A discrepancy between clinical course and magnetic resonance imaging in a case of non-herpetic acute limbic encephalitis

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Abstract

We report the case of a 64-year-old man who presented memory disturbance, low-grade fever, weight loss, and bilateral hand tremors for three months. He was diagnosed with non-herpetic acute limbic encephalitis (NHALE). Follow-up magnetic resonance imaging (MRI) revealed new lesions after symptomatic improvement following steroid pulse therapy. This may indicate that there is a time lag between the disturbance or recovery of neurons and astrocytes. Thus, other lesions might occasionally appear during convalescence in patients with NHALE, even if only minimal lesions were found on the initial MRI.

Case Report

A 64-year-old man was admitted to our hospital for a memory disturbance. He had been treated for hypertension, hypercholesterolemia, gout, and gastroesophageal reflux disease, but he had no history of neurological or psychiatric illness. He occasionally drank alcohol. He had developed a 37-38°C low-grade fever and bilateral hand tremors three months previously and had lost 5 kg of body weight. He had become aware of the memory disturbance and his gait imbalance one month before admission. He showed no symptoms of focal infection such as a common cold or collagen disease, and hyperthyroidism was excluded. Laboratory data showed liver dysfunction and an inflammatory reaction. On admission, his body temperature was 36.9°C; however, a physical examination of the chest and abdomen showed no abnormalities. His state of consciousness was E4, V4, and M6 on the Glasgow Coma Scale. He had no apparent aphasia and presented no abnormalities in the peripheral cranial nerves or hemiparesis of the extremities. Deep tendon reflexes were normal without a pathological reflex. Nuchal rigidity and Kernig’s sign were absent. He had bilateral 7-8 Hz action tremors of the hands. There was no intention tremor in the lower limbs but his gait was unsteady. He was topographically disoriented and could never find his way to the restroom on the ward. Laboratory data, including a complete blood count, renal function, electrolytes, ammonia, thyroid hormones, antinuclear acid, cytoplasmic antineutrophil cytoplasmic antibody, perinuclear antineutrophil cytoplasmic antibody, matrix metalloproteinase-3, rheumatoid arthritis test, immune complex, cytomegalovirus antigenemia, and electrocardiography, were all normal. Liver dysfunction and C-reactive protein had been normalized. A cerebrospinal fluid (CSF) examination showed elevated cell counts, with monocyte levels of 70 µL (polynuclear cells of 0 µL). The CSF protein level was 67 mg/dL. Diffusion-weighted imaging (DWI) and fluid attenuated inversion recovery (FLAIR) of his brain MRI on Day 2 showed hyperintensity in the bilateral medial temporal cortex (Figure 1A). Magnetic resonance angiography (MRA) showed no abnormalities (Figure 1B). N-isopropyl-[123I]iodoamphetamine single photon emission computed tomography (SPECT) showed hypoperfusion in the whole brain, predominantly in the left frontal lobe (Figure 2). An electroencephalogram showed theta and delta waves in the frontotemporal regions bilaterally (Figure 3).

On Day 3, a neuropsychiatric assessment gave the patient a score of 15 on the Mini-Mental State Examination (MMSE). He was disoriented about time and experienced difficulty of recall. But he could draw interlocking pentagons. He scored 12 points on the Frontal Assessment Battery (range 0-18, cut-off score 15), 82 points on the Kohs Block Design Test, and 32 out of 36 points on the Raven’s Colored Progressive Matricies. The patient did not present consciousness disturbance or myelopathy, and the course of his illness was relatively slow. He did not seem to be suffering from acute disseminated encephalomyelitis. A clinical diagnosis of NHALE was made. He received 1000 mg/day methylprednisolone intravenously from Day 2 to Day 4, followed by oral 50 mg/day prednisolone for three days, 40 mg/day prednisolone for 14 days, 35 mg/day prednisolone for seven days, and was taking 25 mg/day prednisolone when he was discharged on Day 38. He also received 5 g/day gamma globulin on Days 8 and 9, and 2.5 g gamma globulin on Day 10. On Day 7, he only had a slight tremor of the hands and his gait was almost normal. On Day 10, he was disoriented about time and place. On Day 12, he lost his way to the restroom on the ward. On Day 13, his disorientation improved. He could tell which month it was and when asked where he was he could answer in hospital. After treatment, the clinical symptoms of memory disturbance, bilateral hand tremors, and unsteady gait gradually improved.

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Figure 1. (A) Magnetic resonance imaging on Day 2 showed hyperintensity in the bilateral medial temporal cortex on diffusion-weighted imaging and fluid attenuated inversion recovery. (B) Magnetic resonance angiography showed no abnormalities. (C) Diffusion-weighted imaging and fluid attenuated inversion recovery on Day 14 revealed other hyperintense lesions around the lateral ventricles. (D) Diffusion-weighted imaging and FLAIR on Day 37 revealed that hyperintense lesions in the bilateral medial temporal cortex became more apparent in fluid attenuated inversion recovery image and lesions around the lateral ventricles remained. (E) Magnetic resonance angiography did not show any abnormal findings. (F) Magnetic resonance imaging 17 months later showed hyperintense lesions in the bilateral medial temporal cortex and on fluid attenuated inversion recovery the lesions around the lateral ventricles remained.
He was eventually able to walk steadily in the ward without losing his way. But DWI and FLAIR on Day 14 revealed other hyperintense lesions around the lateral ventricles (Figure 1C). There have been reports of antibodies to N-methyl-D-aspartate receptor (NMDAR), antibodies to NR2B- and NR2A-containing heteromers of the NMDAR detected by cell-based assay, antibodies against full-length GluR epsilon 2 (B18) and GluR delta 2 subunits confirmed by Western blot, and antibodies against peptides of GluR subunit of NMDAR quantified by an enzyme-linked immunosorbent assay (ELISA). Using an ELISA, we examined serum and CSF antibodies against GluR epsilon 2, delta 2 and zeta 2. Serum and CSF antibodies against GluR epsilon 2-NT2, GluR epsilon 2-CT1, GluR delta 2-NT, GluR delta 2-CT were positive. Serum and CSF antibodies against GluR epsilon 2-M3-4, GluR zeta 1-NT, GluR zeta 1-CT were negative; thus, the patient was diagnosed with NHALE. We did not look for the other antibodies that have been found in patients with autoimmune limbic encephalitis, i.e. using ELISA on HEK293 cell lysates ectopically expressing NR1 or NR1-NR2B heteromers, NMDAR GluR epsilon 2 (NR2B, GluN2B) or GluR zeta 1 (NR1, GluN1) subunits in this study. Using PCR, we did not detect the DNA of HSV type 1, HSV type 2, and human herpes virus 6 in the CSF. Tumor markers, including carcinoembryonic antigen, carbohydrate antigen 19-9, and alpha-fetoprotein were within normal limits. Further examination with abdominal ultrasonography and enhanced computed tomography of the chest and abdomen revealed no abnormal findings.

A follow-up neuropsychiatric examination on Day 29 showed that the MMSE score had improved to 28 points. A neuropsychiatric examination on Day 37 revealed a full-scale intelligence quotient (IQ) score of 100, a verbal IQ score of 100, and a performance IQ of 99 on the Wechsler Adult Intelligence Scale. But DWI and FLAIR on Day 37 revealed that hyperintense lesions in the bilateral medial temporal cortex became more apparent in the FLAIR image and there were still lesions around the lateral ventricles (Figure 1D). MRA did not show any abnormal findings (Figure 1E). The patient was discharged with little sequelae on Day 38. He was taking glimepiride for diabetes mellitus and atorvastatin calcium hydrate for hypercholesterolemia in addition to prednisolone when he was discharged.

A follow-up MRI performed 17 months later showed no abnormalities on DWI, but revealed that hyperintense lesions in the bilateral medial temporal cortex and around the lateral ventricles on FLAIR remained (Figure 1F). We had not performed a whole body positron emission tomography (PET) scan. But the patient had presented no symptoms of malignancy and his symptoms of encephalitis had not recurred.
more than one year after he had stopped taking steroids. Thus, paraneoplastic limbic encephalitis has been ruled out.

Discussion

Takahashi reported 2 cases of NHALE and recognized four clinical features in both cases: i) an episode of preceding infection such as a common cold; ii) the appearance of reversible high signal intensity lesions in bilateral hippocampi and amygdaloid bodies on DWI; iii) elevation of only interleukin-6 in CSF; and iv) marked neurological improvement following intravenous administration of high-dose methylprednisolone.4 Takahashi speculated that the immune reaction of the host might play a significant role in the pathogenesis of NHALE, based on these four clinical features. Our patient showed no symptoms of focal infection such as a common cold or collagen disease, and his low-grade fever might have been caused by NHALE.

Laboratory data in ambulant showed initial liver dysfunction and elevated C-reactive protein, but examination on admission showed that liver dysfunction and C-reactive protein had been normalized. The cause of the liver dysfunction was unknown, although a case of NHALE following a type-2 adenovirus infection that presented high fever and severe liver dysfunction has been reported.12

Steroid pulse therapy and gamma-globulin are effective against non-herpetic acute encephalitis with autoantibodies to GluR delta2 and epsilon2, and these antibodies in the CSF normalize during the clinical course.2,3 Intravenous and oral steroids, in addition to an intravenous gamma globulin infusion, are also effective against acute-onset non-neoplastic limbic encephalitis with hypogammaglobulinemia.13 Okamoto reported a case of paraneoplastic limbic encephalitis caused by an ovarian teratoma with autoantibodies to Glur in the CSF in which signs and symptoms improved following acyclovir and steroid pulse therapy.14 Symptoms of Hashimoto’s encephalopathy with antibodies against the amino terminus of enolase in the serum and those against Glur epsilon2 in the serum and CSF,15 as well as bilateral postural hand tremor, memory impairment, and insomnia caused by limbic encephalitis with the anti-voltage-gated potassium channel antibody,16 also improved following steroid pulse therapy.

According to an MRI study in 91 adult patients with NHALE, DWI lesions were found in 20 of 49 (40.8%) patients at 12.5±9.4 days after onset, and FLAIR lesions were found in 32 of 59 (54.2%) patients at 14.7±17.5 days after onset.17 Follow-up MRI in convalescence showed abnormal findings in bilateral hippocampi and amygdaloid bodies that were reversed on DWI.14 T2-weighted and FLAIR imaging abnormalities decreased or disappeared followed by limbic atrophy during convalescence.5 A T1-weighted MRI three months after onset in a 31-year old woman with NHALE showed a linear high-signal intensity in the hippocampi, and the lesions seemed to be a focal necrosis.12 MRI abnormalities in children with NHALE are also reversible.18,19 Takahashi et al.17 reported that MRI lesions appear in various stages after onset. However, we are unaware of any other case of NHALE in which a follow-up MRI disclosed other lesions during convalescence.

The neuropathological lesions in patients with NHALE were limited to the hippocampus and amygdala. The rostral portion of the hippocampus showed small foci characterized by neuronal loss with immunopositivity for cell cytokerin-5 and 19, suggesting preservation of neuronal structure. The neuropathological lesions in patients with NHALE, even if only a few lesions are found on the initial MRI, may indicate that there is a time lag between the disturbance or recovery of neurons and astrocytes. Thus, other lesions might appear occasionally during convalescence in patients with NHALE, even if only a few lesions are found on the initial MRI.

Conclusions

To our knowledge, this is the first published case of NHALE in which a follow-up MRI revealed that other lesions became more prominent after symptomatic improvement following steroid pulse therapy. The MRI findings of lesions in the temporal cortices were not compatible with those of demyelinating lesions. Although SPECT showed hypoperfusion in the whole brain, MR angiography did not show any abnormal findings on Day 2 or on Day 37. The lesions around the lateral ventricles were irreversible and it is not appropriate to consider them ischemic changes. The appearance of additional lesions after steroid therapy did not match the course of clinical symptoms and may indicate that there is a time lag between the disturbance or recovery of neurons and astrocytes. Thus, other lesions might appear occasionally during convalescence in patients with NHALE, even if only a few lesions are found on the initial MRI.

References


