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SYSTEMATIC REVIEW

Overlap syndrome of anti-aquaporin 4 positive neuromyelitis optica spectrum disorder and primary Sjögren's syndrome: a systematic review of individual patient data

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Abstract

Central nervous system (CNS) involvement can occur in primary Sjögren's syndrome (pSS) due to co-existing neuromyelitis optica spectrum disorder (NMOSD) which has a highly relapsing course requiring indefinite immunosuppression, and if not diagnosed early, damage accrual occurs over time leading to permanent disability and morbidity. In this review, we describe and outline the clinical course and outcomes of anti-aquaporin 4 (AQP4) antibody seropositive NMOSD with pSS overlap cases. To investigate the co-existence of AQP4 + NMOSD with pSS, we conducted a review of individual patient data from case reports and case series found in major databases. The study extracted clinico-demographic features, imaging and laboratory profiles, treatment approaches, and outcomes of these patients. Inclusion criteria for the review required patients to have positivity for anti-AQP4 or NMO-IgG autoantibodies in the blood and/or cerebrospinal fluid (CSF) and exhibit at least one manifestation of both pSS and NMOSD. In this overlap between AQP4 + NMOSD and pSS, 44 patients were included of whom 41 (93.2%) were females. The mean age of pSS onset was 44.8 ± 18.4 years and NMOSD onset was 43.2 ± 19.8 years. In 20 (45.5%) patients, NMOSD preceded pSS onset, 13 (29.5%) NMOSD occurred after pSS onset, and 11 (25%) patients had a simultaneous presentation. 31 (70.5%) patients experienced acute transverse myelitis, 21 (47.7%) optic neuritis, 14 (31.8%) cerebral syndrome, 10 (22.7%) acute brainstem syndrome, 5 (11.4%) area postrema syndrome, and 2 (4.5%) diencephalic clinical syndromes. For the treatment of acute phase, 40 (90.9%) patients received intravenous methylprednisolone, 15 (34.1%) received plasma exchange, and 10 (22.7%) received intravenous immunoglobulin; and for the induction/maintenance therapy, 16 (36.4%) patients received cyclophosphamide, 6 (13.6%) received rituximab, 16 (36.4%) received azathioprine, and 10 (22.7%) received mycophenolate mofetil. Disease course was monophasic in 2 (4.5%) and relapsing in 27 (61.4%) patients. At median (IQR) follow-up duration of 2.4 (6) years, 39 (88.6%) patients showed improvement, 3 (6.8%) showed stabilization and 2 (4.5%) showed worsening of their NMOSD manifestations. In this overlap syndrome of AQP4 + NMOSD and pSS, patients have a neurologically disabling disorder that can mimic neurological manifestations of pSS, frequently occurs prior to the onset of pSS, has a relapsing course, responds well to immunosuppressants, and necessitates indefinite treatment. Collaborative multicentre studies are needed to clarify the natural history and outcomes of this rare overlap syndrome.

Keywords Neuromyelitis optica spectrum disorder · Primary Sjögren's syndrome · Aquaporin 4 · Systematic review

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Introduction

The prevalence of neurological manifestations in primary Sjögren's syndrome (pSS) varies between 10 and 70%, of which 2–25% have central nervous system (CNS) involvement [1, 2]. CNS demyelinating lesions in pSS can occur either due to the disease per se or due to co-existing; multiple sclerosis or neuromyelitis optica spectrum disorders (NMOSD) [3]. The reported prevalence of Sjögren's syndrome (SS) in NMOSD patients was estimated to be between 2 and 30%, which is a highly under-recognized association [4]. NMOSD is an autoimmune astrocytopathy in which patients classically presents with one or more of the six core clinical manifestations and associated with anti-aquaporin 4 (AQP4) antibody which has an important pathogenic, diagnostic and prognostic role [5, 6]. Anti-AQP4 antibody can penetrate the blood–brain barrier (BBB) and react with AQP4 transmembrane receptor located at the astrocytic end-feet. This initiates an immune response which mediates demyelinating lesions, inflammatory cell infiltration, and hyaline degeneration of blood vessels; affecting various brain regions which vary upon the expression of AQP4 receptors, resulting in mosaic clinical presentations [6, 7].

To understand co-existence of SS and NMOSD, some researchers considered that this may be related to the AQP epitope diffusion hypothesis [8]. As AQPs have been detected in the lacrimal and salivary glands of which AQP5 has important role in saliva and tear secretion, and its expression diminished in lacrimal gland of SS patients [9, 10]. AQP4 and AQP5 are structurally homologues with 50% of common genetic sequence [11]. Due to a likely common target, anti-AQP4 antibody binding to both AQP4 and AQP5 in multiple sites of exocrine glands, brain, and other sites. Furthermore, anti-SSA antibody in SS patients react with SSA-antigens present in vascular endothelial cells causing immune-mediated inflammatory reactions destroying the BBB, which is conducive to anti-AQP4 antibody entering the CNS [12]. The resulting subsequent reactions may lead to the co-existence of SS and NMOSD, although the internal mechanism between SS and NMOSD remains to be elucidated.

Diagnosing AQP4 + NMOSD in pSS is crucial as it has a highly relapsing course requiring indefinite immunosuppression, and if not diagnosed early, damage accrual occurs over time leading to permanent disability and morbidity [13]. To date, there has been no systematic reviews that have investigated the relationship between AQP4 + NMOSD with pSS. Therefore, the aim of the present study was to systematically review literature on the overlap syndrome of AQP4 + NMOSD with pSS reported in the form of case reports and case series. And further analyze individual patient data to gain more insight into their clinical course, imaging findings, laboratory parameters, treatment approaches, and outcomes which would equip practitioners to make more informed decisions and decide on patient's management.

Methods

The current systematic review was conducted and is reported in accordance with the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [14].

Eligibility criteria

We included case reports and case series that presented individual patient data on the co-occurrence of primary Sjögren's syndrome (pSS) and anti-aquaporin-4 autoantibody positive NMOSD (AQP4 + NMOSD). To be included in the study, patients were required to exhibit at least one clinical feature of both pSS and NMOSD. We included cases where patients tested positive for antibodies to AQP4 and/or NMO in either their serum or cerebrospinal fluid (CSF). If anti-AQP4 tests were not available and anti-NMO-IgG tests were positive, these cases were also included.

Data sources and search strategy

After preliminary search in PubMed did not identify any published systematic review on pSS with AQP4 + NMOSD, final search strategy was performed in the four databases: PubMed, EMBASE, Scopus, and Ovid MEDLINE to identify the case reports and case series. The keywords and search phrases are tabulated in the supplementary material (Table S1). The search was confined to the articles published in English language, from the inception of database till June, 2022. Additional articles from the relevant references of the included articles were also searched. The initial search included both pSS and systemic lupus erythematosus (SLE). Only the results of pSS with NMOSD are presented here.

Study selection

Independent search was done by both CBP and CRK in the databases as mentioned above and the articles were imported to Mendeley Desktop (v 1.19.8) citation software tool. Duplicates were removed using it, and additional duplicates including conference abstracts later published as full-length articles were removed manually. Case reports and case series with individual patient data were included. Any discrepancies in the search and inclusion of the articles into the final analysis were discussed with AS and DPM as the adjudicators and resolved by consensus.

Quality assessment

The overall quality of included case reports and case series were appraised using standard of Joanna Briggs Institute (JBI) checklist for critical appraisal [15].

Data collection

A proforma for data collection of the relevant outcome variables was made by reviewing relevant articles a priori. Data extracted included demographic and clinical features, imaging findings, laboratory parameters, treatment, and outcome of patients. After entering all the data, the final analysis was executed.

Statistical analysis

Discrete categorical data were represented in form of either a number or a percentage. For continuous data with normal distribution, mean ± SD and, for skewed data, median with IQR (interquartile range) were calculated. The normality of continuous data was checked by the Kolmogorov–Smirnov (KS) test for normality. All the descriptive analysis was performed using IBM SPSS STATISTICS (Version 23.0).

Results

Search results are detailed in Fig. 1 derived from the PRISMA flowchart. After screening and eligibility assessment as per criteria detailed previously, 72 articles (35 article with 46 patients of SLE with NMOSD and 37 article with 44 patients of pSS with NMOSD) were included in the analysis. Results of pSS with NMOSD are presented here. The JBI checklist for appraisal of the individual cases is provided in the supplementary material (Table S2).

Clinical characteristics

A total of 44 patients (Table 1) were included with a mean age of 47.3 ± 17.7 years; 41 (93.2%) were females. The mean age of pSS onset was 44.8 ± 18.4 years and NMOSD onset was 43.2 ± 19.8 years. In 20 (45.5%) patients, first neurological event of NMOSD preceded pSS onset by 3.5 (IQR—8.3) years; in 13 (29.5%) patients, first neurological event of NMOSD occurred after pSS onset by 2 (IQR—7.3) years; and in 11 (25%) patients had a simultaneous presentation. In pSS, dryness was the predominant symptom, with oral dryness being the most common (63.6%), whereas in the core clinical presentation of NMOSD, acute TM was the most commonly experienced by 31 (70.5%) patients; followed by ON in 21 (47.7%), CS in 14 (31.8%), ABC in 10

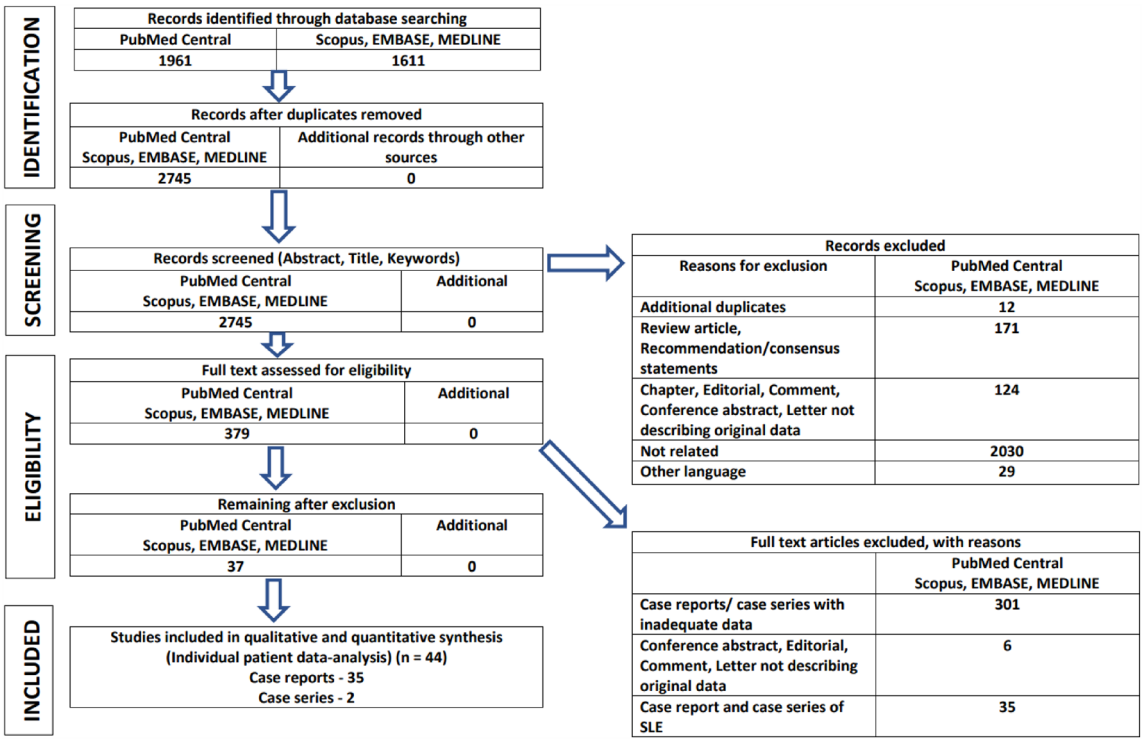

Fig. 1 PRISMA flowchart depicting the study identification, screening, assessment of eligibility, and final inclusion

Table 1 Clinical characteristics of pSS with NMOSD

	Primary Sjögren's syndrome (pSS) ($n=44$)
Female, *n* (%)	41 (93.2)
Age at pSS diagnosis (years), mean ± SD	44.8 (18.4)
Age at NMOSD diagnosis (years), mean ± SD	43.2 (19.8)
NMOSD diagnosis, *n* (%)	
Concurrent with pSS diagnosis	11 (25)
Prior to pSS diagnosis	20 (45.5)
After pSS diagnosis	13 (29.5)
NMOSD diagnosis duration (years), median (IQR)	
Prior to pSS diagnosis	3.5 (8.3)
After pSS diagnosis	2 (7.3)
Clinical manifestation, *n* (%)	
Oral sicca	28 (63.6)
Ocular sicca	22 (50)
Articular	6 (13.6)
Renal	6 (13.6)
Pulmonary	2 (4.5)
Neurological	4 (9.1)
Diagnosis of APS ever	1 (2.3)
NMOSD core clinical presentation, *n* (%)	
Transverse myelitis (TM)	31 (70.5)
Optic neuritis (ON)	21 (47.7)
Area postrema syndrome (APS)	5 (11.4)
Acute brainstem syndrome (ABS)	10 (22.7)
Diencephalic clinical syndrome (DCS)	2 (4.5)
Cerebral syndrome (CS)	14 (31.8)

(22.7%), APS in 5 (11.4%), and in DCS 2 (4.5%) patients. Less than a quarter of patients had other features of pSS as outlined in Table 1.

Laboratory findings

Antinuclear antibodies (ANA) were found in 30 (68.2%) patients. All the patients had anti-Ro/SSA positivity and 27 (61.4%) patients were positive for anti-La/SSB. Hypocomplementemia was seen in 50% of the patients. NMO-IgG/AQP4-IgG autoantibodies were positive in all the patients of which; 7 (15.9%) patients showed positive NMO-IgG, 35 (79.5%) patients with positive serum AQP4-IgG, and 2 (4.5%) patients with positive cerebrospinal fluid (CSF) AQP4-IgG. CSF analysis was available in 30 patients with 60% had pleocytosis. In CSF, 92.3% patients had lymphocytic predominant cells, 59.3% had high proteins, 15.3% had low glucose, and 18.2% had Oligoclonal bands (OCBs). In 84% of patient had positive Schirmer test, 88.9% had positive salivary scintigraphy and 94.7% had positive salivary gland biopsy (Table 2).

Table 2 Laboratory findings of pSS with NMOSD

	Primary Sjögren's syndrome (pSS) ($n=44$)
Positive serology, *n* (%)	
ANA	30 (68.2)
Extractable nuclear antigens (ENA)[a]	
Anti-Ro/SSA	44/44 (100)
Anti-Ro52	4/4 (100)
Anti-La/SSB	27/32 (61.4)
APS profile[a]	
Anticardiolipin (IgM/IgG)	1/15 (6.7)
Anti-beta2-glycoprotein-1 (IgM/IgG)	0/10 (0)
Lupus anticoagulant (LAC)	0/12 (0)
Anti-NMO-IgG/AQP4 IgG	
Anti-NMO-IgG	7 (15.9)
Anti-AQP4 IgG	
Serum	35 (79.5)
CSF	2 (4.5)
Hypocomplementemia[b]	5/10 (50)
Cerebrospinal fluids (CSF) analysis[a]	
White blood cells	
Normocellular (≤ 5 cells/hpf)	12/30 (40)
Cellular (> 5 cells/hpf)	18/30 (60)
Predominant cells	
Lymphocytic	12/13 (92.3)
Neutrophilic	1/13 (7.7)
Elevated proteins	16/27 (59.3)
Hypoglycorrhachia	2/13 (15.3)
OCBs	4/22 (18.2)
Positive Schirmer test[a]	21/25 (84)
Positive salivary scintigraphy[a]	8/9 (88.9)
Positive salivary gland biopsy[a]	18/19 (94.7)

[a] *n/N* (%)

[b] Hypocomplementemia includes—low C3 and/ C4

Imaging findings

In the imaging findings (Table 3) of pSS with NMOSD patients, spinal MRI was available in all the 44 patients of which 32 (72.7%) patients had longitudinally extensive transverse myelitis (LETM) and 2 (4.5%) patients presented with short-segment extensive transverse myelitis (STM). The most common site of spinal cord involvement was the thoracic in 14 (45.2%) patients followed by the cervicothoracic in 12 (38.7%), cervical in 4 (12.9%), and conus medullaris to cauda equina in 1 (3.2%) patient. Brain MRI was available for 38 (86.4%) patients of which 31 (70.5%) patients had abnormal MRI findings. Of this abnormal brain MRI finding, 11 (35.5%) patients had optic nerve involvement, 4 (12.9%) with dorsal medulla/area postrema, 11 (35.5%) with

Table 3 Imaging findings of pSS with NMOSD

	Primary Sjögren's syndrome (pSS) ($n=44$)
MRI lesions, *n* (%)	
Spinal lesions	
LETM[a]	32 (72.7)
STM[b]	2 (4.5)
Cervical[c]	4 /31 (12.9)
Thoracic[c]	14/31 (45.2)
Cervicothoracic[c]	12/31 (38.7)
Whole spine[c]	1/31 (3.2)
Brain lesions[c]	
Optic nerve	11/31 (35.5)
Area postrema/dorsal medulla	4/31 (12.9)
Brainstem	11/31 (35.5)
Diencephalon	6/31 (19.4)
Cerebral	17/31 (54.8)
Diffuse white matter	12/31 (38.7)
Corpus callosum	4/31 (12.9)
Corticospinal tract	1/31 (3.2)

[a]*LETM* longitudinally extensive transverse myelitis (≥3 contiguous vertebral involvement)

[b]*STM* short-segment transverse myelitis (<3 contiguous vertebral involvement)

[c]*n/N* (%)

Table 4 Treatment and outcomes of pSS with NMOSD

	Primary Sjögren's syndrome (pSS) ($n=44$)
Treatment ever, *n* (%)	
Glucocorticoids (oral/IV-MPS)	44 (100)
Oral high dose	38 (86.4)
IV-MPS	40 (90.9)
IVIG	10 (22.7)
PLEX	15 (34.1)
Cyclophosphamide pulse	16 (36.4)
Rituximab	6 (13.6)
Azathioprine	16 (36.4)
MMF	10 (22.7)
Follow-up	
Duration of follow-up (years), median (IQR)	2.4 (6)
Disease course	
Monophasic[a], *n* (%)	2 (4.5)
Relapsing, *n* (%)	27 (61.4)
Relapse rate, median (range)	3 (1–9)
Last visit status, *n* (%)	
Improvement	39 (88.6)
Stabilization	3 (6.8)
Worsen	2 (4.5)
Dead	3 (6.8)

[a]Monophasic were defined if no relapses occurred at least after 5 years of follow-up

brainstem, 6 (19.4%) with diencephalon, and 17 (54.8%) with cerebral (12 with diffuse white matter, 4 with corpus callosal, and 1 with corticospinal tract) involvement.

Treatment and outcomes

For the treatment (Table 4) of NMO-SD in pSS patients, 40 (90.9%) patients received intravenous methylprednisolone (IV-MP), 15 (34.1%) received plasma exchange (PLEX), and 10 (22.7%) received intravenous immunoglobulin (IVIG) for the acute neurological attacks. High doses of oral prednisone were used in 38 (86.4%) patients for induction of remission followed by gradual tapering. Patients also received one or more immunosuppressants during the course of their disease for induction and/or maintenance therapy which included: cyclophosphamide (CYC) in 16 (36.4%), rituximab (RTX) in 6 (13.6%), azathioprine (AZA) in 16 (36.4%), and mycophenolate mofetil (MMF) in 10 (22.7%) patients.

The total median (IQR) follow-up duration was 2.4 (6) years. The disease course was monophasic in 2 (4.5%) and relapsing in 27 (61.4%) patients with median (range) relapse rate of 3 (1–9) per patient. At last follow-up visit, 39 (88.6%) patients showed improvement, 3 (6.8%) showed stabilization, and 2 (4.5%) showed worsening of their NMOSD manifestations. Three patents died, one was due to worsening of NMOSD manifestation with respiratory failure and other due to invasive colonic adenocarcinoma with systemic metastasis; and in one patient, cause was not specified.

Discussion

We have described the features of AQP4 positive NMOSD in pSS patients by performing individual patient data analysis, as it allowed to homogenously include patients who had clinical features of both pSS and AQP4 + NMOSD. Autoantibody positivity without clinical features of pSS is well known in NMOSD, and whether they evolve to clinical pSS remains an area of uncertainty due to sparsity of data and short-term follow-up [16].

In our study, 93.2% of the patients were females, and the age of diagnosis of NMOSD and pSS was in the fourth decade. This is in near concordance with the female: male ratio of 9:1 reported in seropositive NMOSD and 7.6:1 in pSS with NMOSD reported by the previous studies [17, 18]. The mean age of pSS with NMOSD is in the fourth decade compared to pSS without NMOSD is in fifth decade as reported in the literature [17, 18]. We found nearly half of the patients (45.5%) had NMOSD diagnosis prior to pSS. The median

onset of NMOSD was 3.5 years before and 2 years after the pSS diagnosis, this interval period needs to alert the clinician whenever a new onset neurological symptom occur in pSS patients, as the diagnosis of NMOSD portends a relapsing course. Dry eyes and mouth are seen in 70–95% and 84–95% of the pSS without NMOSD [19, 20]; whereas we found lesser proportions of the patients (50% and 63.2%) having sicca symptoms. Similarly, the lesser prevalence of sicca (ocular—53.5% and oral—60.5%) were also noted in another case series of 43 patients of pSS with NMOSD [18]. This difference may arise due to the short follow-up of the patients, as in one study [21] noted that one-third of neurological dominant pSS patients had no sicca symptoms at onset and these may eventually develop over the next 5 years.

Myelitis was seen in 77.3% (34/44) of the patients, with LETM (72.7%) being most common. Myelopathy in pSS is seen in about 1% of the patients [22], which can be due to Sjogren syndrome myelopathy (SSM), multiple sclerosis (MS), NMOSD overlap, or myelin oligodendrocyte glycoprotein antibody-associated myelitis. Overall, in NMOSD, commonly the cervical and upper thoracic followed by lower thoracic and lumbar involvement is seen [23]. Though we found cervical (12.9%), cervicodorsal (38.7%), and dorsal (45.2%) region commonly affected, none had lumbar involvement. In another case series of NMOSD, most commonly cervical cord (63%) involvement was seen followed by dorsal and cervicodorsal [24]. In a Chinese cohort of 43 patients, over 60% of the patients had cervical and dorsal involvement. These differences may be reflected as we did not include the cervicodorsal cases in the only cervical category, leading to overestimation of cervical cord involvement. However, Chee CG et al. [25] in AQP4 positive NMOSD have noted cervical involvement at a lesser frequency (33%), and none had lumbar involvement.

All the patients had anti-Ro positivity and 61.4% were positive for anti-La. Hypocomplementemia was seen in 50% of the patients (5/10), whereas in pSS, it ranges from 4 to 21.7% [19, 20, 26]. The presence of hypocomplementemia in patients with neurological manifestations may perhaps be due to the co-existing NMOSD. We found a lymphocyte dominant (92.3%) cellular CSF picture in 60% (18 out of 30) of the patients, and OCBs were present in 4 of the 22 patients (18.2%) reported. In contrast, Wingerchuk et al. [27] reported that, in NMOSD, 73–82% had cellular CSF with neutrophilic (50–60%) dominant pleocytosis. Another study of Qiao et al. [18] reported lymphocytosis and OCBs in 29.4% and 35.3% of the 34 pSS patients with NMOSD who underwent CSF analysis. A lymphocyte dominant CSF in NMOSD may point toward a co-existing pSS.

NMOSD attacks are often severe, difficult to treat, and leave residual deficits. There is not high-quality study evaluating treatment strategies in overlap syndrome of NMOSD and pSS, so treatment strategies are based on extrapolation from studies in NMOSD. For acute attacks, IV-MP or PLEX followed by high-dose oral steroids are effective treatments [28]. Steroid-sparing agents like RTX, MMF, and AZA are preferred as the first line for preventing relapses [29–31]. In our study, all the reported cases (100%) had used corticosteroids (oral and/or IV steroids). IV-MP was used in 90.9% of patients and fewer than 10% patients had used only oral steroids. PLEX was used in 34.1% of the reported patients, which is commonly deployed in steroid refractory cases. CYC (36.4%) and AZA (36.4%) were the most common steroid sparing agents used followed by MMF (22.7%) and RTX (13.6%). In an observational study of NMOSD patients by Xu et al. [32]; AZA, MMF, and CYC were all effective in decreasing relapses, but only AZA and MMF had a significant impact in reduction of Expanded Disability Status Scale [EDSS] scores. However, one study of NMOSD with connective tissue disease, CYC, outperformed AZA in reducing relapse risk [33]. A network meta-analysis which aimed to compare and rank the effectiveness and tolerability of all preventive therapies for NMOSD reported, RTX was better than AZA in terms of efficacy; and MMF was better tolerated followed by RTX, AZA, and CYC was wort tolerated [34]. EULAR guidelines recommend treatment of CNS involvement due to NMOSD in pSS with CYC as the second line followed by RTX as rescue therapy [35]. RTX targets the B-cell specifically, which underpins the basic pathophysiology of pSS and NMOSD, has shown efficacy in RIN-1 study [29]. Even in the patients who did not have reduction in AQP4 titres and in those with AQP4 negative, RTX was able to prevent relapses, which points that the underlying humoral immune dysregulation is strongly implicated. And also, the humoral dominant immune dysregulation in pSS, RTX may be a better option in this overlapping autoimmune disorder.

Although improvements were seen in the majority (88.6%) of patients, the short follow-up durations make it difficult to accurately assess neurological outcomes, which require long-term follow-up. According to the IPND criteria, monophasic nature of disease is defined prospectively after at least 5 years of relapse free period [5]. Only two cases (4.5%) had a monophasic course of disease after a follow-up of 6.3 years. True monophasic pattern is seen in 10–20% of the NMOSD cohorts [36]. One retrospective case series of 289 Chinese patients, none had monophasic pattern with a mean follow-up duration of 86.9 ± 93.8 months [37]. A study done by Wingerchuk et al. [13] showed that history of autoimmune disease portended a nearly fourfold increased relapse risk. This suggests that less than 5% of the pSS with NMOSD truly have a monophasic course, which slants their course toward a relapsing disease. However, it needs to be emphasized that a fraction of the patients may experience relapse beyond

5 years, up to 2 decades later after the sentinel attack, and the current recommendation from retrospective data is to continue treatment indefinitely [38, 39].

Our study has some limitations. First, due to inclusion of case reports and two case series, which were heterogenous, particularly in terms of the duration of follow-up and reporting of outcome measures; and also, with an inherited selection bias in terms of selective reporting of outcomes. To wrinkle out this issue, individual patient data were extracted to maintain homogeneity of observations. However, the overall quality of evidence remains low, and additional data from a more extensive range of studies are necessary to conduct a more detailed analysis. Second, we have studied the AQP4 + subset of NMOSD only, and have not included AQP4 negative NMOSD, and there may be cases of these subset with pSS overlap which can act as comparison group and enhance our understanding of their underlying pathophysiology. And at last, the outcomes in our review could not be assessed by the type of immunosuppressant used due to the inconsistent regimens, short follow-up of certain patients, and the heterogeneity in reporting of the outcome variables. The standard outcome measure used in demyelinating disease EDSS at 6 months was seldom reported.

Despite these shortcomings, strength of our study is that, for the first time, we have systematically reviewed this uncommon and rare overlap syndrome and described the salient features with a comprehensive summary of the current literature on this topic. We have included the cases after proper quality assessment using the JBI checklist. This review will help clinicians, such as rheumatologist, neurologist, ophthalmologist, and other specialities dealing with such patients to be more sensitized about the mosaic clinical presentation of this overlap syndrome and manage them with appropriate immunosuppressive therapy.

In summary, pSS patients with clinical features of NMOSD should be always tested for AQP4-IgG autoantibodies, as results will impact treatment decisions. As NMOSD co-existing with pSS is rare, collaborative multicentre studies are needed to clarify the exact natural history and outcomes of this overlap syndrome.

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Author contributions CBP, CRK, DPM, and AS contributed to the conception and design of the study. CBP, CRK, GN, VS, DPM, DA, and AS contributed to critical inputs in design and acquisition of data. CBP, CRK, VS, and DPM analyzed and interpreted the data. CBP, CRK, GN, and AS drafted the first manuscript and all the other authors have done a critical review of the content and approved the final version submitted. All the co-authors fulfill the ICMJE 4 authorship criteria. All authors take full responsibility for the integrity and accuracy of all aspects of the work, and no artificial intelligence support was employed.

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Data availability All data relevant to the study are included in the article. Supplementary material contains keywords and search phrases; and Joanna Briggs Institute checklist of included articles. Additional data extracted from database will be made available on request.

Declarations

Conflict of interest None of the authors have any conflict of interest.

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