
**Manuscript Type:** Case Report

**Title:** The role of therapeutic plasma exchange in the treatment of a child with West Nile virus encephalitis

**Running Title:** Therapeutic plasma exchange and West Nile virus

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ABSTRACT

Background
West nile virus (WNV) is a member of the Japanese encephalitis family that causes 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 certain patients, especially those older, who have a chronic disease, have undergone organ transplantation, or are immunocompromised.

Case
Herein, we present a 12-year-old boy with selective immunoglobulin A deficient (sIgAD) and refractory seizures due to WNV encephalitis (WNE), who successfully treated with therapeutic plasma exchange (TPE) together with other immunomodulatory therapies.

Conclusion
WNV can progress like autoimmune encephalitis, and 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.

Key words: West Nile virus, plasma exchange, children, treatment, epilepsy

INTRODUCTION
West Nile virus (WNV) infection is manifested by 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 older, who have a chronic disease, have undergone organ transplantation, or are immunocompromised. The neuropathogenesis of the central nervous system (CNS) involvement in WNV is still poorly understood, and both cytopathic effect and indirect immune-mediated inflammation are postulated to be involved. Although cases of encephalitis associated with WNV infection have been rarely reported, there is no definitive therapy for the disorder. Some studies have been published on the use of...
imunomodulator treatments (intravenous immunoglobulin (IVIG), corticosteroids, interferon) and ribavirin in WNE (1-5). Herein, we present a 12-year-old boy with selective immunoglobulin A deficient (sIgAD) and refractory seizures due to WNV encephalitis (WNE), who 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 in WNE.

CASE REPORT

A 12-year-old boy was admitted to our hospital with a history of convulsion, lethargy and strabismus in both eyes on September, 2017. The patient’s medical history indicated that he was previously healthy but he had a history of tick bites in August and September 2017. His family medical history was also unremarkable. He had a loss of consciousness and orofacial dyskinesia at physical examination. Initial laboratory evaluation was normal. Magnetic resonance imaging (MRI) of the brain revealed only slight leptomeningeal staining. Cerebrospinal fluid (CSF) showed normal protein and glucose concentrations with 20 cells/mm3, with neutrophilic predominance and 480 erythrocyte/mm3. The interictal electroencephalograph was characterised 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 and 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 except for low IgA level 17.9 mg/dl (29-251 mg/dl). The CSF did not show 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 was started on the second day of admission at 0.4gm/kg/day for 5 successive days. Despite the addition of levetiracetam, his seizures continued, and phenytoin, topiramate, clobazam were added sequentially on follow-up, but seizure control was not achieved. Intravenous ketamine and midazolam infusions were started, but seizures recurred. Therefore, corticosteroid treatment was added on day 3 to suppress the autoimmune encephalitis and/or post-viral immunologic process that might have been
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treatment as well as IVIG treatment for sIgAD. On the other hand, corticosteroid treatment was stopped in 3 months and he had been seizure-free for 40 months.

DISCUSSION
According to the established clinical and diagnostic criteria of European Union (EU) for probable and confirmed WNV case definition (European Centre for Disease Prevention and Control), our patient could be considered a confirmed case of WNE due to the detection of WNV IgM and IgG in the serum of the patient in the acute phase of the infection and a 4-fold increase in virus-specific neutralising antibodies in the convalescent phase taken 2 weeks apart (1,2,6). In immunocompetent children, WNV infection is usually benign and self-limiting. However, this virus might be associated with severe neurological disease in certain patients, especially in immunocompromised patients. To date, the pathogenesis of WNE remains unclear. However, emerging evidence suggests that an autoimmune mechanism may be involved in its aetiology. 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 have 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 which did not include any use of TPE in WNE (1-5). Table 1 presents an analysis of the 5 previously documented pediatric cases and our case.

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

It is widely known that viral infections have often been associated with autoimmune diseases, and the best studied example is NMDAR encephalitis following HSV-1 infections. WNV has also been previously reported in patients with various autoimmune diseases. Karagianni et al. reported an adult patient with WNV infection who developed autoimmune encephalitis with positive anti-glycine receptor antibodies (11). On the other hand 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 clear yet (12). Since our patient responded to TPE together with other immunomodulatory treatments, 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 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 child with WNE who was treated with TPE. As well as, this report is the first of a child with WNV infection together with sIgAD.

REFERENCES

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as: Özkale Y, Özkale M, Ceylan Ö, Erol İ. The role of therapeutic plasma exchange in the treatment of a child with West Nile virus encephalitis. Erciyes Med J 2021; DOI: 10.14744/etd.2021.96606.

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Abbreviations: WNV, West nile virus; WNE, west nile virus encephalitis; TPE, Therapeutic plasma exchange;

TABLE
Table I. Treatment and outcome of central nervous system infections of WNV in children.
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Abbreviations of table: WNV, West nile virus; WNE, west nile virus encephalitis; WNVME, west nile virus meningoencephalitis; TPE, Therapeutic plasma exchange; intra venous immunoglobulin, IVIG; CSF; cerebro spinal fluid; AFP, acute flaccid paralysis
Table 1. Treatment and outcome of central nervous system infections of WNV in children

<table>
<thead>
<tr>
<th>Reported Cases No</th>
<th>Spiegel et al²</th>
<th>Thabet et al³</th>
<th>Soldatou et al¹</th>
<th>Hindo et al⁴</th>
<th>Messacar et al⁵</th>
<th>Presented case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)/Sex</td>
<td>4/M</td>
<td>10/M</td>
<td>2/M</td>
<td>14/M</td>
<td>9/M</td>
<td>12/M</td>
</tr>
<tr>
<td>Presenting signs and symptoms</td>
<td>Seizures and motor aphasia</td>
<td>Left leg weakness</td>
<td>Difficulty in walking</td>
<td>Ataxia and altered mental status</td>
<td>Status epilepticus</td>
<td>Seizures, consciousness, lethargy and strabismus</td>
</tr>
<tr>
<td>Neurologic examination</td>
<td>Lethargy, disorientation, neck rigidity and positive brudzinski sign</td>
<td>Left foot drop and weak plantar flexion</td>
<td>Bilateral proximal lower extremity weakness and absent deep tendon reflexes.</td>
<td>Lethargy, disorientated In coherent speech, deviated right eye medially, horizontal nystagmus, diplopia, weakness in left upper and lower extremity</td>
<td>Lethargy, disorientation</td>
<td>Lethargy, orofacial dyskinesia</td>
</tr>
<tr>
<td>Results of brain MRI</td>
<td>-</td>
<td>Unremarkable</td>
<td>-</td>
<td>Slight increase in the size of the right thalamic region without contrast enhancement</td>
<td>Symmetric T2 hyperintensity in the bilateral caudate heads and putamen</td>
<td>Leptomeningeal enhancement</td>
</tr>
</tbody>
</table>

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| CSF analysis | WBC count; 180/mm³; 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 | Cell count; 5/μL, glucose; 34/mg/dL protein; 11 mg/dL | WBC count; 31/mm³; 1% PNL, 99% monocytes, red blood cell; 1 and no blast cells]. glucose; 41/mg/dL protein; 100 mg/dL | WBC count; 41/mm³; 18% PNL, 17% lymphocytes, 48% monocytes, and 15% plasma cells, glucose; 42/mg/dL protein; 256 mg/dL | WBC count; 120/mm³, 60% PNL, 40% lymphocytes, erythrocyte; 480 glucose; 68 mg/dl protein; 18 mg/dl |
| Diagnoses | WNVME | WNV-AFP | WNV-AFP | WNE | WNVME | WNE |
| WNV serology results | WNV IgM and IgG antibodies were positive in the serum | WNV IgM antibody was positive in CSF | WNV IgM and IgG antibodies were positive in the 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 leukaemia | Primary adrenal insufficiency | Selective immunoglobulin A deficient |
| Treatment type/ response | Ribavirin Complete recovery | IVIG Parsiyel recovery | IVIG Complete recovery | Corticosteroids IVIG Omr-IgG-am Death | Antibiotics acyclovir corticosteroids | Corticosteroids IVIG TPE Complete recovery |

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