CASE REPORT

H1N1-associated Acute Necrotizing Encephalopathy of Childhood: Successful Treatment with the "Zipper Method" and Long-Term Outcome

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ABSTRACT

Acute necrotizing encephalopathy of childhood (ANEC) is a devastating childhood disease characterized by rapid neurologic deterioration after a viral febrile illness. Seizures, encephalopathy, and fatal acute necrotizing encephalopathy are well-defined neurologic complications of H1N1 virus infections. Symmetrical, multifocal lesions on cranial magnetic resonance imaging (MRI) are the best-known features of ANEC. Various treatment options include glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange (PEX).

Herein, we present a 45-month-old girl diagnosed with ANEC and treated with a novel immunomodulation technique, the "zipper method." It is a combined treatment method in which PEX and IVIG treatments are used together. In the first session of plasma exchange, one and a half volumes of patients' plasma were removed using 5% albumin as a replacement solution. At the end of the PEX session, 0.4 g/kg IVIG infusion was started. The second PEX session was applied with one volume 24 hours after the end of the IVIG infusion. This plasma exchange–intravenous immunoglobulin cycle was repeated five times. Furthermore, this case report presents her outcome 3-years after discharge: full recovery. This case is a unique example of ANEC treated successfully with the zipper method.

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Introduction

Acute necrotizing encephalopathy of childhood (ANEC) is a para-infectious disease characterized by rapid neurologic deterioration after a viral febrile illness(1). Glucocorticoids, intravenous immunoglobulin (IVIG), and plasma exchange (PEX) are various treatment options (2). Herein, we present a 45-month-old girl diagnosed with ANEC and treated with a novel immunomodulation technique, the "zipper method. Additionally, we aimed to report the patient's prognosis and motor and mental development in the 3-year follow-up.

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Case report

A previously healthy, 45-month-old girl was admitted to the pediatric intensive care unit of our hospital with a decreased level of consciousness and loss of motor control and cognition. She had a history of upper respiratory infection. Personal and familial medical history was unremarkable. She had a fever of 39°C, but other vital signs were normal. Her Glasgow Coma Score (GCS) was 10/15. She had a limited response to the environment and no meaningful words. Bilateral pupils were mydriatic and isochoric and reacted to light weakly. She had an upward gaze. She had increased muscle tone, increased deep tendon reflexes, and a decerebrate posture.

The hemogram and blood gas analysis were normal. Liver function tests noted a mild increase in aminotransferase levels [aspartate aminotransferase (AST) 104 U/L-alanine transaminase (ALT) 68 U/L]. Initial brain magnetic resonance imaging (MRI) (Figure 1) showed multifocal involvement of the basal ganglia and thalamus, brainstem, supratentorial region, and cerebellum. Besides, there was T2-weighted contrast-enhancing swelling (edema) and hemorrhage. Cranial MRI confirmed the diagnosis of ANEC. A lumbar puncture was performed; no cells were observed in the cerebrospinal fluid (CSF), glucose was 68 mg/dL, and protein was 52.5 mg/dL (N: 15-45 mg/dL). Blood, CSF cultures, and the oligoclonal band were negative. Screening for inborn errors of metabolism and heavy metal levels was normal. Influenza A virus (H1N1) was detected in the nasopharyngeal swab polymerase chain reaction (PCR).CSF-PCR was negative for viral etiologies. An electroencephalogram showed background slowing but no epileptic activity.

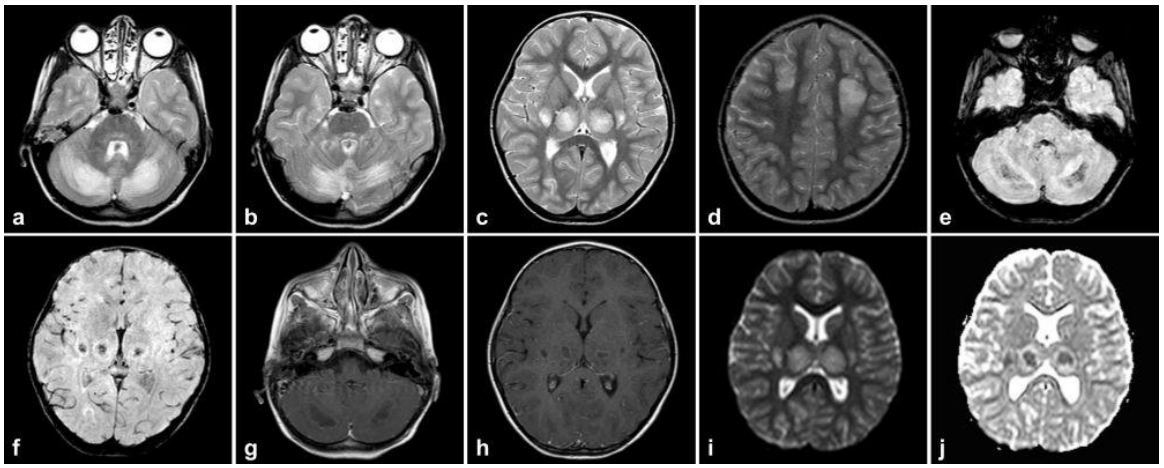

Figure 1a-i: Initial cranial MRI findings on axial T2-weighted images (a) inferior cerebellar hemispheres, (b) superior cerebellar hemispheres, vermis and brain stem, (c) both thalamus and putamen inferior, (d) hyperintense signal changes and widespread edema in subcortical white matter in the plane of both vertexes, (e-f) blood destruction products in the same locations in series showing increased sensitivity, (g-h) environmental contrast involvement, (i-j) diffusion limitation observed in diffusion-weighted series. Findings were assessed as compatible with acute necrotizing encephalitis.

Empirical oseltamivir and antibiotherapy were administered immediately. PEX was started within the first six hours combined with a total of 2 g/kg of IVIG following the zipper protocol and five doses of methylprednisolone (30 mg/kg/daily), followed by oral prednisolone (2 mg/kg) weaning over four weeks. In the first PEX session, 1.5 L volume of the patient's plasma was removed using 5% albumin as a replacement solution. At the end of the PEX session, 0.4 g/kg IVIG infusion was started. A second PEX session was performed with one volume change 24 hours after the end of the IVIG infusion. The zipper treatment was completed with five cycles over nine days.

The patient was admitted to a physiotherapy and rehabilitation center for three months. She could repeat what was said at the end of the three months. She could walk without support five months later (Video 1) and slowly began to speak coherently in the sixth month. In the eighth month, she could eat by herself. In the third year after discharge, she continues attending school; she can read, write, and tend to herself (Video 2).

In the latest neurologic examination after three years, she had good motor and cognitive ability. No tremors, ataxia, speech impairment, spasticity, or focal neurologic signs were observed. All findings had regressed in the follow-up MRI (Figure 2) performed three years later.

Discussion

ANEC is a rare and life-threatening encephalopathy mostly noticed in previously healthy children. It seems

to be triggered by a viral infection such as H1N1 in a genetically susceptible host. Symmetrical, multifocal lesions in the thalami, basal ganglia, and cerebral and cerebellar white matter on cranial MRI are the best-known features of ANEC (2).

The underlying pathogenesis of ANEC remains unknown; the most prevalent hypothesis is hypercytokinemia, known as “cytokine storm” (2,3). Cytokine storms may destroy the blood-brain barrier (BBB), increase vascular permeability, and result in brain edema, petechial hemorrhage, and necrosis. According to flow cytometric analysis of peripheral blood in the recovery phase, patients with ANEC have a high proportion of CD56+ natural killer (NK) cells (3). NK cells are associated with the development of ANEC (3).

No specific therapies are recommended for ANEC. Intensive care, symptomatic treatment, empirical treatment (antiviral therapy), and immunomodulatory agents are stated to be beneficial. Some case reports suggested that administration of corticosteroids, IVIG, plasmapheresis, and induced hypothermia might improve clinical outcomes (2, 4-6).

After the studied patient attended our hospital, we immediately began pulse steroid, IVIG, and PEX treatments within the first six hours. IVIG and PEX treatments were administered in combination with the zipper method, which is a novel treatment protocol that was first used by Kesici et al. in nine intubated children with Guillain-Barré syndrome with a rapid disease course and poor prognosis (7). In the zipper method, PEX removes antibodies intensively from the plasma, controls hypercytokinemia, decreases leukocyte degranulation, and inhibits macrophage activation and phagocytosis. IVIG works through multiple mechanisms to deliver its effects. It inhibits the production of antibodies and supplies anti-idiotypic antibodies that neutralize harmful autoantibodies. Additionally, it suppresses complement activation and the formation of membrane attack complexes. IVIG also modulates the expression and function of Fc receptors on macrophages and other effector cells while suppressing cytokines, chemokines, and adhesion molecules (8). Further, IVIG infusion starts at the end of each PEX course, and plasma autoantibodies are cleaned by performing PEX; however, new antibodies are later synthesized, stimulating the transition from tissue to plasma. IVIG is given immediately after PEX neutralizes these regenerated autoantibodies. Antibody movement from tissue to plasma is completed in 24 hours [7]. The zipper treatment was completed in five cycles over nine days.

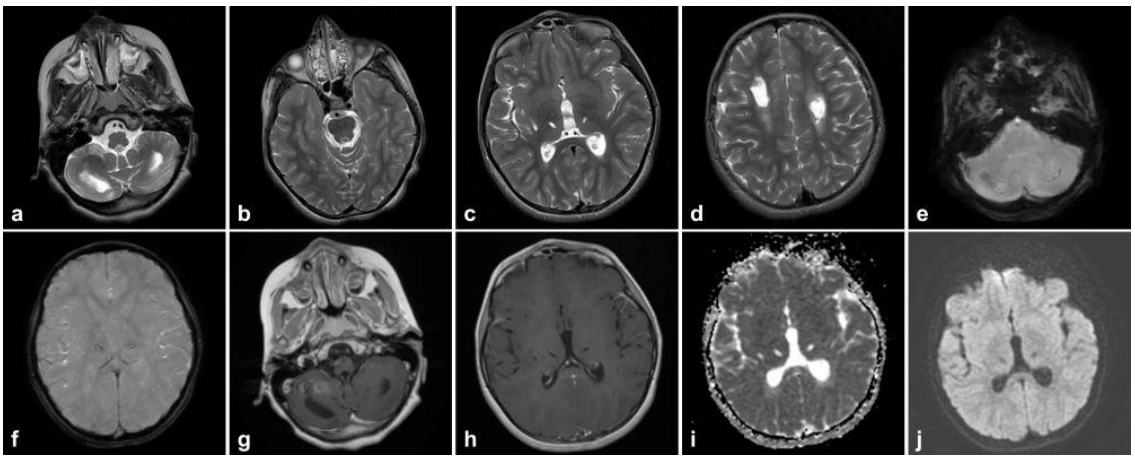

Figure 2a-j: Follow-up MRI findings 3 years after discharge showing regression of lesions. Axial T2-weighted images (a) bilateral cerebellar hemispheres, (b) posterior brain stem, (c) both thalamus and putamen posterior,and(d) hyperintense signal changes and widespread edema in subcortical white matter in the plane of both vertex were markedly regressed, (e-f) blood destruction products in the same locations in series showing decreased sensitivity. (g-h) Environmental contrast involvement and, (i-j) diffusion limitation was not observed in diffusion-weighted series.

Mortality rates for ANEC approach 30% (1). The outcome of ANEC was reported to be usually poor; approximately 65% of affected patients died or were left with severe neurologic sequelae(1, 4), and 90% of survivors were left with permanent neurologic sequelae (9). Motor deficits, movement disorders, and speech impairment frequently develop in the chronic stage [10]. Interestingly, none of these symptoms were observed during the long-term follow-up in the studied patient.

Wong et al. (4) aimed to determine the correlation between MRI and the outcome by performing MRI scoring (0-4) in 12 patients with ANEC. Patients with the highest MR scores had poor clinical outcomes, but those with low scores (1 or 2) had better clinical outcomes. The present patient had an MRI score of 4.

At the time of attendance, necrosis was present in the bilateral basal ganglia, thalami, and hemorrhage in the parenchyma. Hemorrhage and tissue loss are associated with poor prognosis in ANEC (10). The patient had more severe findings than the patients reported in the literature.

In the literature, there is a long-term follow-up for one patient with H1N1-associated ANEC, reporting intention tremor of the left hand, ataxic walking pattern, and left abducens nerve palsy still observed 2 years after onset (11).

In the studied patient, respiratory PCR was positive for H1N1. Both MRI findings and H1N1 positivity are poor prognosis criteria for this patient. Despite this, the patient rapidly improved and recovered without sequelae. Seemingly, the initiation of aggressive treatment within the first 24 hours after the onset of symptoms and the administration of the zipper method was effective in the patient's rapid improvement.

In Conclusion

ANEC is a devastating childhood disease characterized by rapid neurologic deterioration. Timely diagnosis and early treatment reduce mortality and morbidity. This case is a unique example of ANEC treated successfully with the zipper method.

Acknowledgment

None

Authors' Contribution

All authors contributed substantially to the work's concept or design of the work or the acquisition, analysis, or interpretation of data. EA, ÖK, and NG drafted or revised the article critically for important intellectual content. SK, YTY, and AA approved the publication of the version.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/ or publication of this article.

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