

Higher frequency of brain abnormalities in neuromyelitis optica spectrum disorder patients without primary Sjögren's syndrome

Li-na Gu^{1,#}, Min Zhang^{2,#}, Hui Zhu³, Jing-yao Liu^{3,*}

1 Department of Intensive Care Unit, First Hospital, Jilin University, Changchun, Jilin Province, China

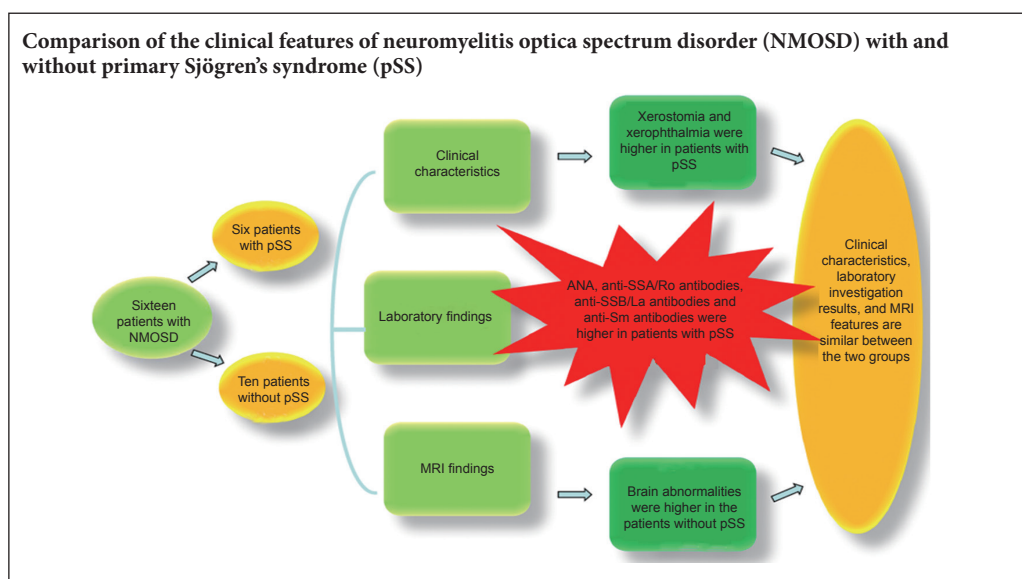
2 Department of Acupuncture and Moxibustion, Changchun University of Chinese Medicine, Changchun, Jilin Province, China

3 Department of Neurology, First Hospital, Jilin University, Changchun, Jilin Province, China

How to cite this article: Gu LN, Zhang M, Zhu H, Liu JY (2016) Higher frequency of brain abnormalities in neuromyelitis optica spectrum disorder patients without primary Sjögren's syndrome. *Neural Regen Res* 11(10):1633-1637.

Open access statement: This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

Graphical Abstract



*Correspondence to:

Jing-yao Liu, Ph.D.,
xiaohua208@sina.com.

#These authors contributed equally to this study.

orcid:

0000-0002-9999-7546
(Jing-yao Liu)

doi: 10.4103/1673-5374.193243

Accepted: 2016-09-12

Abstract

Neuromyelitis optica spectrum disorder often co-exists with primary Sjögren's syndrome. We compared the clinical features of 16 neuromyelitis optica spectrum disorder patients with ($n = 6$) or without primary Sjögren's syndrome ($n = 10$). All patients underwent extensive clinical, laboratory, and MRI evaluations. There were no statistical differences in demographics or first neurological involvement at onset between neuromyelitis optica spectrum disorder patients with and without primary Sjögren's syndrome. The laboratory findings of cerebrospinal fluid oligoclonal banding, serum C-reactive protein, antinuclear autoantibody, anti-Sjögren's-syndrome-related antigen A antibodies, anti-Sjögren's-syndrome-related antigen B antibodies, and anti-Sm antibodies were significantly higher in patients with primary Sjögren's syndrome than those without. Anti-aquaporin 4 antibodies were detectable in 67% (4/6) of patients with primary Sjögren's syndrome and in 60% (6/10) of patients without primary Sjögren's syndrome. More brain abnormalities were observed in patients without primary Sjögren's syndrome than in those with primary Sjögren's syndrome. Segments lesions (> 3 centrum) were noted in 50% (5/10) of patients without primary Sjögren's syndrome and in 67% (4/6) of patients with primary Sjögren's syndrome. These findings indicate that the clinical characteristics of neuromyelitis optica spectrum disorder patients with and without primary Sjögren's syndrome are similar. However, neuromyelitis optica spectrum disorder patients without primary Sjögren's syndrome have a high frequency of brain abnormalities.

Key Words: nerve regeneration; neuromyelitis optica; primary Sjögren's syndrome; neuromyelitis optica spectrum disorder; xerostomia; xerophthalmia; neurological involvements; magnetic resonance imaging; anti-aquaporin 4; neural regeneration

Introduction

Neuromyelitis optica (NMO) is classically described as optic neuritis and longitudinal extensive transverse myelitis, and is associated with other autoimmune disorders in 10–40% of patients (Takahashi et al., 2007; Gono et al., 2011). The diagnosis of NMO spectrum disorder (NMOSD) is greatly facilitated by screening for a specific biomarker for NMO: immunoglobulin G (IgG) antibodies targeting water channel protein aquaporin 4 (AQP4) in the astrocytic foot processes, which contributes to the formation of the blood brain barrier (Wingerchuk et al., 2007; Wang et al., 2014; Kleiter and Gold, 2016).

Despite a prevalence ranging between 1–3% in the general population, approximately 30% of primary Sjögren's syndrome (pSS) patients present with additional autoimmune diseases (Peri et al., 2012). Several studies have reported that organ-specific autoimmune diseases, such as thyroid diseases and myasthenia gravis, and non-organ-specific autoimmune diseases, such as systemic lupus erythematosus, pSS, rheumatoid arthritis, and undifferentiated connective tissue disease, are strongly associated with NMOSD (Takahashi et al., 2007; Pittock et al., 2008; Gono et al., 2011).

pSS is a chronic autoimmune disease of the exocrine glands characterized by focal lymphocytic infiltration and destruction of these glands. The diagnosis of pSS requires a set of rigorous clinical tests. The most widely accepted diagnostic standard is the European criteria of Vitali (Vitali et al., 2002). Sjögren's syndrome is more frequent in women, with a female-to-male ratio of 9:1, and peaks in patients in their mid-50s (Tzioufas et al., 2008). Central nervous system manifestations in pSS are diverse and span the entire neuroaxis. There is no consensus regarding the prevalence of central nervous system involvement in pSS. A few studies have attempted to address the relationship between pSS and NMOSD (Massara et al., 2010). However, the characteristics of different NMOSDs have not been sufficiently investigated. The aim of this study was to investigate the neurological, laboratory, and MRI features of NMOSD patients, with or without pSS, and their clinical outcomes.

Subjects and Methods

Subjects

We retrospectively studied 16 NMOSD patients who were diagnosed and admitted to the First Hospital of Jilin University of China between May 2010 and May 2014.

The following data were collected from the medical records: age at disease onset, age at diagnosis, age at first neurological manifestation, disease duration (calculated from time of disease onset to January 2014), radiological characteristics, laboratory investigations, and treatment. NMO was defined using the 2006 clinical diagnostic criteria (Wingerchuk et al., 2006). Other criteria included: (a) autoantibody analysis conducted, including anti-AQP4 antibody, extractable nuclear antigen, autoantibodies antinuclear (ANA) antibodies, and antineutrophil cytoplasmic antibodies; (b) availability of the following laboratory data: rheumatoid factors, immunoglobulins, complement C3 and C4, and thyroid

hormones; and (c) MRI scan of the brain and spinal cord.

pSS was diagnosed using a set of rigorous clinical and immunologic criteria based on the most widely accepted European criteria of Vitali (Vitali et al., 2002). In addition, NMOSD was defined using the revised clinical diagnostic criteria of Wingerchuk et al. (2007). Owing to the complexity of symptoms, physicians paid special attention to atypical extraglandular symptoms in addition to the classical clinical evidence of xerophthalmia, xerostomia, and laboratory test results, suggesting a systemic autoimmune disease. At the time of pSS diagnosis, minor salivary gland biopsies showed lymphocytic infiltration in all pSS patients.

All patients were evaluated by neurologists/rheumatologists, and neurological manifestations were only attributed to pSS after excluding other causes. The patients were divided into two groups: one with ten NMOSD patients without pSS and the other with six NMOSD patients with pSS. The study was approved by the local Ethics Committee of First Hospital of Jilin University of China (Approval No. 2010-3). Written informed consent was obtained from the participants and their family members.

Laboratory analyses and MRI

Fasting venous blood and cerebrospinal fluid samples were collected from the participants during their visits to the hospital. The following laboratory tests were performed in all patients: serum IgG, complement C3 and C4, cryoglobulins, anti-AQP4, cerebrospinal fluid oligoclonal banding, rheumatoid factors, antinuclear, anti-Sjögren's-syndrome-related antigen A (SSA), anti-Sjögren's-syndrome-related antigen B (SSB), and antiphospholipid antibodies (Wang et al., 2014). A standard MRI examination was performed using a GE MR scanner at 1.5Tesla (GE, Boston, MA, USA), including brain, spinal cord, and enhancement scanning in all patients. Each patient underwent MRI at the time of the initial diagnosis, prior to corticosteroid or immunomodulatory treatment.

Statistical analysis

Statistical analysis was performed using SPSS 17.1 (SPSS, Chicago, IL, USA). The differences between the groups (pSS *versus* without pSS) were analyzed using chi-square tests or Fisher's exact tests for qualitative data. One-way analysis of variance and the least significant difference tests were used to analyze quantitative data. All quantitative data are presented as the mean \pm SD. A *P* value < 0.05 was considered to be statistically significant.

Results

Comparison of clinical manifestations and neurological findings between NMOSD patients with and without pSS

The cohort consisted of five (83%) females, one (17%) male (ratio of females to males, 5:1) in the NMOSD with pSS patient group and nine (90%) females, one (10%) male (ratio of females to males, 9:1) in the NMOSD without pSS patient group. Only one (17%) patient with pSS and two (20%) patients without pSS had visual impairment as the first manifestation of NMOSD. Spinal cord involvement was the first

Table 1 Demographic and clinical characteristics of NMOSD patients with or without pSS

	NMOSD with pSS (<i>n</i> = 6)	NMOSD without pSS (<i>n</i> = 10)	<i>P</i>
Gender (female/male, <i>n</i>)	5/1	9/1	0.675
Age at onset (year)	46.6±14.67	48.69±13.45	0.443
Xerostomia	5(83)*	2(20)	0.034
Xerophthalmia	6(100)*	1(10)	0.017
First neurological involvements at onset			
Optic nerve	1(17)	2(20)	0.884
Optic nerve+spinal cord	2(33)	4(40)	0.629
Spinal cord	2(33)	4(40)	0.629
Brainstem	1(17)	2(20)	0.884

Data for xerostomia, xerophthalmia, and first neurological involvements at onset are expressed as *n*(%), and age at onset data are expressed as the mean ± SD. Qualitative data were analyzed with the chi-square test or Fisher's exact test. **P* < 0.05, vs. NMOSD without pSS. NMOSD: Neuromyelitis optica spectrum disorder; pSS: primary Sjögren's syndrome.

Table 2 Laboratory findings of NMOSD patients with or without pSS

	NMOSD with pSS (<i>n</i> = 6)	NMOSD without pSS (<i>n</i> = 10)
CSF index		
IgG index	1.09(0.6, 2.1)	0.98(0.7, 1.7)
OCB	5(83)	4(40)
Serum index		
CRP (mg/L)	5.63±7.62*	2.33±4.37
ESR (mm/h)	12.90±7.89	14.04±13.39
Number of anti-AQP4-positive patients (percentage)	4(67)	6(60)
Number of ANA-positive patients (percentage)	3(50)*	0
Number of SSA-positive patients (percentage)	4(67)*	0
Number of SSB-positive patients (percentage)	3(50)*	0
Number of RF-positive patients (percentage)	0	0
Number of Sm-positive patients (percentage)	1(17)	0
Number of ANCA-positive patients (percentage)	0	0
C3 (g/L)	1.07±0.24	1.09±0.32
C4 (g/L)	0.21±0.15	0.22±0.15

All data are presented as the mean ± SD or median (range). Other data are presented as *n*(%). Qualitative data were analyzed using the chi-square test or Fisher's exact test. **P* < 0.05, vs. NMOSD without pSS. NMOSD: Neuromyelitis optica spectrum disorder; pSS: primary Sjögren's syndrome; CSF: cerebrospinal fluid; IgG: immunoglobulin G; OCB: oligoclonal banding (CSF OCB investigates inflammation-related proteins in CSF); CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody; SSA: Sjögren's-syndrome-related antigen A; SSB: anti-Sjögren's-syndrome-related antigen B; RF: rheumatoid factor; ANCA: antineutrophil cytoplasmic antibody.

Table 3 MRI findings of lesions in NMOSD patients with or without pSS

Lesion location	NMOSD with pSS (<i>n</i> = 6)	NMOSD without pSS (<i>n</i> = 10)	<i>P</i>
Brain	2(17)*	8(80)	0.023
Spinal cord (all)	5(83)	7(70)	0.743
> 3 segments	4(67)	5(50)	0.813
Cervical cord only	4(67)	6(60)	0.916
Cervical & thoracic	1(16)	1(10)	0.232

Data are presented as *n*(%). Qualitative data were analyzed using the chi-square test or Fisher's exact test. **P* < 0.05, vs. NMOSD without pSS. NMOSD: Neuromyelitis optica spectrum disorder; pSS: primary Sjögren's syndrome.

symptom in two (33%) patients with NMOSD and occurred in four (40%) patients without pSS. The demographic and first neurological involvements at onset were compared between NMOSD patients with and without pSS, and there was no significant difference. Nevertheless, the prevalences of xerostomia and xerophthalmia were significantly higher in NMOSD patients with pSS than in NMOSD patients without

pSS (*P* < 0.05; **Table 1**).

Comparison of laboratory analyses between NMOSD patients with and without pSS

The laboratory findings of the patients are presented in **Table 2**. There were no significant differences in CSF or IgG index between NMOSD with and without pSS.

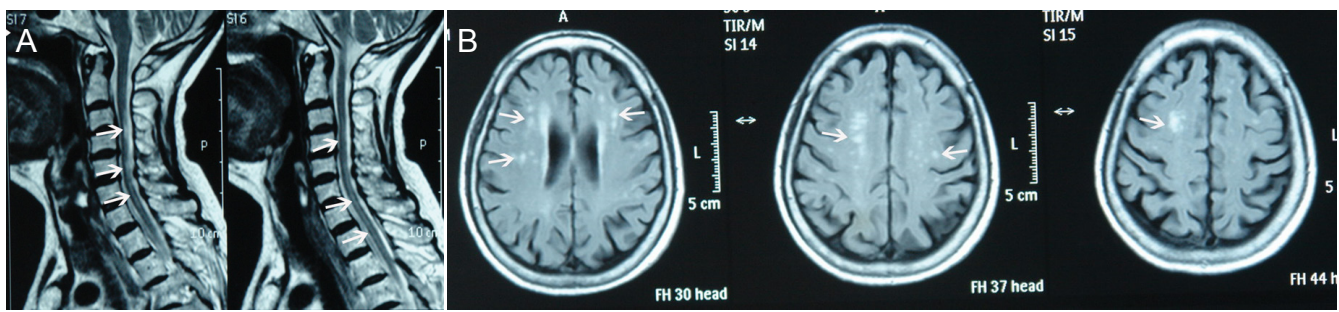


Figure 1 Brain and cervical cord MRI of a 74-year-old female patient with neuromyelitis optica spectrum disorder and primary Sjögren's syndrome.

(A) Sagittal magnetic resonance T2-weighted images show a strip of hyperintensity in the cervical cord (C₃₋₇). (B) Axial fluid-attenuated inversion recovery images show several small hyper-intensities in the white matter near both lateral ventricles in the brain. L: Left; A: anterior; P: posterior.

Serum C-reactive protein levels were significantly higher in NMOSD patients with pSS compared with those without pSS ($P < 0.05$). Moreover, ANA, anti-SSA/Ro antibodies, anti-SSB/La antibodies, and anti-Sm antibodies were significantly higher in NMOSD patients with pSS than those without pSS ($P < 0.05$). Anti-AQP4 was detected in 67% (4/6) of NMOSD patients with pSS and in 60% (6/10) of NMOSD patients without pSS.

Comparison of the neuroimaging features between NMOSD patients with and without pSS

As shown in **Table 3**, more NMOSD patients without pSS had brain abnormalities than those with pSS (80% versus 17%, $P < 0.05$). However, there were no statistical differences between the two groups in other MRI features. Segment lesions (> 3 centrum) on spinal cord MRI scans were noted in 50% (5/10) of NMOSD patients without pSS and in 67% (4/6) of NMOSD patients with pSS. We also observed gray matter lesions in the basal ganglia of NMOSD patients with pSS. Corpus callosum lesions were rarely observed. In cases of acute myelopathy, we frequently observed an extended T2-weighted hyperintensity involving a large part of the cord (**Figure 1**).

Discussion

NMO is an immune-mediated neurological disorder characterized by recurrent episodes of optic neuritis and longitudinally extensive transverse myelitis. A serum biomarker, anti-AQP4, has been specifically associated with NMOSD and is useful in early recognition of the disease and for predicting relapses. Other autoimmune disorders, both organ-specific and generalized, are observed in 20–30% of NMOSD cases (Wang et al., 2014). These disorders, which may become symptomatic before or after the development of NMOSD, are often diagnosed long after the diagnosis of NMOSD. Iyer et al. (2014) identified that pSS and systemic lupus erythematosus were the most common autoimmune disorders co-existing with NMOSD. Thus, central nervous system disorders such as NMOSD, and autoimmune diseases such as pSS may coexist for a long time prior to being diagnosed correctly. This poses a challenge for diagnosis and contributes to a high number of misdiagnosed cases in

young female patients with neurological symptoms.

This study also showed the diversity of manifestations of NMOSD. Although most of the patients with neurological involvement were female, NMOSD patients with pSS or other autoimmune disorders have also been observed in males (Delalande et al., 2004). Neurological involvement precedes the diagnosis of pSS in 25–81% of patients (Gono et al., 2011). The optic nerve, spinal cord and brainstem are involved earliest in NMOSD patients. The most frequently observed clinical manifestations are optic atrophy, motor or sensory deficit, headache, dizziness, intractable hiccups, and nausea. The results of this study demonstrate that the initial neurological involvement at the onset and clinical manifestation with pSS were less frequent than in patients without pSS, although the difference was not statistically significant.

In a previous study, 47% of NMOSD patients had autoantibody markers of pSS (Jacob et al., 2013). Previous reports have shown that although autoantibodies in the serum (particularly ANA, anti-SSA/Ro antibodies, and anti-SSB/La antibodies in this study) can be found in all NMOSD subtypes, the titer varies in different subtypes. Antinuclear antibodies are common in NMOSD patients, especially in those with pSS (Pittock et al., 2008). NMO patients often show concomitant autoantibodies, for example, anti-SSA/Ro antibodies, which are frequently detectable in AQP4-seropositive patients (de Seze et al., 2002). Our observations are in line with these previous findings.

With the recent discovery of the anti-AQP4 antibody, which is considered to be specific for NMOSD, an overlap between patients with pSS and NMOSD has been noted (Massara et al., 2010). Anti-AQP4 antibody was detected in all patients in the present study. Previous studies have suggested that anti-AQP4 autoantibody plays a role in the pathogenesis of NMO: AQP4 expression is absent from NMOSD lesions, and titers of anti-AQP4 appear to correlate with disease activity (Jarius et al., 2008; Ramos-Casals et al., 2008). Autopsies of NMOSD spinal cord lesions have revealed immunoglobulin and complement deposits in the endothelial cell wall (Mandler, 1993). Thus, if optic neuritis, longitudinally extensive transverse myelitis, or multiple lesions are detected in the spinal cord and white matter of pSS patients, anti-AQP4 antibody should be screened for (Taka-

hashi et al., 2007; Kahlenberg, 2011).

The pathophysiological mechanisms of the neurological involvement in pSS are still unclear. The diverse clinical features imply the possibility of distinct pathogenic pathways. In peripheral neuropathy, lymphocytic infiltration of the dorsal ganglia seems to be the main phenomenon involved (Iyer et al., 2014). Griffin et al. (1990) have also described T lymphocyte infiltration of the ganglia with neuronal degeneration. In multiple mononeuropathies, nerve biopsy often reveals vasculitis (Grant et al., 1997), which could explain the good efficacy of corticosteroids and immunosuppressive drugs in these cases. We have previously demonstrated a high concentration of cryoglobulin in sensory motor neuropathy, implying the possible pathophysiologic role of this protein (Hebbar et al., 1995). Many studies have suggested an ischemic mechanism of central nervous system complications in pSS (Alexander, 1993). Bakchine et al. (1991) supported another hypothesis regarding mononuclear cell infiltration in the central nervous system in a pathologic case. Additional mechanisms such as immunologically mediated vascular damage in the central nervous system, the action of anti-neuron antibodies (Mauch et al., 1994), or a direct role of anti-Ro/SSA antibodies, have also been suggested.

In summary, the clinical characteristics, laboratory investigation results, and MRI features are similar in NMOSSD patients with or without pSS.

Declaration of patient consent: *The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.*

Author contributions: LNG and MZ drafted the paper. HZ participated in the study design. JYL helped to draft the paper. All authors approved the final version of the paper.

Conflicts of interest: None declared.

Plagiarism check: *This paper was screened twice using CrossCheck to verify originality before publication.*

Peer review: *This paper was double-blinded and stringently reviewed by international expert reviewers.*

References

- Alexander EL (1993) Neurologic disease in Sjögren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update of immunopathogenesis. *Rheum Dis Clin North Am* 19:869-908.
- Bakchine S, Duyckaerts C, Hassine L, Chaunu MP, Turell E, Wechsler B, Chain F (1991) Central and peripheral neurologic lesions in primary Gougerot-Sjögren syndrome. *Clinicopathological study of a case. Rev Neurol (Paris)* 147:368-375.
- de Seze J, Stojkovic T, Ferriby D, Gauvrit JY, Montagne C, Mounier-Vehier F, Verier A, Pruvo JP, Hache JC, Vermersch P (2002) Devic's neuromyelitis optica: clinical, laboratory, MRI and outcome profile. *J Neurol Sci* 197:57-61.
- Delalande S, de Seze J, Fauchais AL, Hachulla E, Stojkovic T, Ferriby D, Dubucquoi S, Pruvo JP, Vermersch P, Hatron PY (2004) Neurologic manifestations in primary Sjögren syndrome: a study of 82 patients. *Medicine (Baltimore)* 83:280-291.
- Gono T, Kawaguchi Y, Katsumata Y, Takagi K, Tochimoto A, Baba S, Okamoto Y, Ota Y, Yamanaka H (2011) Clinical manifestations of neurological involvement in primary Sjögren's syndrome. *Clin Rheumatol* 30:485-490.
- Grant IA, Hunder GG, Homburger HA, Dyck PJ (1997) Peripheral neuropathy associated with sicca complex. *Neurology* 48:855-862.
- Griffin JW, Cornblath DR, Alexander E, Campbell J, Low PA, Bird S, Feldman EL (1990) Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjögren's syndrome. *Ann Neurol* 27:304-315.
- Hebbar M, Hebbar-Savean K, Hachulla E, Brouillard M, Hatron PY, Devulder B (1995) Participation of cryoglobulinaemia in the severe peripheral neuropathies of primary Sjögren's syndrome. *Ann Med Interne (Paris)* 146:235-238.
- Iyer A, Elson L, Appleton R, Jacob A (2014) A review of the current literature and a guide to the early diagnosis of autoimmune disorders associated with neuromyelitis optica. *Autoimmunity* 47:154-161.
- Jacob A, McKeon A, Nakashima I, Sato DK, Elson L, Fujihara K, de Seze J (2013) Current concept of neuromyelitis optica (NMO) and NMO spectrum disorders. *J Neurol Neurosurg Psychiatry* 84:922-930.
- Jarius S, Aboul-Enein F, Waters P, Kuenz B, Hauser A, Berger T, Lang W, Reindl M, Vincent A, Kristoferitsch W (2008) Antibody to aquaporin-4 in the long-term course of neuromyelitis optica. *Brain* 131:3072-3080.
- Kahlenberg JM (2011) Neuromyelitis optica spectrum disorder as an initial presentation of primary Sjögren's syndrome. *Semin Arthritis Rheum* 40:343-348.
- Kleiter I, Gold R (2016) Present and Future Therapies in Neuromyelitis Optica Spectrum Disorders. *Neurotherapeutics* 13:70-83.
- Mandler RN, Davis LE, Jeffery DR, Kornfeld M (1993) Devic's neuromyelitis optica: a clinicopathological study of 8 patients. *Ann Neurol* 34:162-168.
- Massara A, Bonazza S, Castellino G, Caniatti L, Trotta F, Borrelli M, Feggi L, Govoni M (2010) Central nervous system involvement in Sjögren's syndrome: unusual, but not unremarkable--clinical, serological characteristics and outcomes in a large cohort of Italian patients. *Rheumatology (Oxford)* 49:1540-1549.
- Mauch E, Völck C, Kratzsch G, Krapf H, Kornhuber HH, Laufen H, Hummel KJ (1994) Neurological and neuropsychiatric dysfunction in primary Sjögren's syndrome. *Acta Neurol Scand* 89:31-35.
- Peri Y, Agmon-Levin N, Theodor E, Shoenfeld Y (2012) Sjögren's syndrome, the old and the new. *Best Pract Res Clin Rheumatol* 26:105-117.
- Pittock SJ, Lennon VA, de Seze J, Vermersch P, Homburger HA, Wingerchuk DM, Lucchinetti CF, Zéphir H, Moder K, Weinschenker BG (2008) Neuromyelitis optica and non organ-specific autoimmunity. *Arch Neurol* 65:78-83.
- Ramos-Casals M, Solans R, Rosas J, Camps MT, Gil A, del Pino-Montes J, Calvo-Alen J, Jiménez-Alonso J, Micó M-L, Beltrán J, Belenguer R, Pallarés L; GEMESS Study Group (2008) Primary Sjögren syndrome in Spain: clinical and immunologic expression in 1010 patients. *Medicine (Baltimore)* 87:210-219.
- Takahashi T, Fujihara K, Nakashima I, Mitsu T, Miyazawa I, Nakamura M, Watanabe S, Shiga Y, Kanaoka C, Fujimori J, Sato S, Itoyama Y (2007) Anti-aquaporin-4 antibody is involved in the pathogenesis of NMO: a study on antibody titre. *Brain* 130:1235-1243.
- Tzioufas AG, Mitsias DI, Moutsopoulos HM (2008) Sjögren's syndrome. In: *Rheumatology (Hochberg MC, Silman AJ, Smolen JS, eds). Edinburgh: Mosby.*
- Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons S, Daniels TE, Fox PC, Fox RI, Kassan SS, Pillemer SR, Talal N, Weisman MH; European Study Group on Classification Criteria for Sjögren's Syndrome (2002) Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 61:554-558.
- Wang Y, Wu A, Chen X, Zhang L, Lin Y, Sun S, Cai W, Zhang B, Kang Z, Qiu W, Hu X, Lu Z (2014) Comparison of clinical characteristics between neuromyelitis optica spectrum disorders with and without spinal cord atrophy. *BMC Neurol* 14:246.
- Wingerchuk DM, Lennon VA, Pittock SJ, Lucchinetti CF, Weinschenker BG (2006) Revised diagnostic criteria for neuromyelitis optica. *Neurology* 66:1485-1489.
- Wingerchuk DM, Lennon VA, Lucchinetti CF, Pittock SJ, Weinschenker BG (2007) The spectrum of neuromyelitis optica. *Lancet Neurol* 6:805-815.

Copyedited by Brooks W, Hindle A, Yu J, Qiu Y, Li CH, Song LP, Zhao M