Clinical features of neuromyelitis optica-related atypical optic neuritis in Thammasat hospital.

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Purpose: *To study the clinical features of optic neuritis in patients with neuromyelitis optica (NMO) in Thammasat Hospital.*

Design*: Retrospective case series*

Material and Method*: The author reviewed the medical records of 12 patients who had optic neuritis with atypical features managed at Thammasat Hospital between October 1, 2015 and June 30, 2016. The baseline characteristics including age, gender, underlying systemic diseases, laterality of visual loss, best corrected visual acuity (BCVA), optic disc appearance, color vision, visual fields, positive laboratory investigations, visual evoked potential (VEP), cerebrospinal fluid (CSF) analysis, magnetic resonance imaging (MRI) findings, and serostatus of aquaporin 4-Immunoglobulin G (AQP4-IgG) were analyzed.*

Results*: Five from 12 patients had clinical features of neuromyelitis optica spectrum disorder (NMOSD) diagnostic criteria for adult patients. All were healthy female and they had a mean age of 42.2 years (range 13 to 54 years). Two patients had bilateral simultaneous involvement, one patient had bilateral sequential involvement within 2 years, and another two patients had unilateral involvement. All had severe visual loss, initial BCVA worse than 20/200. Three patients had retrobulbar optic neuritis and two patients had anterior optic neuritis. We cannot perform the color vision and visual field due to the patient had severe visual impairment. The laboratory investigation was positive for anti-cardiolipin IgM in one patient. VEP showed evidence of demyelinating optic neuropathy. The CSF analysis was all normal. All patients had normal brain MRI findings with two patients had bilateral optic nerve enhancing lesions. One patient developed acute transverse myelitis following optic neuritis. All had positive test for AQP4-IgG by using available detection method.*

Conclusions*: The present study demonstrated that patients with atypical clinical features are more likely to develop NMOSD 5 from 12 patients. NMOSD should be suspected in patients with the clinical signs revealed aspects that were not typical for demyelinating optic neuritis.*

Keywords*: Neuromyelitis optica, Optic neuritis, Aquaporin-4, Multiple sclerosis*
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Introduction

Typical optic neuritis is a demyelinating inflammation of the optic nerve that often occurs in isolated or association with multiple sclerosis (MS). Typical clinical features will present as subacute unilateral visual loss that is progressive over several days associated with periorbital pain that precedes visual loss or occur simultaneously.[1] Atypical optic neuritis often occurs in association with infectious, autoimmune, or systemic inflammatory diseases. Atypical clinical features may present as bilateral visual loss, lack of pain, severe pain or severe visual loss, signs of ocular inflammation, or lack of spontaneous visual recovery within one month.

Neuromyelitis optica (NMO) or the new term; neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune demyelinating CNS disorder which primarily attack the optic nerve, spinal cord and causing some part of the brain lesions at certain sites such as the hypothalamus.[2] NMOSD has a higher incidence among non-Caucasians.[3-4] NMOSD-related optic neuritis is most often characterized by episodes of bilateral onset, chiasmal involvement, altitudinal visual field defect, or visual acuity 20/200 or worse. Most patients have serum AQP4-IgG and these specific antibodies are required as one of diagnostic criteria. The criteria for diagnosis of NMOSD are the manifestation at least 1 of 6 CNS regions: optic nerve, spinal cord, area postrema of the dorsal medulla, brainstem, diencephalon, or cerebrum.[5] NMOSD must be differentiated from MS in patients with optic neuritis because no clinical characteristic is pathognomonic of NMOSD such as bilateral simultaneous optic neuritis may also occur in MS. Whether all optic neuritis patients should be tested for AQP4-IgG remains controversial.[6-7]

The objective of the present study was to review the clinical features of optic neuritis in patients with NMO in Thammasat Hospital for the planning of investigations in patients presenting with atypical optic neuritis.

Materials and Methods

The study was approved by the Medical Ethics Committee of Thammasat University (MTU-EC-OP-0-141/58), Pathum thani, Thailand, and was conducted in accordance with the tenets of the Declaration of Helsinki. The author reviewed the medical records of 12 patients who had optic neuritis with atypical features managed at Thammasat Hospital between October 1, 2015 and June 30, 2016. Patients with unilateral or bilateral optic neuritis with visual symptoms for 14 days or less were enrolled. The inclusion criteria included the diagnosis of NMOSD following the International Panel for NMO Diagnosis (IPND) either (1) Diagnostic criteria for NMOSD with AQP4-IgG require at least one of six core clinical characteristics plus AQP4-IgG seropositivity. Six core clinical characteristics included optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with typical diencephalic MRI lesions, and symptomatic cerebral syndrome with typical brain lesions. (2) Diagnostic

criteria for NMOSD without AQP4-IgG or unknown AQP4-IgG status require at least two of six core clinical characteristics in which at least one core clinical characteristic must be optic neuritis, acute myelitis with longitudinal extensive transverse myelitis (LETM), or area postrema syndrome. AQP4-IgG were negative test by using best available detection method. Additional findings for acute optic neuritis in NMO requires brain MRI showing normal findings or only nonspecific white matter lesions, or orbital MRI showing T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over ½ optic nerve length or involving chiasm.

The patients who had any incomplete medical records, duration of follow-up less than 6 months, infectious disease that can cause infectious optic neuropathy such as syphilis, tuberculosis and evidence of alternative diagnoses such as other demyelinating diseases were excluded. The patient data including age, gender, underlying systemic diseases, laterality of visual loss, BCVA, optic disc appearance, color vision, visual fields, positive laboratory investigations, VEP, CSF analysis, MRI findings, and serostatus of AQP4-IgG were collected. The optic disc appearance and the retinal nerve fiber layer (RNFL) were analyzed by stereo optic disc photography and the optical coherence tomography (OCT). Contrast-enhanced MRI brain and orbit with gadolinium were performed in all cases and the enhancing optic nerve lesion was interpreted by a neuroradiologist. Contrast-enhanced MRI spine did was not performed in all cases because the decision to investigate will depend upon the signs and symptoms of spinal cord lesions. Examination of serum AQP4-IgG was done at the Prasart Neurological Institute by using cell-based indirect immunofluorescence assay (CBA) method. The available commercial CBA assay yielded sensitivity of 68% and specificity of 100%. The time to interpretation is about 5 working days. Statistical analysis was performed with SPSS software version 20.0 (IBM Inc, Chicago, IL). Data described in number and range.

Results

Five from 12 patients had clinical features of NMOSD diagnostic criteria for adult patients. All were healthy female and they had a mean age of 42.2 years (range 13 to 54 years). One patient had retrobulbar pain with eye movement. Two patients had bilateral simultaneous involvement, one patient had bilateral sequential involvement within 2 years, and another two patients had unilateral involvement. All had severe visual loss, initial BCVA worse than 20/200. Three patients had normal disc appearance (retrobulbar optic neuritis) and two patients had swollen disc (papillitis or anterior optic neuritis). We cannot perform the color vision and visual field in some patient which had severe visual impairment. VEP showed prolong P100 latency and decreased amplitude in affected eye. One patient had no P100 response in the affected eye with BCVA of no light perception. Investigations of serum inflammatory markers include erythrocyte sedimentation rate, C-reactive protein, and serum autoimmune markers include rheumatoid factor, lupus

anticoagulant, anti-cardiolipin IgM and IgG, anti-double stranded DNA antibody, anti-neutrophil cytoplasmic antibody, and anti-nuclear antibody revealed negative, except one patient was positive for anti-cardiolipin IgM. Routine laboratory tests for starting systemic corticosteroids were all normal. All patients were consulted with neurologist and underwent a lumbar puncture procedure. The CSF analysis revealed normal opening CSF pressure, protein level, sugar level, oligoclonal bands, and cytology. All patients had normal brain MRI findings with 2 patients had bilateral optic nerve enhancing lesions. MRI of whole spine showed no hyperintense intramedullary lesion or cord enlargement in 4 patients, but in one patient who developed episode of numbness and paraparesis of both legs following optic neuritis had hyperintense lesions with focal cord enlargement in cervical 2^{nd}-6^{th} segments which correlated with acute transverse myelitis. All had positive test for AQP4-IgG by using available commercial CBA assay method.

All patients received high-dose intravenous methylprednisolone (IVMP) (1 gram/day) for 3 days in 4 patients and extend for 5 days in one patient. Then patients were received oral prednisolone (1 mg per kg body weight). After the diagnosis of NMO was confirmed by AQP4-IgG seropositivity, the patient was scheduled to continue oral prednisolone for several months then tapered over to azathioprine for long-term treatment. During the follow-up period, one patient developed erythematous skin rash from azathioprine-induce photodermatosis, the drug was stopped and the patient was received long-term corticosteroid instead

Table 1 Patients data

Case	Age	Gender	Laterality	Visual symptoms	Initial BCVA	Final BCVA	Optic disc	MRI findings
1	13	F	Bilateral sequential	10 days	20/20, PL	20/20,20/20	Swollen disc	Enhancing optic nerve(s), cervical cord lesions
2	38	F	Unilateral	5 days	5/200, 20/20	20/50,20/20	Swollen disc	Normal
3	52	F	Unilateral	5 days	HM, 20/50	5/200,20/50	Normal disc	Normal
4	54	F	Bilateral simultaneous	3 days	NPL, Fc1foot	HM,20/200	Normal discs	Enhancing optic nerves
5	54	F	Bilateral simultaneous	1 day	PJ, PJ	5/200,Fc 1ft	Normal discs	Enhancing optic nerves

Selected Case Summaries

Case 1: A 13-year-old female presented with acute visual loss in the left eye preceded by periorbital pain which worsened on eye movement followed by a decreased vision in the right eye vision 2 years later. Initial BCVA were was 20/20 OD and light perception (PL) OS with relative afferent pupillary defect (RAPD) in the left eye. The left optic disc was swollen. MRI of the brain and orbit with gadolinium contrast showed mild enhancement of left optic nerves in T1-weighted images. No evidence of periventricular white matter lesion in FLAIR T2-weighted images (Figure 1). Investigations of serum inflammatory markers revealed to be negative. Lumbar puncture revealed normal CSF analysis and negative oligoclonal bands. We suspected idiopathic demyelinating optic neuritis. The patient received high-dose IVMP (1 gram/day) for 3 days followed by oral prednisolone (1 mg per kg body weight) then taper within few weeks. The BCVA of her left eye was improved to counting fingers at 3 feet and 20/20 at 6 months. Two years later, the patient developed recurrent optic neuritis in her right eye and numbness and paraparesis of both legs. Repeat CSF analysis was all normal. Repeat MRI brain and orbit revealed mild enhancement of right optic nerve without brain lesions (Figure 2). MRI spine revealed hyperintense lesions with focal cord enlargement in cervical 2^{nd}-6^{th} segments which correlated with acute transverse myelitis (Figure 3). Serum AQP4-IgG was positive. The patient received pulse IVMP again and continued oral prednisolone for several months then tapered over to azathioprine for long-term treatment. The final visions were 20/20 OU with bilateral optic atrophy. The color visions were normal in both eyes. The visual field defects were inferior altitudinal defect in the right eye and normal field in the left eye (Figure 4).

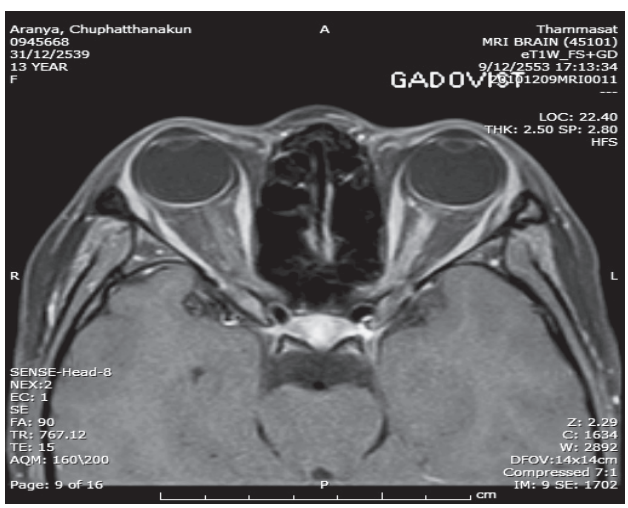

Figure 1 shows gadolinium-enhancing left optic nerve lesions in fat-suppressed T1-weighted orbital MRI.

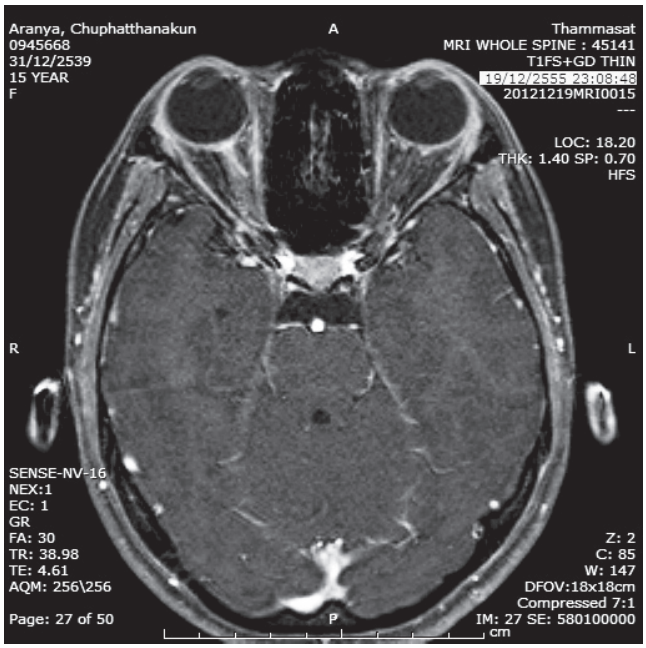

Figure 2 shows gadolinium-enhancing right optic nerve lesions in fat-suppressed T1-weighted orbital MRI.

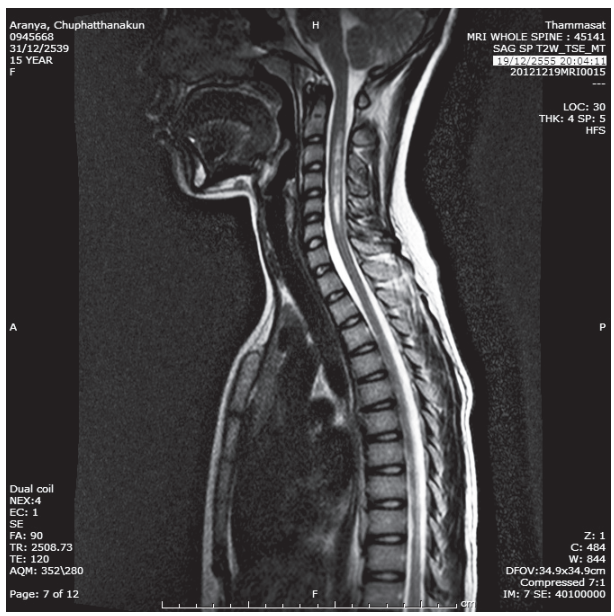

Figure 3 show hyperintense lesions with focal cord enlargement in cervical 2nd-6th segments in whole spine MRI.

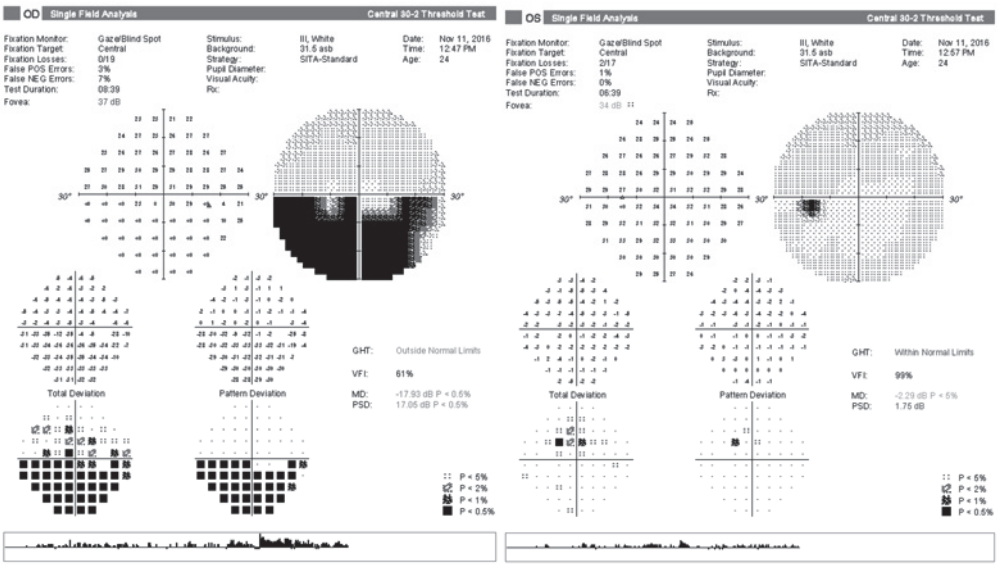

Figure 4 shows visual field of inferior altitudinal defect in the right eye and normal field in the left eye

Case 2: A 54-year-old female presented with acute bilateral simultaneous painless visual loss. Initial BCVA were was no light perception (NPL) OD and counting fingers at 1 foot OS with RAPD in the right eye. The optic discs were normal appearance. MRI of the brain and orbit with gadolinium contrast showed enhancement of intraorbital part of bilateral optic nerves without brain lesions (Figure 5). Investigations of serum inflammatory markers revealed positive for anti-cardiolipin IgM. Lumbar puncture revealed normal CSF analysis and negative oligoclonal bands. We suspected NMOSD-related optic neuritis. VEP showed no P100 response in the right eye and prolong P100 latency in the left eye. The patient received high-dose IVMP (1 gram/day) for 5 days followed by oral prednisolone (1 mg per kg body weight). After the diagnosis of NMO was confirmed by AQP4-IgG seropositivity, the patient was scheduled to continue oral prednisolone for several months then tapered over to azathioprine for long-term treatment. At 6 months, the BCVA were NPL OD, count finger counting fingers at 2 feet OS. At one year after initial attack, the BCVA were improved to hand motion (HM) OD and 20/200 OS with bilateral optic atrophy (Figure 6). We cannot could not perform the color vision and visual field tests due tobecause the patient still had suffered from severe visual impairment.

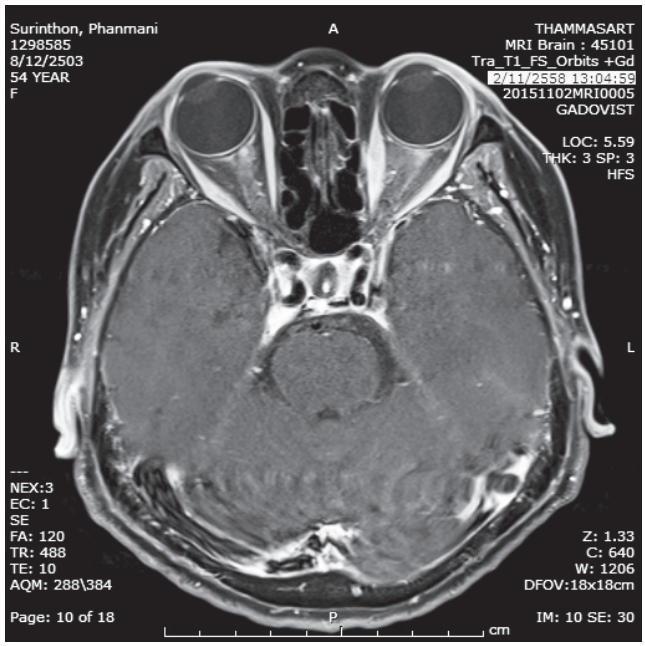

Figure 5 shows bilateral gadolinium-enhancing optic nerve lesions in fat-suppressed T1-weighted orbital MRI.

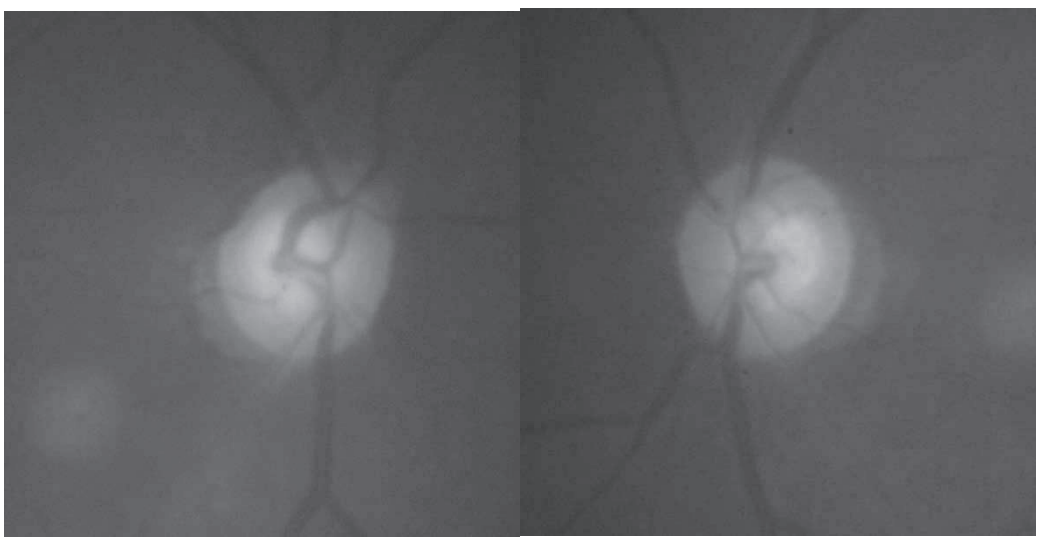

Figure 6 shows bilateral optic atrophy

Discussion

Optic neuritis was characterized with decreased vision, dyschromatopsia, RAPD and visual field defect. The optic disc may appear normal or swelling, the term retrobulbar optic neuritis and papillitis was used respectively. When the clinical features suggest typical optic neuritis, at young ages (18-45 years old) patients will present with acute/subacute unilateral visual loss that progressive over several days. Most patients (92%) have associated periorbital pain which may precede the visual loss by days or occur simultaneously, and pain was worsened by eye movement. These features can help for help in the clinical diagnosis in that typical optic neuritis is mostly related to isolated or demyelinating disorders particularly MS.

In NMOSD, the immune-mediated inflammation primarily attacks the AQP4 water channels resulting in loss of astrocytic AQP4 and disruption of water homeostasis. The pathophysiology features of NMOSD include perivascular deposition of immunoglobulin and activated complement, leukocytes migration and macrophage infiltration and secondary demyelination with axonal loss. NMOSD had characterized by optic neuritis and transverse myelitis and some part of the brainstem involvement. The disease can be monophasic or relapsing-remitting form.[8] In monophasic form, optic neuritis and transverse myelitis occur simultaneously or within days of each other. In relapsing form, patients often have a relapse weeks or months after the initial attack.[9] NMOSD rarely has a secondary progressive phase without remission. Optic neuritis are often more severe after an NMO attack than an MS attack and some patients have permanent visual loss.[10] Acute treatment is high-dose corticosteroids; IVMP 1 g for 5 days followed by prednisolone (1 mg per kg body weight). If the AQP4-IgG titers return as positive, prednisolone should be continued and immunosuppressant agents should be considered to prevent relapse. Some patients may need a low dose of prednisolone to maintain remission. Most patients need prednisolone at dose 0.5-1 mg/kg for up to 3 months after an attack, and then a slow tapering off over 6-12 months.[11]

We reported five cases of seropositive NMOSD related-optic neuritis. All were healthy female and they had age range of 13-54 years which is correlated to the demographic data of NMOSD including a predilection of female gender and the typical age range usually 15-50 years. Four patients lacked retrobulbar pain with eye movement which could be related to the clinical features of atypical optic neuritis. Most cases had bilateral involvement; one of five patients had recurrent episode of visual loss in the fellow eye (relapsing form) and this patient also had optic neuritis and transverse myelitis which occur simultaneously. These findings could be related to the clinical features of the high frequency of bilateral involvement and lack of the retrobulbar pain with eye movement in the early phase of NMOSD, respectively. All had severe visual impairment in the initial phase, two patients had delayed good visual recovery and three patients had delayed insufficient visual recovery

which could be related to the clinical features of severe disability in NMOSD.[12] All had no underlying systemic disease, but one patient was positive for anti-cardiolipin IgM which could be related to the clinical features of NMOSD that is frequently associated with systemic autoimmune disorders, or with the presence of serum autoantibodies. All patients had normal brain MRI findings with 2 patients having bilateral optic nerve enhancing lesions although the enhancing lesions not extending did not extend over ½ optic nerve length or involving chiasm. Enhancing the gadolinium of optic nerve lesion is found about 90 percent of optic neuritis, which can be found on average 30 days after the onset of visual symptoms.[13] The duration ofqueue for an the MRI order in our hospital sometimes can be as long it's quite a long time can is long, at times lasting about 1 to 2 weeks. Some patients in the present study received intravenous corticosteroids treatment before they underwent MRI, so only 2 patients had optic nerve enhancing lesions. One patient had hyperintense lesions with focal cord enlargement equal or more than 3 contiguous vertebral segments which could be related to the clinical features of longitudinal extensive transverse myelitis (LETM) in NMOSD.[14] All had positive test for AQP4-IgG by using available commercial CBA assay method which could be indicate that AQP4-IgG is directly related to optic neuritis in our cases.

The major limitation of the present study is the small sample size. Only 12 participants enrolled within 9 months, which may be explained from by the insufficient numbers of number of case of optic neuritisoptic neuritis cases in our hospital is still insufficient and we should extend the time period for the further study. In conclusion, the present study demonstrated that patients with atypical clinical features are more likely to develop NMOSD in 5 from 12 patients. NMOSD should be suspected in patients with the clinical signs revealed aspects that were not typical for demyelinating optic neuritis.

References

1. Voss E, Raab P, Trebst C, Stangel M. Clinical approach to optic neuritis: pitfalls, red flags and differential diagnosis. Ther Adv Neurol Disord. 2011 Mar;4(2):123-34.
2. Etemadifar M, Nasr Z, Khalili B, Taherioum M, Vosoughi R. Epidemiology of neuromyelitis optica in the world: a systemic review and meta-analysis. Mult Scler Int.2015;174720.
3. Marrie RA, Gryba C. The Incidence and Prevalence of Neuromyelitis Optica. International Journal of MS Care. 2013; 15(3): 113–118.
4. Etemadifar M, Nasr Z, Khalili B, Taherioum M, Vosoughi R. Epidemiology of neuromyelitis optica in the world: a systemic review and meta-analysis. Mult Scler Int.2015;174720.
5. Wingerchuck DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for

neuromyelitis optica. Neurology.2006;66:1485-9.
6. Galetta SL, Cornblath WT. Should most patients with optic neuritis be tested for neuromyelitis optica antibodies and should this affect their treatment? J Neuroophthalmol. 2010;30:376-378.
7. Chong HT, Kermode AG, Tan CT. The role of anti-aquporin-4 antibody in Asian patients with multiple sclerosis: confusions and controversies. Neurology Asia. 2007;12:135-139.
8. Poppe AY, Lapierre Y, Melancon D. “Neuromyelitis optica with hypothalamic involvement” Multiple Sclerosis. 2005;11(5):617-621.
9. Ghezzi A, Bergamaschi R, Martinelli V. “Clinical characteristics, course and prognosis of relapsing devic's neuromyelitis optica,” Journal of Neurology. 2004;251(1):47-52.
10. Levin MH, Bennett JL, Verkman AS. Optic neuritis in neuromyelitis optica. Prog Retin Eye Res.2013;36:159-71.
11. Malik A, Ahmed M, Golnik K. Treatment options for atypical optic neuritis. Indian J Ophthalmol.2014;62:982-4.
12. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (devic's syndrome). Neurology. 1999; 53(5): 1107-1114.
13. Hickman SJ, Toosy AT, Miszkiel KA, Jones SJ, Altmann DR, MacManus DG, et al. Visual recovery following acute optic neuritis—a clinical, electrophysiological and magnetic resonance imaging study. J Neurol 2004;251:996-1005.
14. Wang Y, Zhang L, Zhang B, Dai Y, Kang Z, Lu C, Qiu W, Hu X, Lu Z. Comparative clinical characteristics of neuromyelitis optica spectrum disorders with and without medulla oblongata lesions. J Neurol 2014; 261(5):954-62