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ORIGINAL COMMUNICATION

Impact of comorbid Sjögren syndrome in anti-aquaporin-4 antibody-positive neuromyelitis optica spectrum disorders

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Abstract

Background Neuromyelitis optica spectrum disorders (NMOSD) are autoimmune neurological diseases of the central nervous system, which are characterized by the presence of serum anti-aquaporin-4 autoantibodies (AQP4-IgG). An association between Sjögren syndrome (SjS) and AQP4-IgG-positive NMOSD has been proposed, but the rate of coexistence has not been determined.

Methods In this study, 4,447 patients suspected of having NMOSD with acute neurological episodes were evaluated for the positivity of serum AQP4-IgG, serum SS-A/Ro antibody, and the presence of SjS-related symptoms (dry eye, dry mouth).

Results Of the 4,447 patients, 1,651 were positive for serum AQP4-IgG, and the remaining 2,796 were negative. A significantly higher proportion of AQP4-IgG-positive patients were positive for serum anti-SSA/Ro antibody (26.3 vs. 4.5%; $p < 0.0001$) and anti-SSB/La antibody (7.2 vs. 1.2%; $p < 0.0001$) and had dry eye (9.1 vs .4.9%; $p < 0.0001$) and dry mouth symptoms (8.9 vs. 3.7%; $p < 0.0001$). More than 80% of the patients with SjS with acute neurological events such as myelitis or optic neuritis were AQP4-IgG positive. AQ4-IgG-positive patients with comorbid SjS showed a higher female rate (97.1 vs. 89.0%; $p = 0.0062$), a higher positivity rate for oligoclonal bands (15.4 vs. 7.5%; $p = 0.029$), and a higher relapse frequency ($p = 0.027$) than AQP4-IgG-positive patients without comorbid SjS.

Conclusions The prevalence of SjS is higher among AQP4-IgG-positive than AQP4-IgG-negative patients, with the potential prevalence of 10–20% at the diagnosis of AQP4-IgG-positive NMOSD. Comorbid SjS is more prevalent in females, and it has a higher relapse frequency among AQP4-IgG-positive patients.

Keywords Anti-aquaporin-4 antibodies · Anti-SSA/Ro antibody · Comorbidity · Neuromyelitis optica spectrum disorders · Sjögren syndrome

Introduction

Neuromyelitis optica spectrum disorders (NMOSDs) are autoimmune neurological diseases characterized by the presence of serum anti-aquaporin-4 autoantibodies (AQP4-IgG) that predominantly binds around the blood–brain barrier and supposedly to primarily disturb the functions of astrocytes in the central nervous system (CNS) [13, 19–21, 40]. Most patients with AQP4-IgG-positive NMOSD experience repeated clinical episodes based on CNS lesions, represented by optic neuritis (ON), acute myelitis, and area postrema syndrome (APS), often with incomplete recovery [1, 24, 32]. Because the progression of neurological disturbance in AQP4-IgG-positive NMOSD occurs almost exclusively during clinical attacks [4, 26, 41, 42], long-term administration

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of immunosuppressants for relapse prevention to avoid irreversible neurological sequelae is critical [14, 37].

The exact mechanism underlying the clinical manifestations of AQP4-IgG-positive NMOSD has not been fully elucidated yet. Several possible risk factors and triggers of attacks have been reported in several articles recently [2, 11]. Among the suggested risks and triggers are comorbid autoimmune diseases such as Sjögren syndrome (SjS) [6, 8, 25, 43]. SjS is an autoimmune systemic disease characterized by the presence of serum anti-SSA/Ro antibody and dry eye and dry mouth symptoms [31, 33]. More than 90% of patients with SjS are females; the disease is usually seen in middle-aged post-menopausal females [39], but the age of onset varies widely [7, 27]. SjS is a very common autoimmune disease with an estimated prevalence of approximately 0.5% to 1.0% of the general population [38]. Patients with SjS often have co-existing autoimmune diseases (e.g., rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, scleroderma) or hematologic diseases (e.g., malignant lymphoma). Traditionally, the disease has been considered to be characterized by exocrine dysfunction based on glandular damage with lymphatic infiltration, but more recent studies have suggested that there is a discrepancy between lymphocytic infiltration and the level of secretory dysfunction [28]. Moreover, the disease is known to present with several extra-glandular manifestations, including central nervous system disturbances.

An elevated frequency of coexisting SjS among the patients with AQP4-IgG-positive NMOSD has been proposed [26], and such coexisting non-organ-specific autoimmunity was supposed to independently present distinct clinical manifestations based on a different pathomechanism [25]. Meanwhile, until now, the exact clinical impact of comorbid SjS on the manifestations of AQP4-IgG-positive NMOSD or the exact rate of coexistence of these two diseases has not yet been determined. In this study, we enrolled a large number of subjects with neurological conditions with possible inflammatory involvement and compared the rates of comorbid SjS in those with and without serum AQP4-IgG. We further evaluated the clinical impact of comorbid SjS on the severity and relapse frequency of AQP4-IgG-positive NMOSD.

Methods

Patients

In this study, we enrolled a total of 4,447 patients (1,208 males and 3,239 females) with neurological symptoms suspected to be MS or other related demyelinating diseases (e.g., optic neuritis, acute myelitis) who were evaluated for the positivity of serum AQP4-IgG. The means and standard deviations (SDs) of the ages of onset and the ages at AQP4-IgG titration of the enrolled patients were 41.2 ± 17.1 years and 46.2 ± 16.7 years, respectively. The serum samples were sent to our laboratory for testing AQP4-IgG from around the country from 2006 to 2012. Some clinical and laboratory data, which included questionnaire responses on SjS-related autoantibodies and symptoms, were sent to us with the sera.

Collected information

Serum AQP4-IgG positivity was assessed using the cell-based assay method in all the enrolled 4,447 patients, as previously reported [29, 35, 36]. In addition, the following data were collected during AQP4-IgG evaluation: age, sex, previous times of neurological episodes, details of the neurological episodes, presence and locations of brain lesions on brain MRI, the latest Expanded Disability Status Scale (EDSS) scores for the acute to subacute phases, positivity of oligoclonal bands (OCB) in the cerebrospinal fluid, positivity of serum anti-SSA/Ro antibody, positivity of serum anti-SSB/La antibody, presence of dry eye symptoms, and presence of dry mouth symptoms.

Statistical analyses

Comparisons of qualitative data, such as the prevalence of serum antibody and clinical symptoms, of the two groups were performed using the chi-squared test. Comparisons of quantitative data, such as age or the EDSS score, of the two groups were performed using the Student's t test or Mann–Whitney U test based on the patterns of distribution of the evaluated variables. p values less than 0.05 were regarded as statistically significant in this study. The statistical analyses were performed using IBM SPSS Statistics version 22 (IBM Corp., USA) or MATLAB R2015a (MathWorks, USA).

Results

Demographic and clinical data by AQP4-IgG positivity

Of the 4,447 enrolled patients, 1,651 patients (37.1%; 95% confidence interval [CI] 35.7. 38.6%) were positive for serum AQP4-IgG, and the remaining 2,796 patients (62.9%; 95% CI 61.4. 64.3%) were negative. The demographic and clinical data for the positivity of serum AQP4-IgG are listed in Table 1. Patients with serum AQP4-IgG were more likely to be female and have an older onset, longer disease duration with more clinical episodes, and more severe neurological disturbances than those without serum AQP4-IgG. Given the SjS-related variables, the prevalence of anti-SSA/Ro

Table 1 Demographic and clinical data stratified by AQP4-IgG positivity

	AQP4-IgG (+) ($n=1,651$)	AQP4-IgG (−) ($n=2,796$)	p values
Male: Female	173 (10.5%): 1,478 (89.5%)	1,035 (37.0%): 1,761 (63.0%)	< 0.0001
Age at clinical onset	46.1 ± 15.9 years	38.3 ± 17.2 years	< 0.0001
Age at titration	52.6 ± 14.9 years	42.5 ± 16.5 years	< 0.0001
Disease duration at titration[a]	3 (1–10) years	1 (1–6) years	< 0.0001
EDSS at titration (acute phase)[a]	5.0 (3.0–7.5)	2.5 (1.0–4.5)	< 0.0001
OCB positivity (Pos: Neg)	70 (8.8%): 728 (91.2%)	310 (23.9%): 989 (76.1%)	< 0.0001
Previous times of neurological episodes[a]	2 (1–5)	1 (1–3)	< 0.0001
(optic neuritis[a])	(1 [0–2])	(0 [0–1])	< 0.0001
(acute myelitis[a])	(1[1–3])	(1[1–2])	< 0.0001
Anti-SSA/Ro antibody (positive: negative)	300 (26.3%): 839 (73.7%)	83 (4.5%): 1,777 (95.5%)	< 0.0001
Anti-SSB/La antibody (positive: negative)	80 (7.2%): 1,033 (92.8%)	21 (1.2%): 1,785 (98.8%)	< 0.0001
Dry eye (Yes: No)	140 (9.1%): 1,399 (90.9%)	128 (4.9%): 2,503 (95.1%)	< 0.0001
Dry mouth (Yes: No)	136 (8.9%): 1,384 (91.1%)	95 (3.7%): 2,492 (96.3%)	< 0.0001
SjS suspected (Yes: No)	105 (9.2%): 1,034 (90.8%)	27 (1.5%): 1,833 (98.5%)	< 0.0001

AQP4-IgG anti-aquaporin-4 antibodies, *EDSS* Expanded Disability Status Scale, *OCB* oligoclonal bands

[a]Median and interquartile range (i.e., 25–75 percentile range)

antibody positivity, anti-SSB/La antibody positivity, dry eye symptoms, and dry mouth symptoms were significantly higher in AQP4-IgG-positive than in AQP4-IgG-negative patients ($p < 0.0001$ for all variables). Consequently, the number of cases of suspected comorbid SjS with serum anti-SSA/Ro antibody and at least one SjS-related clinical symptom was significantly higher in the AQP4-IgG-positive than in the AQP4-IgG-negative patients ($p < 0.0001$). The estimated 95% CI of the anti-SSA/Ro antibody positivity of the AQP4-IgG-positive cases was 23.9. 29.0%, which was higher than that of the AQP4-IgG-negative cases with neurological conditions (3.6. 5.5%). For reference, the estimated range of anti-SSA/Ro antibody positivity among the AQP4-IgG-negative cases in this study was slightly higher than what was previously reported in the normal population (i.e., less than 2–3%) [30].

Demographic and clinical data stratified by comorbid SjS

The demographic and clinical data of the enrolled patients (irrespective of the eventual results of AQP4-IgG positivity) were stratified by comorbid SjS (Table 2). More than 95% of patients with suspected comorbid SjS were females, which was significantly higher than that of those without comorbid SjS. The age of onset and the latest EDSS score for the acute phase were also significantly higher in those with comorbid SjS. The positivity rate of serum AQP4-IgG was higher

Table 2 Cohort data stratified by the comorbidity of Sjögren syndrome

	With suspected SjS ($n=132$)	Without SjS ($n=2,867$)	p values
Male: Female	3 (2.3%): 129 (97.7%)	801 (27.9%): 2,066 (72.1%)	< 0.0001
Age at clinical onset	47.4 ± 15.9	41.5 ± 16.7	< 0.0001
Age at titration	52.7 ± 14.2	46.5 ± 16.2	< 0.0001
Disease duration at titration[a]	2.0 (1.0–7.0)	2.0 (1.0–7.0)	0.649
EDSS at titration (acute phase)[a]	5.0 (2.5–7.5)	3.0 (2.0–6.0)	< 0.0001
OCB positivity (Pos: Neg)	13 (16.5%): 66 (83.5%)	286 (17.6%): 1,335 (82.4%)	0.787
Previous times of neurological episodes[a]	2 (1–4)	2 (1–4)	0.151
AQP4-IgG (Pos: Neg)			
Total	105 (79.5%): 27 (20.5%)	1,034 (36.1%): 1,833 (63.9%)	< 0.0001
Among those with myelitis	83 (86.5%): 13 (13.5%)	513 (47.9%): 557 (52.1%)	< 0.0001
Among those with ON	50 (89.3%): 6 (10.7%)	826 (42.4%): 1,123 (57.6%)	< 0.0001

AQP4-IgG anti-aquaporin-4 antibodies, *EDSS* Expanded Disability Status Scale, *OCB* oligoclonal bands, *ON* optic neuritis, *SjS* Sjögren syndrome

[a]Median and interquartile range (i.e., 25–75 percentile range)

among those with comorbid SjS than among those without comorbid SjS (79.5 vs. 36.1%, $p < 0.0001$). The QP4-IgG-positivity rate of those with episodes of myelitis was also higher among those with comorbid SjS than those without comorbid SjS (86.5 vs. 47.9%, $p < 0.0001$). The rate of ON episodes was higher in those with SjS than in those without SjS (89.3 vs. 42.4%, $p < 0.0001$).

Effect of comorbid Sjögren syndrome on the manifestation of NMOSD

Of the 1,651 patients with serum AQP4-IgG, 1,139 patients had complete clinical information on serum anti-SSA/Ro antibody and dry eye and dry mouth symptoms. Those with serum anti-SSA/Ro antibody and at least one of the dry eye and dry mouth symptoms were suspected of having SjS. As a result, 105 (9.2%) of the 1,139 patients with AQP4-IgG had suspected comorbid SjS; the remaining 1,034 (90.8%) had no suspected comorbid SjS. The demographic and clinical data based on the presence of suspected comorbid SjS are listed in Table 3. The female predominance was higher among those with suspected comorbid SjS, with a comparable rate for the general population of patients with SjS, irrespective of NMOSD. Moreover, the rate of OCB positivity was slightly higher in those with suspected SjS (15.4 vs. 7.5%, $p = 0.0293$). Other variables related to the severity and clinical manifestations of NMOSD were not different in patients with suspected comorbid SjS and those without SjS on univariate analysis. To visually assess the relationship between attack frequency and the presence of comorbid SjS, scatter plots and approximation lines depicting the presence of comorbid SjS are shown in Fig. 1. The attack frequency was irrespective of the presence of comorbid SjS during the early disease stages, but the frequency gradually increased for more than 5 years after the disease onset. Analysis of covariance (ANCOVA) for the AQP4-positive patients with disease duration of 5–20 years, after setting the disease duration as a covariate and the presence of comorbid SjS as the fixed factor, showed an increase in the attack frequency in NMOSD with comorbid SjS ($p = 0.0270$).

Discussion

In this study, the demographic backgrounds of patients with SjS and those with AQP4-IgG-positive NMOSD were similar. The female rates were 90–95% and the onset ages were mostly above 40 years of age for both diseases. The prevalence of comorbid SjS was higher in those with AQP4-IgG than in those without AQP4-IgG. These suggest that these two diseases have common mechanisms or share susceptibility factors for disease expression during their early stages. Moreover, this study demonstrated that the attack frequency in patients with AQP4-IgG-positive NMOSD increased with comorbid SjS. These suggest that the two diseases have common underlying mechanisms or susceptibility factors. Meanwhile, this study failed to show an increase in the latest EDSS scores in NMOSD patients with comorbid SjS compared with NMOSD patients without comorbid SjS, possibly because the collected EDSS scores were the latest during the acute or subacute phase. In NMOSD, the peak EDSS score during the acute phase is worse than the subsequent EDSS score in a later chronic phase after steroid pulse therapy. If the subsequent EDSS scores in the chronic phase were followed, those of the patients with comorbid SjS may have been worse than those of the patients without comorbid SjS. Consequently, the results were not sufficient to encourage the potentiation of treatments for relapse prevention in

Table 3 AQP4-IgG-positive patient data stratified by the comorbidity of Sjögren syndrome

	AQP4-IgG-positive with suspected SjS ($n = 105$)	AQP4-IgG-positive without SjS ($n = 1,034$)	p values
Male: Female	3 (2.9%): 102 (97.1%)	114 (11.0%): 920 (89.0%)	0.0062
Age at clinical onset	47.7 ± 16.7 years	46.3 ± 15.8 years	0.416
Age at titration	53.2 ± 14.3 years	52.8 ± 14.9 years	0.810
Disease duration at titration[a]	2 (1–7) years	3 (1–10) years	0.182
EDSS at titration (acute phase)[a]	5.0 (3.0–7.5)	5.0 (2.5–7.5)	0.315
OCB positivity (Pos: Neg)	10 (15.4%): 55 (84.6%)	44 (7.5%): 541 (92.5%)	0.0293
Cerebral lesions (Pos: Neg)	8 (38.1%): 13 (61.9%)	54 (26.6%): 149 (73.4%)	0.306
Brainstem lesions (Pos: Neg)	8 (38.1%): 13 (61.9%)	88 (43.3%): 115 (56.7%)	0.818
Previous times of neurological episodes[a]	2 (1–5)	3 (1–5)	0.426
(Optic neuritis[a])	(1 [0–2])	(1 [0–2])	0.458
(Acute myelitis[a])	(1[1–2])	(1[1–3])	0.150

AQP4-IgG anti-aquaporin-4 antibodies, *EDSS* Expanded Disability Status Scale, *OCB* oligoclonal bands, *SjS* Sjögren syndrome

[a]Median and interquartile range (i.e., 25–75 percentile range)

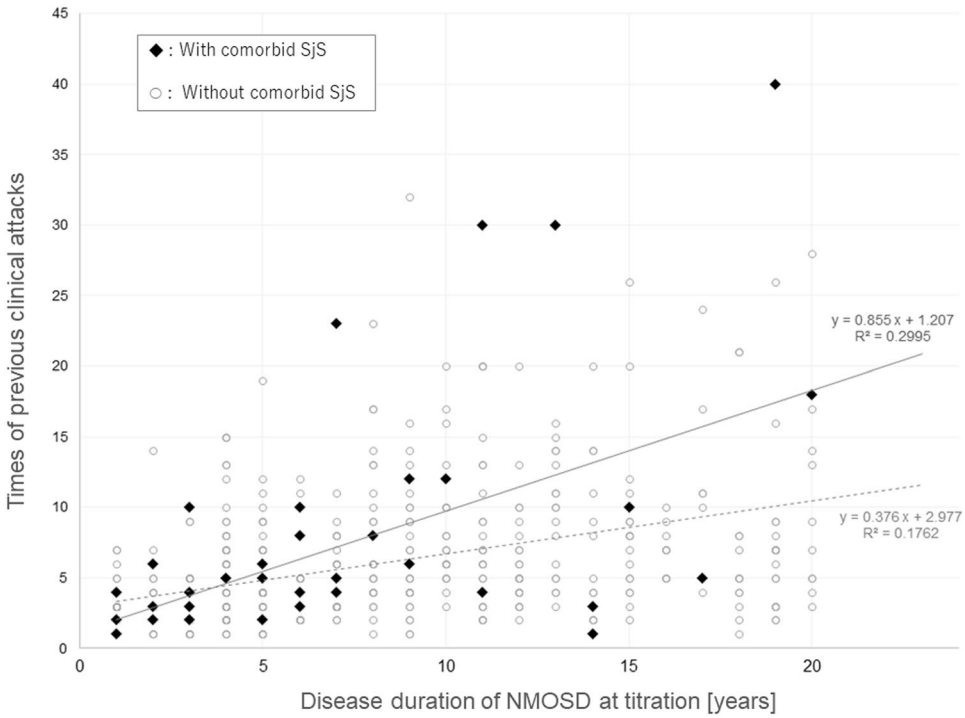

Fig. 1 Correlation between disease duration and NMOSD attack times stratified by the suspected coexistence of Sjögren syndrome. The attack frequency was not significantly affected by comorbid SjS during the early disease stages, but it gradually increased during later disease stages. NMOSD: neuromyelitis optica spectrum disorder; SjS: Sjögren syndrome

patients with NMOSD suspected of having comorbid SjS. Further longitudinal cohort studies will be needed to conclude on the necessity for strengthening relapse prevention treatments in NMOSD patients with comorbid SjS.

The severity and relapse rates of SjS and AQP4-IgG-positive NMOSD exacerbate during the period after delivery [12, 17, 18]. This implies that these diseases have mechanisms related to bodily fluid dynamics or serum estrogen levels. Previous reports have demonstrated that lower estrogen levels are associated with the exacerbation of SjS [15]. Additionally, an animal model of AQP4-IgG-positive NMOSD showed lower serum levels of estrogen [10, 34]. Furthermore, chloride imbalance between the serum and cerebrospinal fluid was observed during the acute phase of ON in AQP4-IgG-positive NMOSD [3, 5]. Considering these, the pathogenesis of NMOSD is considered to be multifactorial, involving several environmental or acquired (e.g., infections, changes in bodily hydrodynamics, childbirth) and hormonal factors. Similarly, the mechanism of SjS is also thought to be multifactorial, involving genetic, environmental, or hormonal predisposing factors [23, 28]. The multistep process elicits proportional, functional, and morphological changes in lymphocytes with persistent abnormal immune responses. These changes eventually cause lymphocytic infiltration (i.e., T cells, B cells, and dendritic cells) in the exocrine glands and the formation of ectopic lymphoid structures with germinal centers in non-lymphoid organs that may partially contribute to the perpetuation of abnormal immune responses in target organs [16, 22]. These immune cell infiltrations and ectopic lymphoid structures are also observed in patients with NMOSD [9, 21]. In total, both diseases may have partially similar pathophysiological mechanisms that subsequently cause the initiation and perpetuation of abnormal immune cell responses. This may account for the similar demographic backgrounds and the high rate of comorbidity of SjS and AQP4-IgG-positive NMOSD.

There are some limitations to this study. Almost all the enrolled subjects were of Asian ethnicity. As a result, the observed high rates of comorbidity of these two diseases may not be generalizable to Caucasian and African-American populations. Another limitation is that the diagnosis of SjS was not based on the latest diagnostic criteria by the 2016 American College of Rheumatology/European League Against Rheumatism (ACR-EULAR) [31]. Schirmer's test and the measurement of salivary flow with or without salivary gland biopsy were used to correctly diagnose patients with SjS. However, based on the observed higher rates of anti-SSA/Ro antibody positivity and dry eye/mouth symptoms in AQP4-IgG-positive than in AQP4-IgG-negative patients, a higher rate of comorbidity of SjS and AQP4-IgG-positive NMOSD than the expected comorbidity rate by chance is undoubted.

In conclusion, the rate of comorbidity of SjS and AQP4-IgG-positive NMOSD was estimated to be 10–20% at the diagnosis of NMOSD, which was higher than that expected by chance. More than 80% of patients with SjS who present with acute neurological episodes involving the central nervous system are positive for serum AQP4-IgG. The comorbidity of SjS and AQP4-IgG-positive NMOSD is more frequent in females, and it is associated with a higher relapse

frequency. AQP4-IgG-positive NMOSD and SjS share some susceptibility factors that result in more severe clinical manifestations when they coexist.

Compliance with ethical standards

Conflicts of interest None.

Ethics approval This study was approved by the Institutional Review Board of the Tohoku University School of Medicine. Written informed consent was obtained from all enrolled patients and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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