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Acute limbic encephalitis: A new entity?

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Abstract

Clinical cases similar to herpes simplex virus (HSV) encephalitis have accumulated in Japan. Detailed examinations have failed to demonstrate HSV infection. Recently, these cases have been named "non-herpetic acute limbic encephalitis". Only a single autopsy case was so far reported in an abstract form, because many cases showed a good prognosis. The case presented here was that following fever, a 59-year-old woman developed disturbance of consciousness and uncontrollable generalized seizures. Brain MRI revealed abnormal signals in the bilateral medial temporal lobe and along the lateral part of the putamen. Autoantibody against the NMDA glutamate receptor (GluR) IgM-ε2 was detected in the serum, and the GluR IgG-δ2 antibody was positive in cerebrospinal fluid. She died 12 days after onset. An autopsy examination revealed scattered foci consisting of neuronal loss, neuronophagia and some perivascular lymphocytic infiltration in the hippocampus and amygdala, but no haemorrhagic necrosis in the brain. HSV-1, -2 and human herpes virus-6 were negative immunohistochemically. We believe that our autopsy case may contribute to understanding the neuropathological background of non-herpetic acute limbic encephalitis.

Keywords: Acute encephalitis; Status epilepticus; Autopsy; Non-herpetic acute limbic encephalitis; Herpes simplex encephalitis

Limbic encephalitis is usually considered to be paraneoplastic, occurring subacutely in association with specific neuronal antibodies [2]. Among the cases with reversible acute or subacute non-paraneoplastic limbic encephalitis, voltage-gated potassium channel (VGKC) antibodies have been reported [12]. Autoantibodies against the NMDA glutamate receptor (GluR), which is considered to be related causally to partial seizures [11], were detected in the acute non-herpetic encephalitis [3].

In Japan, acute encephalitis, in which the clinical picture was comparable with that of herpes simplex virus (HSV) encephalitis but where evidence of HSV infection was not demonstrated, has been reported [5]. Recently, these cases have been named "non-herpetic acute limbic encephalitis" as a possible new subgroup of limbic encephalitis [5,9]. It has been proposed that mild infections and immunological process are the cause of this disease from clinical findings and cerebrospinal fluid (CSF) cytokine levels, elevated level of interleukin-6 [5,9] and unelevated level of interferon-γ [1]. Moreover, it has been indicated that acute limbic encephalitis, HSV encephalitis and other acute limbic encephalitis were etiologically interrelated, because cases of limbic encephalitis similar to non-herpetic acute limbic encephalitis were reported [1,9].

Many previously reported cases of non-herpetic acute limbic encephalitis have shown a rather favorable prognosis [1,4,5,7,8,10]. For this reason, only a single autopsy case was so far reported in an abstract form [7]. We believe that this report contributes to understanding the neuropathological background of the acute limbic encephalitis of unknown etiology.

One week after a fever, a 59-year-old woman developed progressive disturbance of consciousness following generalized tonic seizures. The brain computed tomography showed no abnormalities. CSF examinations showed mononuclear cells 10 μl/l, protein 50 mg/dl and glucose 143 mg/dl. The seizures continued, even though multiple anticonvulsants were administered and mechanical ventilation was performed. Eight days after the onset of unconsciousness and seizures, brain magnetic resonance imaging (MRI) with T2-weighted and FLAIR images revealed high signal intensities in the bilateral medial temporal lobes and along the lateral part of the putamen (Fig. 1). She was admitted to our hospital 10 days after the onset of the seizures. She showed marked emaciation and pneumonia complications. Recurrence of generalized tonic seizures

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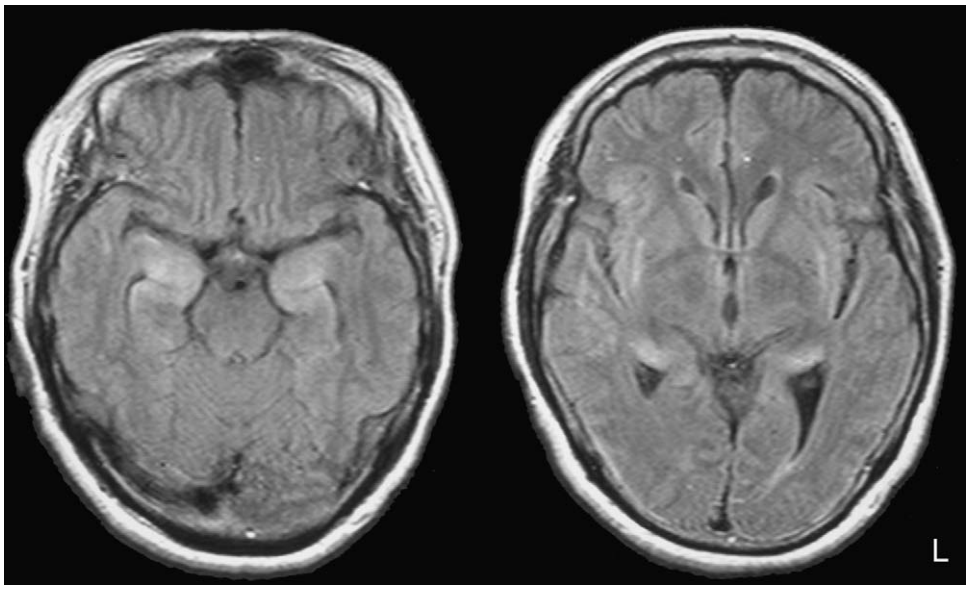

Fig. 1. FLAIR MRI images. High signal intensity is seen in the bilateral medial temporal lobe and the lateral part of the putamen.

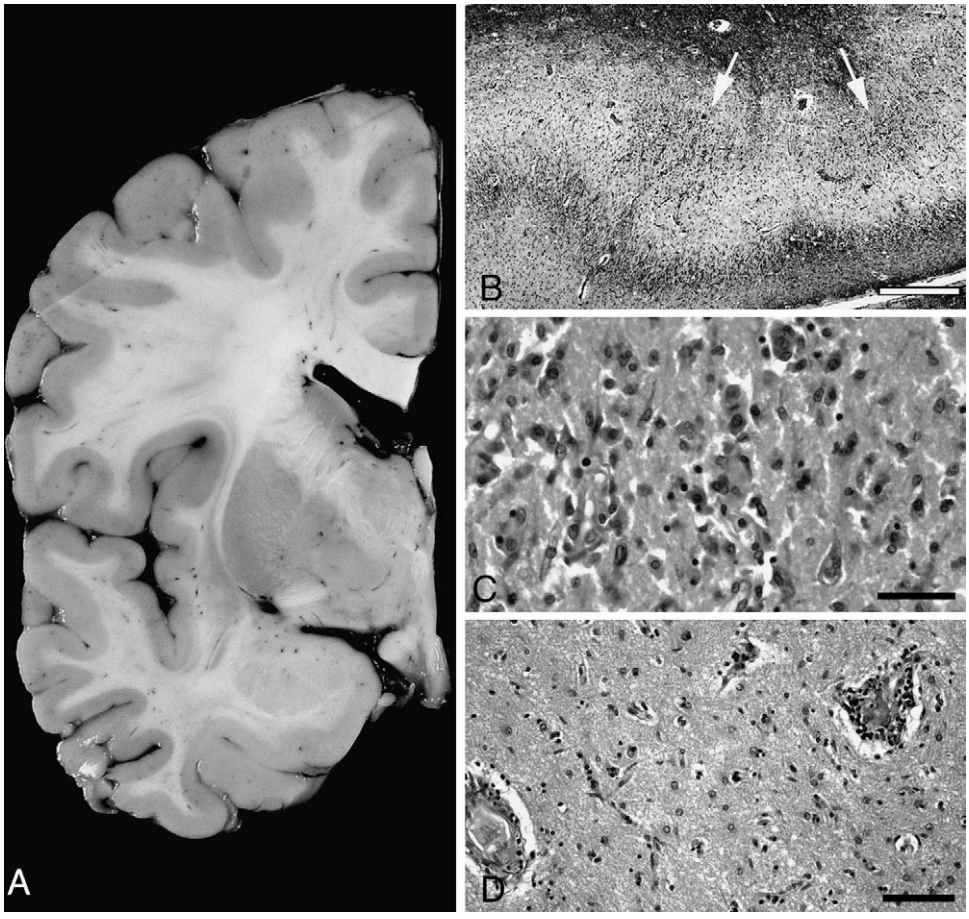

Fig. 2. Neuropathological findings: (A) coronal slice through the left cerebrum. No lesions visible on macroscopic examination; (B) foci of neuronal loss (arrows) surrounded by spongy state in the rostral CA1 of hippocampus. Klüver–Barrera staining (Bar 500 μm); (C) foci of neuronal loss and neuronophagia in the rostral CA1 of hippocampus. Hematoxylin and eosin (HE) staining (Bar 50 μm) and (D) neuronal loss, fibrillary astrocytosis and lymphocytic perivascular cuffing were seen in the rostral part of amygdala. HE staining (bar 50 μm).

failed to be controlled with propofol and acyclovir in addition to the anticonvulsants. An electroencephalogram revealed multifocal spikes without periodic synchronous discharges and periodic lateralized epileptiform discharges. Autoantibodies, including antinuclear antibody, anti-SS-A/B antibodies, and anti-Hu antibodies were all negative. Autoantibody against the GluR IgM-ε2 [11] in the serum was positive, autoantibody against GluR IgG-δ2 in the CSF was positive, and VGKC antibody and P/Q-type voltage-gated calcium channel antibodies were negative in the serum and CSF. Antibodies for several viruses including HSV in the serum and CSF were negative 10 days after the onset of seizures. She had acute renal failure complications and died 12 days after the onset of the seizures.

The direct cause of death was acute renal tubular necrosis and purulent pneumonia. Both laboratory data and pathological examination revealed that the patient did not have any malignant tumors or collagen disease. The brain, weighing 1183 g, was macroscopically unremarkable except for mild swelling (Fig. 2A). Microscopically, there were no leptomeningitis. The amygdala and hippocampus showed small foci of neuronal loss with neuronophagias, proliferation of microglias and hypertrophic astrocytes (Fig. 2B and C). These foci were surrounded by a spongy state. Only a few lymphocytic perivascular cuffings occurred in the amygdala (Fig. 2D). No intranuclear inclusion bodies were found anywhere. Immunohistochemistry for HSV-1, -2 and human herpesvirus-6 was negative. No tissue necrosis or haemorrhage were found in the cerebral cortex including the cingulate, insular, and parahippocampal cortex.

Besides demonstrating evidence of HSV infection, HSV encephalitis shows extensive necrosis with haemorrhage in the medial temporal lobe, insular and cingulate gyri bilaterally [6], where the brain MRI shows high signal intensities. Furthermore, the lesions are bilateral, but not always symmetrical in distribution. In our case, however, abnormal signal intensities were limited in the hippocampus and amygdala bilaterally and symmetrically. No haemorrhagic necrosis was found anywhere, even though there would not have been sufficient time for our patient to develop it. Finally, there were no intranuclear inclusions or immunohistological evidence of HSV infection.

Recently, it is suggested that the presence of autoantibodies against the GluR-ε2 in the CSF of non-herpetic acute encephalitis involves in autoimmune pathogenic mechanism [3,9]. In the CSF of this patient, autoantibody against the GluR-ε2 was negative, while the autoantibody against the GluR-δ2, which is against cerebellar Purkinje cell-specific antibody [11] was positive. The other similar cases as shown in Table 1 [1,4,5,7,8,10] were not examined for the presence of these antibodies. Unfortunately, it remains obscure that this antibody played a role in development of the disease in our case.

There has been only one pathological report of a patient similar to our case: a 53-year-old woman who died 36 days after the onset of illness, and showed neuronal loss in the hippocampus, and neuronophagia and gliosis in the amygdala [7]. As seen in the present patient, this patient showed no evidence of HSV infection, no apparent necrosis in the brain, and the

Table 1
Clinical characteristics and MRI abnormalities of patients with non-herpetic acute limbic encephalitis

Patients	Kohira et al. [4]	Kusuhara et al. [5]				Asaoka et al. [1]						Nonaka et al. [8]	Takahashi et al. [10]		Maki et al. [7]	Present case
		Case 1	Case 2	Case 3	Case 4	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6		Case 1	Case 2		
Age (year)	25	40	38	38	53	34	60	73	35	23	18	42	25	58	53	59
Sex	M	M	F	M	F	M	F	F	M	M	F	F	F	M	F	F
Clinical symptoms																
Impaired consciousness	2+	3+	3+	+	3+	2+	+	2+	2+	2+	2+	3+	+	+	3+	3+
Seizures	2+	2+	3+	+	–	+	+	+	2+	+	3+	3+	2+	–	3+	3+
Cerebrospinal fluid																
Cells (mm^3)	52	17	47	9	10	10	5	32	8	5	320	10	1	76	normal	10
Protein(mg/dl)	25	325	55	27	50	72	32	29	41	28	86	40	15	45	normal	50
MRI abnormalities																
Hippocampi	B	B	B	B	L	B	R>L	B	B	B	L>R	B	B	B	B	B
Amygdalae	B	B	B	B	L	B	R>L	B	B	B	L>R	B	B	B	B	B
Cingulate gyri	–	–	L	–	–	–	–	B	–	–	–	–	–	–	–	–
Sequelae	+	+	+	+	+	+	2+	2+	+	+	+	+	+	+	died	died

M: male; F: female; B: bilateral; L: left; R: right, (−): negative; (+): mild; (2+): moderate and (3+): severe.

lesions were exclusively limited to the hippocampus and amygdala. In this regard, similar clinical cases with acute encephalitis have accumulated in Japan, as shown in Table 1 [1,4,5,7,8,10]. Many cases with this type of encephalitis showed good prognosis, although patients died because of uncontrollable generalized seizures during the clinical course. It is likely that our case showed the neuropathological changes of non-herpetic acute limbic encephalitis as a possible clinicopathological new entity.

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