Steroid-Responsive Limbic Encephalitis

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Abstract

A 71-year-old man presented with gradually progressing cognitive decline following acute febrile exanthematous disorder. The MRI showed an abnormality in the bilateral limbic systems. An elevation of cerebrospinal fluid (CSF) protein with lymphocyte pleocytosis was noted. Immunoblot of the CSF revealed the presence of anti-white matter antibodies that mainly recognized astrocytes. Intravenous steroid followed by oral steroid reduced the symptoms to a remarkable degree. The patient has now been successfully sustained with steroid for more than two years. We considered that this case is classified as non-paraneoplastic limbic encephalitis, and acquired autoimmunity played a major role in the pathogenesis of this case.
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Key words: encephalitis, dementia, MRI, limbic system, white matter, autoimmunity

Introduction

Among patients with encephalitis or encephalopathy of unknown etiology, there exist those who predominantly show cognitive decline with a sub-acute to chronic clinical course and who show an excellent response to steroid without obvious autoimmune disorders or steroid-dependent endocrinopathy. Consideration of the possibility of various types of encephalitis/encepalopathy as well as steroid-dependent cognitive impairment is easier when these conditions occur in a younger population than in older patients. This is because cognitive impairment in elderly patients might be diagnosed as being merely senile or presenile dementia. Actually, there have been several reports of senile or pre-senile dementia that has been successfully treated with steroids, i.e. so called steroid-responsive dementia (1) or steroid-sensitive dementia (2).

We encountered such a case with cognitive impairment, one who responded excellently to both intravenous and oral steroid administrations, and who furthermore showed limbic abnormalities on MRI. Cerebrospinal fluid (CSF) analyses revealed the presence of autoantibodies that selectively recognized central nervous system (CNS) components, especially astrocytes. We considered that the patient had limbic encephalitis. There was, however, no evidence of any malignant neoplasm. Furthermore, antoantibodies found in this case differed from the ones found in the patients with paraneoplastic limbic encephalitis (PLE) (3). This case should be meaningful regarding encephalitis associated with limbic abnormalities, steroid sensitivity and autoantibodies in limbic encephalitis. We therefore report the details of this case, as well as a literature review of similar cases.

Case Report

A 71-year-old man experienced low-grade fever and fine tremors in both hands at the end of December 1996. One week after the onset, five or six red spotty eruptions were noticed which looked as if he had been stuck by a needle in the left femoral cutis. The eruptions disappeared after several days without any treatment. Five days later, he became aware of an itching pain in the bilateral femoral regions, and he complained that this was unbearable even when his own clothes rubbed against the femoral cutis. The next day, the same pain spread to the left temporal skin of his scalp. On January 12, he was admitted to another hospital with a 38°C fever, a shaking chill and loss of appetite. The patient had lost 7 kg in weight since the onset. Several days after admission, he could not remember how, why and with whom he had been admitted to the hospital. The unbearable pain in the head and femoral cutis disappeared after use of a non-

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steroidal anti-inflammatory agent. He was discharged from the hospital on January 26, although a minor fever still persisted. On February 14, about six weeks after onset of the initial symptoms, he was admitted on foot with his family's support to our hospital's department of internal medicine. On admission, he displayed no abnormality on physical examination except for oral moniliasis. Routine admission studies, including urinalysis, hemogram, blood chemistries, erythrocyte sedimentation rate, chest X-ray and electrocardiogram, were all normal and the blood examination at this time was the first since the onset. Physical and serological examination ruled out collagen diseases, infectious endocarditis, sarcoidosis, Behçet disease and tuberculosis. During hospitalization his memory loss and disorientation were markedly worsened. He often mistook his hospital room and could not remember the names of inquirers. After further consultancy he was transferred to the neurology division.

At the first neurological examination, the patient's consciousness was alert but severe disorientation was noticed. He could not say what day of the week it was, nor tell us his own age or birthday. Revised Hasegawa's dementia scale (HDS-R) indicated 10 (full score is 30 and anything under 20 is suspected as dementia). Neither aphasia, apraxia, nor agnosia were present. Cranial nerves were intact except for the bilateral papilloedema. There was a mild degree of Barré's sign in his right arm but no laterality in his deep tendon reflexes. Planter responses were flexor. Mild rigidity was noticed bilaterally in his arms. There was no abnormality in the sensory or cerebellar systems. An electroencephalograph (EEG) showed slow, diffuse activity with paroxysmal slow wave bursts. Somatosensory evoked potentials, brainstem auditory evoked potentials and visually evoked potentials indicated no abnormalities. Lyme disease antibody, Tsutsugamushi disease antibody and Weil-Felix reaction were all negative. CSF analyses revealed initial pressure 80 mmH_2O, total protein 92 mg/dl, sugar 57 mg/dl, lymphocytes 33/μl, polymorph nuclear (PMN) cells 6/μl, and red blood cells 0/μl. Viral antibodies in CSF (HTLV-1, HIV, eccho, coxsackie, mumps, measles, rubella, varicella zoster, herpes simplex, Epstein-Barr, Japanese encephalitis, and cytomegalo virus) were all within normal limits. Myelin basic protein was 4.9 ng/ml (normal<4.0 ng/ml). Anti-neuronal-cell antibodies seen in paraneoplastic syndrome, including anti-Hu antibodies were absent in the CSF. Cranial MRI revealed bilateral limbic system abnormalities, with low signal intensity on T1-weighted image (T1WI) and high signal intensity on T2WI (Fig. 1A, B, C, and D).

EEG abnormalities were improved by valproate sodium therapy; however, amnesic symptoms showed no obvious change. After confirming no beneficial effect of the intravenous administration of aciclovir (1,000 mg daily for 10 days), a course of methylprednisolone (500 mg/day for 3 days) followed by oral prednisolone (30 mg/day) was started. As a result of the methylprednisolone treatment, malaise disappeared and low grade fever was completely resolved. Confusion and amnesia gradually receded. Papilloedema also disappeared. This fact might indicate that intracranial hypertension existed for a certain period of time. HDS-R increased to 19 on May 21. MRI was followed up on May 29, 1997 (Fig. 1E and F). Abnormal signal intensities in the limbic systems showed improvement, while cerebral atrophy and white matter hyperintensity along the lateral ventricles became obvious. He was discharged on June 1, 1997. On outpatient examination several months later, a marked improvement was noted in both HDS-R (28 point) and CSF analysis (protein: 60 mg/dl, lymphocytes: 5/μl and PMN cells: 0/μl). The prednisolone doses were gradually decreased and suspended altogether from late October 1997. The memory deficits subsequently reappeared, however. HDS-R decreased to 10 points. CSF analysis showed protein 91 mg/dl, lymphocytes 18/μl, and PMN cells 0/μl. Prednisolone 10 mg was consequently restarted on December 1, 1997. Subsequently HDS-R recovered to 22 points on December 22 and 24 points on May 31 1998. The patient now visits our hospital once a month and shows no neurological deficits with a daily 7.5 mg intake of prednisolone and the patient and his family have no complaints. His wife says that previously he was very shy and reticent before the onset of the disease but that subsequently he has become a talkative and jolly person. We consider that the patient's mental alteration is a consequence of the disease rather than any adverse effect of steroid therapy. We could not rule out the possibility that this patient was suffering from PLE, because paraneoplastic symptoms sometimes precede the appearance of any evident neoplasm (3). Using immunoblotting we subsequently analyzed the CSF derived from the patient to confirm whether or not there were antibodies that recognized the CNS components as in a previous report (4) (Fig. 2A). As a consequence we found antibodies that mainly react with human white matter extract at 38 to 42 kDa fractions. There were several indistinct bands in the white matter at 38 to 50 kDa and in the gray matter at 42 kDa. These antibodies did not react with non-CNS tissues or cells.

Immunohistological procedures (4) involving staining according to the avidin-biotin peroxydase complex (ABC) method showed that the autoantibodies reacted with a cytoplasm of astrocytes in an acetone-fixed specimen derived from frozen rat cerebrum (subpial, cortico-medullary junction and other whole cerebral regions) (Fig. 2B). These results seemed to correspond to the white matter abnormalities in the MRI examination.

Discussion

This case showed some characteristic findings: an excellent response to steroid, MRI abnormalities in the limbic systems, and the presence of anti-white matter antibodies. Caselli et al (5) reported on five patients with progressive cognitive decline, psychosis, and unsteady gait that proved to be an excellent example of steroid responsiveness known as nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM). The authors indicated that the NAIM might con-

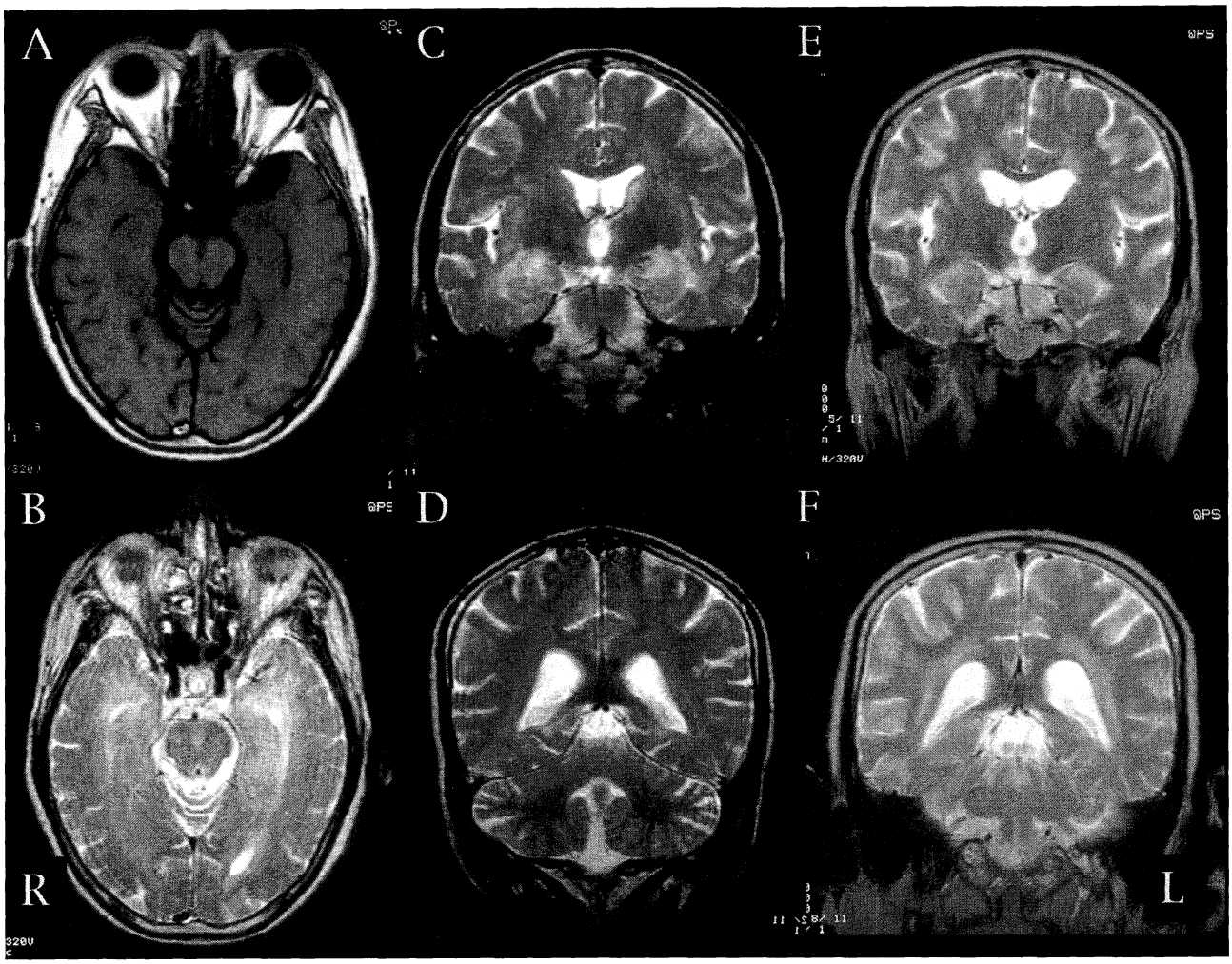

Figure 1. MR images. A, B, C, and D were taken on April 27 1997; E and F were taken on May 29 1997. A: axial T1WI; B: axial T2WI; C: coronal T2WI at the anterior horn level; D: coronal T2WI at the middle portion of lateral ventricles; E: coronal T2WI at the anterior horn level; F: coronal T2WI at the middle portion of lateral ventricles. MR images showed abnormal signal loci (low signal in T1WI and high signal in T2WI) in bilateral amygdala and hippocampus (A, B, C, and E). These lesions revealed no enhancement with gadolinium (data not shown). Moderate cerebral atrophy with periventricular high-signal area in T2WI became evident in later series of MR images (E and F).

tain meningoencephalitides associated with Sjögren's syndrome, hypereosinophilic syndrome, Hashimoto's disease and systemic lupus erythematosus. These disease states share similar features in their symptoms and, most importantly, steroid responsiveness. Unlike the present case, however, these five cases did not show any MRI abnormalities.

The clinical pictures of the present case have a certain similarity to PLE (3), the limbic dysfunction associated with malignant neoplasm. Throughout more than two years of observation, there was no evidence of cancer in the present case and thus it would not be classified as PLE. Nevertheless, there have been a few reports presenting demented patients with encephalomyeloneuritis (6) or encephalomyeloneuropathy (7) with limbic abnormality and with the absence of cancer (non-paraneoplastic limbic encephalitis or encephalopathy: non-PLE). Just as with PLE, non-PLE discloses peripheral nerve involvement with high frequency (6, 7). The etiological candidate of non-PLE is considered to be autoimmunity or an infectious agent. Due mainly to the rarity of the cases, the application of steroids for these conditions is not mentioned. As rare cases whose affected lesions were restricted in the limbic systems, Kohler et al (8) reported on two cases of limbic encephalitis without malignancy. One patient developed progressive dementia and died 8 months after the onset. The other patient showed amnesic syndrome that was stabilized with high-dose dexamethasone treatment over 12 months. These two also had epileptic seizures and showed signs of mild lymphocytic pleocytosis in the CSF. The authors concluded that limbic encephalitis is caused not only by the remote effect of a neoplasm but also

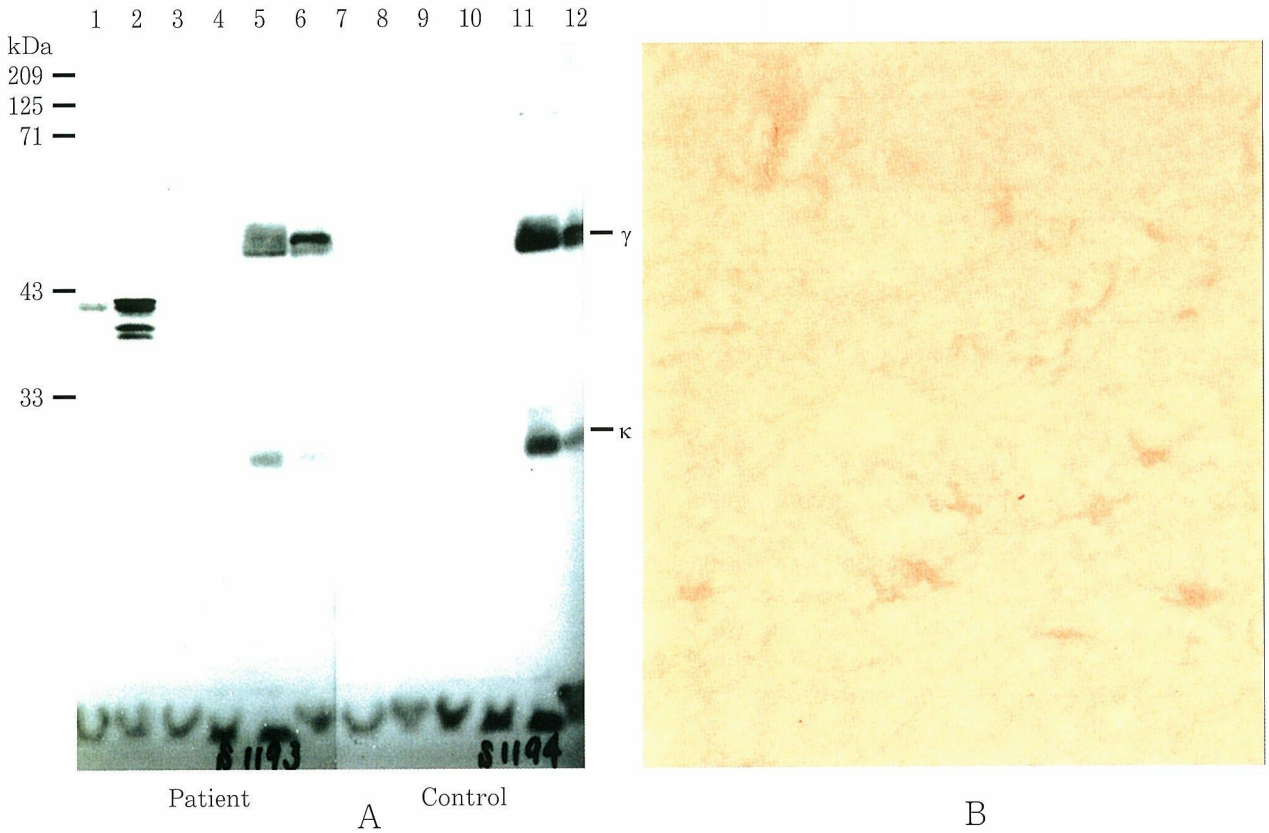

Figure 2. A: Immunoblot analysis. Immunoblotting stained with CSF from the patient and an age-matched disease control was performed using biotinized anti-human IgG (H + L) as the second antibody. Each lane of the blot contained 50 μg of total protein. Lanes 1 and 7: human cerebral gray matter; lanes 2 and 8: human cerebral white matter; lanes 3 and 9: mouse cerebellum; lanes 4 and 10: human neuroblastoma cells (NB1); lanes 5 and 11: human liver; and lanes 6 and 12: human peripheral nerve (sciatic nerve). In lane 2 (human white matter), there were four obvious bands at 38 to 42 kDa and several indistinct bands at 38 to 50 kDa. In human gray matter (lane 1), two indistinct bands at 42 kDa were also observed. The bands of gamma and kappa in the figure indicate the endogenous immunoglobulin that reacts to the second antibody. B: Immunohistochemistry. Acetone-fixed frozen rat cerebellum was stained with CSF diluted 1:50 as the first antibody and biotinized anti-human IgG (H and L) as the second antibody and detected with the ABC method. The autoantibodies in CSF reacted diffusely with the cytoplasm of astrocytes.

by immunological mechanisms, and that the use of steroids may be beneficial in this condition. Recently, Mori et al (9) reported a 21-year-old woman who subacutely developed memory loss subsequent to gastroenteritis as non-PLE. Combined immunosuppressive treatment with plasmapheresis and immunoglobulin improved the patient's clinical symptoms.

Western blot and immunohistochemical analyses of CSF obtained from such patients reveal the presence of antibodies that react to between 38 and 50 kDa astrocyte components. In Table 1, we summarized the representative autoantibodies related to PLE. Antibodies found in our case differ from any antibodies listed in the Table 1 with regard to antigen-expressing cell types or the molecular weight of the antigens. Regarding the presence of the anti-white matter antibodies, Kaneko et al (10) reported a demented patient who had serum autoantibody that reacted to a 48 kDa nuclear protein in human astrocytes and neurons. The patient exhibited white matter abnormalities in MRI, a finding that resembles the present case. However, the symptoms of the patient did not respond to oral steroid therapy. On the other hand, in three patients with ordinary PLE in the absence of anti-Hu antibodies, Honnorat et al (11) identified the presence of antibodies that recognized a cytoplasmic antigen in a subpopulation of glial cells in the white matter, especially oligodendrocytes. Whether or not the anti-white matter antibodies play an essential role in the pathogenesis of these cases, or are merely an immunological reaction following the destruction of the white matter components, is unknown. However the glial cells, as well as neurons, seem to be potential targets of the immuno-mediated attacks.

In a literature review with regard to steroid sensitive encephalitis/encephalopathy without malignant neoplasm, and autoantibodies that selectively recognize CNS compo-

Table 1. Characteristics of Autoantibodies in Paraneoplastic Limbic Encephalitis

Antibody	Antigen	M.W.	Malignancy	Reference
Anti-Hu	Neuronal nuclear proteins	35 to 40 kDa	SCLC, breast, etc.	12
Anti-Ma2 (Ta)	Granular structures in neuronal cytoplasm	40 and 50 kDa	Testis, breast	13
Anti-CV2	Cytoplasm of oligodendrocytes	66 kDa	SCLC	11
Anti-amphiphysin	Cytoplasmic surface of synaptic vesciles	128 kDa	SCLC	14
Anti-VGKC	VGKC	*	SCLC, Thymoma	15
	Cytoplasm of astrocytes	38 to 50 kDa	–	Present case

M.W.: molecular weight, SCLS: small cell lung cancer, VGKC: voltage-gated potassium channel, *usually undetectable in immunoblot.

nents and relate to cognitive impairment, some of the cases reviewed seem to be related to para- or post-infectious conditions, while others seem to be related to autoimmunity. In particular, in the present case, the episode occurred in the course of an acute exanthematous disorder. We do not recommend patients with cognitive impairment and putatively with immunological abnormalities to undergo a course of empirical corticosteroids, or other immunosuppressive therapies. However, it is important to note that there are a few patients who exhibit an excellent response to steroids, and who, therefore, are potentially treatable.

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