupus anticoagulant, and bacterial culture revealed no abnormalities. The analyses of serum and CSF showed the absence of viruses, such as herpes simplex, herpes zoster and Epstein-Barr viruses. DNA analyses of such viruses also confirmed their absence. Consciousness disturbance gradually developed. Thereafter, she also devel-

oped left hemiparesis and had epileptic movements of the extremities. EEG revealed paroxysmal delta activities in the right frontal lobe where no radiological abnormalities were detected. Methylprednisolone (1,000 mg/day) was administered for three days, 12 days after the onset of the third episode. Although her left hemiparesis improved two weeks after the onset, consciousness disturbance did not improve. Therefore, the three-day course of methylprednisolone was repeated at three and five weeks after the onset of the symptoms. Her consciousness disturbance gradually improved, although psychiatric symptoms such as irritability remained. The lesions partly disappeared, as determined by MRI, 5 months after the onset of the third episode.

Discussion

Her clinical symptoms were indicative of recurrent meningoencephalitis with obvious lesions in the left basal ganglia. The clinical characteristics of this case were a very long symptom-free interval between the second episode in childhood and the third episode in adolescence, and the reappearance of lesions in the same brain regions as determined by MRI.

Patients with recurrent episodes of CNS symptoms are often diagnosed as having multiple sclerosis (MS) or systemic diseases with CNS involvement such as collagen diseases. However, specific symptoms indicative of a systemic disease and autoantibodies indicative of collagen diseases, such as CNS lupus, neuro-Behçet's disease, ANCA-associated vasculitis and antiphospholipid syndrome, were all absent in the present case. MS and ADEM are two representative demyelinating diseases. Sometimes it is very difficult to distinguish these two diseases, particularly in recurrent cases, and an initial diagnosis of ADEM is often changed to MS after a recurrence (5, 6). Hynson et al (7) suggested that a viral prodrome, early-onset ataxia and the absence of oligoclonal IgG bands are highly indicative of ADEM. In addition, Dale et al (3) described that polysymptomatic presentation, pyramidal signs, encephalopathy, bilateral optic neuritis and blood leukocytosis are more commonly observed in ADEM. In the present case, prodromal symptoms, ataxia and optic neuritis were not observed. However, the other characteristics described in these two reports agree with the present case. Moreover, MRI abnormality was prominent in the basal ganglia, which is rare in MS and is sometimes observed in ADEM (8–10). Another rare condition that resembles MS and recurrent ADEM is multiphasic disseminated encephalomyelitis (MDEM), which has repeated episodes of neurological syndrome (3, 11, 12). Although the symptoms observed in each episode in MDEM resemble those in ADEM, MDEM is not always symptomatically stereotyped as recurrent ADEM. Therefore, it is our conclusion that this patient had recurrent ADEM. The analysis of a brain biopsy obtained during her first episode did not reveal typical demyelinating lesions. The reason for this was not clear, but it could be that the disease process

was still in the early stage when the biopsy was performed.

Cohen et al (4) studied the features of five patients with recurrent ADEM. They reported that in a relapse, the brain territory involved tends to be the same as that affected before, and neuropsychiatric symptoms may be among the main presentations of a relapse, as in the present case. They speculated the existence of an area abnormally vulnerable to relapse or a residual area of subclinical disease activity. Hynson et al (7) performed a follow-up study of four patients with recurrent ADEM using MRI. Lesions in the patients of these two studies decreased in size, but did not disappear completely. In the present case, the lesions detected by MRI clearly disappeared after the second episode. The resolution of MRI used in the first and second episodes was lower than that of the latest MRI. Therefore, the residual lesions were possibly not radiologically detected after the second episode. On the other hand, the pathological findings in the first episode were only of minor significance for ADEM. Consequently, these findings possibly explained the complete remission.

The longest interval of 30 months between episodes was reported by Cohen et al (4). The 12-year interval in the present case is surprisingly much longer than that in previously reported cases. We could not clearly determine the precise reason for this long interval. She had the first and second episodes in childhood and the third episode in adolescence. Only minor differences, such as the presence of a prior infection, between children and adult ADEM patients have been reported (3, 7).

The relapse after a very long symptom-free interval in a patient with ADEM suggests the presence of previously undetected pathological conditions. A long-term follow-up study of children with ADEM is necessary to clarify these conditions.

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