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An infant with steroid-refractory cytomegalovirus-associated ADEM who responded to immunoglobulin therapy

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Abstract. – Acute disseminated encephalomyelitis (ADEM) develops via an immunological mechanism. We encountered a 10-month-old infant with a rare pathogenesis of cytomegalovirus (CMV)-related ADEM. The patients complaints were; protracted fever; counsciousness disorder; and affected cervical stability. Cerebral magnetic resonance imaging (MRI) 9 days after onset, revealed a disseminated lesion, suggesting ADEM. Pulse therapy with methylprednisolone at 30 mg/kg was performed for 3 days. However, its clinical efficacy was not marked. Therapy with immunoglobulin (IVIg) at 400 mg/kg/day was started 15 days after onset, and continued for 5 days. This markedly improved the consciousness level and muscle strength, and the infant was discharged without neurological sequelae. ADEM showed a monophasic course, and the infant's subsequent growth has been favorable. Altough the number of case reports is small, massive-IVIg therapy should be considered in patients with steriod-refractory ADEM, as demonstrated in this case study.

Key Words:
Cytomegalovirus, Acute disseminated encephalomyelitis, Immunoglobulin.

Introduction

Acute disseminated encephalomyelitis (ADEM) represents monophasic allergic encephalomyelitis with a disseminated white matter lesion. Autoimmune disorders with inflammatory demyelination in response to myelin antigen in the central nervous system may be involved in the various pathogenesis[1,2]. We herein report the clinical course of an infant with a rare pathogenesis of cytomegalovirus (CMV)-related ADEM. Steroid therapy is usually effective for conventional cases of ADEM[3]. However, methylpredonisolone pulse therapy was not effective in the present case, and this infant responded better to immunoglobulin (IVIg) therapy. We discuss the clinical course of this infant who was diagnosed with neuroradiological method using MRI, MRS, ^{99m}Tc-ECD SPECT analysis.

Case Study

The infant was a 10-month-old boy. His development was normal, and neither the medical nor family history was contributory. The infant was admitted for fever and poor sucking at 6 days after onset. Consciousness on admission consisted of repeated excitation with crying and somnolence. On consultation, pharyngeal flare was observed. The eyes were frequently fixed on the median line, and sometimes, there was no pursuit eye movement. The light reflex was normal. General muscle strength was reduced, and neck stabilization was impossible. The deep tendon reflex of the upper limbs was normal, but that of the lower limbs was enhanced. Neither brain CT on day 7 after onset revealed any abnormal densities. Hematology showed a WBC of 19,600, a CRP level of 0.6, an AST level of 117, and ALT level of 224. The electrolyte, glucose and blood gas levels were normal. The infant was positive for serum CMV-specific IgM antibody. CSF was negative for myelin basic protein and oligoclonal bands, with a cell count of 5/3 and a protein level of 22 mg/dl. Concerning the consciousness level at 8 days after onset, the infant's eyes opened when his body was shaken, and Jouvet Coma Scale JCS) was evaluated as 20. On EEG, a 2-Hz slow wave was predominant as the background activity. At nine days after onset, brain MRI revealed an abnormal disseminated intensity, thus, suggesting ADEM (Figure 1A). Steroid pulse therapy (30 mg/kg/day) was performed for 3 days. A respiratory disorder related to a submerged tongue root occurred 10 days after onset, and intubation was, thus, performed. In the Magnetic Resonance Spetroscopy (MRS) findings on the 12th day, abnormal signals remained in the

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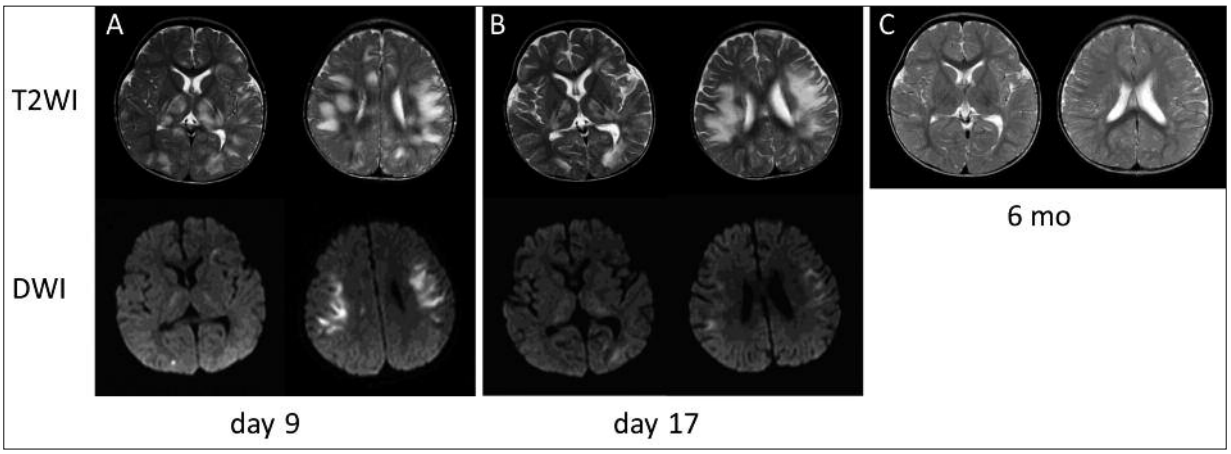

Figure 1. A, The MRI findings of the day 9: Multiple high intensity areas were observed in the T2WI, almost symmetrically, on both sides of the thalamus, periaqueductal gray matter, on the right side of the pons, both sides of the cerebral hemisphere's white matter and the cerebellar dentate nucleus. These signals presented as high signals in the diffusion-weighted images (DWI) and low signals in the ADC-map, thus representing a finding of cellulous edema. ***B,*** In the MRI findings of day 17: Although abnormal signals were observed at multiple areas on both sides of the subcortical white matter in the DWI, there was more of a tendency toward contraction than previously observed. In the T2WI findings, abnormal signals remained almost symmetrical at the thalamus and in the temporal lobe subcortical white matter and the long T2 lesion in the brain stem disappeared. ***C,*** The MRI from 6 months after onset showed normal findings.

thalamus and elsewhere, and a lactic acid peak was detected at both echo times of 135 and 30 (Figure 2A). In the ^{99m}Tc-ECD SPECT findings of the same day, uneven images of cerebral hypoperfusion were observed at both sides of the basal ganglion, thalamus brain stem and in the cerebellum region (Figure 3A). To treat convulsion, continuous intravenous injection of midazolam at 0.3 mg/kg/hr was performed. The neck stability remained low 15 days after onset, and there was no improvement in the consciousness levels from 20 days after onset. Subsequent treatment, massive doses of immunoglobulin therapy at 400 mg/kg were administered for 5 days from the 15th to 19th day. MRI scans were taken on the 17th day. Although abnormal signals in the T2 weighted images remained, when looking at the diffusion-weighted image, the abnormal signals, including the subcortical white matter, demonstrated a contractive tendency (Figure 1B). In the MRS findings on the 19th day, both echo times of 135 and 30 tended to improve with respect to the lactic acid levels (Figure 2B). Head shaking movements gradually occurred from 21 days after onset, and the eyes became persistently open in the absence of stimulation. Neck stabilization

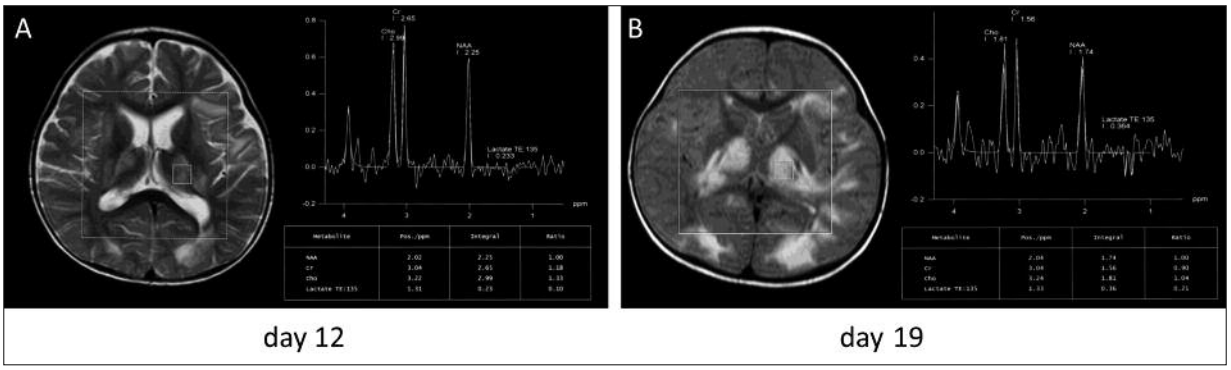

Figure 2. The MRS from day 12 ***(A)*** and day 19 ***(B)***. The measurement site was a long T2 lesion of the left thalamus. At TE = 135, the Lac/NAA rate was observed to have decreased from 0.21 to 0.1. At TE = 30, the Lac/NAA reduced from 0.31 to 0.14 and the peak of lactic acid decreased by half.

became possible at 28 days after onset. In the SPECT findings on the 35th day, the cerebral hypoperfusion image on both sides of the basal ganglion showed no improvement (Figure 3B). Rehabilitation treatment was started, and it became possible to maintain the sitting position by 41 days after onset. The infant could stand while grasping something at 43 days after onset, and he was discharged 44 days after onset. Six months later, brain the MRI findings have also normalized (Figure 1C) and a cerebral perfusion image in both basal ganglion and thalamus were improved (Figure 3C). Currently, the boy is 4 years old, no neurological sequelae have been observed, and his motor and intellectual development was normal.

Discussion

Acute disseminated encephalomyelitis (ADEM) presents as a monophasic clinical course characterized by allergic encephalomyelitis with a disseminated white matter lesion. In the pathogenesis, autoimmune disorders with inflammatory demyelination in response to myelin antigen in the central nervous system may be involved. ADEM is classified into 3 types by etiological factors: post-infection ADEM[4,5], post-prophylactic vaccination ADEM[6], and idiopathic ADEM[1,2]. Various etiological factors for ADEM have been reported but in post-viral infection CMV-related ADEM is considered to be rare[7-11]. There have been few reports of ADEM occurring due to a cytomegalovirus infection and there have only been a few cases of infant patients with a related background of immunosuppressive condition bone marrow transplant or renal transplantation[11]. In our infant, methylpredonisolone steroid pulse therapy was initially performed, but its clinical efficacy was found to be insufficient. Thereafter, massive doses of immunoglobulin therapy were administrated which successfully, improved the consciousness level and general muscle strength. There were no adverse reactions to the immunoglobulin therapy. The subsequent development was, thus, normal without any neurological sequelae. In this infant, ADEM showed a monophasic clinical course. Recent studies have reported the efficacy of immunoglobulin therapy not only for the treatment of ADEM but also for the treatment of various autoimmune disorders[12]. Unfortunately, the detailed pharmacological mechanism of immunoglobulin for ADEM remains unclear. However, massive doses of immunoglobulin therapy should be considered in the early stages of the disease to treat steroid-refractory ADEM, as demonstrated in our infant, although the number of such clinically reported patients is still small. As a result, further clinical studies of a larger number of patients are, thus, called for before any definitive conclusions can be made.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

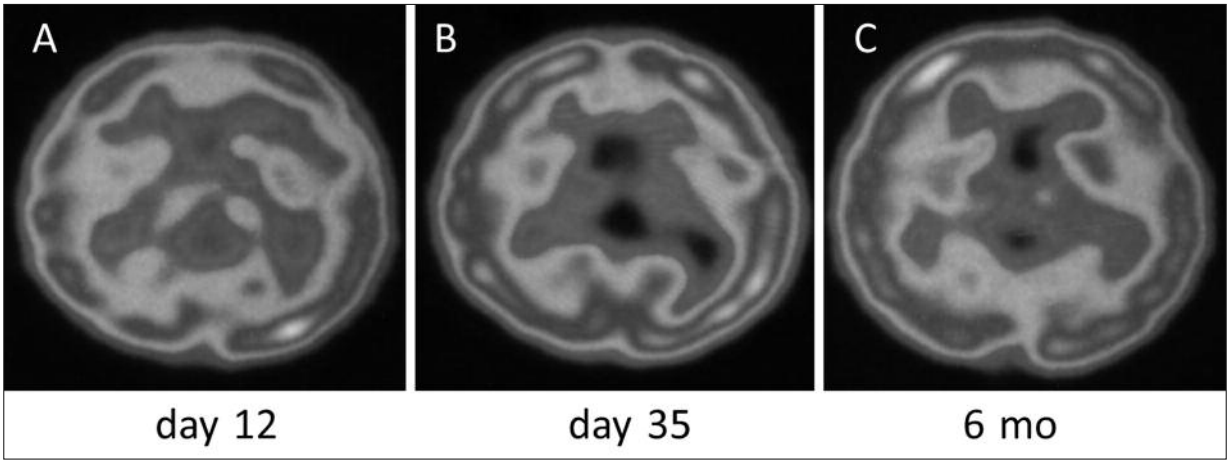

Figure 3. SPECT findings using ^{99m}Tc-ECD on day 12 ***(A)*** shows uneven images of cerebral hypoperfusion on both sides of the basal ganglion, thalamus brain stem and cerebellum region. In the SPECT findings on day 35, the cerebral hypoperfusion image was particularly well observed on both sides of the thalamus. ***C,*** The ^{99m}Tc-ECD SPECT findings on the 6 months after onset showed improvement of cerebral perfusion in both side of basal ganglia and thalamus.

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