Association between Sjögren’s syndrome and neuromyelitis optica spectrum disorders: a systematic review and meta-analysis

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Abstract

Objectives: This meta-analysis was performed to determine the association between Sjögren's syndrome (SS) and neuromyelitis optica spectrum disorders (NMOSD).

Methods: A systematic review of all published English-language observational studies was performed. This included cross-sectional, prospective, retrospective cohort and case-control studies. Three databases (EMBASE, PubMed and Cochrane Library) up to June 2022 were searched for data collection. The study protocol was registered in PROSPERO (ID: CRD42022346810).

Results: From a total of 471 retrieved articles, 4 studies with 806 patients were eligible for this meta-analysis. 83 patients had SS with NMOSD, 52 had NMOSD without SS, and 671 had SS without NMOSD. NMOSD patients with SS had a significantly higher percentage of positive ANA (OR = 19.27, 95% CI: 4.66-79.66, p < 0.0001, I² = 0%), anti-SSA (OR = 131.84, 95% CI: 19.66-884.13, p = 0.0001, I² = 0%) and anti-SSB antibodies (OR = 34.92, 95% CI: 4.09-297.91, p = 0.001, I² = 0%) than NMOSD patients without SS. Significant differences were found for dry eyes (OR = 0.52, 95% CI: 0.28-0.94, p = 0.03, I² = 0%) and dry mouth (OR = 0.31, 95% CI: 0.17-0.59, p = 0.0003, I² = 4%) when SS patients with NMOSD were compared to those without NMOSD.

Conclusion: NMOSD patients with SS had a significantly higher percentage of positive results for ANA, anti-SSA and anti-SSB antibodies than those without SS. SS patients with NMOSD had less dry mouth and eyes than those without NMOSD, which may pose a significant diagnostic and therapeutic challenge in clinical practice.

Key Message

1. NMOSD may be a common comorbidity in patients with SS;
2. Anti-SSA/Ro antibodies are common in NMOSD patients and may be one of the poor prognostic factors;
3. SS patients with NMOSD have less dry mouth and eyes which may pose a significant diagnostic and therapeutic challenge in clinical practice.

1. Introduction

Sjögren's syndrome is a systemic autoimmune disease that mainly affects women, particularly those in their 50s. It can present as primary Sjögren's syndrome (pSS) or secondary to other underlying connective tissue diseases, most commonly rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE). Approximately 20%-25% of the patients also have neurological manifestations. SS is associated with a variety of central nervous system manifestations, sometimes involving the entire neuroaxis.

Neuromyelitis optica (NMO), classically described as optic neuritis and longitudinally extensive transverse myelitis, is associated with other autoimmune diseases in 10%-40% of the patients. However, NMO is now recognised as a spectrum disease (NMOSD) that can affect other regions of the CNS and encompasses more diverse clinical presentations due to the presence of a disease-specific autoantibody against aquaporin-4 (AQP4). NMOSD and SS continue to be intertwined both clinically and pathologically. In patients with SS and NMOSD, it is unclear whether NMOSD is merely the neurological manifestation of SS or whether the two diseases coexist as independent entities. Studies in adult patients have shown that transverse myelitis is a relatively common neurological manifestation of SS apart from optic neuritis. However, recent studies have suggested NMOSD as an independent disease coexisting with SS. Pathological analysis of a patient diagnosed with pSS and NMOSD showed active demyelination with oedematous changes rather than vasculitis, further supporting the notion that these two diseases coexist as independent entities.

To date, there has been no systematic reviews to have investigated the relationship between SS and NMOSD. Therefore, the aim of the present study was to systematically review the literature on the characteristics of SS and NMOSD to gain more insight into their clinical features.

2. Materials And Methods

2.1 Protocol registration

This review has been registered in PROSPERO (Registration ID: CRD42022346810), an international database that provides a platform for researchers to prospectively register systematic reviews in health and social care.

2.2 Data sources and search strategy

This systematic review included all published English-language observational studies, including cross-sectional, prospective, retrospective cohort and case-control studies, that evaluated the association between Sjögren's syndrome and NMOSD that was independent of serum AQP4-IgG from onset to June 2022. EMBASE, PubMed and the Cochrane Library were searched for eligible studies. The language of the literature was limited to English. The search strategies included the following terms and synonyms "Sjögren's syndrome", "sicca syndrome", "Sjögren's disease", "Sjögren's syndrome", "Sjogren's syndrome", "neuromyelitis optica (NMO) spectrum disorder", "Devic disease", "Devic syndrome", "myelopticoneuropathy", "myelopticoneuropathy", "neuromyelitis optica", "neuropatomegalitis" and "optic neuromyelitis". This trial was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

2.3 Study selection and data extraction
Studies were included according to the following criteria:

- they were published up to June 2022;
- they were classified as observational case-control studies (regardless of whether the study design was retrospective, cross-sectional, prospective, or combined);
- their main aims were to analyse the clinical manifestations between Sjögren's syndrome and NMOSD;
- their study population was patients with Sjögren's syndrome or NMOSD.

Exclusion criteria included: studies that included secondary Sjögren's syndrome or did not report the clinical features, conference abstracts and cases.

The retrieved articles were exported to Endnote 20 to exclude duplicate literature. Then, two authors (Zhihong Wu and Dong Wang) independently screened the remaining literature. The initial screening was performed by reviewing the titles and abstracts of the studies, and studies of interest were further assessed by reading the full text. Any discrepancies were resolved by discussion with a third author (Lirong Chen). The full text of potential studies was accessed to confirm inclusion. Two authors extracted data from the trials. Briefly, all relevant data from each study, including author, year of publication, study parameters, patient characteristics, detailed laboratory reports and outcomes, were extracted and summarised in tabular form.

2.4 Assessment of quality

The methodological quality of observational studies was assessed independently by two study investigators using the Newcastle-Ottawa scale, which scores studies in three categories: selection (four questions), comparability of study groups (two questions), and ascertainment of the outcome of interest (three questions). All questions with a score of 1, except for comparability of study groups (maximum 2 points), were scored separately. The quality assessment of all included studies is shown in Table 1.

2.5 Statistical analysis

Statistical analyses were performed using the Review Manager (Revman) v5.4 software. All effect measures were calculated with a 95% confidence interval. The Q statistic and $I^2$ (p < 0.10 was considered statistically significant) were used to quantify the heterogeneity of effect estimates across trials. The $I^2$ is the ratio of true heterogeneity to total observed variation, and values greater than 50% were considered significant heterogeneity.

3. Results

3.1 Study characteristics

The literature search strategy initially identified 471 potential studies. Of these, only 4 met the inclusion criteria. All studies were observational, of which 3 were retrospective studies and only one was a cross-sectional study. Figure 1 illustrates the entire selection process.

The four eligible studies included 806 participants, including 730 women, of whom 83 had SS with NMOSD, 52 had NMOSD without SS, and 671 had SS without NMOSD (those with a diagnosis of SS, probably with some neurological episodes that did not meet the diagnostic criteria for NMOSD). Two studies compared NMOSD with SS and without SS, while another two compared SS with and without NMOSD. Of the included studies, three were from China and one from the USA, and the characteristics of the four selected studies are shown in Table 1.

3.2 SS and NMOSD

As shown in Figure 2, two studies reported changes in the serum autoantibodies in NMOSD patients with and without SS, showing that NMOSD patients with SS had a significantly higher percentage of positive results for ANA (OR = 19.27, 95% CI: 4.66-79.66, p < 0.0001, $I^2 = 0$%), anti-SSA antibody (OR = 131.84, 95% CI: 19.66-884.13, p < 0.0001, $I^2 = 0$%) and anti-SSB antibody (OR = 34.92, 95% CI: 4.09-297.91, p = 0.001, $I^2 = 0$%) than NMOSD patients without SS. However, no significant differences were observed for serum anti-AQP4 antibody positivity (OR = 1.83, 95% CI: 0.57-5.86, p = 0.73, $I^2 = 0$%) and oligoclonal banding (OR = 2.81, 95% CI: 0.52-15.16, p = 0.23, $I^2 = 33$%). Furthermore, no correlation was observed between the presence or absence of SS in the affected part of the brain on MRI in NMOSD patients (OR = 0.65, 95% CI: 0.26-1.62, p = 0.36, $I^2 = 59$%).

As shown in Figure 3, two studies involving 831 patients with SS evaluated the effect of NMOSD and compared the clinical features of SS patients with and without NMOSD. Significant differences were found for dry eyes (OR = 0.52, 95% CI: 0.28-0.94, p = 0.03, $I^2 = 0$%) and dry mouth (OR = 0.31, 95% CI: 0.17-0.59, p = 0.0003, $I^2 = 4$%) between the two groups. They also reported changes in the serum autoantibodies in SS patients with or without NMOSD. However, no significant differences were observed in ANA (OR = 1.37, 95% CI: 0.63-2.99, p = 0.43, $I^2 = 0$%) and anti-SSB antibodies (OR = 0.57, 95% CI: 0.31-1.05, p = 0.07, $I^2 = 54$%). The percentage of positive anti-SSA antibodies showed a strong tendency towards statistical significance (OR = 2.70, 95% CI: 1.02-7.18, p = 0.05, $I^2 = 3$%).

3.3 Sensitivity analysis and publication bias

Given that the number of studies in this meta-analysis was <10, no visual inspection of funnel plots was performed as an indicator of publication bias, and as only two studies were analysed in each group, no sensitivity analysis was performed.
4. Discussion

To the best of our knowledge, this is the first meta-analysis to investigate the association between SS and NMOSD. SS is a systemic autoimmune disease that typically presents with xerophthalmia and xerostomia. Neurological involvement is a common comorbidity in patients with SS, particularly in the central nervous system (CNS). NMOSD is a disabling inflammatory autoimmune disease of the CNS characterised by the demyelination of the optic nerves and spinal cord. The coexistence of NMOSD with other autoimmune diseases has been widely recognised. The literature review by Sareh et al. showed that systemic lupus erythematosus (SLE), SS and autoimmune thyroid disease (AITD) were the most common associated diseases of NMOSD. Mendelian randomization (MR) analysis revealed a causal relationship between AITD, SLE and SS and NMOSD susceptibility, and Ontology (GO) enrichment analysis revealed that MHC class I-related biological processes and the interferon-gamma-mediated signalling pathways may be involved in the pathogenesis of NMOSD in association with AITD, SLE, and SS.

NMOSD has also been described as an autoimmune CNS astrocytopathy due to the production of pathogenic antibodies directed against aquaporin-4 (AQP4) expressed on the foot of the astrocytes. The prevalence of SS was found to be higher in AQP4 IgG positive patients than in AQP4 IgG negative patients, with a potential prevalence of 10%-20% at the diagnosis of AQP4-IgG-positive NMOSD. Pittock et al. reported an increased frequency of coexisting SS in patients with AQP4-IgG-positive NMOSD. However, another study suggested that anti-SSA/Ro antibodies may be a risk factor for relapse and poor EDSS performance in NMOSD patients, suggesting that the coexistence of anti-SSA/Ro antibodies in NMOSD patients may be one of the poor prognostic factors.

Our results showed that NMOSD patients with SS had a significantly higher percentage of positive results for ANA, anti-SSA and anti-SSB antibodies than those without SS. Regarding the relapse activity of NMOSD in patients with SS, Zhong et al. found that the annual relapse rate and the time from disease onset to EDSS scores of 4.0 and 6.0 were not significantly different in NMO patients with SS compared with those without SS. However, Akaishi et al. found that comorbid SjS had a higher relapse frequency in AQP4-IgG-positive patients. Gu et al. found that NMOSD without pSS had a high frequency of brain abnormalities, although other clinical features of NMOSD with and without pSS were similar.

When SS patients with NMOSD were compared with those without NMOSD, dry mouth and dry eyes were found to be less common in the former, suggesting that sicca symptoms may occur after the onset of myelitis. This finding is consistent with studies reporting initial neurological manifestations before the development of other features of SS. Similarly, Alhomoud et al. reported that up to 33% of patients with pSS and CNS involvement did not have sicca symptoms at the time of presentation, but eventually developed these symptoms over a 5-year follow-up period. This may represent a significant diagnostic and therapeutic challenge in the clinical practice. To date, the potential immune mechanisms in SS patients with NMOSD may be unclear. Qiao et al. found that serum clusterin and complement factor H (CFH) may play important roles in the pathogenesis and may be potential biomarkers for pSS patients with NMOSD.

There were several limitations to this study. Firstly, three of the included studies were from China, which may have caused some bias in the combined statistics. Secondly, three of the included studies were retrospective and one was cross-sectional. There were no high-quality RCT studies because the complication of NMOSD and SS is relatively rare. Finally, we observed that the diagnostic criteria for NMOSD were not consistent among the included studies. Prospective, multicentre and large-scale studies are needed to confirm the relationship between SS and NMOSD in the future.

To the best of our knowledge, this is the first meta-analysis to investigate the association between SS and NMOSD. Despite some limitations, the study provides a comprehensive summary of the current literature on this topic.

In conclusion, this study showed that NMOSD patients with SS had a significantly higher percentage of positive results for ANA, anti-SSA and anti-SSB antibodies than those without SS. When SS patients with NMOSD were compared with those without NMOSD, dry mouth and dry eyes were less common, which may lead to delayed diagnosis and treatment clinically, and particular attention should be paid to patients with SS who present with neurological symptoms, as this may suggest a diagnosis of NMOSD, which would alter the treatment plan and prognosis.

Declarations
Conflict of interest: The authors declare no conflict of interest.

Funding: There was no funding.

Data availability statement: There are no new data associated with this article.

References
## Tables

Table 1. The characteristics of the four extracted studies included in this systematic review

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<th>Items</th>
<th>Country</th>
<th>Year</th>
<th>Study type</th>
<th>Diagnosis criteria</th>
<th>Sample size</th>
<th>Age (SD, range or mean)</th>
<th>Gender(F/M)</th>
<th>Outcome</th>
<th>Quality assessment</th>
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<td>10</td>
<td>China</td>
<td>2016</td>
<td>Retrospective</td>
<td>SS: American-European Consensus Criteria(^{28}) NMO: the diagnostic criteria described by Wingerchuk et al.(^{29}).</td>
<td>65</td>
<td>SS(+)NMO:43.9 (26.6)</td>
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<td>SS(+)NMO: 36 6</td>
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<td>Retrospective</td>
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<td>pSS(+)NMO:46.6±14.67</td>
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<td>Clinical features, CSF index, serum index, MRI findings</td>
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<td>pSS(+)NMO:48.69±13.45</td>
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<td>America</td>
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<td>Cross-sectional</td>
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<td>NMOSD(+)SS:49.5</td>
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<td>Retrospective</td>
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<td>NMOSD(+)pSS:40.1</td>
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<td>NMOSD(+)pSS:49.7</td>
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Note: SS, Sjögren’s syndrome; pSS, primary Sjögren’s syndrome; NMO, neuromyelitis optica; NMOSD, Neuromyelitis Optica Spectrum Disorder.

## Figures
Figure 1

The flowchart of this study.
Figure 2

Meta-analysis of the presence of ANA (A), anti-SSA antibody (B), anti-SSB antibody (C), serum anti-AQP4 antibody positivity (D), oligoclonal banding (E) and abnormal brain MRI (F) between patients with NMOSD with or without SS. The size of squares is proportional to the weight of each study. The horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI; OR, odds ratio; SS, Sjögren’s syndrome; NMOSD, neuromyelitis optica spectrum disorder; ANA, antinuclear antibody.
Figure 3

Meta-analysis for the presence of dry eyes (A), dry mouth (B), ANA (C), anti-SSA antibody (D) and anti-SSB antibody (E) between patients with SS with or without NMOSD. The size of the squares is proportional to the weight of each study. The horizontal lines indicate the 95% CI of each study; diamond, the pooled estimate with 95% CI; OR, odds ratio; SS, Sjögren’s syndrome; NMOSD, neuromyelitis optica spectrum disorder; ANA, antinuclear antibody.

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