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CASE REPORT – OPEN ACCESS

Plasma Exchange in the Treatment of A Child with West Nile Virus Encephalitis: A Case Report

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ABSTRACT

Background: West Nile virus (WNV) is a member of the Japanese encephalitis antigenic complex of the family *Flaviviridae* that can cause a wide range of clinical symptoms, from asymptomatic disease to severe meningitis, encephalitis flaccid paralysis, and death. In immunocompetent children, WNV infection is usually benign and self-limiting. However, this virus is also associated with severe neurological disease in some patients, especially those who are older, have a chronic disease, have undergone organ transplantation, or are immunocompromised.

Case Report: A 12-year-old boy with selective immunoglobulin A-deficiency (SIgAD) and refractory seizures due to WNV encephalitis (WNE) was successfully treated with therapeutic plasma exchange (TPE) in conjunction with other immunomodulatory therapies.

Conclusion: WNV can progress like autoimmune encephalitis. TPE appears to be safe and effective for treating children with WNE. To our knowledge, this report is the first of a child with WNV infection and SIgAD.

Keywords: Children, epilepsy, plasma exchange, treatment, West Nile virus

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INTRODUCTION

West Nile virus (WNV) infection can manifest with a wide spectrum of clinical symptoms, including asymptomatic, flu-like illness and fever. In immunocompetent children, WNV infection is usually benign and self-limiting. However, this virus is also associated with severe neurological disease in certain patients, especially those who are older, have a chronic disease, have undergone organ transplantation, or are immunocompromised. The neuropathogenesis of central nervous system (CNS) involvement in WNV is still poorly understood; involvement of a cytopathic effect and indirect immune-mediated inflammation have been postulated. Although there have been rare cases of encephalitis associated with WNV infection reported, there is no definitive therapy for the disorder. Some studies have described the use of immunomodulator treatments (intravenous immunoglobulin [IVIG], corticosteroids, interferon) and ribavirin in WNE (1–5). This report presents the case of a 12-year-old boy with selective immunoglobulin A deficient (SIgAD) and refractory seizures due to WNV encephalitis (WNE), who was successfully treated with therapeutic plasma exchange (TPE) together with other immunomodulatory therapies. To the best of our knowledge, this is the first report of TPE treatment for WNE.

CASE REPORT

A 12-year-old boy was admitted to the hospital with a history of convulsions, lethargy, and strabismus in both eyes. The patient's medical history indicated that he had previously been healthy, but had a recent history of tick bites. His family medical history was also unremarkable. Loss of consciousness and orofacial dyskinesia were observed in the physical examination. The results of the initial laboratory evaluation were normal. Magnetic resonance imaging (MRI) of the brain revealed only slight leptomeningeal staining. Evaluation of the cerebrospinal fluid (CSF) showed normal protein and glucose concentrations (20 cells/mm^3), with a neutrophilic predominance and 480 erythrocyte/mm^3. An interictal electroencephalograph recording was characterized by electrographic seizure activity arising from the right and left hemisphere. Acyclovir, ceftriaxone, and levetiracetam were administered empirically. Laboratory investigations for metabolic and connective tissue disease as well as serum markers for viruses (i.e., herpes simplex virus, cytomegalovirus, *Varicella zoster*, mumps, rubella, measles and Epstein-Barr virus), *Borrelia burgdorferi*, and *Mycoplasma pneumonia* were all normal. Serum immunoglobulin levels were normal, with the exception of a low IgA level 17.9 mg/dL (29–251 mg/dL). The CSF assessment did not reveal any oligoclonal banding. Based on the results of the MRI and clinical examination, including orofacial dyskinesia, the patient was diagnosed with autoimmune encephalitis, and IVIG therapy was initiated on the second day of admission at 0.4 gm/kg/day for 5 successive days. Despite the addition of levetiracetam, his seizures continued, and phenytoin, topiramate, clobazam

were added sequentially, but seizure control was not achieved. Intravenous ketamine and midazolam infusions were initiated, but the seizures recurred. Therefore, corticosteroid treatment was added on day 3 to suppress the autoimmune encephalitis and/or post-viral immunological process that might have been responsible for this clinical condition. Intravenous methylprednisolone (20 mg/kg/day) was administered for 5 days and followed by oral prednisolone (1 mg/kg per day), but seizures and stupor persisted. Screening for neural autoantibodies, including antibodies to glutamic acid decarboxylase (anti-GAD), anti N-methyl-D-aspartate receptor (NMDAR), anti-glutamate receptor (AMPA 1 [Glu 1] and AMPA 2 [Glu 2]), anticontactin-associated protein-like 2 (CASPR2), anti-leucine-rich glioma inactivated 11 (LGI1), anti-gamma-aminobutyric acid-B receptor antibodies 1 (anti GABA B [GABABARB1/B2], and a paraneoplastic panel, including anti-amphiphysin, anti-CV2, anti-PNMA2 (Ma2/Ta), anti-Ri (Nova1), anti-Yo, anti-Hu, anti- recoverin, anti-SOX1, anti-titin, anti-Zic4, anti-GAD65 and anti-Tr (DNER) was normal. The number of seizures decreased, but they were not fully eliminated during follow-up and the patient's confusion continued. TPE treatment was started at 8 days of admission. With written informed consent from the family, a central venous catheter was inserted into the internal jugular vein. TPE was performed at an estimated 1–1.5 times the plasma volume using a Spectra Optia v.11.3 apheresis system (Terumo Corp., Tokyo, Japan) with continuous centrifugation. The plasma volume was calculated using the body surface area (calculated from height and weight), gender, and hematocrit values. Fresh frozen plasma was used as the volume replacement fluid, and acid citrate dextrose (dilution: 1:10–1:20 g/L) was used for anticoagulation. To avoid severe hypocalcemia, an intravenous infusion of calcium gluconate 10% was also administered. After 4 sessions of TPE, the patient remained seizure-free with antiepileptic treatment. On the 23rd day of admission, a serologic evaluation was positive for human WNV immunoglobulin M (IgM) and IgG in the serum. A test had also been conducted at admission. Since other closely related viral infections may lead to IgM and IgG positivity due to cross-reaction, a test was scheduled to be compared with the neutralization test in 2 weeks. After 30 days, the patient was discharged from the hospital with topiramate, clobazam, phenytoin, and levetiracetam treatment. At the time of discharge, the patient was seizure-free, and the results of a neurologic examination were normal. On the 44th day of outpatient follow-up, the serologic evaluation for WNV was repeated and revealed a 4-fold increase in WNV virus-specific neutralizing antibodies. Although immunology of the CSF for WNV could not be performed, the diagnosis of WNE was strongly supported by the serologic results. At the time of writing, the patient was still taking daily topiramate, clobazam, phenytoin, and levetiracetam as well as IVIG treatment for SIgAD. The corticosteroid treatment was terminated at 3 months, and he had been seizure-free for 40 months.

DISCUSSION

According to the established clinical and diagnostic criteria of the European Centre for Disease Prevention and Control for probable and confirmed WNV case definition, our patient could be considered a confirmed case of WNE due to the detection of WNV IgM and IgG in the serum during the acute phase of the infection and a 4-fold increase in virus-specific neutralizing antibodies during the convalescent phase, measured 2 weeks apart (1, 2, 6). In immunocompetent children, WNV infection is usually benign and self-limiting. However, this virus can be associated with severe neurological disease in some patients, particularly those who are immunocompromised. To date, the pathogenesis of WNE remains unclear. However, emerging evidence suggests that an autoimmune mechanism may be involved in the etiology. Antiviral antibodies and autoreactive antibodies targeting cerebellar neurons (possibly auto-antibodies specific for the centrosome protein pericentrin) have been detected in the CFS (1, 2, 7). Therefore, the treatment of neurological manifestations of WNV infection has primarily included corticosteroids and/or immunoglobulins. However, this treatment plan relies on data from previous case reports, and the clinical benefit of immunomodulatory therapy has not yet been sufficiently established in the literature for children. After conducting a search of the medical literature using the terms of "neurological disorders associated with WNV" and "treatment outcome in children," we identified 5 previously published reports, none of which included any use of TPE in WNE (1–5). Table 1 presents an analysis of these previously documented pediatric cases and our case.

Sava et al. (8) reported on the use of a double-filtration plasmapheresis method in the treatment of a female patient aged 59 years with a diagnosis of WNE. This case was the first and only known case of WNE treated using plasmapheresis. TPE has been successfully used in various pediatric neuroimmunological diseases in children. The American Society for Apheresis has provided guidelines on definite indications for TPE in neuroimmunological diseases. According to the 2019 guidelines, NMDA receptor encephalitis, the best-characterized type of autoimmune encephalitis, is a category I indication, which means that TPE should be considered a first-line therapeutic option (9). We previously reported our experience with the use of TPE in the treatment of neurological disease, such as inflammatory neuropathies and autoimmune CNS disorders, which resulted in significant neurological recovery in the majority of affected children (10).

It is widely known that viral infections can be associated with autoimmune diseases, and the best studied example is NMDAR encephalitis following herpes simplex virus 1 infection. WNV has also been reported in patients with various autoimmune diseases. Karagianni et al. (11) reported an adult patient with WNV infection who developed autoimmune encephalitis with positive anti-glycine receptor antibodies. Patients with SIgAD have a higher incidence of autoimmune disease as well as increased prevalence of autoantibodies without symptoms of overt autoimmune disease. However, the relationship between autoimmunity and IgA deficiency is not yet clear (12). Since our patient responded to TPE in combination with other immunomodulatory treatment, we speculated that the post-viral immunologic process might have been responsible for his clinical condition. We also believe that the pre-existing SIgAD significantly contributed to the development of the immunologic process during the WNV infection.

CONCLUSION

Firstly, we highlighted that WNV can progress like autoimmune encephalitis. Therefore, it should be included in differential diagnosis of autoimmune-like encephalitis with refractory seizures. Secondly, TPE appears to be safe and effective for treating children with WNE. To the best of our knowledge, this is the first report of a child with WNE treated with TPE. In addition, this report appears to be the first of a child with WNV infection and comorbid SIgAD.

Table 1. Treatment and outcome of central nervous system infections of WNV in children

Reported cases **No**	**Spiegel et al. (2)** **1**	**Thabet et al. (3)** **2**	**Soldatou et al. (1)** **3**	**Hindo et al. (4)** **4**	**Messacar et al. (5)** **5**	**Presented case** **6**
Age (y)/sex	4/M	10/M	2/M	14/M	9/M	12/M
Presenting signs and symptoms	Seizures and motor aphasia	Left leg weakness	Difficulty walking	Ataxia and altered mental status	Status epilepticus	Seizures, loss of consciousness, lethargy, and strabismus
Neurologic examination	Lethargy, disorientation, neck rigidity, and positive Brudzinski sign	Left foot drop and weak plantar flexion	Bilateral proximal lower extremity weakness and absent deep tendon reflexes	Lethargy, disoriented, incoherent speech, deviated right eye medially, horizontal nystagmus, diplopia, weakness in left upper and lower extremities	Lethargy, disorientation	Lethargy, orofacial dyskinesia
Results of brain MRI	–	Unremarkable	–	Slight increase in the size of the right thalamic region without contrast enhancement	Symmetric T2 hyperintensity in the bilateral caudate heads and putamen	Leptomeningeal enhancement
CSF analysis	WBC count 180/ mm^3, 60% PNL, 40% lymphocytes, glucose 55 mg/dL, protein 109 mg/dL	WBC count 33% PNL, 67% lymphocytes, glucose 62 mg/dL, protein 137 mg/dL	CSF cell count 5/μL, glucose 34 mg/dL, protein 11 mg/dL	WBC count 31/ mm^3, 1% PNL, 99% monocytes, red blood cell 1 and no blast cells), glucose 41 mg/dL, protein 100 mg/dL	WBC count 41/ mm^3, 18% PNL, 17% lymphocytes, 48% monocytes, and 15% plasma cells, glucose 42 mg/dL, protein 256 mg/dL	WBC count 20/ mm^3, 60% PNL, 40% lymphocytes, erythrocyte 480 glucose 68 mg/dL protein 18 mg/dL
Diagnosis	WNVME	WNV-AFP	WNV-AFP	WNE	WNVME	WNE
WNV serology results	WNV IgM and IgG antibodies were positive in serum	WNV IgM antibody was positive in CSF	WNV IgM and IgG antibodies were positive in serum	WNV IgM antibody in CSF and serum	WNV IgM antibody in CSF and serum	WNV IgM and IgG antibodies were positive in the serum
Comorbid disease	Hodgkin's lymphoma	–	–	Acute lymphocytic leukemia	Primary adrenal insufficiency	Selective immunoglobulin A deficient
Treatment type/ response	Ribavirin/ Complete recovery	IVIG/ Partial recovery	IVIG/ Complete recovery	Corticosteroids IVIG Omr-IgG-am/ Death	Antibiotics acyclovir corticosteroids	Corticosteroids IVIG TPE/ Complete recovery

AFP: Acute flaccid paralysis; CSF: Cerebrospinal fluid; Ig: Immunoglobulin; IVIG: Intravenous immunoglobulin; MRI: Magnetic resonance imaging; PNL: Polymorphonuclear neutrophilic leukocyte; TPE: Therapeutic plasma exchange; WBC: White blood cell; WNE: West Nile virus encephalitis; WNV: West Nile virus; WNVME: West Nile virus meningoencephalitis

Informed Consent: Written, informed consent was obtained from the patient's family for the publication of this case report and the accompanying images.

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