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Case Report

Hyperammonemia in a case of herpes simplex and anti-N-methyl-D-aspartate receptor encephalitis

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Abstract

Herpes simplex encephalitis (HSE) is a widely accepted risk factor for anti N-methyl-D-aspartate receptor (NMDAR) encephalitis. Association of inherited metabolic disease has never been reported in a patient with HSE and anti-NMDAR encephalitis. Herein, we report a case of pediatric HSE complicated by development of anti-NMDAR encephalitis; this patient showed subsequent recurrent, unexplained episodes of encephalopathy associated with hyperammonemia. The patient was diagnosed with lysinuric protein intolerance (LPI), a rare inborn metabolic disorder. Although it would be difficult to make conclusions regarding the casual link of HSE and anti-NMDAR encephalitis with LPI from a single case, there have been many reports that autoimmune diseases and immunologic abnormalities are frequently associated with LPI. Thus, we speculate that LPI may contribute to the development of anti-NMDAR encephalitis following HSE.

Keywords: Herpes simplex encephalitis; Anti-N-methyl-D-aspartate receptor encephalitis; Lysinuric protein intolerance

1. Introduction

Although anti N-methyl-D-aspartate receptor (NMDAR) encephalitis was originally described in the context of paraneoplastic syndrome, tumors are rare in pediatric patients [1]. Viral encephalitis, specifically herpes simplex encephalitis (HSE), may be a trigger for anti-NMDAR, because approximately 20% of HSE patients suffer from this condition [2]. The currently postulated mechanism is that exposure to neural antigens released from viral-induced neural destruction may initiate an autoimmune process [2]. However, because only a small proportion of patients develop anti-NMDAR encephalitis after HSE, undefined genetic predisposition may contribute to this sequence.

Dysfunction in the innate immune response has been known to play an important role in HSE susceptibility [3]. Specifically, toll-like receptor 3 (TLR3) and TLR3 pathway gene mutation was found in 6 of the 120 pediatric HSE patients [4]. Interestingly, dysfunction in macrophage TLR signaling was reported in LPI patients, although the TLR3 pathway has not been studied [5]. Thus, dysfunction in the innate immune response associated with LPI in some patients might be linked with HSE susceptibility.

Herein, we report the case of a 20-month-old girl diagnosed with anti-NMDAR encephalitis following

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HSE. During our investigation into the etiology of hyperammonemia that complicated her neurologic recovery, a rare metabolic disorder, lysinuric protein intolerance (LPI, OMIM#222700), was identified. We discuss the contributing role of LPI to the development of HSE and anti-NMDAR encephalitis.

2. Case report

A 20-month-old girl presented with fever and seizure. The patient was born after an uncomplicated pregnancy at 38 weeks gestation. Her early developmental trajectory was reported as normal, without any episodes of altered consciousness. She developed a high fever without any prodromal symptoms. The day after fever onset, a left-sided tonic–clonic seizure lasted for 20 min, and her mental status became drowsy. Brain magnetic resonance imaging (MRI) revealed cortical swelling and increased signal intensity in the right temporo-occipital area (Fig. 1A). Cerebrospinal fluid (CSF) examination showed increased white blood cell (WBC) count ($324/mm^3$) with lymphocyte predominance (98%). CSF protein was also mildly elevated (77 mg/dL). She was treated with intravenous acyclovir. CSF PCR result was positive for Herpes simplex virus type 1. Her mental state subsequently improved, and she was treated with acyclovir for three weeks. However, three weeks after initial fever onset, fever developed again. She became extremely irritable, and her mental status deteriorated. She also showed orofacial dyskinesia and choreic limb movement. CSF examination and brain MRI were repeated. WBC counts and CSF protein were within normal limits. Brain MRI revealed encephalomalcic change of the right temporo-occipital area, but no new lesion was detected (Fig. 1B). As we were under the impression that she had autoimmune post-HSE, she was treated with intravenous immunoglobulin (400 mg/kg/day for five days) and methylprednisolone (30 mg/kg/day for three days). Anti-NMDAR antibody was positive in both serum and CSF. Antibody titer in CSF was 1:1280. Because her neurologic status had not improved, rituximab (375 mg/m^2 BSA weekly × 5 doses) and cyclophosphamide infusion (750 mg/m^2 BSA monthly × 5 doses) were subsequently administered. Follow-up anti-NMDAR antibody titer in CSF decreased to 1:80. During 10 months of treatment and rehabilitation, her neurologic status gradually improved. She became alert and reacted responsively. However, she could not communicate verbally. She also had difficulty swallowing. She could sit alone and stand with assistance. Irritability and dyskinesia were partially improved but persisted. There were no definite abnormalities on neurologic examination except truncal and extremity hypotonia. Upon discharge, she was treated with topiramate and azathioprine. During outpatient follow-up, she was stable and receiving physiotherapy until she presented to the emergency department with sudden aggressive behavior and irritability at age 37 months. Her height, weight, and head circumference were 97 cm (50–75th percentile), 12.7 kg (10–25th percentile), and 47.5 cm (10–25th percentile), respectively. Initial evaluation showed hyperammonemia, with a level of 521 μg/dL. When reviewed retrospectively, serum ammonia level was either within normal range or mildly increased (Fig. 2). Considering a possible link with drugs and hyperammonemia, topiramate was changed to levetiracetam, and azathioprine was discontinued. She suffered from recurrent episodes of hyperammonemia for the next 10 months.

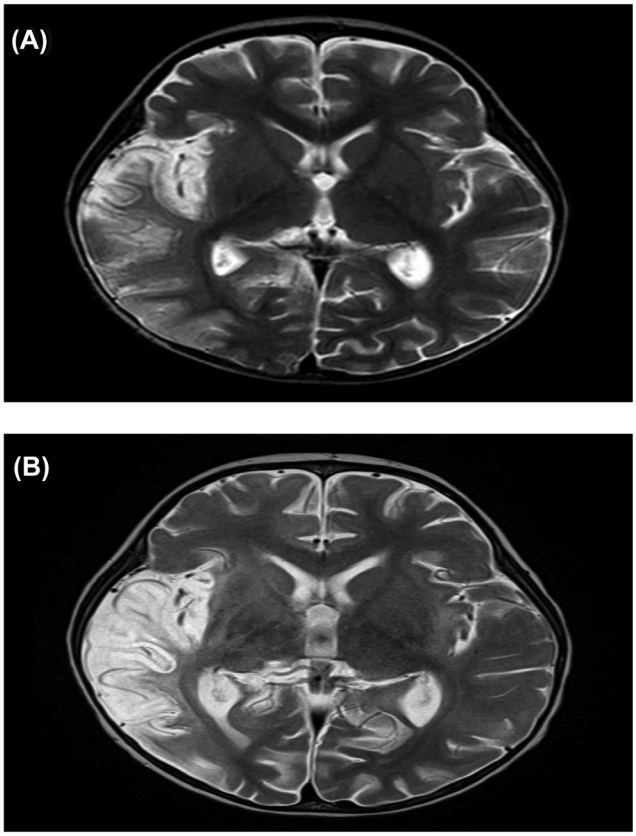

Fig. 1. Brain MRI findings (A) T2 axial brain MRI performed at the onset of herpes simplex encephalitis showed diffuse swelling and high signal intensity in the right temporo-occipital lobe; (B) T2 axial brain MRI performed one month after fever onset, showing diffuse encephalomalcic changes to the right temporo-occipital lobe.

Serum amino acid analysis showed elevated alanine, glutamine, and citrulline, although lysine, arginine and ornithine levels were in the lower ends of the normal ranges. Mild urinary excretion of orotic acid varied between repeated analyses, and lysine, arginine, and ornithine were markedly excreted in urine. Except for mildly elevated serum ferritin (209 ng/mL), the patient did not have anemia, leukopenia, or neutropenia, and her hemoglobin, serum iron concentration, liver enzymes, protein and albumin levels, fibrinogen, and

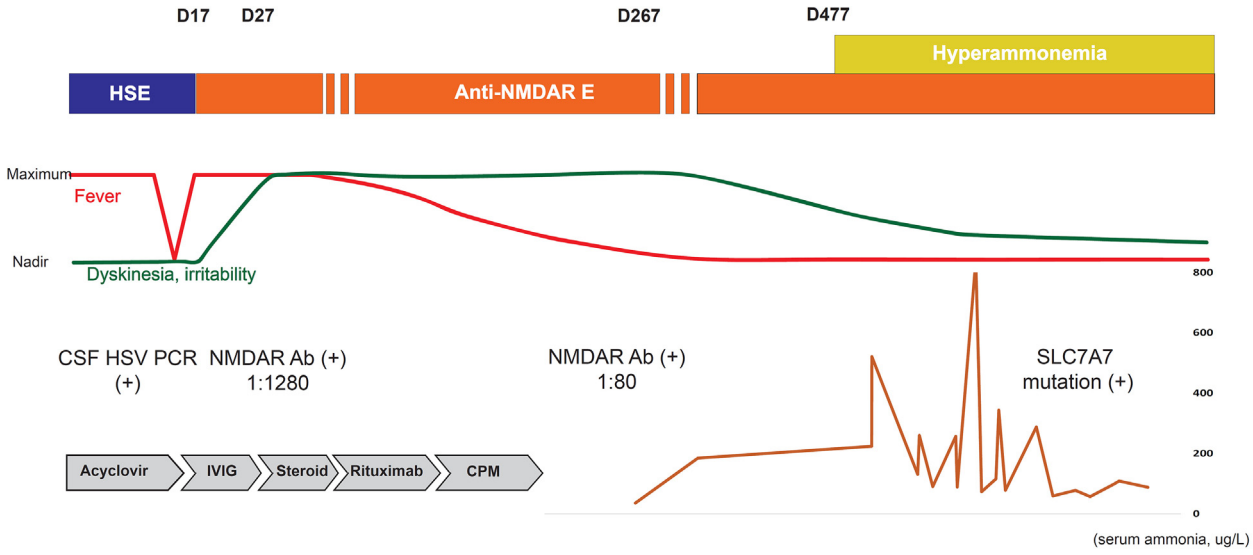

Fig. 2. Time schematic showing symptoms and signs, laboratory results, and treatments. HSV, herpes simplex virus; HSE, herpes simplex encephalitis; NMDAR, N-methyl-D-aspartate receptor; CPM, cyclophosphamide.

lipid profiles were normal. Serum immunoglobulin levels (IgG, IgA, and IgM), IgG subclass levels (IgG1, IgG2, IgG3, IgG4), T cell subset count (CD3, CD4, and CD8), B cell count (CD19), and NK cell count (CD16/CD56) were all within reference range. Herpes simplex virus IgG antibody and Varicella zoster virus IgG antibody were measured as positive. Abdominal sonography did not identify hepatosplenomegaly and only indicated increased medullary echogenicity in both kidneys, although albuminuria was absent and serum creatinine levels were normal. Simple radiographs showed normal findings for the lungs, and there was no osteopenia of the spine.

Target gene panel sequencing was focused on inherited metabolic disorders accompanying hyperammonemia, and the patient was found to be a compound heterozygote with a likely novel pathogenic variant, c.1330dup (p.Leu444Profs*24), and a known pathogenic variant, c.625+1G>A, in *SLC7A7* (Fig. 3). A written informed consent was obtained from the parents. Her parents were heterozygous carriers of two variants each. Oral arginine supplementation and intravenous sodium benzoate infusion with 10% glucose solution and 20% lipid emulsion were initiated for acute management of hyperammonemia. After the ammonia level was normalized and the diagnosis of LPI was confirmed, a low-protein diet and oral supplementation of sodium benzoate, citrulline, and L-carnitine have been maintained with topiramate. After initiation of metabolic management, there have been no acute episodes of metabolic derangement. Hemoglobin, leukocyte, serum ferritin, and ammonia levels have remained within normal ranges.

3. Discussion

Despite slow and incomplete neurologic recovery, we expect that extensive tissue destruction from HSE was

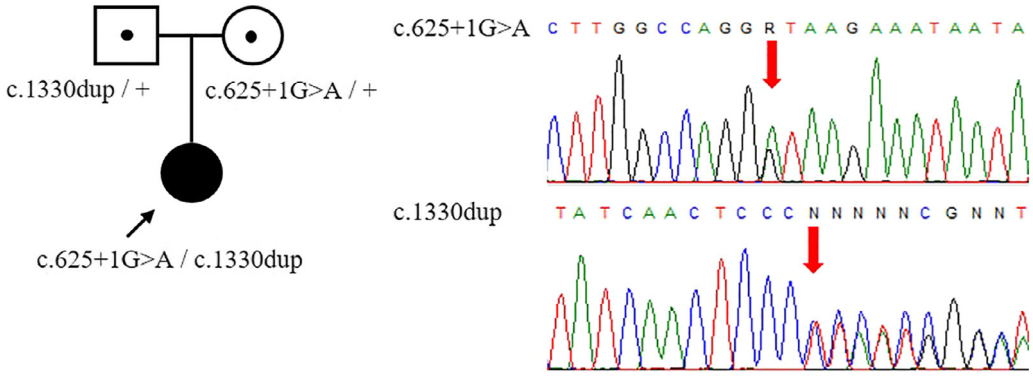

Fig. 3. Family pedigree carrying two compound heterozygous *SLC7A7* mutations, confirmed by Sanger sequencing. *SLC7A7* alleles represented by "+" (wild type), "c.625+1G>A", and "c.1330dup (p.Leu444Profs*24)".

partially responsible for the patient's clinical course. Furthermore, the titer of anti-NMDAR antibody decreased from 1:1280 to 1:80, suggesting that the patient was responding to immunotherapy. However, recurrent encephalopathy episodes, along with fluctuating serum ammonia level, were mysteries unexplained by complication from either encephalitis or immunotherapy. Coexistence of an inherited metabolic disease was not initially prioritized, because the patient did not show other features of metabolic disease, such as hepatosplenomegaly, failure to thrive, episodes of altered consciousness, or developmental delay before the onset of HSE. Thus, until the target gene panel sequencing revealed a compound heterozygous pathogenic variant in *SLC7A7*, we could not have suspected a diagnosis of LPI.

LPI diagnosis in the present case not only resulted in etiology-specific treatment but also provided insight into a genetic predisposition to HSE and anti-NMDAR encephalitis. Autoimmune complications, including lupus nephritis, vitiligo, and immune thrombocytopenic purpura have been regarded as cardinal clinical features in LPI patients [6]. Defects in phagocytosis and humoral immune response have also been reported in LPI patients, which may support the notion of a predisposition of those with this disease to autoimmunity [7,8]. Although anti-NMDAR encephalitis has never been reported in an LPI patient, these immunologic abnormalities may contribute to central nervous system autoimmunity initiated by exposure to neural antigens released from HSE-induced neural destruction. Thus, anti-NMDAR encephalitis could be regarded as one of the autoimmune diseases that may be associated with LPI.

Although there has been no report describing HSE in patients with LPI, defects in humoral immunity and innate immune response reported in LPI patients could also affect the development of HSE. Unfortunately, we could not find any evidence of immunologic dysfunction in our case that could be linked with HSE. However, further extensive study including TLR signaling analysis and genotyping of TLR3 pathway genes would be needed to support this relationship.

Our case could extend the phenotypic spectrum of LPI resulting from immune dysfunction. Our case could also provide the insight for linking inherited metabolic disorder to HSE and anti NMDAR encephalitis. Because the phenotypic spectrum of LPI may be broader than previously reported, serum ammonia level needs to be monitored, especially in pediatric anti-NMDAR encephalitis patients. This course could lead to identification of a rare but manageable contributing factor.

Acknowledgements

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We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.03.013.

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