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REVIEW ARTICLE

Neuromyelitis Optica Spectrum Disorders: Diagnostic Issues in Korea

Ju-Hong Min, MD, PhD

Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

ABSTRACT

Neuromyelitis optica (NMO) is a CNS demyelinating disorder, characterized by optic neuritis and acute myelitis. A specific autoantibody of NMO, NMO-IgG was recently detected, which resulted in the revision of the diagnostic criteria of NMO, proposed in 1999. The new diagnostic criteria emphasized the long cord lesion over 3 vertebral segments and the presence of NMO-IgG. In addition, with the positivity of NMO-IgG in longitudinal extensive myelitis, recurrent optic neuritis and autoimmune disorders, the spectrum of NMO-related disorders were broadened. The review for NMO spectrum disorders and NMO-IgG will provide a help to understand NMO, this rapidly disabling disease.
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Key Words: Neuromyelitis optica, Myelitis, Optic neuritis

Introduction

Neuromyelitis optica (NMO), known as Devic syndrome (or Devic disease) was identified in the 19th centry.[1] The traditional term NMO was applied to patients with a monophasic event consisting of bilateral simultaneous optic neuritis (ON) and acute myelitis, but sparing the remainder of the central nervous system.[2] However, NMO is now recognized to typically evolve as a relapsing disorder that also includes patients with unilateral ON and those with index events of ON and myelitis occurring weeks or even years apart.[2] Recently, the detection of NMO immunoglobulin G (NMO IgG), an autoantibody, in the serum of patients with NMO, is known to distinguish NMO from other demyelinating diseases.[3] Moreover, this antibody is also found in other NMO-related disorders, which suggests of the need to reestablish the spectrum of NMO.

Diagnostic criteria of neuromyelitis optica (NMO)

In 1984, Devic and Gault described the *sine qua non* clinical characteristics of neuromyelitis optica: ON and acute transverse myelitis. The patients had monophasic or relapsing courses of NMO.[4] The definition of NMO developed from the recognition that attacks of ON are more commonly unilateral than bilateral, and that attacks of ON and myelitis usually occur sequentially rather than simultaneously. A previous diagnostic criteria of NMO, which has been most widely used and replicated, was the result of a retrospective study published in 1999 by Wingerchuk et al (Table 1).[5] These include the absolute requirement that a patient experiences both ON and myelitis but without clinical symptoms or signs implicating other CNS structures. Major and minor supportive criteria, including characteristics of the attacks (bilateral ON, attack severity and recovery), brain and spinal cord MRI features, and the CSF profile, were also proposed to enhance the specificity of the diagnostic schema. However, the criteria have limitations, and international experience generally has concurred with this fact. In 2006, Wingerchuk et al proposed revised diagnostic criteria for NMO (Table 2).[6] In this proposal, several criteria has been removed or changed, 'No clinical disease outside of optic nerves and spinal cord',

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Address for correspondence: Ju-Hong Min
Department of Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea
Tel: +82-2-3410-3599, Fax: +82-2-3410-0052, E-mail: juhongm@gmail.com

Table 1. Proposed diagnostic criteria for neuromyelitis optica (1999)

Diagnosis requires all absolute criteria AND
One major supportive criterion or 2 minor supportive criteria
Absolute criteria
1. Optic neuritis
2. Acute myelitis
3. No clinical disease outside of the optic nerves and spinal cord
Major supportive criteria
1. Negative brain MRI at disaese onset (normal or not meeting radiological diagnostic criterai for MS)
2. Spinal cord MRI with T2-signal abnormality extendnig over > 3 vertebral segments
3. CSF pleocytosis (> 50 * 106 WBC/L) or > 5 * 106 neutrophils/L
Minor supportive criteria
1. Bilateral optic neuritis
2. Severe On with fixed visual acuity worse than 20/200 in at least 1 eye
3. Severe, fixed, attack-related weakness (MRC grade 2 or less) in 1 or more limbs
Potential criteria revisions
1. Allowance for extraoptic-spinal clinical symptoms and signs or brain MRI lesions if other criterai satisfied
2. Requirement for > 3 segment spinal cord MRI lesion
3. Integration of NMO-IgG serologic status into diagnostic schema

Table 2. Revised diagnostic criteria of neuromyelitis optica

Definite NMO
Optic neuritis
Acute myelitis
At least two of three supportive criteria
1. Contiguous spinal cord MRI lesion extending over 3 vertebral segements
2. Brain MRI not meeting diagnostic crietria for multiple sclerosis
3. NMO-igG seropositive status

'negative brain MRI at disease onset', 'CSF pleocytosis', and 3 minor supportive criteria. Newly incorporated criteria are 'NMO-IgG status' and 'brain MRI not meeting diagnostic criteria for MS'.

Neuromyelitis optica antibody (NMO-IgG)

NMO-IgG is a disease-specific autoantibody for NMO and binds selectively to aquaporin-4 (AQP4), a CNS water channel protein, which is found in astrocyte foot processes (blood-brain border), the glia limitans (subarachnoid cerebrospinal fluid-brain border) and ependyma (ventricular cerebrospinal fluid-brain border). This antibody was reported to be 76% sensitive and 94% specific for clinically defined NMO, by Lennon et al.[3] Two independent groups have since reported experience with the assay introduced by Lennon and co-workers11 using recombinant human aquaporin 4 as the antigen.[7,8] Takahashi and co-workers reported that with 1:4 dilutions of patient serum, the immunofluorescence assay of transfected HEK280 cells described by Lennon and co-workers[9] was 91% sensitive and 100% specific for NMO, with clinical diagnosis as the reference standard.[8] However, even with the most sensitive assays, 10-25% of patients clinically diagnosed with NMO are seronegative for NMO-IgG. Whether the lack of NMO-IgG in these patients is indicative of inadequate clinical diagnostic criteria, suboptimal assay sensitivity, or it represents a closely related autoimmune disorder that targets a different autoantigen in the glia limitans is not clear.

Table 3. Neuromyelitis optica spectrum disorders

Neuromyelitis optica
Limited forms of neuromyelitis optica
Idiopathic single or recurrent events of longitudinally extensive myelitis (vertebral segment spinal cord lesion seen on MRI)
Optic neuritis : recurrent or simultaneous bilateral
Asian optic-spinal multiple sclerosis
Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)

Neuromyelitis optica spectrum disorders (NMOSDs)

NMO-IgG, a specific serologic marker for NMO, is also detected in the serum of patients with disorders related to neuromyelitis optica, including Asian optic-spinal multiple sclerosis, recurrent myelitis associated with longitudinally extensive spinal cord lesions, recurrent isolated optic neuritis, and optic neuritis or myelitis in the context of certain organ-specific and non-organ-specific autoimmune diseases (Table 3).[4]

1. Limited forms of neuromyelitis optica

The term, "limited forms of NMO" usually indicates 'idiopathic single or recurrent events of longitudinally extensive myelitis

(LEM)' and 'recurrent or simultaneous bilateral ON'. In the study of Lennon et al. which described NMO-IgG first, NMO-IgG was detected in a half of patients with recurrent LEM and in a quarter of patients with recurrent ON.[3] Another study to confirm the previous results for NMO-IgG in Oxford, NMO-IgG was also observed in 4 of 5 patients with isolated LEM.[10] Moreover, NMO-IgG was positive in patients with progressive necrotizing myelopathy.[11] A recent observation showed that some of patients with immune-mediated optic neuritis, such as chronic relapsing inflammatory ON, relapsing isolated ON and single isolated ON had NMO-IgG, compared to the negative results in patients with ON in the context of MS.[12] More importantly, Weinschenker et al. reported that approximately 40% of LEM patients were NMO-IgG seropositive and these patients were at high risk for relapse.[13]

2. Asian optic-spinal multiple sclerosis (OSMS)

Multiple sclerosis (MS) in Asian population is characterized by the selective involvement of the optic nerve and spinal cord and 15-40% of them especially in Japan have been of 'optico-spinal' type.[14] This form of MS has a higher age at onset and a higher female to male ratio than conventional MS. However, recently many neurologists suggested that OSMS is NMO, but no more MS.[14,15] One of evidences of this was that NMO-IgG was found in more than half of Japanese patients with OSMS.[3,16] However, some Japanese neurologists suggested that OSMS is not same with NMO, because interferon is effective in Japanese OSMS patients and NMO-IgG was detected in a few Japanese patients with conventional MS.[17-19] Moreover, recently, it was suggested that anti-AQP4-positive patients are immunologically distinct from anti-AQP4-negative OSMS patients in Japan.[20] However, there are still debates for the relationship between OSMS and NMO.

3. Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease

The association of NMO and autoimmunity was well described in a previous paper published by Pittock et al.[21] In NMO patients, anti-nuclear antibody is observed in 52% and anti-extractable nuclear antigen in 17%, without having systemic lupus erythematosus (SLE) or Sjogren's syndrome (SS). They observed that patients meeting diagnostic criteria for SLE or SS, but not having ON or LEM were NMO-IgG seronegative. Therefore, the coexistence of NMO and autoimmune disorders was strongly suggested. Moreover, there were reports where NMO was the initial presentation of SLE or Sjogren's syndrome.[22-24]

4. Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem) (Fig. 1)

MRI findings of the brain at the onset of NMO are typically normal (except for optic nerve enhancement by intravenously

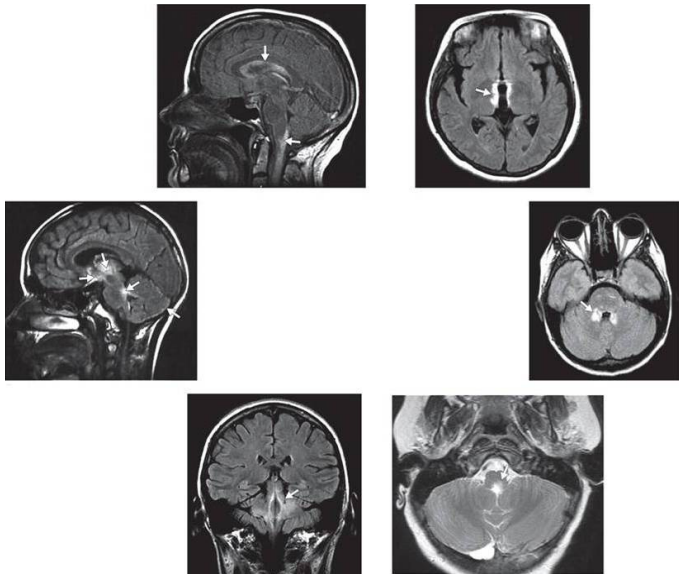

Figure 1. Brain lesions typical of neuromyelitis optica. Periependymal corpus callosal lesions, hypothalamic lesions, and periventricular brainstem lesions adjacent to the 3rd and 4th ventricles, known to have high AQP4 expression, are observed in neuromyelitis optica patients.

administered gadolinium during an acute attack of optic neuritis), in contrast to MS, or they show non-specific, white matter lesions that do not satisfy neuroimaging criteria for the diagnosis of MS.[5,25,26] Hence, asymptomatic brain lesions are commonly found in NMO and symptomatic brain lesions do not exclude the diagnosis of NMO.[27] In addition, several brain lesions atypical for MS, but characteristic for NMO were observed and these lesions are known to be localized at sites of high expression of aquaporin 4, the target for NMO-IgG.[28]

Diagnostic issues of NMOSDs in Korea

The recent study by Korean MS study group showed that SS patients with recurrent CNS involvement have brain abnormalities characteristic of NMO and AQP4-Ab in Korea.[22] This suggests that the coexistence of NMO should be explored in SS patients with recurrent CNS manifestations, even without optic neuritis or myelitis. Another study performed in a single center, also demonstrated that patients with SS and myelitis have poor prognoses with high mean annual relapse rates, and most seemed to have the clinical and immunological characteristics of NMO.[29] In our study for SS, brain lesions typical of NMO were observed in all 12 patients with optic neuritis or myelitis, 8 of whom were checked for AQP4-Ab and 6 of 8 were positive for this antibody.[22]

1. Relation to systemic autoimmune disorders

The Korean MS study group has concentrated on the relationship of NMO and systemic autoimmune disorders, especially SS and studied 'brain abnormalities of primary SS with recurrent CNS manifestations : association with neuromyelitis optica'.[22] This study included 12 patients with SS who had recurrent CNS manifestations with brain involvement. In the analysis of brain MRI, neurologic and serologic findings, it was found that all patients had common brain lesions characteristic of NMO, as follows: (1) the involved sites adjacent to the ventricles and in the internal capsule, (2) unique configurations,

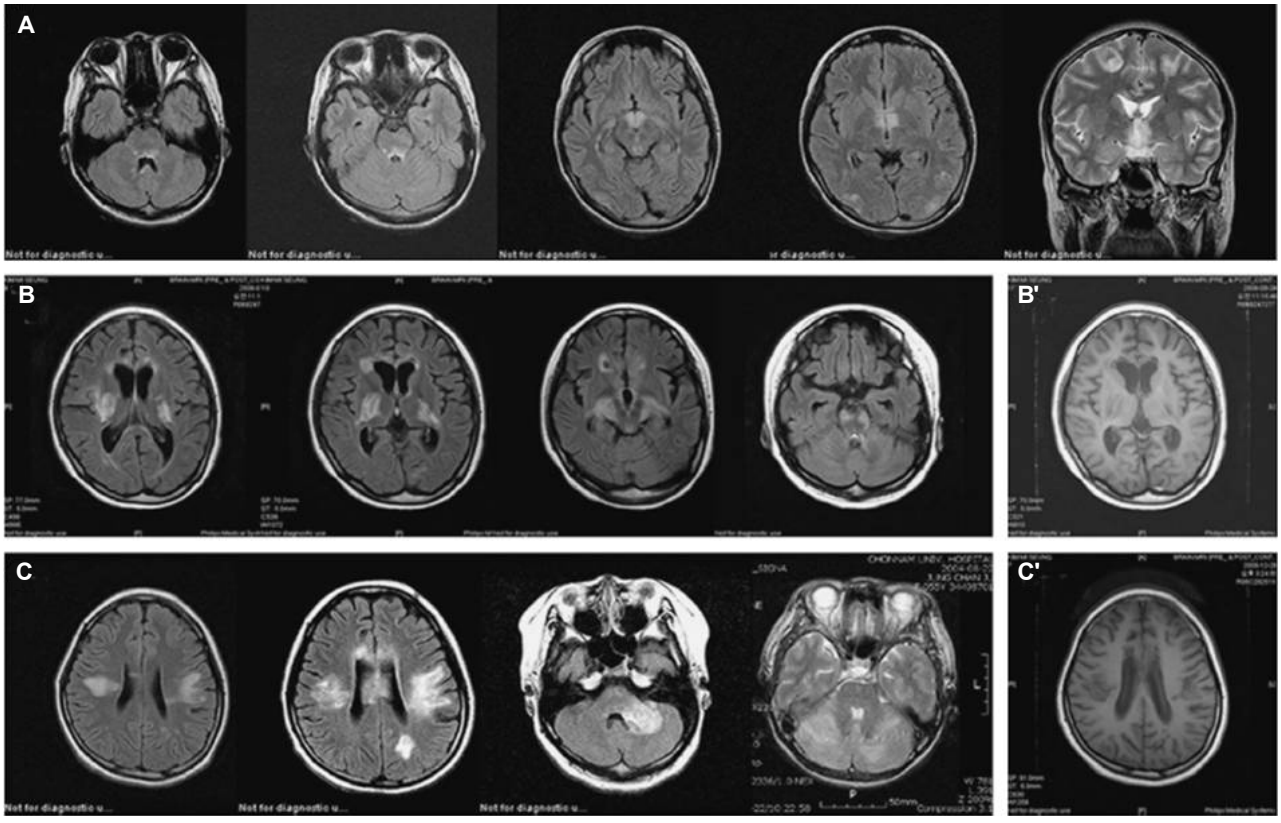

Figure 2. Brain lesions characteristic of NMO in Korean Sjogren's syndrome patients with recurrent CNS involvement. (A) Adjacent lesions to the 3rd and 4th ventricles, (B) Longitudinal lesions involving corticospinal tract from internal capsule to cerebral peduncle, (C) Extensive large lesions over 3cm in diameter in hemisphere, cerebellum and corpus callosum.

such as the longitudinally course from the internal capsule to the midbrain, large lesions and cavity-like formations (Fig. 2). Anti-aquaporin 4-antibody (AQP4-Ab, measured by P. Waters and A. Vincent at Oxford Biomedical Research Center) was positive in six of eight patients, tested. All patients with myelopathy revealed LEM, which was shown as over three vertebral segments (8.3±2.7, meand±SD) and located in the central portion of the cord. Four patients met the revisited criteria of NMO and nine had features of NMOSDs. This study demonstrated that SS with CNS recurrence shows frequent characteristic findings of NMO and these brain lesions suggest of NMOSDs. Hence, the detection of NMO-IgG and brain lesions characteristic of NMO in those patients may support the coexistence of NMO and autoimmune disorders. More interestingly, among 12, there was one SS patient who had AQP4-ab and brain abnormalities characteristic of NMO, but did not suffer ON or LEM. However, this patient developed ON and LEM one year after the positivity of AQP4-ab; therefore this case suggests that brain MRI lesions characteristic of NMO and positive AQP4-Ab may predict LEM and ON in SS.[30] Next, another study for "SS with myelitis (SSM)" in Korea, also showed that patients with SSM had poor prognoses with high mean annual relapse rates, and most seemed to have the clinical and immunological characteristics of NMO.[29]

2. Brain abnormalities in NMOSD

The 1st study, commented above, showed that patients including those with NMOSDs had brain lesions characteristic for NMO. Among those, 4 NMO patients also revealed signal abnormalities in diffusion weighted image (DWI) and they all were AQP4-Ab seropositive. MRIs performed between 3 to 7 days after symptom onset, showed high signal intensities in DWI and apparent diffusion coefficient (ADC) maps with different enhancement patterns. It is suggested that these lesions may be reflective of vasogenic edema, from interruption of blood-brain barrier, not vasculitis itself as observed in other systemic autoimmune disorders. This vasogenic edema in extensive hemispheric or periependymal lesions has been reported in several studies.[31,32] The lesions in patients with NMO-IgG showed no enhancement, which suggests of intact blood-brain barrier and dysfunction of AQP4 water channel.[31] Also, the unique enhancement pattern, "cloud-like enhancement" is observed in Japanese patients with NMO, which may help to differentiate from MS.[32]

Conclusion

Most of all, the result of NMO-IgG must be important for the diagnosis NMO as well as NMOSD, although the role of NMO-IgG has not been fully elucidated. The specificity of NMO-IgG as a marker for NMO and its immunoreactive sites in the spinal cord suggests of a true pathogenic role rather than being a secondary phenomenon.[14,15] Finally, NMO is now considered as distinct from prototypic MS, despite the fact that most patients with NMO have a relapsing-remitting course and satisfy diagnostic criteria for MS.[5,26] Therefore, the differentiation of NMO or NMOSD from MS could help the early diagnosis and the proper management.

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REFERENCES

1. Cree BA, Goodin DS, Hauser SL. Neuromyelitis optica. *Semin Neurol* 2002;22:105-122.
2. de Seze J. Neuromyelitis optica. *Arch Neurol* 2003;60:1336-1338.
3. Lennon VA, Wingerchuk DM, Kryzer TJ, Pittock SJ, Lucchinetti CF, Fujihara K, et al. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. *Lancet* 2004; 364:2106-2112.
4. Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinshenker BG. The spectrum of neuromyelitis optica. *Lancet Neurology* 2007;6:805-815.
5. Wingerchuk DM, Hogancamp WF, O'Brien PC, Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). *Neurology* 1999;53:1107-1114.
6. Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinshenker BG. Revised diagnostic criteria for neuromyelitis optica. *Neurology* 2006;66:1485-1489.
7. Matsuoka T, Matsushita T, Kawano Y, Osoegawa M, Ochi H, Ishizu T, et al. Heterogeneity of aquaporin-4 autoimmunity and spinal cord lesions in multiple sclerosis in Japanese. *Brain* 2007; 130 Pt 5:1206-1223.
8. Takahashi T, Fujihara K, Nakashima I, Misu T, Miyazawa I, Nakamura M, et al. Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 2007;130 Pt 5:1235-1243.
9. Lennon VA, Kryzer TJ, Pittock SJ, Verkman AS, Hinson SR. IgG

marker of optic-spinal multiple sclerosis binds to the aquaporin-4 water channel. *J Exp Med* 2005;202:473-477.
10. Jarius S, Franciotta D, Bergamaschi R, Wright H, Littleton E, Palace J, et al. NMO-IgG in the diagnosis of neuromyelitis optica. *Neurology* 2007;68:1076-1077.
11. Okai AF, Muppidi S, Bagla R, Leist TP. Progressive necrotizing myelopathy: part of the spectrum of neuromyelitis optica? *Neurol Res* 2006;28:354-359.
12. Petzold A, Pittock S, Lennon V, Maggiore C, Weinshenker BG, Plant GT. Neuromyelitis optica-IgG (aquaporin-4) autoantibodies in immune mediated optic neuritis. *J Neurol Neurosurg Psychiatry* 2010;81:109-111.
13. Weinshenker BG, Wingerchuk DM, Vukusic S, Linbo L, Pittock SJ, Lucchinetti CF, et al. Neuromyelitis optica IgG predicts relapse after longitudinally extensive transverse myelitis. *Ann Neurol* 2006;59:566-569.
14. Kira J. Multiple sclerosis in the Japanese population. *Lancet Neurology* 2003;2:117-127.
15. Lucchinetti CF, Mandler RN, McGavern D, Bruck W, Gleich G, Ransohoff RM, et al. A role for humoral mechanisms in the pathogenesis of Devic's neuromyelitis optica. *Brain* 2002;125 Pt 7:1450-1461.
16. Nakashima I, Fujihara K, Miyazawa I, Misu T, Narikawa K, Nakamura M, et al. Clinical and MRI features of Japanese patients with multiple sclerosis positive for NMO-IgG. *J Neurol Neurosurg Psychiatry* 2006;77:1073-1075.
17. Kikuchi S, Fukazawa T. "OSMS is NMO, but not MS": confirmed by NMO-IgG? *Lancet Neurology* 2005;4:594-595.
18. Saida T, Tashiro K, Itoyama Y, Sato T, Ohashi Y, Zhao Z. Interferon beta-1b is effective in Japanese RRMS patients: a randomized, multicenter study. *Neurology* 2005;64:621-630.
19. Tanaka K, Tani T, Tanaka M, Saida T, Idezuka J, Yamazaki M, et al. Anti-aquaporin 4 antibody in selected Japanese multiple sclerosis patients with long spinal cord lesions. *Mult Scler* 2007; 13:850-855.
20. Matsushita T, Isobe N, Matsuoka T, Shi N, Kawano Y, Wu XM, et al. Aquaporin-4 autoimmune syndrome and anti-aquaporin-4 antibody-negative opticospinal multiple sclerosis in Japanese. *Mult Scler* 2009;15:834-847.
21. Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, et al. Neuromyelitis optica and non organ-specific autoimmunity. *Arch Neurol* 2008;65:78-83.
22. Min JH, Kim HJ, Kim BJ, Lee KW, Sunwoo IN, Kim SM, et al. Brain abnormalities in Sjogren syndrome with recurrent CNS manifestations: association with neuromyelitis optica. *Mult Scler* 2009;15:1069-1076.
23. Karim S, Majithia V. Devic's syndrome as initial presentation of systemic lupus erythematosus. *Am J Med Sci* 2009;338:245-247.
24. Rabadi MH, Kundi S, Brett D, Padmanabhan R. Neurological pictures. Primary Sjogren syndrome presenting as neuromyelitis optica. *J Neurol Neurosurg Psychiatry* 2010;81:213-214.
25. O'Riordan JI, Gallagher HL, Thompson AJ, Howard RS, Kingsley DP, Thompson EJ, et al. Clinical, CSF, and MRI findings in Devic's neuromyelitis optica. *J Neurol Neurosurg Psychiatry* 1996;60:382-387.
26. de Seze J, Stojkovic T, Ferriby D, Gauvrit JY, Montagne C, Mounier-Vehier F, et al. Devic's neuromyelitis optica: clinical, laboratory, MRI and outcome profile. *J Neurol Sci* 2002; 197:57-61.
27. Pittock SJ, Lennon VA, Krecke K, Wingerchuk DM, Lucchinetti CF, Weinshenker BG. Brain abnormalities in neuromyelitis optica. *Arch Neurol* 2006;63:390-396.
28. Pittock SJ, Weinshenker BG, Lucchinetti CF, Wingerchuk DM, Corboy JR, Lennon VA. Neuromyelitis optica brain lesions localized at sites of high aquaporin 4 expression. *Arch Neurol* 2006;63:964-968.
29. Kim SM, Waters P, Vincent A, Kim SY, Kim HJ, Hong YH, et al. Sjogren's syndrome myelopathy: spinal cord involvement in Sjogren's syndrome might be a manifestation of neuromyelitis optica. *Mult Scler* 2009;15:1062-1068.
30. Min JH, Kim SH, Park MS, Kim BJ, Lee KL. Brain MRI lesions characteristic of neuromyelitis optica and positive anti-aquaporin 4-antibody may predict longitudinal extensive myelitis and optic neuritis in Sjogren's syndrome. *Mult Scler* 2010;16: 762-764.
31. Eichel R, Meiner Z, Abramsky O, Gotkine M. Acute disseminating encephalomyelitis in neuromyelitis optica: closing the floodgates. *Arch Neurol* 2008;65:267-271.
32. Ito S, Mori M, Makino T, Hayakawa S, Kuwabara S. "Cloud-like enhancement" is a magnetic resonance imaging abnormality specific to neuromyelitis optica. *Ann Neurol* 2009;66:425-428.