

Case Report

Diagnosis and Management of Devic's Disease

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ABSTRACT

Background: To report diagnosis and management of Devic's Disease with good visual outcome.

Case Illustration: A 51 years-old male came with sudden blurred vision of his right eye since 3 days. The patient also complained of lower limbs weakness, urinary retention, and defecation disorder. Ophthalmology examination revealed visual acuity of no light perception in the right eye and 6/12 in the left eye. Light reflex of both eyes decreased. Funduscopy examination of the right eye showed an indistinct edge and hyperemic optic nerve head, cup-disc ratio was hard to be evaluated, artery/vein ratio of 2/3, macular reflex was positive and the retina was good. Funduscopy of the left eye was within normal limit. No pathological finding in brain Magnetic Resonance Imaging (MRI). Thoracolumbal MRI support longitudinal transverse myelitis. The patient was diagnosed as Devic's Disease and treated initially with intravenous methylprednisolone 1 g/day for five days followed by methyl prednisolone orally.

Conclusion: Early diagnosis of Devic's Disease is important because immediate therapeutic intervention is required to get excellent result, prevent relapse and further disability.

Devic's disease, also known as neuromyelitis optica (NMO), is a serious idiopathic demyelinating disease of the central nervous system (CNS) selectively attacking the spinal cord and optic nerves.¹ The association between acute myelitis and optic nerve disorder was first described by Albutt in 1870. In 1884 Eugene Devic proposed the identity of pathological process involving both spinal cord and optic nerves named the syndrome *neuro-myelite optique*. The eponym Devic disease was suggested by Acchiote in 1907.²

Devic's disease is a rare disease which has a worldwide distribution and estimated prevalence of 1-2/100,000.³ There are very few epidemiological studies in NMO, but case report and series have been reported from many countries. Devic's disease is more prevalent in areas with black, Asian and Indian population.² Although NMO cases are usually sporadic,

familial NMO has been reported in 3% of some cohort.⁴ Devic's disease is up to 9 times more prevalent in women than it is in men. The median age of onset is 39 but also occurs in children and elderly people.¹

Devic's disease is clinically characterized by severe optic neuritis and transverse myelitis, causing severe visual impairment usually with poor prognosis. Optic neuritis in patients with recurrent Devic's disease has a severe and acute onset, with predominantly unilateral lesions. In the long term, the disease leads to severe bilateral visual impairment. Patients also show signs of longitudinal extensive transverse myelitis with severe clinical disability, demonstrated by paraparesis or tetraparesis and sphincter disturbances.^{4,5}

Diagnostic criteria for Devic's disease that have been proposed by Wingerchuck and Col requires three absolute criteria: 1) optic neuritis; 2) acute myelitis; and 3) no evidence of clinical disease

outside the optic nerve or spinal cord as well as at least one of the following major supportive criteria: 1) negative brain MRI at onset; 2) spinal cord MRI with signal abnormality extending over 3 vertebral segments; 3) CSF pleocytosis of >50 WBC/mm³ or >5 neutrophils/mm³; or two of the following minor supportive criteria: 1) bilateral optic neuritis; 2) severe optic neuritis; 3) severe, fixed, attack-related weakness in one or more limbs.⁶

Table 1. Diagnostic criteria by Wingerchuk and Col

Absolute Criteria
<ul style="list-style-type: none"> ● Optic neuritis ● Acute myelitis ● No evidence of clinical disease outside the optic nerve or spinal cord
Major Supportive Criteria
<ul style="list-style-type: none"> ● Negative brain MRI at onset ● Spinal cord MRI with signal abnormality extending over 3 vertebral segments ● CSF pleocytosis of >50 WBC/mm³ or >5 neutrophils/mm³
Minor Supportive Criteria
<ul style="list-style-type: none"> ● Bilateral optic neuritis ● Severe optic neuritis ● Severe, fixed, attack-related weakness in one or more limbs

Devic's disease can have differential diagnosis with Multiple Sclerosis. Clinical, laboratory, immunological, and pathological characteristics distinguish multiple sclerosis from Devic's disease. Early diagnosis of Devic's disease is important because immediate therapeutic intervention is required, since Devic's disease has a poor prognosis and requires immunosuppressive treatment.⁷

Considering the high rates of mortality and morbidity of Devic's disease, all therapeutic efforts should be considered as possible treatments during the acute phase of optic neuritis or transverse myelitis and as prevention of severe events.⁵ Treatment of Devic's disease need to be started as early as possible to avoid new relapse and further disability. Intravenous corticosteroid therapy is commonly used as the initial treatment for acute attacks of optic neuritis or myelitis. Plasmapheresis has been used as an alternative therapy when high dose intravenous corticosteroid therapy is ineffective.^{1,7}

The purpose of this case presentation is to report diagnosis and management of Devic's disease with good visual outcome.

CASE ILLUSTRATION

A 51 years-old male came to Ophthalmology Clinic at RSCM Kencana on July 12, 2012 with

a blurred vision of his right eye since 3 days before admission. There was sudden visual loss followed by weakness of both lower limbs.

Seven days before admission he complained of urinary retention. He went to Abdi Waluyo Hospital and underwent bladder function examination and low abdomen ultrasonography, the results were within normal limit. A foley catheter was inserted due to his urinary retention. Three days before admission the patient complained blurred vision on his right eye followed by weakness of both lower limbs but he was still able to walk. He went to Abdi Waluyo hospital, underwent brain MRI and tuberculosis examination. The results were within normal limit. The patient also went to Jakarta Eye Center (JEC) due to his blurred vision. He underwent fundus photograph and macular OCT examination. Funduscopy examination of the right eye showed an indistinct edge and hyperemic optic nerve head, cup-disc ratio was hard to be evaluated, artery/vein ratio of 2/3, macular reflex was positive and the retina was good (Figure 1A). Funduscopy of the left eye showed the fundus was within normal limit (Figure 1B). Macular OCT examination of both eyes were within normal limit (Figure 2). He was consulted to Neuro-ophthalmology division in RSCM. There were no histories of diabetes mellitus, hypertension, alcohol consumption, nor trauma.

On admission, initial clinical examination revealed visual acuity of the right eye was no light perception and the left eye was 6/12. Light reflex of both eyes was decreased. Funduscopy examination of the right eye showed an indistinct edge and hyperemic optic nerve head, cup-disc ratio was hard to be evaluated, artery/vein ratio of 2/3, macular reflex was positive and the retina was good. Funduscopy of the left eye showed the fundus was within normal limit.

The patient also complained lower limb weakness, he was not able to walk and couldn't move his lower limb. The patient also had urinary retention and defecation disorder. The patient was suspected with Devic's disease or neuromyelitis optica. He was consulted to the Neurology and Internal Medicine Department. The patient was planned to undergo thoracolumbal MRI and blood examination. The patient was treated initially with intravenous methylprednisolone (1g/day for five days).

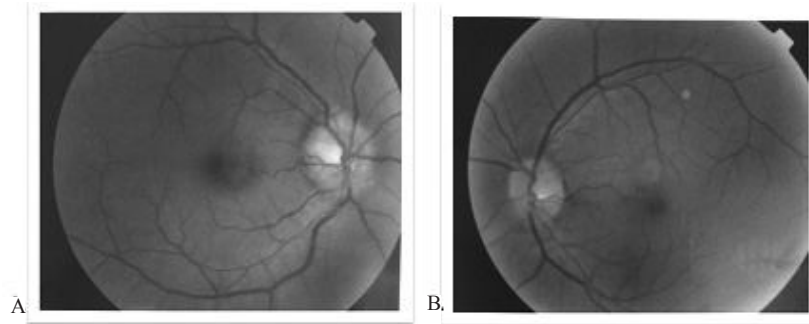


Fig 1A. Funduscopy examination of the right eye showed round optic nerve head, blurry edge, hyperemic, CDR was hard to be evaluated, aa/vv 2/3 macular reflex was positive and the retina was gold. **1B.** Funduscopy of the left eye showed the fundus was within normal limit.

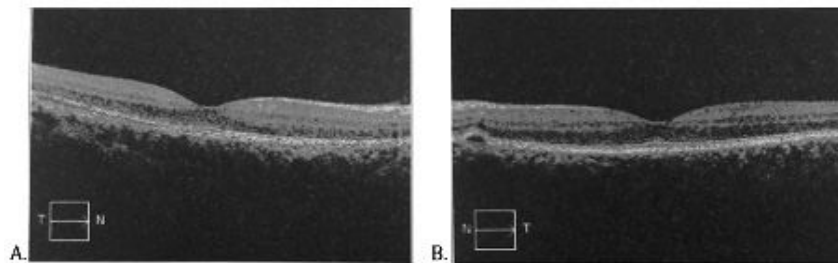


Fig 2. The OCT examination of the right eye (A) and the left eye (B) were within normal limit.

Thoracic spine MRI supported the diagnosis of transverse myelitis and revealed spondylosis thoracolumbalis with degenerative disc disease on L4-5 and L5-S1, bulging intervertebral disc of C5-6 with compression of medula spinalis, right and left radix, bulging disc of L4-L5 with right and left radix compression, protrusion of L5-S1 disc with compression of right and left radix especially on the left radix with anular tear discus L5-S (Figure 3). Brain MRI from Abdi Waluyo hospital showed no pathological findings (Figure 4).

Epstein Barr virus IgG and IgM tests in serum revealed no pathological values. Immunological tests of ANA was 1:100 and anti-dsDNA were within normal limit (3 IU/ml). IgE test was high 1,806.7 ng/ml while IgA test was within normal limit. Prostate specific antigen (PSA) test was within normal limit and acid fast stain in sputum was negative.

An initial improvement in patient's clinical status was noted after administration of IV corticosteroid (1 gr methylprednisolone) in five days. Five days after therapy, the visual

acuity was 1/60 of the right eye and 6/12 of the left eye. The optic nerve head was within normal limit. By the fifth day he was able to move his lower limbs horizontally, but still unable to withstand gravity. The therapy continued with methylprednisolone orally.

Ten days after therapy, the visual acuity was 6/60 of the right eye and 6/12 on the left eye. The optic nerve head was within normal limit. Eleven days after injection, the right eye visual acuity was 6/60 and the left eye was 6/12. The fundus of the right eye were within normal limit. Two weeks after injection, the best corrected visual acuity (BCVA) of the right eye was 6/10 and the best corrected visual acuity (BCVA) of the left eye was 6/6. He required a foley catheter and bowel program for his incontinence. On July 26, 2012, 16 days after injection the BCVA of both eyes were 6/6. The optic nerve head were within normal limit. On July 27, 17 days after injection the patient was allowed to go home.

On August 8, 2012, 1 month after therapy the patient said that he had no complain about his eye. Best corrected visual acuity of both eye



Fig 3. T2 weighted MRI show longitudinally spinal cord lesion, intramedullary enhancement C2-T1 (white arrow), spondylosis thoracolumbalis with degenerative disc disease of L4-5 and L5-S1 (blue arrow), bulging intervertebral disc of C5-6 (red arrow) with compression of medula spinalis, right and left radix, bulging disc of L4-L5 with compression of right and left radix, protrusion of L5-S1 disc with compression of right and left radix, especially on the left radix with annular tear disc L5-S1, there was no pathological intramedullary enhancement.

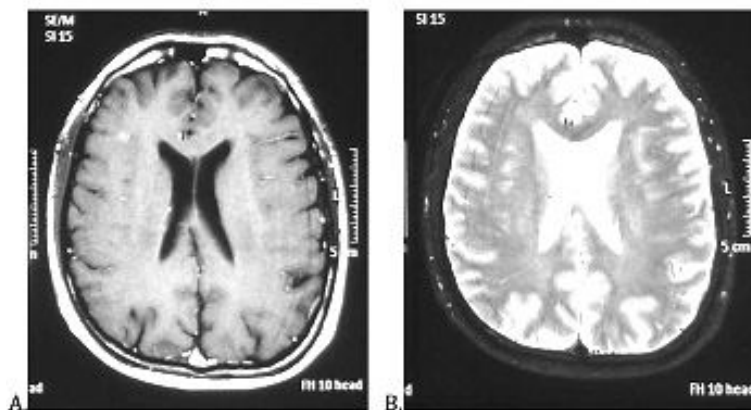


Fig 4. T1 (A) and T2 (B) weighted brain MRI demonstrated no pathological finding

were 6/6. His lower limb motoric muscle power improved, but he still complained urinary and defecation disorder. On January 31, 2013, 6 months after therapy the visual acuity was 6/6. The patient was able to walk but he still felt paresthesia on his upper and lower limbs.

DISCUSSION

Devic's disease (neuromyelitis optica) is an idiopathic, severe, demyelinating disease of the central nervous system that preferentially affects the optic nerve and spinal cord. Devic's disease is

clinically characterized by severe optic neuritis and transverse myelitis, causing severe visual impairment usually with poor prognosis. Patient also shows signs of longitudinal extensive transverse myelitis with severe clinical disability, demonstrated by paraparesis or tetraparesis and sphincter disturbances.⁴ Neuromyelitis optica has a worldwide distribution, poor prognosis and has long been thought of as a variant of multiple sclerosis. Clinical presentations, laboratory and immunological examination, and pathological characteristic can distinguish them.⁸

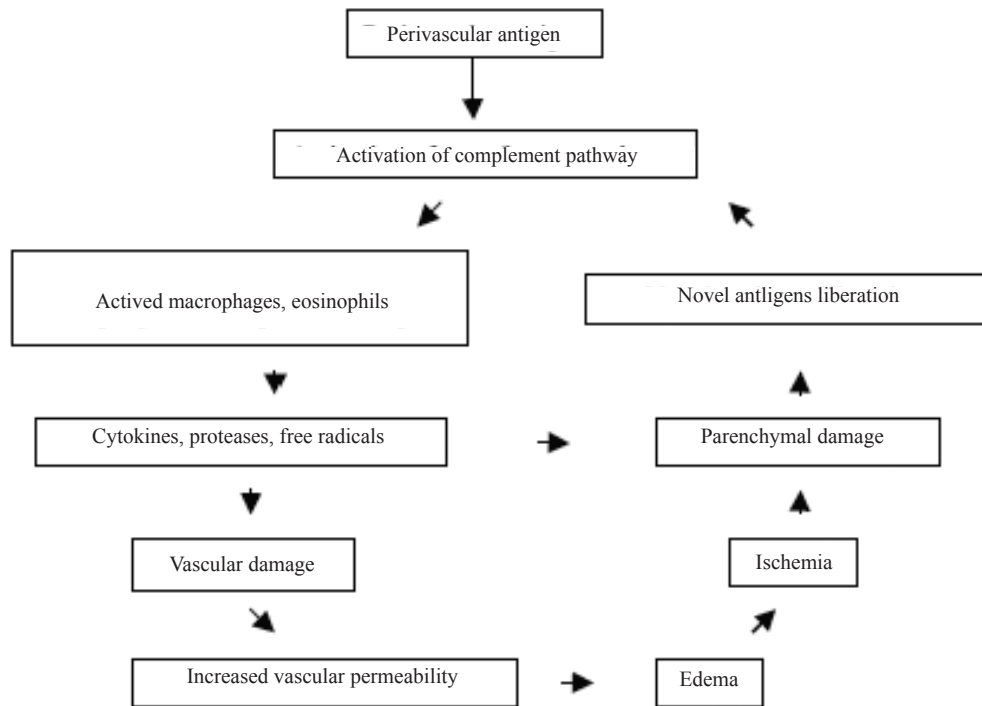


Fig 5. Mechanism of parenchymal damage in neuromyelitis optica²

The pathological features of Devic’s disease in acute phase include diffuse swelling and softening extending over multiple spinal segments and occasionally over the entire extension of the cord. Histopathological examination discloses necrosis of both grey and white matter with macrophage infiltration associated with myelin and axonal loss.²

There are several criteria to definite Devic’s disease from Wingerchuck and Col and Criteria from International Consensus Diagnostic criteria for NMO. Wingerchuck in Revised Diagnostic Criteria for Neuromyelitis Optica proposed the criteria require Optic neuritis, transverse myelitis and at least two of three supportive criteria contiguous spinal cord lesion in the magnetic resonance imaging (MRI) extending over three vertebral segments, brain MRI not meeting diagnostic criteria for multiple sclerosis (MS), serum positive for AQP-4 antibody.^{1,7,9}

Other diagnostic criteria for NMO that had been proposed by Wingerchuck and Col requires three absolute criteria: 1) Optic neuritis; 2) acutemyelitis; and 3) no evidence of clinical disease outside the optic nerve

or spinal cord, as well as at least one of the following majorsupportive criteria: 1) negative brain MRI at onset; 2) spinal cord MRI with signal abnormality extending over 3 vertebral segments; 3) CSF pleocytosis of >50WBC/mm³ or >5neutrophils/mm³, or two of the following minor supportive criteria: 1) bilateral optic neuritis; 2) severe optic neuritis; 3) severe, fixed, attack-related weakness in one or more limbs.⁶

Criteria from International Consensus Diagnostic criteria for NMO required three major criteria (all required): optic neuritis in one or more eye, transverse myelitis, exclusion of other syndromes, minor criteria (at least one required) brain MRI not fulfilling McDonald diagnostic criteria, positive test for NMO IgG/ Aquaporin 4 antibodies in serum or CSF.¹⁰

This patient came with monocular visual loss with lower limb weakness and urinary retention. Funduscopy examination of the right eye showed an indistinct edge and hyperemic optic nerve head, cup-disc ratio was hard to be evaluated, artery/vein ratio of 2/3, macular reflex was positive and the retina was good.

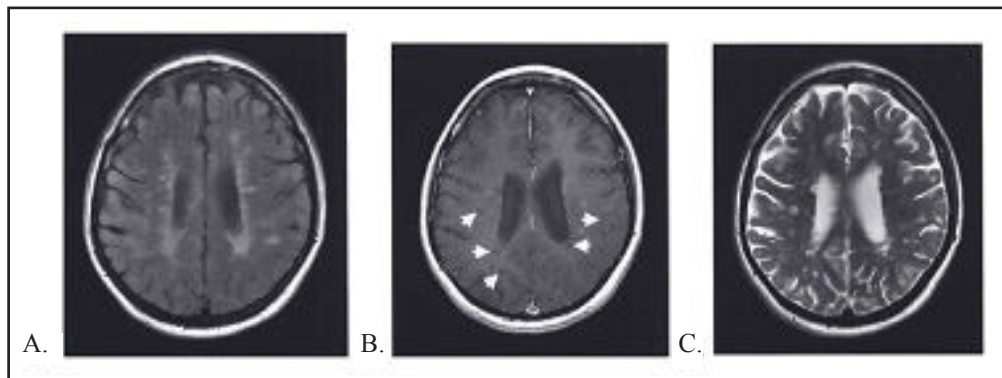


Fig 6. Example of Axial brain MRI scans of a patient with multiple sclerosis shows demyelinating plaques. A: T1-weighted MRI postgadolinium demonstrates enhancing white matter lesions bilaterally, as well as "black holes" (*arrows*). B: T2-weighted MRI shows periventricular multifocal hyperintense white matter lesions consistent with demyelination. C: A fluid-attenuation inversion recovery (FLAIR) scan confirms periventricular white matter lesions.¹²

Spinal cord magnetic resonance imaging (MRI) examination at that time on this patient showed contiguous spinal cord lesion in the MRI, this supported the diagnostic of transverse myelitis and also appropriate with the clinical finding of this patient.

Brain MRI findings of the brain at the onset of Devic's disease are typically normal although some studies have reported multiple sclerosis like lesions in about 10-30% of Devic's disease patients. Cranial lesions in brain MRI appeared in acute relapses of NMO but they were transient, different from MS and disappeared with time. Brain CT scan in this patient showed there was within normal limit. We can exclude the possibility of multiple sclerosis as differential diagnostic because in multiple sclerosis usually we can find white matter lesion (Figure 6).¹¹⁻¹³

Magnetic resonance spectroscopy (MRS) is a non invasive complement magnetic resonance imaging (MRI) that uses the signal from hydrogen protons to determine the concentration of brain metabolites such as N-acetyl aspartate (NAA), choline (Cho), creatine (Cr) and lactate in the tissue examined.¹⁴ Although MRS is rarely used to diagnose Devic's disease, Seze et al¹³ found that Magnetic Resonance Imaging spectroscopy could differentiate between MS and Devic's disease where NAA is frequently decreased and choline increased in Devic's disease patient.

The other examination that would support the diagnostic of Devic's disease (neuromye-

litis optica) is the serum autoantibody NMO-immunoglobulin G (IgG) that binds to Aquaporin-4. Aquaporin 4 (AQP4) is the major water channel in the central nervous system that recently discovered in central nervous system and highly concentrated in the astrocytes foot process. Aquaporin 4 is the autoantigen target in NMO. The peripheral immunoglobulin pool contains NMO-IgG. These immunoglobulins have limited access to the CNS parenchym, either through endothelial transcytosis or at areas of relative blood brain barrier permeability or injury, the astrocytes foot process makes extracellular aquaporin 4 channels accessible to any NMO-IgG entering this region. Increased permeability of the blood brain barrier caused by complement activation, makes infiltration of leucocytes, including polymorphonuclear cells (eosinophils and neutrophils). Massive leucocytes are detected in the CSF in the acute phase of neuromyelitis optica. The combined complement-mediated injury and cellular influx cause demyelination, severe neuronal injury and necrosis. There is low prevalence of oligoclonal IgG band in CSF patient with Devic's. It can't differentiate Devic's disease with multiple sclerosis (Figure 7). An IgG autoantibody (NMO IgG) or Anti aquaporin 4 that binds aquaporin 4 (AQP4) has been identified in the serum of a significant number of Devic's patients.^{1,2,4,15,16} Unfortunately, the patient were not willing to do the anti aquaporin 4 (NMO IgG).

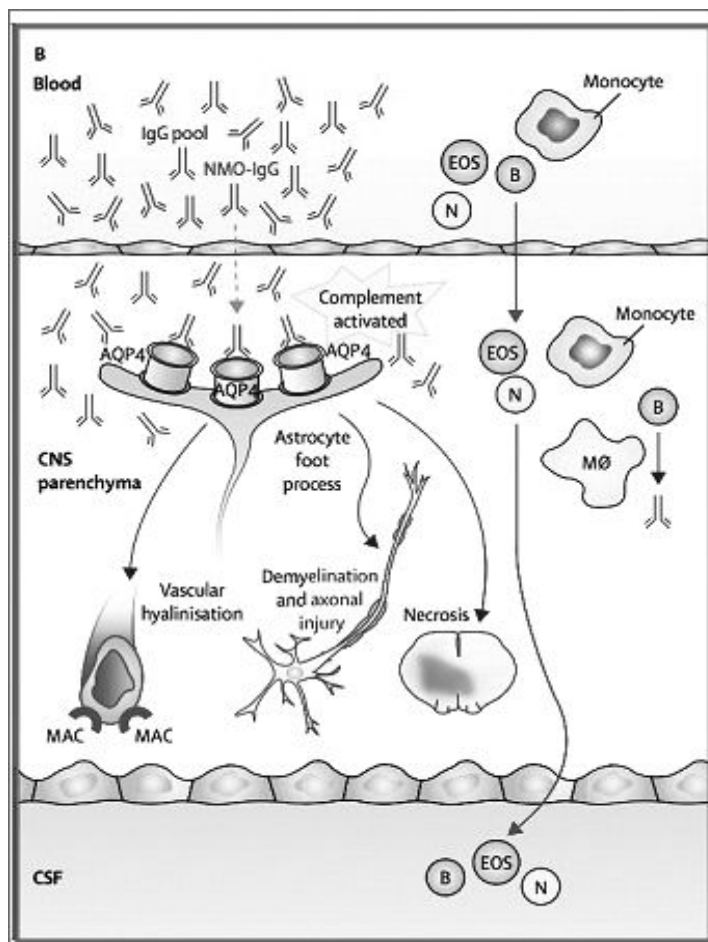


Fig 7. Pathogenesis of neuromyelitis optica. B (Basophil), EOS (Eosinophil), N (Neutrophil), MAC (Membrane Attack Complex), AQ4 (Aquaporin 4).¹

In most NMO patients CSF analysis exhibits some abnormalities. Pleocytosis (>5 WBC/mm³) was present in 79% of the patients and was greater than 50 WBC/mm³ in 35%. Cell count varies broadly and can reach figures over 2,000 cells/mm³. Neutrophils are commonly found, and even the presence of eosinophils can be noted. Protein content and some cytokines as interleukin IL-17 and IL-8, and the numbers of IL-5 and IL-6, IgG and IgM secreting cells are increased. CSF features may be helpful in distinguishing NMO from MS. Pleocytosis greater than 50 WBC/mm³ rarely occurs during MS relapses, and oligoclonal bands, present in over 90% of MS patients, are found in less than 20% of patients with NMO. Similarly, IgG index which is usually elevated in MS is normal in patients with NMO.^{1,2} In this patient the CSF examination was not done.

Neuromyelitis optica can be associated with autoimmune diseases.¹⁷ Immunological tests for this patient showed ANA titer was 1:100 and ds-DNA were within normal limit. This patient did not fulfill criteria for diagnosis of Systemic lupus erythematosus (SLE) so it could be ruled out. If Neuromyelitis optica associated with SLE, it is difficult to determine whether NMO is a separate entity, or neurologic symptoms refer to SLE. NMO specific anti-aquaporin-4 antibody positivity can help confirming diagnosis.¹⁷

Viral and bacterial disease that associated with Devic's disease have been described. Transverse myelitis and optic neuritis both symptoms of Devic's disease, have been reported subsequent to mumps infection or mumps virus vaccination. Some reports have suggested an association of optic neuritis with mumps

virus. No reports have described an association between NMO and mumps virus, but one case report has described a patient who presented transverse myelitis and optic neuritis after mumps virus meningoencephalitis.¹⁸ There were also case report which describe two patients with severe neurological manifestations associated with Epstein Barr virus (EBV) infection.^{19,20} In this patient testing for Epstein Barr virus IgG and IgM in serum revealed no pathological values. This patient also had sputum bacterial testing for Tuberculosis before admission and it was negative.

Devic's disease and Multiple sclerosis need to be differentiated because the medical condition of Devic's disease is more severe than MS and the principles of treatment are different. A combination of clinical, laboratory, and neuroimaging features helps to discriminate NMO from MS and facilitates accurate prognosis and treatment.^{1,21}

Nakajima et al²² found that patients with Devic's disease usually showed higher incidence of non central scotoma than MS, and altitudinal hemianopia may be characteristic of optic neuritis occurring in NMO.²² In this patient, due to the systemic and visual acuity condition of the patient, the visual field examination can't be done.

Other examination that can be use as diagnostic tool in optic nerve neuropathies is visual evoked potential (VEP). Visual evoked potential can help to establish a proper diagnosis very early, before typical clinical signs of Devic's disease is found.^{23,24} Neto et al²⁴ proposed the evaluation of VEP in patients with Devic's disease and revealed a pattern that was different from that of MS in characterized by the absence of responses, or decreased amplitude with normal latency.

Devic's disease treatment has two main objectives, one is to control the inflammatory damage in acute attacks and the other one is to maintain treatment to avoid relapse. Controlling the inflammatory damage in acute attacks is based on high dose intravenous corticosteroids and plasmapheresis, to avoid relapse we can use low dose corticosteroids and immuno-suppressants. Although Devic's disease attacks are related to severe disability, there are some evidences that

NMO patients remain neurologically stable without progressive deterioration like in MS. Therefore, it is crucial to start the treatment as early as possible to avoid new relapse and further disability. Intravenous corticosteroid therapy is commonly the initial treatment for acute attacks of optic neuritis or myelitis. Patient who does not respond to corticosteroid treatment can be considered to get the plasmapheresis. Once the diagnosis of NMO is established, acute management of a subsequent relapse is important. Many patients have permanent and severe disability after the very first episode. Management of relapse is with early corticosteroid treatment, typically 1 g of intravenous methylprednisolone for 5 days followed by oral prednisone (1 mg per kg body weight) for a month, and then a gradual tapering off over a 6-12 month period.^{7,21} This patient showed improvement five day after treatment with intravenous methylprednisolone. The therapy was continued with methylprednisolone orally.

The mechanism of action of corticosteroids is not completely understood. The positive effects of corticosteroids in NMO, inducing a reduction of inflammation, apoptosis of leukocytes, suppression of migration of polymorphonuclear leukocytes and reversal of increased capillary permeability.⁷

Plasmapheresis has been used as an alternative therapy for autoimmune diseases when high dose intravenous methylprednisolone is not effective. Plasma exchange is an extracorporeal blood purification technique designed to remove antibodies, complement, cytokines and chemokines from the plasma. Plasma exchange is an invasive therapeutic procedure and carries some complications like hypotension, pulmonary edema, hypocalcaemia, coagulation abnormalities, infection and catheter related issues.^{7,25} In this case, the patient showed initial improvement after administration of IV corticosteroid 1 gr methylprednisolone in 5 days. The plasmapheresis in this patient was not done.

Interferon beta is not currently recommended for Devic's disease because it maybe harmful and increasing the relapse rate. Interferon beta has been used in multiple sclerosis treatment.⁷

There are 80-90% of patients with neuromyelitis optica have relapsing episodes

of optic neuritis and myelitis. Relapse occurs within 1 year in 60% of patients and within 3 years in 90%. Most relapses of neuromyelitis optica worsen over several days and then slowly improve in the weeks or months after the maximum clinical deficit is reached. However, recovery is usually incomplete, and most patients have disability due to frequent and severe relapses. Within five years of disease onset, more than 50% of patients with relapsing neuromyelitis optica are blind in one or both eyes or require ambulatory help.^{1,5,15}

Rehabilitation is an important aspect of the disease. Disabilities occurred often after the very first episodes are often irreversible. A special multidisciplinary team is needed to manage and follow up patient with neuromyelitis optica.^{4,26}

Predictors of a worse prognosis of neuromyelitis optica include the number of relapses in the first 2 years of disease activity, the severity of the first attack, also having systemic lupus erythematosus or a related non-organ-

specific autoimmune disorder or autoantibodies. Age at disease onset and genetic factors are likely to be important in determining clinical outcomes in NMO disease.^{1,15} This patient had a good visual outcome and his lower motoric muscle power improved, and didn't have a relapse within 6 month of follow up.

CONCLUSION

We have to consider the possibility of Devic's disease with patients with sudden blurred vision accompanied by limb weakness. Early diagnosis of Devic's disease is important because immediate therapeutic intervention is required, since NMO has a poor prognosis and requires immunosuppressive treatment. Multidisciplinary team collaboration is needed to diagnose and treat appropriately and immediately because treatment for NMO is need to started as early as possible to achieve good result, avoid new relapses and further disability.

Table 2. Definition and characteristics of multiple sclerosis and neuromyelitis optica¹

	Multiple sclerosis	Neuromyelitis optica
Definition	Central nervous system symptoms and signs that indicate the involvement of the white-matter tracts Evidence of dissemination in space and time on the basis of clinical or MRI findings No better explanation	Transverse myelitis and optic neuritis At least two of the following: brain MRI, non-diagnostic for multiple sclerosis; spinal cord lesion extending over three or more vertebral segments; or seropositive for NMO-IgG
Clinical onset and course	85% relapsing-remitting 15% primary-progressive Not monophasic	Onset always with relapse 80–90% relapsing course 10–20% monophasic course
Median age of onset (years)	29	39
Sex (F:M)	2:1	9:1
Secondary progressive course	Common	Rare
MRI: brain	Periventricular white-matter lesions	Usually normal or nonspecific white-matter lesions; 10% hypothalamic, corpus callosal, periventricular, or brainstem lesions
MRI: spinal cord	Short-segment peripheral lesions	Longitudinally extensive (≥ 3 vertebral segments) central lesions
CSF white-blood-cell number and differential count	Mild pleocytosis Mononuclear cells	Occasional prominent pleocytosis Polymorphonuclear cells and mononuclear cells
CSF oligoclonal bands	85%	15–30%

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