Severe Depression as an Initial Symptom in an Elderly Patient with Acute Disseminated Encephalomyelitis

Masayuki Matsuda*,**, Jun Miki*, Ken-ichi Tabata* and Shu-ichi Ikeda**

Abstract

We report a 63-year-old man with acute disseminated encephalomyelitis (ADEM), initially showing depression for one and a half months but subsequently meningoencephalitis followed by acute-onset myelopathy. Neuroradiological examinations of the brain demonstrated no focal lesion causative for his depression, while cerebrospinal fluid revealed elevated levels of inflammatory cytokines in parallel with disease activity. Because depression is usually a rare initial symptom for patients with ADEM, an increased production of inflammatory cytokines in the central nervous system as well as age-related alterations of immune response might have played an important role in the development of depression in this elderly patient.

Case Report

A 63-year-old man with no previous psychiatric history abruptly developed depression, poor concentration, sleep disturbance, irritability, appetite loss and excessive sweating at night following common cold-like symptoms from the middle of August 1999 with no apparent precipitating cause. He was admitted to a neighboring psychiatric hospital and diagnosed as having endogenous depression because there was no abnormal finding in brain computed tomography, electroencephalogram (EEG), blood chemistry or endocrine functions. Although he was taking anti-depressive drugs, his symptoms progressed gradually with anxiety, hypersensitivity and irritability after discharge from that hospital. He was admitted to our department in the middle of October because of a continuous fever above 38°C and consciousness disturbance with hiccups since the end of September.

On physical examination, his body temperature was 38.5°C with no abnormal findings in either the chest or the abdomen. He was in a drowsy state with irritability, intractable hiccups, paretic dysarthria and dysphagia, with no paresis in the extremities and no signs of meningeal irritation. All deep tendon reflexes were reduced with negative Babinski’s sign on both sides. There were no abnormal findings in routine laboratory data, including urinalysis, hematology, blood chemistry, hypopituitary hormones and thyroid function, except for CRP (1.6 mg/dl) and WBC (14,000/mm³). Angiotensin-converting enzyme and lysozyme in serum were normal, and autoantibodies, including the anti-nuclear antibody, and antibodies against either human immunodeficiency virus or human T-lymphotropic virus type 1 (HTLV-1) were not detected. Cerebrospinal fluid (CSF) showed pleocytosis (108/mm³) with a predominance of mononuclear cells and an increased level of total protein (168 mg/dl), IgG (36.4 mg/dl) and myelin basic protein (MBP, 4.6 ng/ml, normal value less than 4.0 ng/ml), with a positive oligoclonal IgG band and negative cytology and bacterial culture. Detection of cytokines revealed high levels of interferon (IFN)-γ (240 IU/ml), interleukin (IL)-6 (134 pg/ml) and tumor necrosis factor (TNF)-α (42 pg/ml) in CSF. We could...
not find any significant change in serial examinations of titers of antibody against either cytomegalovirus or herpes simplex virus in either sera or CSF. MRI demonstrated a high intensity signal from the lower medulla to the upper cervical cord with age-related periventricular changes in the cerebrum on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig. 1). We could not find any abnormal lesion in either hypothalamus or limbic systems on MRI. EEG showed diffuse slow activities over the cortex, while neither somatosensory nor visual evoked potential demonstrated abnormal findings suggestive of subclinical focal lesions in the cerebrum. On single photon emission computed tomography (SPECT), we could not find any focal decreased uptake of tracer in the CNS.

Although we treated him with antibiotics and aciclovir (1,500 mg/day) for about two weeks from his admission to our department, he showed no improvement in the high fever, consciousness disturbance or hiccups. CSF showed a decrease in the cell count, while total protein and IgG were remained at a high level for one month after the admission. From the beginning of November he showed paraparesis and urinary obstruction due to the spinal cord lesion. Because MRI performed at this time demonstrated multiple high-intensity signals irregularly distributed along the cervical and thoracic cord (Fig. 2) on the T2-weighted image, we tried intravenous administration of methylprednisolone (1,000 mg/day) for three days followed by oral prednisolone (50 mg/day) after cessation of the aciclovir and antibiotics. All of his symptoms promptly improved in parallel with decreases in the levels of total protein, IgG and inflammatory cytokines in CSF (Fig. 3). He showed no exacerbation in symptoms or CSF findings during the tapering of prednisolone.

Figure 1. MRI demonstrates a high-intensity signal from the lower medulla to the upper cervical cord (A and B, arrowheads), and age-related periventricular changes in the cerebrum (C) on fluid-attenuated inversion recovery (FLAIR) image (0.5 Tesla, TR/TE=8,000/120).

Figure 2. When the patient showed paraparesis and urinary obstruction, MRI demonstrated multiple high-intensity signals irregularly distributed along the cervical (A, 0.5 Tesla, TR/TE=3,500/120) and thoracic cord (B, 0.5 Tesla, TR/TE=3,500/105) on T2-weighted image.
Severe Depression in ADEM

<table>
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<th>Therapy</th>
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<tr>
<td>Aciclovir 1,500 mg/day</td>
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Common cold-like symptoms
Depression
Fever
Consciousness disturbance
Hiccup
Paraparesis

<table>
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<tr>
<th>WBC (×/mm³)</th>
<th>CRP (mg/dl)</th>
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<tr>
<td>10,000</td>
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<tr>
<td>5,000</td>
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<tr>
<td>Cell count in CSF</td>
<td>TP (mg/dl)</td>
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<td></td>
<td>IgG (mg/dl)</td>
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<td>Myelin basic protein in CSF (ng/ml)</td>
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<td>Oligoclonal IgG band in CSF</td>
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<tr>
<td>IFN-γ in CSF (IU/ml)</td>
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<tr>
<td>IL-6 in CSF (pg/ml)</td>
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<td>91</td>
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<tr>
<td>TNF-α in CSF (pg/ml)</td>
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Figure 3. Clinical course. CSF: cerebrospinal fluid, IFN: interferon, IL: interleukin, TP: total protein.

Discussion

This patient showed high fever, consciousness disturbance and intractable hiccups possibly due to meningoencephalitis following depression for one and a half months. Because he manifested paraparesis and urinary disturbance two weeks after the appearance of meningoencephalitis, with abnormal intensity signals in the lower medulla and along the cervical and thoracic cord on MRI, his multiple CNS lesions were considered to be progressive and to have induced the clinical symptoms. We found increases in the levels of MBP and a positive oligoclonal IgG band in the CSF with no significant changes in any examined anti-viral antibody, and although his symptoms did not improve with aciclovir they did so promptly with steroid therapy, suggesting that he suffered from an autoimmune demyelinating disease in the CNS. Other steroid-responsive diseases with multiple CNS lesions, such as sarcoidosis,
Behçet’s disease, vasculitides and HTLV-1-associated myelopathy, were excluded from the diagnosis on the basis of systemic signs and laboratory findings. He showed a monophasic clinical course with high fever due to meningoencephalitis, which was distinct from multiple sclerosis, leading to the diagnosis of ADEM. Although we could not identify a causative agent for common cold-like symptoms in this patient, the preceding infection was considered to play an important role in the pathogenesis of ADEM.

Because ADEM is usually regarded as a purely neurological disorder, attention has not been drawn to psychic manifestations. Patients with ADEM, however, frequently show neuropsychiatric symptoms, including confusion, unspecified behavioral changes and irritability, during the course of the illness (1-4). According to recent case reports of ADEM with prominent psychic symptoms, several patients presented initially with psychiatric features alone before the development of neurologic symptoms (5-7). Although patients with ADEM can manifest various types of psychic symptoms, depression is quite rare especially as an initial symptom (4). The most characteristic point of this patient is, therefore, that he showed severe depression as an initial symptom before the appearance of a high fever and consciousness disturbance. Because he showed no depression after the improvement of consciousness disturbance and CSF findings, this psychic symptom might not be ascribed to endogenous depression but rather to the ADEM.

The acute or subacute depression can be induced also by the postviral fatigue syndrome (PVFS), which is one of the complications after viral infections as well as ADEM (8). The depression associated with PVFS is fundamentally different from that seen in the primary psychiatric disorder in the following points: sleep disturbance, lack of guilt, the ability for enjoyment and to experience pleasure, and irritability (9). Although the depression in this patient is similar to that in PVFS in its clinical pattern of irritability and sleep disturbance, he cannot be diagnosed as having PVFS because he did not show either myalgia or severe fatigue, which are essential to its diagnosis (9), through the course of illness.

Concerning the pathogenetic mechanism underlying depression in this patient with ADEM, it is necessary to address this from the view of host-disease relationship. One possible explanation is that focal brain lesions due to ADEM might directly contribute to depression. Depression is one of the symptoms included in the frontal lobe syndrome, which can be frequently induced by either bilateral or unilateral lesions (10). Nevertheless, we could not find any evidence suggesting that this patient had a focal brain lesion, including frontal lobes, because he showed no other symptoms of the frontal lobe syndrome and no abnormal findings in the cerebrum on MRI and SPECT. The second possible explanation is that elevated inflammatory cytokines in the CSF might relate to the pathogenesis of depression. Recently there have been several reports demonstrating that depression is accompanied by an immune response with an increased production of inflammatory cytokines (11-13). Because this patient showed elevated levels of inflammatory cytokines, including IFN-γ, IL-6 and TNF-α, in the CSF in parallel with disease activity, ADEM might have contributed indirectly to the pathogenesis of depression with respect to the production of these cytokines. Another possible explanation is that depression is a common initial symptom for elderly patients with ADEM as in this case. Children or young adults with ADEM usually develop consciousness disturbance and fever as an initial symptom, while there have been several reports showing that mental change is a frequent clinical manifestation in middle-aged to elderly patients with ADEM (14-16). Because CNS lesions in ADEM have striking similarities to those of experimental allergic encephalomyelitis (17), ADEM is considered to be a cell-mediated autoimmune disease. Considering that the human immune response would change with age, the age-related alteration of cell-mediated immunity might contribute to a clinical manifestation distinct from children or young adults.

In conclusion, ADEM might be able to manifest itself with acute or subacute psychosis including depression as an initial symptom in middle-aged to elderly patients. When a patient with psychic symptoms shows a high fever and consciousness disturbance, it is recommended to investigate the CSF and do MRI of the CNS for a possible diagnosis of ADEM as soon as possible, because treatment with corticosteroid in the early phase can improve all symptoms promptly with no neurological sequelae.

References

13) Kubera M, Kenis G, Bosmans E, et al. Plasma levels of interleukin-6,
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