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Progressive Multifocal Leukoencephalopathy With Hyper-IgM Syndrome in a 6-Year-Old Boy

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HIGHLIGHTS

- Children with hyper-immunoglobulin M (IgM) syndrome may develop progressive multifocal leukoencephalopathy.
- Progressive multifocal leukoencephalopathy requires caution as it worsens quickly.

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The authors have no potential conflicts of interest to disclose.

ABSTRACT

Hyper-immunoglobulin (Ig) M syndrome is a congenital immunodeficiency disorder characterized by increased serum IgM with low serum IgG, IgA, and IgE. We report the case of a 6-year-old boy with hyper-IgM syndrome as an underlying disease who showed progressive multifocal leukoencephalopathy findings on brain magnetic resonance imaging after visiting the hospital due to left upper extremity muscle weakness, gait disturbance, and speech impairment. At the time of hospitalization, he was treated with steroids and intravenous immunoglobulin, and his condition improved somewhat, but 6 months later, he visited the hospital with rapid deterioration.

Keywords: Progressive Multifocal Leukoencephalopathy; Hyper-IgM Syndrome; Child

INTRODUCTION

Progressive multifocal leukoencephalopathy (PML) is a demyelinating disease of the central nervous system caused by John Cunningham (JC) virus, a human neurotropic polyomavirus [1]. The majority of patients with PML (85%) are human immunodeficiency virus (HIV) carriers [2], while 15% have hematologic malignancies, a history of bone marrow transplantation, or primary immunodeficiency disorders [3]. Herein, we report the case of a 6-year-old boy with hyper-immunoglobulin (Ig) M syndrome who visited the hospital for left-sided weakness and speech impairment, and was diagnosed with PML through magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) tapping. Most cases of PML reported in Korea are related to HIV injection, and there have been no case reports related to hyper-IgM syndrome. Hence, we would like to share this novel case.

CASE REPORT

A 6-year-old boy had no significant family or birth history; however, he had frequent otitis media since approximately 12 months after birth. After admission to another hospital for pertussis at approximately 30 months of age, laboratory tests showed an IgG level < 170.0 mg/dL (reference range, 345–1,236 mg/dL), an IgM level of 307 mg/dL (reference range, 43–207 mg/dL), and an IgA level of 19 mg/dL (reference range, 14–159 mg/dL). In December

2017, he was diagnosed with hyper-IgM syndrome and was administered intravenous immunoglobulin (IVIG), with a dose of 0.4 mg/kg once a month. After November 2020, he was scheduled to receive IVIG once every 3 months, but was lost to follow-up. He showed no specific neurological deficits or other signs, such as fever, rash, or arthralgia, and showed normal development until then.

At the beginning of June 2021, the patient experienced sagging, a lack of energy, and a lack of concentration; therefore, he underwent psychological therapy. Since then, he has not been able to properly urinate in the toilet, and since June 6, 2021, he has not been able to effectively use his left arm. He was hospitalized on June 23, 2021, with left upper limb weakness, gait disturbance, and decreased verbal output.

At the time of admission, the patient was alert and well-oriented. He spoke very little, but nodded to respond. He had left facial palsy; the corners of his mouth were drooping, and food spilled out of his lips while eating. All other cranial nerve functions remained intact. On physical examination, the left upper extremity briefly overcame gravity with a manual muscle test (MMT) grade 4, but that improvement did not last long. The left lower extremity muscle strength was MMT grade 4, and the patient was noted to limp during walking. The range of motion and spasticity did not show specific findings, but the Babinski sign was positive on his left foot.

In blood chemistry tests performed after hospitalization, the serum IgG level was 14.8 mg/dL, the serum IgA level was 5.5 mg/dL, which was lower than the normal levels, and the serum IgM level had increased to 539.2 mg/dL. All other results were within the normal range. MRI of the brain showed multifocal, bilateral, but asymmetric low signal intensities in T1-weighted imaging; high signal intensities in T2-weighted and fluid-attenuated inversion recovery imaging; a partly high and partly low signal on diffusion-weighted imaging; and focal mild peripheral contrast-enhanced lesions in the frontal, temporal, and parietal white matter (WM), basal ganglia, thalamus, and midbrain (**Fig. 1**). Additionally, CSF tapping revealed an elevated CSF glucose level (75 mg/dL) and CSF IgG level (2.6 mg/dL). Polymerase chain reaction (PCR) was performed to confirm viral infection in the CSF, and positive results were found for the JC virus; however, a cytology study was negative for malignant cells. Therefore, PML was diagnosed in this patient.

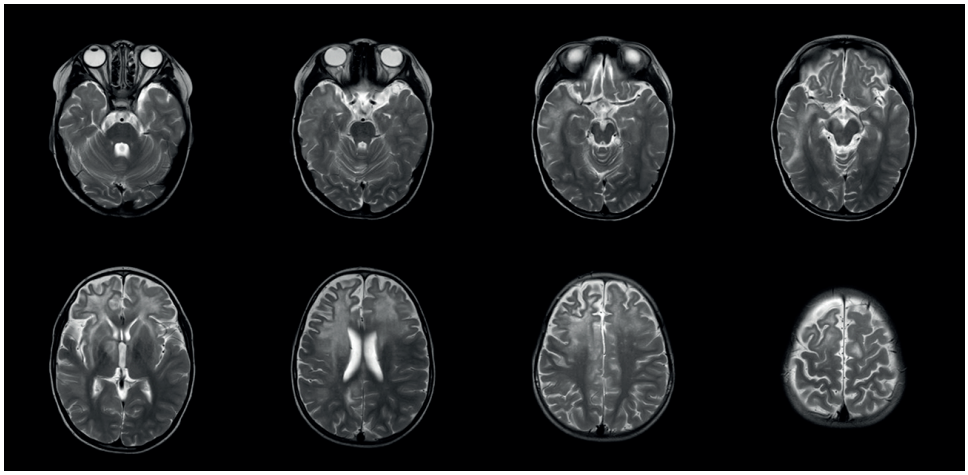

Fig. 1. MRI of the brain. T2-weighted MRI shows hyperintensity in the bilateral frontal, temporal, and right parietal white matter, as well as the bilateral basal ganglia, thalamus, and right midbrain.
MRI, magnetic resonance imaging.

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Following diagnosis, intravenous (IV) acyclovir and IV cefotaxime were initiated. The patient's symptoms did not improve, so IV methylprednisolone (15 mg/kg) was administered. On day 5 (June 28, 2021), 0.4 mg/kg of IVIG was administered with approval from a pediatrician. The patient showed slight improvement, but no overall improvement in grip strength was noticeable. The left corner of his mouth still drooped, but he could eat without spilling rice while eating. On day 7 (June 30, 2021), his facial paralysis improved slightly, but no verbal expression was noted.

The patient was discharged on day 8. During hospitalization, IV cefotaxime and IV acyclovir were administered for 6 days (June 25–30, 2021), and IV methylprednisolone pulse treatment was administered for 5 days (June 25–29, 2021), and once on June 30, 2021, at 1 mg/kg. The patient was thereafter discharged.

On January 14, 2022, the patient was brought for a follow-up visit at the outpatient clinic, but his condition had notably worsened. Muscle strength dropped to MMT grade 1 in both limbs, and muscle tone was flaccid. In addition, there were no meaningful speech sounds, with a Korean version of the Western Aphasia Battery score of 0. A tracheostomy tube was inserted, and percutaneous endoscopic gastrostomy was performed due to weak respiratory muscles and decreased swallowing function.

DISCUSSION

PML is a rare opportunistic infection of the central nervous system caused by the JC virus, which is a DNA virus [4,5]. Primary infection with the JC virus is usually asymptomatic [6]. However, infected B lymphocytes may carry the JC virus into the brain, infecting oligodendrocytes and astrocytes [7]. Disease-related demyelination of the brain is caused by the lysis of oligodendrocytes [8].

In addition to cognitive impairment, common signs and symptoms include paralysis, visual field defects, speech disorders, ataxia, and brain stem-related defects. With these symptoms, typical MRI findings and the detection of JC virus DNA in the CSF are sufficient conditions for diagnosis [4]. On MRI, the lesions show low signal intensity on T1-weighted images and high signal intensity on T2-weighted images, and tend to occur in the subcortical areas of the parieto-occipital lobes, but may also appear in other areas such as the cerebrum, cerebellum, brain stem, and spinal cord [9]. Even though CSF studies showed no abnormalities, the application of PCR to CSF samples is a promising diagnostic tool [9,10]. Furthermore, patients with this condition usually die within an average period of a few months. A better prognosis is associated with a higher CD4 T lymphocyte count and the absence of brainstem involvement [10].

Hyper-IgM syndrome is an underlying immunodeficiency disorder that contributes to JC virus activation. Hyper-IgM syndrome presents as a wide spectrum of clinical symptoms. These symptoms usually develop in infants before 2 years of age, presenting as susceptibility to recurrent infections. In addition, these patients are prone to pulmonary complications, gastrointestinal symptoms, autoimmune disorders, hematologic abnormalities, lymphatic proliferation, and malignancies [11].

In this patient, the JC virus resulted in PML in the frontal, temporal, and right parietal WM, as well as the basal ganglia, thalamus, and right midbrain. This soon resulted in left-sided

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weakness, facial paralysis, and speech disorders at the time of initial onset, but later resulted in a serious course of invasion to both limbs and respiratory muscles. A rapid diagnosis was made, and steroid pulse therapy was initiated; however, the prognosis was poor.

In conclusion, when a patient with underlying immunodeficiency shows neurological abnormalities, such as cognitive impairment, paralysis, visual impairment, or speech impairment, MRI should be performed immediately, and CSF tapping should be done if necessary. If the JC virus is detected in the CSF, the possibility of invasion of the respiratory muscle should be considered, and steroid pulse therapy should be initiated as soon as possible.

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