VISUAL OUTCOME POST THERAPEUTIC PLASMA EXCHANGE IN NEUROMYELITIS OPTICA PATIENTS: A CASE SERIES

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ABSTRACT
Background: The Purpose of this case series was to present several cases of neuromyelitis optica that are treated with therapeutic plasma exchange (TPE).

Case Presentation: This was a retrospective study of 5 cases in DR Kariadi Hospital. Data were collected from medical records in patients diagnosed with neuromyelitis optica (NMO) treated with TPE during 1 year. Diagnosis of NMO is established with the presence of optic neuritis, transverse myelitis, and MRI contrast of the brain and the whole spine. The TPE protocol specifies the treatment of 4 cycles administered within 1 week. All of NMO patients treated with TPE were female, aged between 19-43 years (mean 33.6). Patients had chief complain of an average of 3 months before initial therapy. The initial vision averaged of finger counting and increased after treatment. All complaints of myelitis comprised of paraparesis but some experienced paresthesia. All patients received intravenous steroids and TPE.

Conclusion: All patients with NMO who underwent TPE had vision improvement.

BACKGROUND
Neuromyelitis optica (NMO) and NMO spectrum disorders (NMOSDs) are autoimmune inflammatories or demyelinating disorders of the central nervous system that mainly target astrocytes and predilection for the optic nerves and spinal cord. In 2004, the discovery of aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) made them independent from multiple sclerosis as a disease entity. NMO spectrum disorders (NMOSD) are mostly severe optic neuritis (ON) or recurrent ON and longitudinally extensive transverse myelitis or relapsing, which often occur in young adults with a relapsing-remitting course of neurologic deficits and also some encephalitic presentation. NMOSD are unified by detection in serum or cerebro spinal fluid (CSF) of NMO-IgG (AQP4-antibody). The New Consensus The International Panel for NMO Diagnosis (IPND) 2015 reaffirmed the decision to unify the terms NMO and NMOSD. Given the greater degree of diagnostic uncertainty and potential heterogeneity of seronegative NMOSD, criteria were developed for both NMOSD with AQP4-IgG and NMOSD without AQP4-IgG. An additional category of NMOSD with unknown AQP4-IgG status maybe used for patients in whom serologic testing is unavailable. The nomenclature allows for future modifications based on potential discovery and validation of other biomarkers in AQP4-IgG-seronegative patients who have otherwise typical NMOSD clinical syndromes.¹³

The newest incidence and prevalence NMO published by meta analysis and systematic review with the results highest estimates of incidence and prevalence of NMO in Afro-Caribbean 0.73/100.000 person-years, the lowest incidence, and prevalence of NMP were found on Australia and New Zealand 0.037/100.000 person-years, that was prominent female in middle-age.⁴

The major treatment in patients with
NMOSD shows a good response with steroids and therapeutic plasmapheresis (TPE) and maintenance with immunosuppressant therapy. Aggressive treatment after initial attacks is considered an important measure that could heavily influence the long-term prognosis of patients. Therapeutic plasmapheresis (TPE) add-on in NMO therapy is more effective because TPE eliminates circulating antibodies and inflammatory cytokines, which are the principal mediators of NMOSD attack. Several nonrandomized studies have suggested the role of TPE as rescue therapy or even first-line therapy.5

**CASE PRESENTATION**

This was a retrospective study of 5 cases in DR Kariadi Hospital in Neuroophthalmology division who treated by therapeutic plasma exchange (TPE) during 1 years.

<table>
<thead>
<tr>
<th>Table 1. Demographic data</th>
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<tbody>
<tr>
<td><strong>Data</strong></td>
</tr>
<tr>
<td>Sex</td>
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<tr>
<td>Age</td>
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C : case, F: female, y : years

From table 1, demographic data showed all cases were female with range age of 19-43 yo (table 1)

The diagnosis of NMO was obtained from the presence of optic neuritis, transverse myelitis, and ancillary testing. The symptoms of optic neuritis that were collected from history taking such as blurred vision, the onset of the symptoms, ocular pain, and lack of contras or and colorvision. These symptomsof myelitis such asparasthesia, paresis, sensory disfunction, bladder dysfunction and an unexplained hiccup or nausea vomiting.

<table>
<thead>
<tr>
<th>Table 2. Clinical Symptoms</th>
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<tr>
<td><strong>Data</strong></td>
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<tr>
<td>Onset</td>
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<tr>
<td>Ocular pain</td>
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<tr>
<td>Dyscro</td>
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<tr>
<td>Myelitis</td>
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Mo: month, Dyscro: Dyschromatopsia, p: parasthesia, P: Paresis

The mean onset of TPE is around 3 months after initial attack. All of the patients had ocular pain, dyschromatopsia complaints. Myelitis complaints are found to vary, 2 of 5 patients had paresthesia and others complained of paresis. (table 2)

Physical examination in all of patients performed with visual acuity check, fundus photography, color vision test used Ishihara, Lea book contrast sensitivity, Humphrey visual field analyzer (Hvfa), and Head MRI and Whole spine MRI + contras.

<table>
<thead>
<tr>
<th>Table 3. Physical examination and ancillary test</th>
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<tr>
<td><strong>Data</strong></td>
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<tr>
<td>Fc</td>
</tr>
<tr>
<td>HvFa</td>
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<tr>
<td>Isch</td>
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<td>SC</td>
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In table 3 show all of the patients had papillitis in funduscopy, with visual field defects like paracentral scotoma and superior altitudinal. Almost all of them had a decreased contrast sensitivity and color vision disturbances.
Figure 2 present 1 of 5 cases with unusual optical coherence tomography (OCT) findings displaying temporal thinning. The remaining 4 present the most common finding in patients with NMO which is thinning of peripapillary retinal nerve fiber layer (pRNFL). Damage effects all quadrants, mainly superior and inferior quadrant. Three of 5 patients present with ganglion cell inner plexiform layer (GC-IPL) thinning (Figure 3).

Figure 3 shows MRI brain with contrast shows some a normal brain (b) and MRI whole spine shows interventricular lesion in segment C5-C7.
**Table 4. Visual acuity pre and post TPE**

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<thead>
<tr>
<th>Data</th>
<th>CI</th>
<th>CII</th>
<th>CIII</th>
<th>CIV</th>
<th>CV</th>
</tr>
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<tbody>
<tr>
<td>VA pre TPE</td>
<td>4/60</td>
<td>1/60</td>
<td>T'</td>
<td>1/60</td>
<td>1/60</td>
</tr>
<tr>
<td>VA post TPE</td>
<td>6/48</td>
<td>6/12</td>
<td>2/60</td>
<td>6/60</td>
<td>1/60</td>
</tr>
</tbody>
</table>

VA pre TPE : Visual acuity pre Therapeutic plasma exchange, VA post TPE : Visual acuity post Therapeutic plasma exchange

**DISCUSSION**

This case series reports 5 cases of patients with a diagnosis of NMO who were treated with TPE. Because of in this case series with unknown AP4-IgG status so, NMO diagnosis refers to an International Panel for NMO Diagnosis (IPND) published the consensus diagnostic for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status.

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. at least 1 core clinical characteristic must be optic neuritis, acute myelitis with longitudinally extensive transverse myelitis lesion (LETM), or area postrema syndrome
   b. dissemination in 2 space
   c. fulfillment of additional MRI requirements, as applicable
2. Negative test or unavailable AQP4-IgG
3. Exclusion of alternative diagnoses.

Optical coherence tomography (OCT) is a noninvasive tool to check the retinal layer. In NMO patients usual finding OCT with thinning of peripapillary nerve fiber layer (pRNFL) and damage affects every quadrant mainly the superior and inferior quadrant. Three of 5 patients show the ganglion cell inner plexiform layer (GC-IPL) thinning.

All of the patients had core clinical characteristics such as optic neuropathy, acute myelitis like paresthesia, and paresis but no one had area postrema syndrome and acute brainstem syndrome. Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status from anamnesis and clinical features, and MRI showed in the brain with normal and some nonspecific white matter lesion. But all of the patients MRI spine showed extending ≥3 contiguous segments. Transverse myelitis is defined as spinal cord dysfunction developing over hours to days in the absence of a structural spinal cord lesion. Typically characterized by systematic paraparesis or quadriplegia, bladder dysfunction and sensory loss below the level of spinal cord lesion.

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status from IPND:

1. Acute optic neuritis: MRI brain showing: normal or only nonspecific white matter lesions OR with T2 - hyperintense lesion or T1 weight gadolinium-enhancing lesion extending over > ½ Optic Nerve length or involving optic chiasm.
2. Acute myelitis: intramedullary MRI lesion extensive over ≥3 contiguous segments LETM OR ≥
3 contiguous segments of focal spinal cord atrophy in patients with history acute myelitis
3. area postrema syndrome: requires associated dorsal medulla/area postrema lesions
4. acute brainstem syndrome: requires associated periependymal brainstem lesions.

The major treatment in patients with NMOSD shows good response with steroids and therapeutic plasmapheresis (TPE) more in the acute setting; however, 90% of patients will eventually have clinical relapses and accrue permanent disability. In the acute initial presentation or exacerbation of NMO, the typical treatment is the administration of intravenous methylprednisolone therapy (IVMP; 1,000 mg daily for 3–5 days). If there is no significant clinical improvement on steroids, plasma exchange is effective for both ON and TM associated with NMO. Typically, 5 cycles are administered daily or every other day, but in this case series, all of the patients had 4 cycles of TPE. A recent study comparing IVMP monotherapy with IVMP in combination with TPE treatment for cases of ON associated with NMO demonstrated IVMP and TPE in combination being more efficient than IVMP alone. High-contrast visual acuity, visual fields, and temporal retinal nerve fiber layer thickness improved significantly with TPE treatment. In the other previous study in 52 NMOSD patients reported that patients who were TPE responders or non-responders had a significantly lower relapse rate at 6 months than those who used IVMP alone.9-11

Many systematic reviews and meta-analysis showed the benefit of TPE during the NMO attack with a significantly improved disability status immediately and improve visual acuity after treatment and during follow-up. Therapeutic plasma exchange is the filtration of the plasma, which is removed, replaced by artificial plasma, and reinfused to the patient—the plasma exchange. The goal of the filtration step is to remove a given volume of patient’s plasma and to return an artificial plasma substitute in its place. That explains the improvement post-TPE immediately, the elimination of various antibodies, complements, and cytokines which are the circulating pathogenic inflammatory mediators such as autoantibodies, complement and several cytokines of NMOSD is probably the primary mechanism of TPE that leads to the observed beneficial effect. Because NMO lesions are associated with a strong IgG, IgM, and complement deposition, typical of the pattern II in the Lassmann classification. The NMO-IgG is involved in complement-dependant toxicity against the astrocytes. All of these components—IgG, IgM, and complement—are targeted by plasma exchanges. Employing 5 exchanges, all the exchanged molecules will drop to less than 20% of their initial level.12-14

TPE effectiveness was associated with the duration between disease and the initiation of PE, and the optimal timing for PE initiation is 8 to 23 days after the onset of the disease, But in this case series, almost all of patients had 3-5 mo onset to get initially TPE and still have a better visual acuity after treatment. The previous study showed The duration between the onset of an attack and the initiation of treatment is key. Early initiation of PE treatment was associated with a good prognosis in a study on CNS demyelination. A previous study showed that the EDSS score reductions were significantly greater in groups receiving PE on days≤15 and days 16–30 than in those receiving on days 31–60 and days 61–90.14-16
The long-term benefit after TPE may partly be explained by B-cell depletion. Since AQP4 antibodies are produced by B cell differentiation to plasma cells and B cells are also potent antigen-presenting cells for AQP4-reactive pathogenic T cells, this current knowledge explains the scientific rationale for using B cell depletion therapy for long-term prevention. The depletion of B-cell by TPE helps to prevent auto-reactive B-cell re-expansion, which consequently helps to decrease AQP4 production in the long term like other B-cell depletion therapy. Many studies have indicated that patients who underwent TPE had a lower level of AQP4 autoantibody titer. However, the level of AQP4 autoantibody can rise during follow-up due to the nature of the disease. Of all current knowledge, it may explain the reduction of disability in NMOSD patients after receiving TPE. Therefore, TPE, which is typically used in the prevention of disease, seems to be advantageous as a therapy for acute relapse as well.

These case series show the visual outcome after TPE had improvement just1 patient had a still 1 meters finger counting. The systematic review and meta-analysis reported visual pre and post-treatment visual outcomes among patients with NMOSD who underwent TPE, and had consistently demonstrated the benefit of TPE with improved VA and/or LogMAR after treatment. The other previous study reported a TPE as a first line therapy in acute attack NMO had 73% visual improvement. Minor side effects like rashes, paresthesias were present in 40% of patients, but only two serious reactions resulted in premature PLEX interruption. Although it has side effects like other treatments, TPE is still safe and effective.\textsuperscript{15,16}

**CONCLUSION**

Most cases of NMO had improved vision after TPE therapy despite delayed administration of TPE. In Previous studies showed NMO have a good responds with TPE and TPE effectiveness was associated with the duration between disease and initiation of PE, and the optimal timing for PE initiation is 8 to 23 days after onset of the disease.

**REFERENCES**