MANAGEMENT FOR DECLINING VISUAL OUTCOME AFTER SEQUENTIAL BILATERAL OPTIC NEURITIS DUE TO NEUROMYELITIS OPTICA

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ABSTRACT
Background: To report a management and follow-up plan for a female patient presented with history of sequential optic neuritis (ON) and longitudinally extensive transverse myelitis (LETM) after inadequate treatment during COVID-19 limitation period.
Case Presentation: A twenty-nine-years old female patient presented with chief complaint constriction of visual field in right eye for one month. One year ago, she had the same issue on the left eye with poor visual aquity outcome. She was admitted due to flaccid paraplegia and incontinence urine/alvi. Whole spine MRI found LETM more than three vertebral segments (VC7-VTh8). She was diagnosed with neuromyelitis optica spectrum disorder (NMOSD) based on IPND 2015 with an unknown AQP4-Ab status. IVMP was given for five days followed by prednisone and azathioprine orally. Decreasing retinal function and anatomy were noted by visual function, HVF, and OCT during follow-up. One month follow-up after initial treatment, best corrected visual acuity of right eye was improved though the fundus examination showed pallor disc.
Conclusion: Ophthalmologist should concern with Asian female patient with sequential bilateral optic neuritis as a sign of demyelinating disease. Satisfying clinical improvement after the appropriate initial and maintenance management was achieved in this patient. Humphrey visual field (HVF) and optical coherence tomography (OCT) could be deployed as a follow-up tool for estimating the visual outcome objectively, especially after limitation period which hinder the patient to check-up regularly.
Keyword: bilateral optic neuritis, longitudinally extensive transverse myelitis, neuromyelitis optica spectrum disorder, multiple sclerosis

BACKGROUND

NMOSD is an autoimmune entity which disrupts the astrocytic membrane with ON, LETM, and brain stem lesions manifestation. ON as the first sign of NMOSD can arise in other illnesses, such as MS, viral infections, or autoimmune diseases. Estimated to be between 0.037 and 10 per 100,000, the prevalence of NMO is modest based on population-based and epidemiological studies.[1] NMO accounts for a minor fraction of demyelinating illness in Caucasians (1–2%), whereas it accounts for a significant proportion in Asians (20–48%).[2] The initial presentation may be similar, but NMO is believed to result in severe bilateral vision impairment and injury to the optic nerve. Here, we described this uncommon clinical condition in our institution for the management and follow-up to prevent further visual morbidity.

CASE PRESENTATION

A 29-year-old woman consulted to our department with the chief complaint of progressive visual field constriction in the right eye. A month prior to the presentation, both of her legs were numb and tingling, combined with a visual complaint that worsened over time and left her immobile. Later, she lost control of her urination and defecation which made her rush to the emergency department (ED). The patient was alert and aware of time, location, and person. No objective deficit in memory. The patient was then admitted for one week in the Neurology wing with high dose

methylprednisolone intravenous injection. Her visual acuity improved after admission, but two weeks after discharged, her visual function field shrunken, particularly on the peripheral. This was her third incident of visual disturbance in the past two years. The patient denied having a fever, stiff neck, or headache. The family history of spectacles, trauma, previous surgery, and a similar disorder was unremarkable.

Her complaint began when she was unable to straighten her knee for three months prior the first presentation. One month later, she suffered sudden blurriness and movement-related pain in her left eye. A week after the blurring, her vision field became completely dark. The patient was referred to our facility after experiencing no improvement from earlier medical therapy. Her symptoms started to improve after receiving oral medication. After two follow-ups, the patient was unable to visit our institution at the onset of the pandemic; hence, she stopped taking the prescription. Five months later, her right eye suffered a similar incident, which was followed by hospitalization and the administration of medication through injection for three days. Vision was improved following treatment and no further therapy was consumed after discharge.

Comprehensive ophthalmologic examination was done with the patient's right and left eyes were able to read $^{1}/_{40}$ on the ETDRS chart and light perception only. Confrontation test with counting fingers on right eye medial side was observed. Anterior segment showed rounded pupils with 4 mm and 6 mm diameter, light reflex positive with sluggish movement on left eye. A funduscopic examination revealed on both eyes pale optic discs with no background alterations, indicating bilateral optic atrophy (**Fig.1**). In addition to BCVA and a standard eye exam, perimetry with HVF 3 (Carl Zeiss Meditec AG, Jena, Germany) and pRNFL-macula thickness with a Cirrus OCT (Carl Zeiss Meditec AG, Jena, Germany) were collected. From 2020 to 2021, her RNFL, macular cube, and GCA with OCT demonstrated a significant thinning. Her GPA RNFL and ONH report contained further quantitative information. The ganglion cell layer (GCL) of the macula also exhibits the same modification. In the meantime, her HVF tests revealed right-eye temporal anopia with a decreasing MD value.

Neurology examination showed flaccid paraplegia with hyperesthesia on the sixth thoracic vertebrae and below. The right and left proprioceptive lower extremities were affected. Incontinence alvi and urine also exhibited with urine catheter inserted. Other cranial nerves are within the standard range. The results of the complete blood count, urinalysis, serum liver biochemical, and renal function tests were normal. The HIV, hepatitis B, and hepatitis C virus serological tests, ANA test (10,47), and thorax plain photo were ordinary. Due to unavailability at our hospital, neither Aquaporin 4 immunoglobulin G (AQP4-IgG) nor myelin oligodendrocyte glycoprotein (MOG) were not examined. Imaging of the whole spine was performed on admission, revealing transverse myelitis affecting more than three segments and central cord involvement (**Fig. 2**). Her earlier brain imaging revealed a left optic nerve kinking without involvement of the chiasm or posterior segment, and no brain tissue abnormality was seen (**Fig.3**). A second MRI of the brain was performed following discharge. Multiple lesions near the left lateral ventricle that were T1 hypointense and T2 hyperintense, and the left centrum semiovale that was isointense at T1W1/T2 and hyperintense at T2 with no contrast enhancement on FLAIR were suggestive of a non-specific brain lesion because they did not meet the criteria for either NMOSD or MS brain lesion (**Fig.4**).

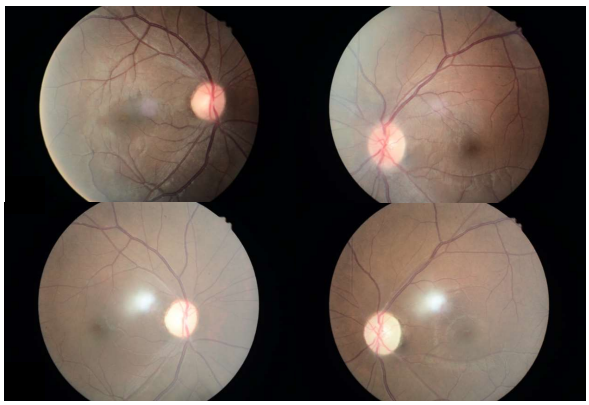

Figure 1. A. Fundal photography one year ago showed OS hyperemic disc with blurred margin. B. Photography during the last presentation with left eye slight pallor than right eye

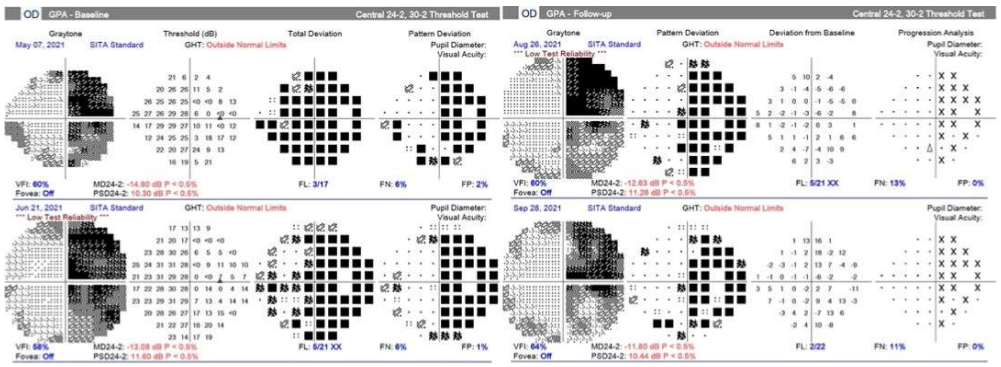

Figure 1. GPA HVF in four consecutive follow-ups showed temporal anopia. Even though VFI didn't show much differences, her MD value over time was decreasing more than -2 dB

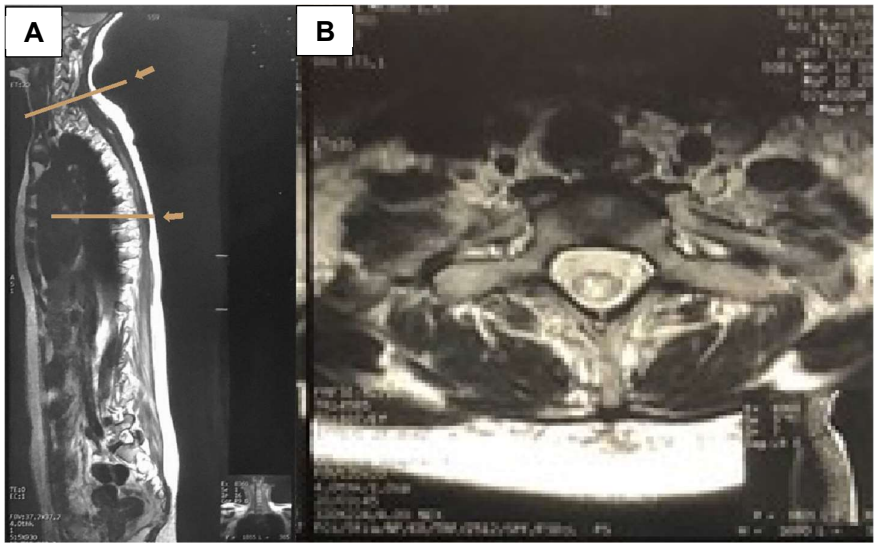

Figure 2. Whole Spine MRI 1,5 T during admission with T2 Sagittal (A) and T2 Axial (B) with transverse myelitis more than 3 segments of vertebrae and involvement of the central cord.

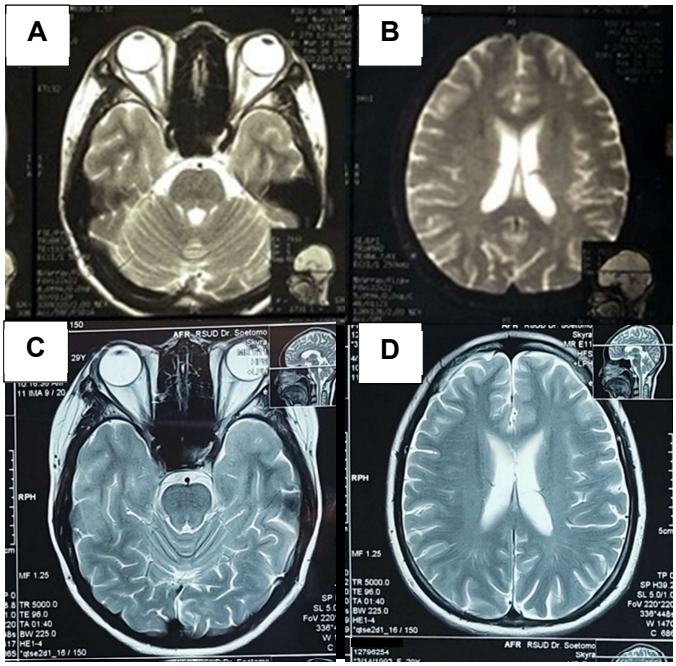

Figure 3. A and B MRI Brain 1,5 T on the first attack with OS Optic Neuritis and no sign of MS in brain area. C and D Brain MRI 3T with contrast on April 30th, 2021 with multiple lesions near left lateral ventricle T1 hypointense and T2 hyperintense, and left centrum semiovale isointense at T1W1/T2W1, hyperintense at T2, FLAIR no contrast enhancement

After excluding other potential causes, NMOSD with unknown AQP4-IgG status was diagnosed using the IPND Diagnostic Criteria. Injections of methylprednisolone 4x125 mg were administered for three days, followed by 4x250 mg injections for four days. After then, prednison 4x15 mg orally was given and tapered off every two weeks following discharge. Since admission patients have been administered azathioprine, an antimetabolite, 2x250 mg to prevent the relapsing. Her visual acuity (VA) at the emergency room was 2 metres counting finger in her right eye and improved to $^{5}/_{40}$ (Peek Acuity app) prior to discharge. After six months follow-up, she could maintain $^{5}/_{6}$ best corrected visual acuity (BCVA) with stable visual field.

DISCUSSION

Optic neuritis (ON) is an acute inflammatory demyelinating central nervous system condition (CNS).[3] Optic neuritis attack population ages between 20 and 45.[4] There are several causes of inflammation of the optic nerve, including autoimmune, infection, granulomatous illness, paraneoplastic diseases, and demyelination.[5] It is essential to determine the cause of optic neuritis quickly in order to execute early and effective treatment. Bilateral optic neuritis and whole spine MRI transverse myelitis were strongly indicative of demyelinating illness, with differential diagnosis including NMOSD, neurosarcoidosis, multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM), and idiopathic transverse myelitis (ITM).[6,7] Extensive research has been conducted over the past few decades to gain a deeper knowledge of ON. Previously there were unclassifiable case identified in studies prior to the autoantibody biomarkers aquaporin-4 (AQP4) immunoglobulin G (IgG) MOG.[3,8]

Eugène Devic and Fernand Gault named the condition as neuromyelitis optica in 1894, which was derived from *neuro-myélite optique aigu*. Therefore, the disease was formerly known as Devic's disease.[5] The condition is distinguished by optic neuritis and longitudinally contiguous transverse myelitis from IPND 2015 criteria.[9] Unlike MS, NMOSD accounts for high incidence of demyelinating disease cases in African ethnicity than Caucasian.[1] Extensive investigations have revealed that NMOSD is associated with severe visual impairment; consequently, early diagnosis and intensive treatment are required for the best chance of preserving the visual and neurologic function.[5,10,11]

The Brain MRI of our patient during the first episode revealed left Optic Neuritis without MS-typical brain lesions which didn't meet McDonald criteria.[12] The entire spine was subsequently imaged during the third attack, which revealed transverse myelitis affecting more than three segments and central cord involvement. Two months later, a second brain MRI was performed and compared to the initial scan as a baseline, revealing several brain lesions that had not previously been seen, but did not meet NMOSD or MS criteria. Our patient filled the diagnostic criteria for NMOSD without AQP4-IgG / unknown AQP4-IgG status with core clinical features of LETM acute myelitis involving more than three continuous spinal segments and exclusion of other potential diagnoses.

The loss of retinal axons and ganglion cells continues up to six months after acute ON. The GCIP is a particularly robust measure for quantifying retinal neuro-axonal damage, three months after acute ON due to consistent damaged by edema. Recent evidence suggests that the inner nuclear layer (INL) swells due to inflammation in CNS autoimmune diseases that manifest as ON.[13] Recurrent ONs in NMOSD result in significantly diminished pRNFL and GCIP.[14] In cases of severe optic nerve atrophy caused by multiple ON assaults and pRNFL values below 30 μm.[15] Our patient had RNFL OCT, macular cube, and GCL-IPL thickness measurements. Though the thickness was above 30 μm, there was a decrease in thickness and volume compared to the 2020 record. This finding was correlated with visual impairment.

Although the patient did not meet the age criterion, she had histories of sequential bilateral optic neuritis with significant declining function in both eyes. Despite the fact that the acute attack subsided, the damage persisted as seen by optic pallor and additional retinal thinning as measured by OCT. AQP4-Ab or IgG-AQP4 and MOG tests are advisable if another attack occurs in the future. To assess the extent of neuronal damage, follow-up particularly six to twelve months after the incident, is essential.

She was observed for six months following her last optic neuritis. Each appointment included an ophthalmic examination, OCT, and HVF to evaluate her visual function. Her visual acuity increased from 1/60 to 5/6 during observation period. Although her visual acuity improved, her visual field deteriorated according to the Humphrey perimetry test. As noted previously, more recent publications have demonstrated that OCT is a potential approach for differential diagnosis of MS and monitoring disease progression. Our finding in our patient with RNFL thickness compromised in superior and inferior quadrants is parallel to study by Oertel *et al.*[15], Mateo *et al.*[16], Bennet *et al.*[17], and Simao *et al.*[18] But, Matsumoto *et al*.[19] claimed no significant association in inferior quadrant RNFL thickness. Reduction macula GCL is also observed in patients with NMOSD. Even though the change is also observed in other neurodegenerative diseases, such as Alzheimer's and MS, the NMOSD drop in

GCL thickness is more alarming as a result of more severe inflammation and necrosis.[13,16] RNFL and GCC thickness in seropositive patient is more apparent. Our patient exhibited the same characteristics with seropositive patient.

Despite the fact that altitudinal visual field defects are more prevalent in NMOSD patients,[9] we discovered another pattern. Her HVF tests indicated temporal anopia on the right eye, which indicates chiasmal or left optic tract impairment from earlier optic neuritis episode.[20,21] Matsumoto et al. found changes in HVF parameters between AQP4-IgG seropositive and seronegative NMOSD patients, with MD value of seropositive four times fold, respectively -40.00~-1.69dB and -10.54~0.66dB.[19] Her MD value revealed a severe visual loss consistent reduction of more than -2 dB in nine months, indicating that her visual function was rapidly deteriorating .[22]

Due to the test's unavailability and affordability in Indonesia, we did not implement AQP4-IgG to our patient. IPND 2015 criteria for unclear NMOSD status are useful in health centers of lower-middle income countries, such as Indonesia, where some resources are scarce. MRI, OCT, and HVF are crucial tools for initial patient diagnosis, further management, therapy decision, and patient's education.

CONCLUSION

As our knowledge, this is the first case report of Indonesian NMOSD patient with sequential recurrent optic neuritis which employed OCT and HVF for follow-up. The limitation of this case report is the limited previous data when patient was lost to follow-up due to COVID-19 pandemic. NMOSD is a rare neurological condition which comprise of bilateral optic neuritis and LETM. Ophthalmologist should be concerned when an Asian female patient presented with history of relapsing bilateral optic neuritis either simultaneously or sequentially, as a sign of demyelinating disease. This patient was diagnosed NMOSD based on diagnostic criteria IPND 2015 with unknown AQP4-Ab status, supporting by clinical symptoms, brain-whole spine MRI imaging, and exclusion of other competing diagnosis. High-dose intravenous methylprednisolone is a mainstay therapy, followed by oral prednisolone which tapered off over time. Azathioprine is an antimetabolite which approved in various studies, when combined with prednisone will have a bigger chance to prevent relapse. Temporal anopia in her HVF test, could guide us the probable site of the second attack and the extensiveness of the damage. This case report showed the effect how devastating visual impact of the disease compared to MS. OCT and HVF completed our long-term follow-up.

ABBREVIATION

AQP4	aquaporin-4
AQP4-ab	aquaporin-4 antibody
AQP4-IgG	aquaporin-4 immunoglobulin g
CNS	central nervous system
CSF	cerebrospinal fluid
GCIP/GCIPL	ganglion cell and inner plexiform layer thickness or volume
HVF	Humphrey Visual Field Analyzer
IPND	International Panel for NMO Diagnosis
LETM	longitudinally extensive transverse myelitis
MD	Mean Deviation
MOG	myelin oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NMOSD	neuromyelitis optica spectrum disorders
OCT	optical coherence tomography
ON	optic neuritis
ONH	optic nerve head
ONTT	Optic Neuritis Treatment Trial
RNFL	retinal nerve fiber layer
SD-OCT	spectral domain OCT

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