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Case report

The first pediatric anti-lactosylceramide antibody-positive encephalomyeloradiculoneuropathy

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ABSTRACT

Introduction: The anti-lactosylceramide (LacCer) antibody is an anti-neutral glycolipid antibody that is involved in the pathogenesis of encephalomyeloradiculoneuropathy (EMRN). It causes acute and subacute injuries to both the central and peripheral nerves. However, no pediatric cases of anti-LacCer antibody-positive EMRN have been reported so far.

Case: A 12-year-old girl presented with signs of meningitis. She subsequently showed disturbance of consciousness and flaccid tetraplegia and was placed on mechanical ventilation due to respiratory failure. MRI showed lesions in the cerebral white matter, basal ganglia, medulla oblongata, as well as the anterior horn of the spinal cord at the C2 to Th1 and Th11 to L1 levels. Nerve-conduction studies showed axonal neuropathy of the motor nerves. After steroid pulse therapy, high-dose immunoglobulin therapy, and plasma exchange, the lesions gradually regressed, and the neurological symptoms improved steadily. The neurological sequelae were minimal at 6 months after disease onset. Although serum anti-aquaporin 4 and anti-myelin oligodendrocyte glycoprotein antibodies were negative, she showed positive anti-lactosylceramide antibody in both serum and cerebrospinal fluid, indicating that these antibodies may be involved in the pathogenesis of this disease.

Conclusion: The first pediatric case of anti-LacCer antibody-positive EMRN showed similar features to the same disease in adults. Anti-neutral glycolipid antibodies should be measured in children presenting with a wide range of neurological symptoms involving both central and peripheral nerves.

1. Introduction

The anti-lactosylceramide (LacCer) antibody is an anti-neutral glycolipid (Ngl) autoantibody involved in the pathogenesis of encephalomyeloradiculoneuropathy (EMRN), an acute and subacute neurological disorder involving both central and peripheral nerves. Adults with anti-LacCer antibody-positive EMRN show muscle weakness, disturbances of consciousness, autonomic symptoms, and multiple peripheral neuropathies and present with a relatively good response to immunotherapy. Here, we report the first pediatric case of anti-LacCer antibody-positive EMRN.

2. Case

A 12-year-old girl presented with fever, headache, and posterior neck pain that appeared two weeks before admission to our hospital. Cerebrospinal fluid (CSF) examination revealed a cell count of 242/μL and a protein level of 86 mg/dL. The IgG index was 0.45, and the myelin basic protein (MBP) level was 1380 pg/mL. Despite methylprednisolone pulse therapy (IVMP), she showed impaired consciousness, flaccid tetraplegia with loss of deep tendon reflexes, disturbances of the bladder and bowel functions, and rapid progression of respiratory failure. She was transferred to our hospital for further evaluation and treatment.

Upon examination, her Glasgow coma scale was E3VTM6, with a tendency toward somnolence, but she was able to follow commands. She showed no spontaneous breathing, a body temperature of 39 °C, and short-term fluctuations in blood pressure and pulse rate. Cranial nerve examination revealed limited abduction of the left eye. She had flaccid paralysis of all four limbs, and a manual muscle strength test (MMT) showed that only her left upper arm had a score of 2, while the remaining scores were 0, indicating complete paralysis. There seemed to be no sensory disturbance. Urinary retention and anal sphincter relaxation were observed, indicating bladder and rectal disturbances.

Test results showed that the CSF had a high cell count of 68/μL, protein level of 75 mg/dL, MBP of 754 pg/ml, IgG index of 0.51, negative

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oligoclonal band, and negative bacterial culture. MRI showed T2 and Fluid-attenuated inversion recovery (FLAIR) high-signal lesions in the cerebral white matter, basal ganglia, medulla oblongata, as well as the anterior horn of the spinal cord at the C2 to Th1 and Th11 to L1 levels (Figure 1). No abnormal contrast enhancement was observed. Peripheral nerve-conduction study (NCS) showed decreased compound muscle action potential (CMAP) in all tested nerves, predominantly in the lower extremities, and F-waves showed prolonged latency and decreased rate of appearance in the tibial nerve (Table 1). The values for all sensory nerves were within the normal limits. EEG, brainstem auditory evoked potential, and visual evoked potential test were normal. Enterovirus PCR of the CSF, sputum, and stool were negative. Tests for serum anti-ganglioside,

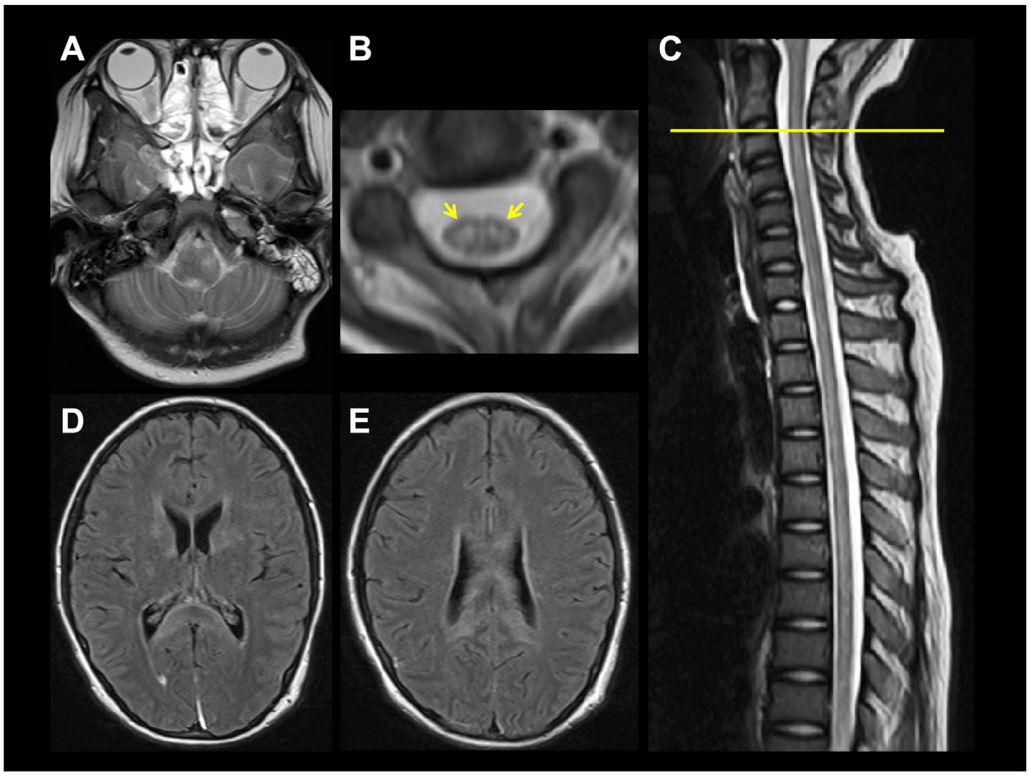

Figure 1. MRI of the brain and spinal cord. (A—C) T2-weighted images of the brainstem and spine. (B) Axial image derived from the C2/C3 level in (C). Symmetrical high signal is seen in the anterior horn (arrow). (D, E) FLAIR images of the cerebrum.

Table 1. Nerve conduction studies. Abbreviations; CMAP, compound muscle action potential; D, distal; MCV, motor nerve conduction velocity; P, proximal; NE, non-evoked.

Nerve	Day 16	Day 35	Day 75	Day 264	Day 372
Motor nerve					
Distal latency (ms)					
Median	2.8/–	3.6/3.5	3.2/3.0	3.4/3.6	3.0/2.7
Ulnar	2.5/–	2.8/2.5	2.6/2.6	2.7/2.8	2.9/2.2
Tibial	2.9/3/2	3.5/3.8	NE/NE	5.0/4.8	8.4/5.5
CMAP (mV)					
Median	3.8(D)3.4(P)/–	1.9(D)1.8(P)/6.5(D)5.4(P)	6.7(D)6.6(P)/8.7(D)8.1(P)	11.9(D)10.0(P)/13.6(D)8.1(P)	16.1(D)16.0(P)/16.0(D)14.6(P)
Ulnar	2.1(D)2.6(P)/–	1.0(D)1.1(P)/5.0(D)4.9(P)	4.5(D)4.3(P)/6.9(D)6.2(P)	8.3(D)7.5(P)/10.4(D)7.0(P)	11.4(D)10.6(P)/12.4(D)11.8(P)
Tibial	4.5(D)7.8(P)/5.4(D)/6.7(P)	0.9(D)1.9(P)/0.4(D)NE(P)	NE/NE	0.3(D)0.3(P)/0.6(D)0.3(P)	0.15(D)NE(P)/0.10(D)NE(P)
MCV (m/sec)					
Median	47.3/–	47.0/50.6	48.4/54.7	51.3/51.6	48.3/58.1
Ulnar	54.8/–	49.6/51.9	50.4/55.1	53.8/51.0	55.6/61.1
Tibial	45.2/45.0	39.0/NE	NE/NE	40.1/42.3	NE/NE
F latency (ms)					
Median	–/–	27.6/26.7	27.6/26.0	28.7/27.0	26.0/24.8
Tibial	49.6/50.5	NE/NE	NE/NE	NE/NE	53.4/52.2
F wave occurrence (%)					
Median	–/–	50/100	66/50	70/56	90/90
Tibial	83/83	0/0	0/0	0/0	100/100

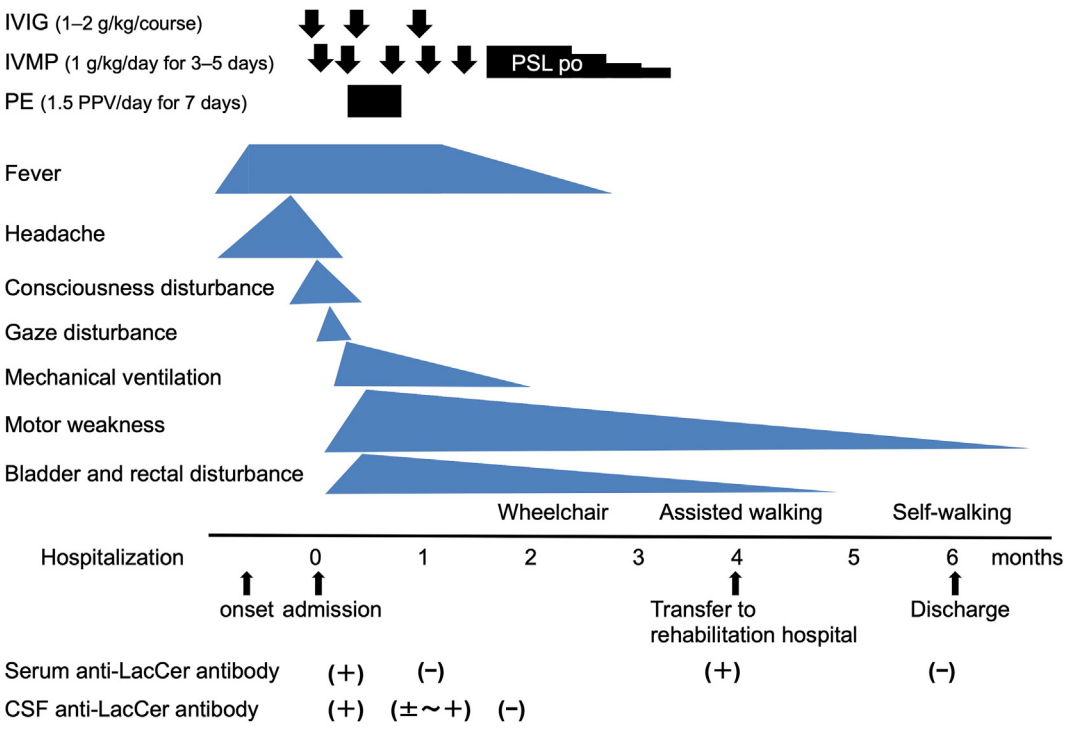

Figure 2. Clinical course of the patient. Abbreviations: anti-LacCer antibody, anti-lactosylceramide antibody; CSF, cerebrospinal fluid; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; PE, therapeutic plasma exchange; PPV, predicted plasma volume; PSL, prednisolone.

anti-aquaporin 4, and anti-myelin oligodendrocyte glycoprotein antibodies were negative, but both serum and CSF samples were positive for anti-LacCer antibodies.

For treatment, five courses of IVMP (1000 mg/dose for 3–5 days), three courses of high-dose intravenous immunoglobulin therapy (1–2 g/kg/course), and seven rounds of plasma exchange (1.5 estimated plasma volume/dose) were administered. The disturbance of consciousness and limitation of left eye abduction improved promptly after treatment initiation. The fever, which was considered to be caused by both the intracranial inflammation and autonomic neuropathy, lasted for a long time, and finally resolved approximately 2 months after the onset. One month after the onset, the patient had MMT score of 1 and required tracheostomy for respiratory muscle weakness. Her muscle strength improved steadily with immunotherapy and intensive rehabilitation. The tracheal hole was closed at 3 months, and the patient was able to walk with assistance at 4 months after onset. Six months after onset, she was able to walk unaided with an MMT score of 4 with disappearance of anti-LacCer antibodies from serum. No cognitive impairment or bladder and rectal dysfunction is noted (Figure 2). The disease has not relapsed for 1.5 years, with persistently negative anti-LacCer antibodies from serum.

MRI at 1 month of onset showed that the lesions in the cerebral white matter and basal ganglia had become inconspicuous, but heterogeneous T2 and FLAIR high-signal lesions were observed in the brainstem from the cerebral peduncle to the pons, and spinal MRI showed continuous T2 and FLAIR high-signal lesions from C2 to Th12. Two months after onset, the signal abnormalities in the brainstem and spinal cord tended to disappear, and all signal abnormalities disappeared within six months after onset. No obvious spinal cord atrophy was observed.

NCS showed that, at 1 month after onset, CMAPs were markedly decreased with disappearance of the F wave of the tibial nerve. At 3 months after onset, CMAP decreased in the right upper extremity, while CMAP was not derived in the lower extremity. At 8 months after onset, the upper limb nerves had almost normalized, and CMAP and F waves of the tibial nerve began to be slightly elicited (Table 1).

3. Discussion

Here, we report the first pediatric case of anti-LacCer antibody-positive EMRN. The patient developed meningitis symptoms, followed by disturbance of consciousness and symptoms resembling brainstem encephalitis and acute myelitis. The acute, monophasic findings and successful immunotherapy initially led us to consider acute disseminated encephalomyelitis (ADEM) as a tentative diagnosis. However, the loss of deep tendon reflexes and NCS findings also suggested axonopathy-type polyneuritis, which led us to the diagnosis of EMRN. Although the patient required tracheostomy, ventilation, and a urinary catheter for bladder disturbances one month after disease onset, the neurological sequelae were minimal at 6 months after disease onset.

In 1968, Blennow et al. reported three children with good prognosis in which both central and peripheral nerves were affected, and proposed the concept of EMRN [1]. In 2014, Shima et al. reported the possible involvement of anti-Ngl antibodies in the pathogenesis of EMRN [2]. Since then, several cases of anti-LacCer antibody-positive EMRN have been reported in adults, who showed acute and subacute muscle weakness, impaired consciousness, autonomic symptoms, spinal cord injury, and peripheral neuropathies. They responded well to immunotherapy, and treatment resulted in disappearance of lesions and improvement of clinical symptoms in the course of weeks to months [2, 3, 4]. The symptoms and disease course of our first pediatric case of confirmed anti-LacCer antibody-positive EMRN were similar to those of adult cases. One distinguishing characteristic of this case is that the fever persisted for up to 2 months after onset. The fever might have been due to long-lasting dysautonomia, but we also considered the fever as an indicator of disease activity of this immune-mediated disease and continued immunotherapy

until it resolved. It is also known that anti-LacCer antibody-positive EMRN can relapse [4]. Since the CSF anti-LacCer antibodies show an earlier response than serum antibodies at the time of recurrence, it would be desirable to measure anti-LacCer antibodies in the CSF when relapse is clinically suspected in this patient.

LacCer, which is one of the targets of anti-LacCer antibodies, is sialic acid-free glycolipid that, together with acidic glycolipids, is essential for the formation of lipid membrane rafts and ensure efficient intracellular and extracellular signal transduction. Mutoh et al. recently found that in patients with EMRN, there was a marked increase in activated C5 complement, C5a levels in serum and significant accumulation of ceramide exhibiting specific acyl chain length in fatty acid moieties in CSF. These findings well illustrated the significance of the abnormal activation of complement and species-specific accumulation of neurotoxic ceramides as the possible pathomechanisms of EMRN [5]. Thus, the presence of antibodies against these Ngls may interfere with normal raft function. Ngls are distributed in the myelin sheaths of central and peripheral nerves and in the cell membranes of neurons and immune cells, such as neutrophils, and are involved in inflammation of the nervous system [6, 7]. Indeed, anti-LacCer antibodies against human neutrophils alter the phagocytic activity and peroxide production of neutrophils [8], and anti-galactosylceramide antibodies induce demyelination in rabbits [9].

NCS is considered highly useful in the diagnosis of EMRN. Nanaura et al. reported that five out of nine EMRN cases showed axonopathy and three cases showed mixed peripheral neuropathy, and most of them showed decreased CMAP and loss of the F wave [4]. The present case also showed loss of the F wave and axonopathy. The axonal deficits were persistent in the lower limbs which showed a slight tendency to improve approximately 1 year after onset. NCS abnormality in patients with central nervous system inflammation should prompt measurement of anti-Ngl antibodies to facilitate diagnosis of EMRN [10, 11].

MRI of this case were characterized by a long spinal cord lesion with anterior horn predominance and bilateral symmetry. This is similar to an adult anti-Ngl antibody-positive case who showed a long spinal cord lesion with gray matter predominance [12]. Conditions showing high signal intensity in the anterior horn of the spinal cord on T2-weighted images include spinal cord injury, anterior spinal artery infarction, Hirayama's disease, epidural arachnoid cyst, spinal cord hernia, and anterior hornitis due to viral infections such as enteroviruses [13]. We propose that anti-Ngl antibody-positive EMRN should also be considered in the differential diagnosis of such cases.

4. Conclusion

The first pediatric case of anti-LacCer antibody-positive EMRN showed neurological features similar to those of the same disease in adults, but unlike the adult case, the fever, presumably caused by both intracranial inflammation and dysautonomia, persisted for a long time and finally resolved about 2 months after onset. Anti-Ngl antibodies should be measured in children presenting with a wide range of neurological symptoms involving both central and peripheral nerves.

Declarations

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article.

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Data availability statement

Data included in article/supp. material/referenced in article.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Consent

Both the patient and her guardian provided consent for publication.

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