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Case Report

Cerebellar symptoms in a case of acute limbic encephalitis associated with autoantibodies to glutamate receptors δ2 and ε2

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1. Introduction

Glutamate, the major excitatory neurotransmitter in the mammalian central nervous system, activates both ion-channel-forming (ionotropic) and G-protein-coupled (metabotropic) glutamate receptors (GluRs). Pharmacological and molecular techniques have been used to identify a large variety of ionotropic and metabotropic GluRs. Ionotropic GluRs can be grouped into the following categories according to their agonist selectivity and sequence homology: α-amino-3-hydroxy-5-methyl-4-isoxazole propionate-type receptors (GluRα), N-methyl-D-aspartate (NMDA)-type receptors (GluRζ, GluRχ, and GluRε), kainate receptors (GluRβ and GluRγ), and GluRδ2. Within these GluRs, autoantibodies to NMDA-type GluR have recently been recognized as biomarkers for non-herpetic acute limbic encephalitis (NHALE) [1]. Indeed, the autoantibody to GluRε2 has been detected in patients with NHALE, who typically show psychiatric symptoms. However, the cerebellar symptoms associated with autoantibodies to GluR have not been emphasized in the literature. We herein report a rare case of acute limbic encephalitis with cerebellar symptoms associated with autoantibodies to GluRε2 and δ2.

2. Case report

A 36-year-old woman had lower back pain with fever, and 2 days later presented with a flat mood. She consulted our department 4 days after the onset of emotional disturbances. On admission, her temperature was 38.7 °C; other vital signs and general examination were normal. Cranial nerve examination revealed no abnormalities. Seizure-like movements of the extremities were observed. No cerebellar sign was detected. Her muscle power was full, with normal tendon reflexes. No sensory deficits or evidence of meningeal signs were observed. Her blood examination was notable for a mildly elevated in white blood cell count (12,750/μL with 83% neutrophils). A cerebrospinal fluid (CSF) examination showed a mild elevation in cell count of 21/μL (95% lymphocytes) with normal glucose level (75 mg/dL) and protein level (26 mg/dL). Both the oligoclonal immunoglobulin G (IgG) band and myelin basic protein were negative. Brain magnetic resonance imaging (MRI) showed no abnormalities. After admission, she progressively lost consciousness and a generalized seizure followed, which was resolved by propofol. An electroencephalogram showed slow-wave abnormalities (2–6 Hz polymorphic delta and theta activity) without epileptic activity. Mechanical ventilation was required because she developed hypoventilation. On day 7, brain MRI showed a hyperintense area in the right insula on a fluid attenuated inversion recovery (FLAIR) image (Fig. 1A) and in the cerebellum on a diffusion weighted image (DWI). Abdominal MRI showed no abnormalities, including ovarian teratoma. Aciclovir 10 mg/kg body weight every 8 h was started for possible herpes simplex virus (HSV) encephalitis. IgG and IgM

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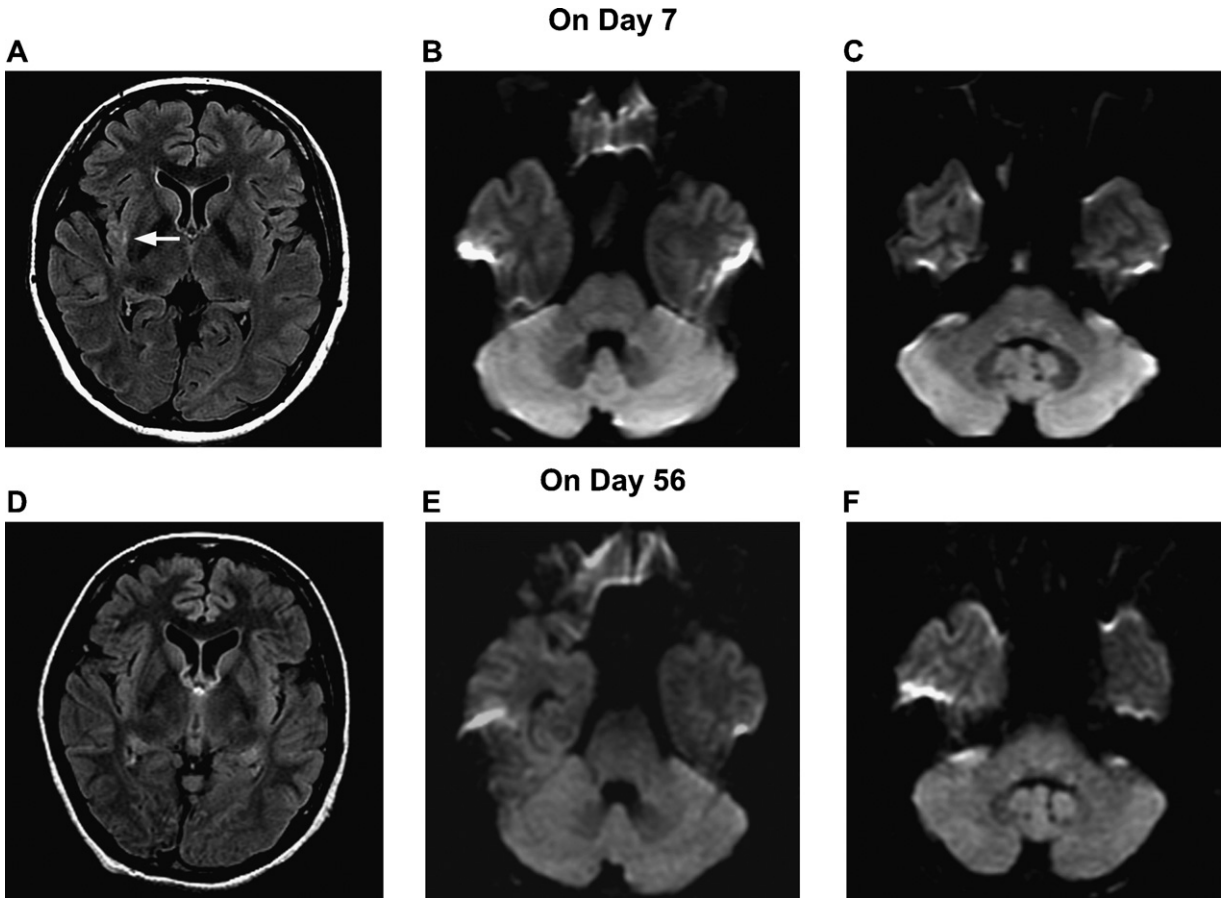

Fig. 1. Serial MRI of the patient. (A–C) MRI finding on day 7. The hyperintense area in the right insula (white arrow) was observed on a FLAIR image (A), and the hyperintense area in the cerebellum was observed on a DWI (B, C). (D–F) MRI findings on day 56. There were no abnormalities in MRI findings.

antibodies to HSV were negative in both the CSF and serum, and aciclovir was discontinued. Tests for autoantibodies to GluR δ2 and ε2 were positive in the CSF (sampled on day 3) (Table 1).

We subsequently performed plasma exchange for possible autoimmune limbic encephalitis. After the fifth plasma exchange (on day 30), the patient gradually regained consciousness and the generalized seizures subsided, allowing the discontinuation of propofol. However, she subsequently presented with cerebellar signs. She exhibited ocular overshoot, gaze-evoked nystagmus, and dysarthria with scanning speech. There was severe limb and truncal ataxia with intention tremor. Finger-to-nose and heel-to-knee test showed mild dysmetria and decomposition of limbs. Muscle tone was hypotonic; and deep tendon reflexes were normal. She could not sit upright or maintain an erect posture without support due to severe cerebellar symptoms. After the seventh plasma exchange, her neurological complications were resolved, and she became able to sit upright or maintain an erect posture without support. On day 56, a brain MRI showed no apparent abnormities in either the insula (Fig. 1D) or the cerebellum (Fig. 1E and F). We made a diagnosis of acute limbic encephalitis with cerebellar symptoms associated with autoantibodies to GluRδ2 and ε2. She was discharged on day 73.

3. Discussion

To our knowledge, this is the first case of acute limbic encephalitis with cerebellar symptoms associated with autoantibodies to GluRδ2 and GluRε2. Our case started with prodromal symptoms, followed by early symptoms like emotional disturbances, fever and movement disorders. Later on, she developed loss of consciousness, seizures and hypoventilation. These clinical features resemble those reported in association with anti-NMDA receptor (NMDA-R) encephalitis. Previous studies suggested that NMDA-R encephalitis is associated with the autoantibody to the NR1–NR2 heteromers (GluRζ1/GluRε2), and the main epitope targeted by this autoantibody is in the extracellular N-terminal (NT) domain of the NR1 or NR2 subunits [1]. The autoantibody to GluRε2-NT2 was positive in our case (Table 1) while the autoantibody to the NR1–NR2 heteromers was not detected. The cerebellar symptoms became clinically evident after this classical pattern of NMDA-R encephalitis disappeared. The CFS and MRI findings in our case suggest that cerebellar symptoms become visible after other symptoms resolve. Taken these findings together, it is supposed that acute limbic encephalitis with cerebellar symptoms is an atypical form of anti-NMDA-R encephalitis.

Table 1
Optical density of antibody to GluR.

	GluRε2-NT2	GluRε2-CT1	GluRδ2-NT	GluRδ2-CT
CFS	0.823 (0.162 ± 0.055)	0.909 (0.189 ± 0.061)	0.961 (0.172 ± 0.086)	0.847 (0.261 ± 0.100)
Serum	0.346 (0.432 ± 0.133)	0.517 (0.556 ± 0.140)	0.502 (0.583 ± 0.148)	0.817 (0.638 ± 0.202)

Optical densities assessed by ELISA are shown (mean ± standard deviation for control data).

Regarding the relationship between the cerebellum and GluR, it is known that GluRδ2 is expressed predominantly in cerebellar Purkinje cells and plays a crucial role in cerebellar functions [2]. In addition, a previous study suggested that 6% of NMDA-R encephalitis had MRI-abnormalities of the cerebellum, although cerebellar symptoms have not been noted in the literature [1]. In contrast to GluRδ2, the expression of GluRε2 mRNA is restricted to the forebrain including the cerebral cortex and limbic system after birth, and GluRε2 is associated with memory and learning [3]. We thus inferred that the cerebellar symptoms were associated with the autoantibody to GluRδ2. Our case provides clinical evidence for the anatomical and functional significance of GluRδ2 for the cerebellum. Further studies should establish the relation between deficits in cerebellar functions and the autoantibody to GluRδ2.

Recent literature has reported a case of anti-NMDA-R encephalitis presenting with cerebellar symptoms such as scanning speech, square-waves jerks on ocular pursuit, bilateral hypermetria, and gait ataxia [4]. In that case, tests for autoantibodies to NMDA-R were positive in the serum. It was notable that, as in our case, the cerebellar symptoms became clinically evident only after the patient regained consciousness. The authors concluded that the cerebellar symptoms observed in that case could be explained by a disabling action on glutamate NMDA-R by the antibody to NMDA-R. However, the significance of the autoantibody to GluRδ2 in NHALE presenting with cerebellar symptoms was not emphasized in this report. Therefore, our case is a novel one that may have important implications: namely, that the autoantibody to GluRδ2 is critical for cerebellar symptoms in NHALE including anti-NMDA-R encephalitis.

It has been supposed that immunotherapy such as plasma exchange, corticosteroids, and intravenous immunoglobulin (IVIg) is an effective therapy for NMDA-R encephalitis [1]. A recent study suggests starting with IVIg or plasma exchange, combined with steroids. If no proper reaction is seen in 10–14 days, they suggest continuing with secondary therapy like rituximab or cyclophosphamide [5]. Indeed, our case showed relatively rapid recovery from her neurological complications after the seventh plasma exchange, although there was no apparent malignancy on clinical examination. These observations suggest the effectiveness of plasma exchange for resolving cerebellar as well as psychiatric symptoms, although spontaneous improvement cannot be completely ruled out.

4. Conclusion

We report a case of acute limbic encephalitis having cerebellar symptoms associated with autoantibodies to GluRδ2 and GluRε2. Acute limbic encephalitis with cerebellar symptoms is presumably an atypical form of anti-NMDA-R encephalitis. Extensive assessments of cerebellar symptoms would be valuable for planning effective rehabilitation programs for these patients.

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