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REVIEW ARTICLE

Primary Sjögren syndrome-related peripheral neuropathy: A systematic review and meta-analysis

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Abstract

Background and purpose: Primary Sjögren syndrome (pSS) is a chronic, systemic, autoimmune disorder characterized by lymphocytic infiltrates of the exocrine organs, leading to sicca symptoms and parotid enlargement. pSS has been linked to various neurological manifestations, including peripheral neuropathy (PN). We aimed to provide a comprehensive analysis of the currently available evidence regarding pSS-related PN.

Methods: A literature search in the PubMed database was performed, and 49 papers were eligible to be included in this systematic review and meta-analysis.

Results: The pooled prevalence of PN in pSS is estimated to be 15.0% (95% confidence interval = 10.7%–20.7%). The mean age of pSS patients at PN diagnosis is 59 years. Among the patients with pSS and PN, 83% are females. Neuropathic symptoms usually precede or lead to the pSS diagnosis at a 2:1 ratio in patients with pSS-related PN. The commonest type of pSS-related PN is distal axonal polyneuropathy (80% of patients with pSS-related PN), followed by sensory ganglionopathy. Peripheral and cranial mononeuropathies—particularly trigeminal—are also frequent. Risk factors for developing PN include increasing age and presence of vasculitis. Immune-mediated pathogenetic mechanisms are discussed. Glucocorticoids are the most commonly used treatment option for managing pSS-related PN, when associated with vasculitis, followed by the use of intravenous immunoglobulin.

Conclusions: PN is very common in pSS patients. Evidence on long-term prognosis of PN in pSS is limited, and further research is needed. Research into the use of immunosuppressive medication in nonvasculitic neuropathies in the context of pSS merits further consideration.

KEYWORDS
neurological manifestations, peripheral neuropathy, prevalence, primary Sjögren syndrome (pSS), small fiber neuropathy

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INTRODUCTION

Sjögren syndrome (SS) is a chronic, systemic, autoimmune disorder characterized by lymphocytic infiltrates of the exocrine organs, including the salivary, lacrimal, and parotid glands, leading to sicca symptoms and parotid enlargement [1, 2]. The prevalence of SS in the general population varies from 0.1% to 3% [3]. Women are mostly affected (female to male ratio = 9:1), with the majority of cases being diagnosed in the 5th or 6th decade of life [4–6]. SS can occur as a primary condition or secondary to other rheumatic diseases such as rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis.

Primary SS (pSS) is marked by immunologic abnormalities of the innate and adaptive immune system resulting in B-cell stimulation, production of autoantibodies, and inflammation of salivary glands and multiple other organs [7]. Lymphocytic infiltration of exocrine and extraglandular organs is the principal histopathologic feature of the disease [7].

Patients with pSS present with a wide range of clinical manifestations, the most common of which are symptoms linked to exocrine gland dysfunction, such as dry eyes (keratoconjunctivitis sicca), dry mouth, fatigue, and joint pain [8]. Neurological involvement of both the central nervous system (CNS) and the peripheral nervous system (PNS) is frequently observed in pSS patients and may precede the diagnosis of pSS, posing a diagnostic challenge [9, 10]. One of the commonest, if not the most common, CNS manifestation of pSS is cerebellar ataxia, affecting 1.5% of this population [11].

The term peripheral neuropathy (PN) refers to disorders of the PNS, which initially manifest—in the majority of cases—with sensory symptoms such as tingling, pins and needles, numbness, tightness, burning, and pain. Based on the electrophysiological assessments and the pathological findings (e.g., nerve and skin biopsy), PN can be broadly classified into pure small fiber neuropathy (SFN), where unmyelinated C and thinly myelinated Aδ fibers are affected, and large fiber neuropathy, where myelinated Aα and Aβ fibers are affected along with a variable degree of small fiber dysfunction. With regard to PNS involvement, several studies have attempted to assess PN in pSS patients; however, to our knowledge, no systematic review and meta-analysis study has been conducted.

Therefore, the aim of this systematic review and meta-analysis is to characterize and comprehensively describe pSS-related PN.

METHODS

Protocol registration

This review was registered in PROSPERO, an international database of prospectively registered systematic reviews in health and social care. The registration number for this review is CRD42021229166.

Literature search strategy

A systematic literature search in the PubMed database was performed on 22 December 2021 using two Medical Subject Headings terms. Term A was "neuropathy OR polyneuropathy OR mononeuropathy OR mononeuritis OR ganglionopathy OR neuronopathy OR polyradiculoneuropathy OR CIDP"; term B was "Sjogren OR Sjögren OR pSS". Human subjects, English language, and full-text filters were applied. The reference lists of eligible papers and relevant reviews were also meticulously searched to include further studies reporting on neuropathy attributable to pSS.

Inclusion and exclusion criteria and screening process

Articles eligible to be included in this review were required to meet the following criteria: (i) papers described patients with pSS diagnosed based on established criteria: (ii) papers studied PN attributable to pSS, including mononeuropathies and polyneuropathies; (iii) diagnosis of PN was made based on objective clinical signs and was confirmed electrophysiologically; (iv) human subjects were involved; and (v) the article was written in English.

The exclusion criteria were (i) presence of comorbidities that could be associated with PN, (ii) case series/cohorts with fewer than 10 patients diagnosed with pSS, (iii) duplicated papers or papers referring to the same patient population, (iv) nonoriginal articles (review, medical hypothesis, letter to the editor, etc.), and (v) articles where full text was not available.

All article titles and abstracts were screened by three authors in a blinded fashion. Those found not complying with the inclusion criteria were removed, and any controversies were resolved by consensus through discussion, in which the abstracts were reviewed. A fourth author verified the eligibility of included studies.

This study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [12].

Data collection process

Three authors extracted data in a structured coding scheme using Excel to record type of study, population size, gender and age distribution, first diagnosis, type of PN, clinical manifestations at first diagnosis, mean age at each diagnosis, means of diagnosis for each condition, electrophysiological findings, means of treatment, and response to treatment.

Synthesis of results

This study used aggregate data where possible. Statistical calculation of pooled proportions was conducted in R language using the default

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settings of the "meta" package and the "metaprop" function with a random effects model [13]. Forest plots are presented for each meta-analysis along with the I^2 statistic, which is used to evaluate heterogeneity [14]. This statistic suggests whether chance or study heterogeneity is responsible for the variation. Negative I^2 values are put equal to zero, and values range between 0% and 100% [14]. Heterogeneity can be quantified as low, moderate, and high, with upper limits of 25%, 50%, and 75% for I^2, respectively [14]. Often, data did not lend itself to meta-analysis, and therefore a narrative approach was taken.

Nomenclature

Across the included studies, different terms have been used to describe the various clinical and neurophysiological types of PN in pSS patients. Three authors carefully examined all papers to distinguish and group the various types as discussed below. Controversies were resolved by consensus through discussion.

With the term "large fiber neuropathy," we considered polyneuropathy that was diagnosed and confirmed with nerve conduction studies, which showed clear axonal or demyelinating damage. As axonal, we considered polyneuropathies that were reported as axonal by the authors of the study and/or where the sensory nerve action potentials and/or the compound muscle action potentials were attenuated in amplitude. As demyelinating, we considered polyneuropathies that were reported as such by the authors of the study.

Various terms have been used to describe the phenotypes of the neuropathies, including the terms "glove and stocking" distribution, distal, proximal, symmetrical, asymmetrical, length-dependent, and non-length-dependent. When enough information was available, we distinguished distal/length-dependent and symmetrical neuropathies from non-length-dependent/asymmetrical neuropathies. Some papers used the terms ganglionopathy/neuronopathy/ganglionitis/pure sensory mononeuritis multiplex and sensory ataxic neuropathy to describe sensory large fiber neuropathies affecting the cell bodies of the sensory neurons located in the dorsal root ganglia; for the purposes of this review, these were grouped together under the term "ganglionopathy." Such neuropathies are characterized by a pure sensory and usually asymmetrical involvement, and certain clinical and electrophysiological criteria must be met [15, 16]. The terms mononeuritis multiplex/multiple mononeuropathy and mononeuropathia multiplex have been used to describe sensorimotor large fiber neuropathies that are asymmetric and usually secondary to vasculitis; for the purposes of this review, these were grouped together under the term "mononeuritis multiplex."

All terms described above have been extracted for each included study and are available in Appendix S1.

Quality assessment of included studies

We evaluated the methodological quality of prevalence studies using a checklist adapted from Hoy et al. [17]. It consists of nine questions that assess the representativeness of the sample, the sampling technique, the response rate, the data collection method, the measurement tools, the case definitions, and the statistical reporting. Each checked question was scored either as "0" or "1" corresponding respectively to "low risk of bias" and "high risk of bias." The total score ranged from 0 to 9, with the overall score categorized as follows: 7–9, "high risk of bias"; 4–6, "moderate risk"; and 0–3, "low risk" [18]. The quality assessment is available in Appendix S1.

Compliance with ethical guidelines

The article is based on previously conducted studies. Thus, there were no ethical concerns in respect to this study, nor was approval of the research protocol from an ethics committee required.

RESULTS

The study selection process is illustrated in the PRISMA chart (Figure 1). All of the 49 studies that met our inclusion criteria [19–67] were of an observational nature. The majority of the papers were published by research teams that included both rheumatologists/internists and neurologists ($n = 31$) followed by research teams that included either only rheumatologists/internists ($n = 12$) or only neurologists ($n = 6$). This information is available in Appendix S1.

Among the included papers, 20 were case series/cross-sectional studies, seven were case–control studies, and 22 were cohort studies. In total, these 49 studies included 5617 patients with pSS (90% females). The mean number of pSS patients per study was 115 ± 195 (range = 12–1115). The mean age at pSS diagnosis was 53 years.

Epidemiology

Large fiber PN in pSS

Figure 2 shows the pooled prevalence of large fiber PN in non-selected populations of patients with pSS, following the meta-analysis of 29 available studies [20–23, 25–28, 30–32, 35, 36, 40–42, 45, 46, 48, 50, 52, 54, 56–59, 61, 63, 66] assessing a total of 4874 patients. The pooled prevalence was 15.0% (95% confidence interval [CI] = 10.7%–20.7%). However, there was high heterogeneity across these studies ($I^2 = 93\%$). The mean age of pSS patients at large fiber PN diagnosis was 59 years. Among the patients with pSS and large fiber PN, 83% were females. Among patients with pSS-related large fiber PN, neuropathic symptoms usually precede or lead to the pSS diagnosis at a 2:1 ratio [19, 20, 31, 33, 40, 43, 47, 48, 60, 61, 65].

Among the pSS patients with large fiber PN, 50% had sensorimotor distal axonal PN and 50% a sensory neuropathy. Less than 1% of the patients had pure motor neuropathy. In eight studies [21, 30, 32, 40, 42, 46, 48, 59], the researchers clearly distinguished pure

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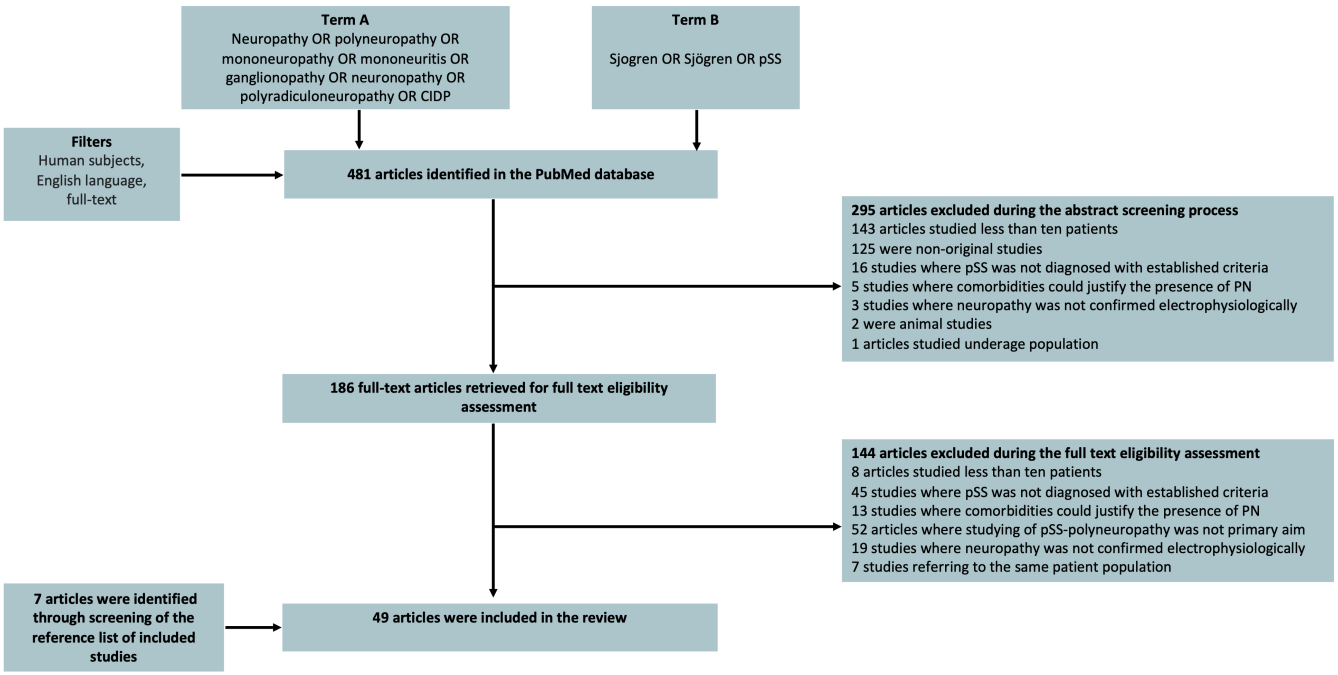

FIGURE 1 PRISMA chart detailing the inclusion/exclusion process. CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; PN, peripheral neuropathy; pSS, primary Sjögren syndrome

sensory PN as sensory neuronopathies (or sensory ganglionopathies) or distal sensory axonal polyneuropathy, revealing a 2:3 ratio, respectively.

Prevalence of peripheral mononeuropathy in pSS

Figure 3 shows the pooled prevalence of peripheral mononeuropathies, all concerning entrapment of the median nerve at the wrist (carpal tunnel syndrome) in nonselected populations of patients with pSS, following the meta-analysis of 11 available studies [23, 25, 30–32, 35, 46, 52, 59, 61, 63] assessing a total of 733 patients. The pooled prevalence was 12.8% (95% CI = 7.2%–21.8%). However, there was high heterogeneity across the included studies (I^2 = 85%).

Prevalence of cranial neuropathy in pSS

Figure 4 shows the pooled prevalence of cranial nerve involvement in nonselected populations of patients with pSS, following the meta-analysis of 16 available studies [21–23, 25, 30, 31, 35, 36, 41, 42, 46, 54, 57, 59, 61, 63] assessing a total of 1430 patients. The pooled prevalence was 5.4% (95% CI = 3.3%–8.9%). However, there was high heterogeneity across the included studies (I^2 = 72%).

The majority of cranial mononeuropathies in pSS patients involve the trigeminal nerve. As shown in Figure 5, the pooled prevalence of trigeminal neuropathy following the meta-analysis of 10 available studies [22, 23, 25, 30, 35, 36, 42, 54, 57, 63], assessing a total of 935 patients, was 3.9% (95% CI = 2.2%–6.9%). However, there was high heterogeneity across the included studies (I^2 = 52%).

Prevalence of SFN

Few studies evaluated pSS patients for small fiber dysfunction, using a variety of means including quantitative sensory testing (QST) and skin biopsy [22, 28, 54, 57, 58]. Only in the study performed by Sène et al. did the authors clearly describe the prevalence of pure small fiber involvement in their cohort. Specifically, when a pure SFN was suspected, the patients underwent additional neurophysiologic testing, including somatosensory laser-evoked potentials, QST using thermal stimuli, and autonomic nervous system testing [54]. The diagnosis of pure SFN according to established criteria was estimated to be 9.2%.

Clinical phenotypes

Distal axonal PN

The commonest type of pSS-related PN is distal axonal PN (length-dependent), accounting for almost 80% of patients with pSS-related large fiber PN.

The clinical symptoms vary and depend on the type of fibers that are involved. Pain, resulting from Aδ and C fiber involvement, is usually burning [35, 38, 46, 49, 55] and can be associated with allodynia [42, 49, 55] and itching [38, 55]. Pain is usually worse at night and at rest [38]; however, paroxysmal attacks can occur during the day. Pain can be very disabling and interfere with mobility [19].

Large fiber involvement manifests with diminished proprioception [34, 42, 47, 51], tingling [35, 38, 55], pins and needles sensation [38, 55], and numbness [34, 35, 38, 46, 47, 55].

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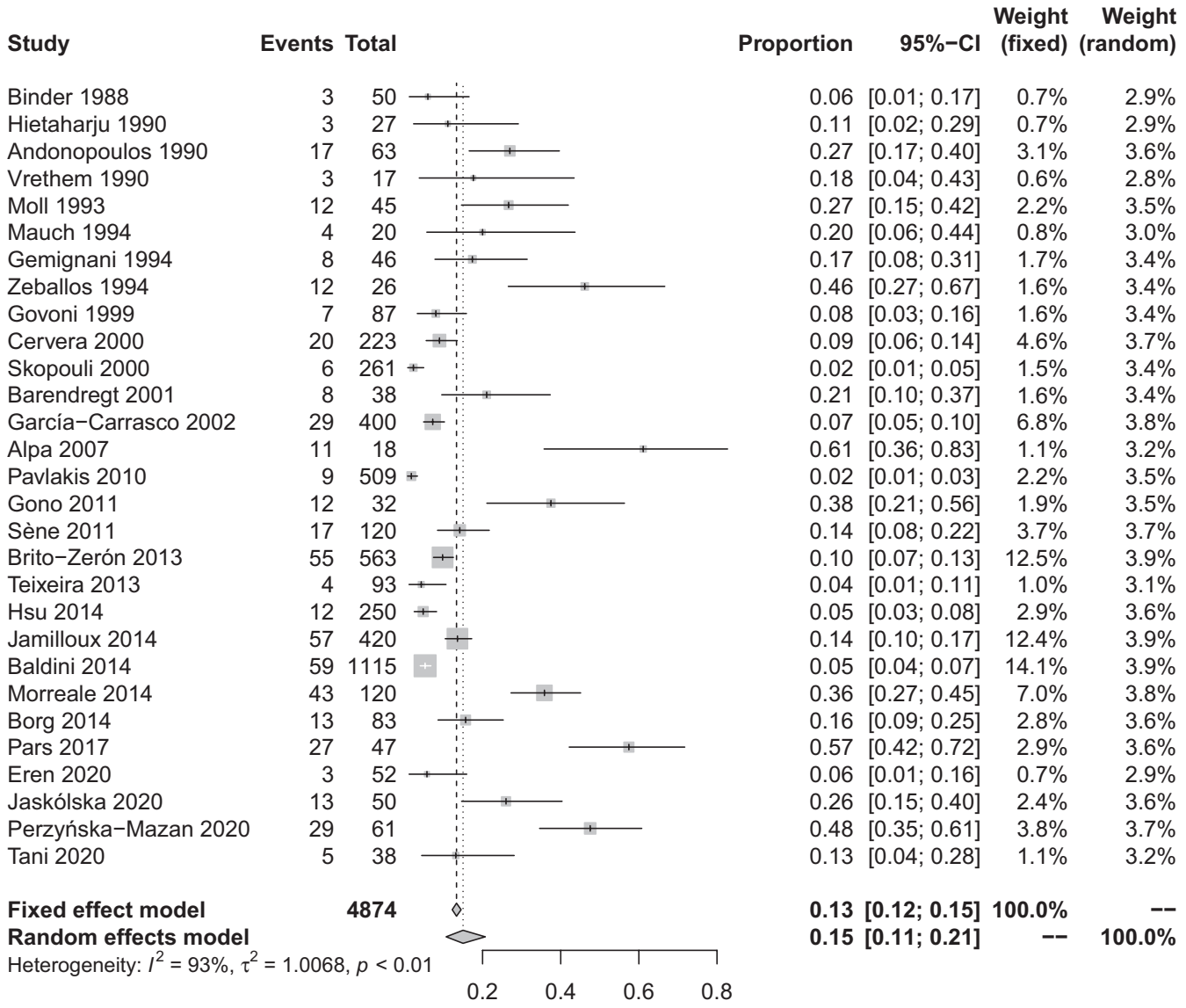

FIGURE 2 Forest plot for the prevalence of peripheral neuropathy in nonselected populations of patients with primary Sjögren syndrome, following the meta-analysis of 29 available studies. CI, confidence interval

Patients with more severe neuropathy may suffer from motor symptoms including muscle weakness, atrophies [19, 36, 42], and cramps [34].

Sensory neuronopathy

The second commonest type of pSS-related PN, accounting for 20% of cases, is sensory neuronopathy. This type of neuropathy manifests as an asymmetrical, non-length-dependent, pure sensory neuropathy and is caused by sensory ganglia involvement [68]. The most striking symptom is the impaired balance due to loss of proprioception (sensory ataxia) [19, 33, 36, 42, 44]. Furthermore, simultaneous involvement of the cerebellum is not uncommon [69].

Other types of PN

Other types of neuropathy account for <1% of pSS patients with PN. Mononeuritis multiplex is an asymmetrical sensorimotor PN that has been reported in pSS patients with comorbid vasculitis [21, 22, 30, 40, 41, 46, 57]. Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) has been described in isolated cases [40, 42, 65]. Pure motor neuropathy has also been reported in a few studies [20, 30, 58]; however, the diagnostic criteria for this type were not well defined.

Pure SFN

Presence of neuropathic pain is the hallmark of SFN [39]. Similarly to large fiber PN, SFN can be distal and symmetrical or diffuse and

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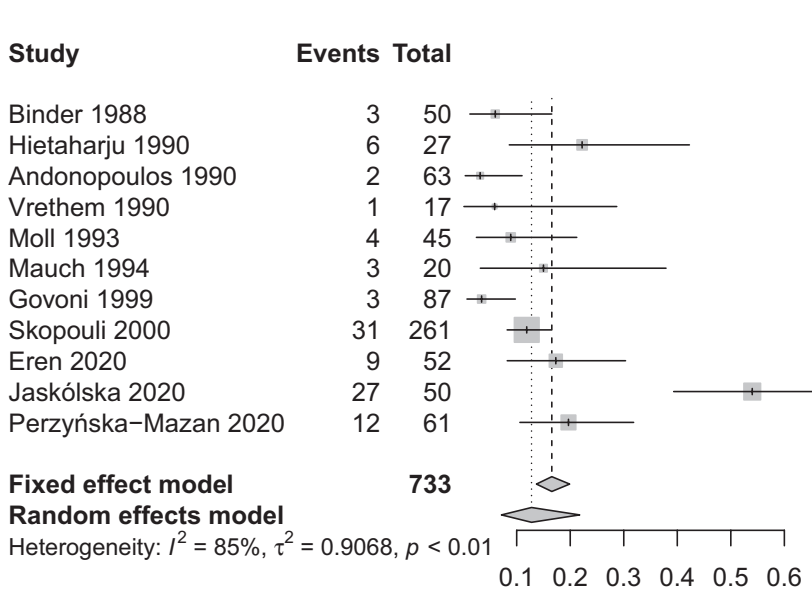

FIGURE 3 Forest plot for the prevalence of peripheral mononeuropathies, all concerning entrapment of the median nerve at the wrist (carpal tunnel syndrome) in nonselected populations of patients with primary Sjögren syndrome, following the meta-analysis of 11 available studies. CI, confidence interval

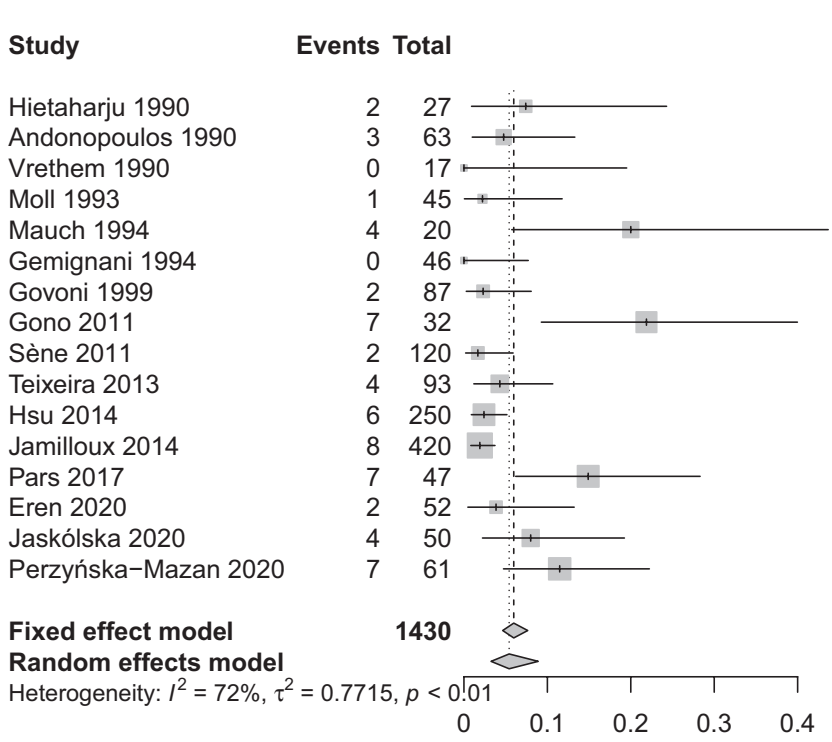

FIGURE 4 Forest plot for the prevalence of cranial nerve involvement in nonselected populations of patients with primary Sjögren syndrome, following the meta-analysis of 16 available studies. CI, confidence interval

asymmetrical, with a 2:3 ratio among cases with pure SFN [37, 38, 49, 62, 67]. Among the patients with pSS and pure SFN, 89% were females. Among patients with pSS-related pure SFN, symptoms usually precede or lead to the pSS diagnosis at a 4:1 ratio [55].

In patients with neurophysiologically confirmed small fiber dysfunction, more intense squeezing and pressure sensations, more frequent dynamic mechanical allodynia (pain provoked by brushing), and a higher prevalence of restless leg syndrome are noted, suggesting sensitization of relatively spared large Aβ fibers and second-order nociceptive neurons [38].

Neuropathic pain associated with small fiber involvement might be accompanied by other neuropathic symptoms that can be

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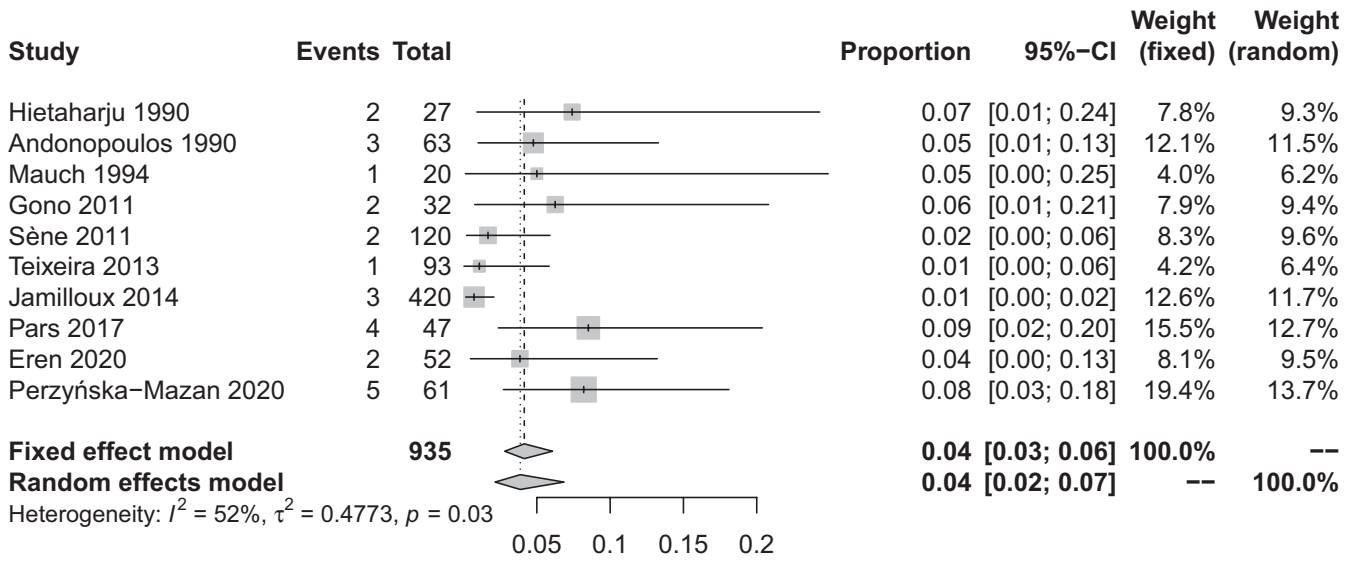

FIGURE 5 Forest plot for the prevalence of trigeminal neuropathy in nonselected populations of patients with primary Sjögren syndrome, following the meta-analysis of 10 available studies. CI, confidence interval

attributed to small fiber dysfunction such as allodynia [38, 39], hyperalgesia, and itchiness but also by symptoms that clinically indicate large fiber involvement (i.e., numbness), despite normal nerve conduction studies [39]. Ng Wing Tin et al. reported that a higher prevalence of restless leg syndrome is also noted, suggesting sensitization of relatively spared large Aβ fibers and second-order nociceptive neurons [38]. These findings probably indicate that small fiber involvement might be an early manifestation of a subsequent large fiber PN. Additionally, Zouari et al. showed that patients with pSS-related SFN had reduced electrochemical skin conductance, suggesting sympathetic small fiber dysfunction [39].

Cranial mononeuropathies

Trigeminal neuropathy is the commonest cranial mononeuropathy in the context of pSS; however, cases of optic, oculomotor, abducens, facial, vestibulocochlear, glossopharyngeal, and vagus neuropathy have been reported [21–23, 25, 30, 31, 35, 36, 41, 42, 46, 54, 57, 59]. Mori et al. suggested that trigeminal involvement may be associated with a ganglioneuropathic process [19] in the context of a generalized sensory ganglionopathy.

Biopsy correlates

Nerve biopsies in patients with neuropathy attributable to pSS disease show predominantly axonal loss [19, 21, 37, 42, 55], although occasionally features of demyelination have been demonstrated [29, 37].

Skin biopsies, when performed, have shown a decrease of the intraepidermal nerve fiber density mostly evident in patients with symptomatic PN [22, 37], including patients with distal length-dependent pain in the lower limbs [37, 38, 55].

Nerve biopsies have also revealed lymphocytic infiltration [43, 44, 51] and lymphocytic nonnecrotizing [43, 44] or necrotizing vasculitis [43, 53].

Risk factors and proposed pathophysiological mechanisms

Risk factors are less commented upon in the literature. Most studies have explored risk factors to describe possible pathophysiological mechanisms that may be involved in the pathogenesis of neuropathy in patients with pSS.

Increasing age

Increasing age is a risk factor for the development of polyneuropathy in pSS patients. Gemignani et al. suggested that a possible explanation is microangiopathic changes in the endoneurial vessels [21].

Antibodies

Font et al. suggested that the presence of antinuclear antibodies (ANAs) and anti-Ro/Sjogren's syndrome A (SSA) is associated with the development of pure sensory neuropathy in patients with pSS [47]. However, this was not confirmed by a more recent study conducted by Gono et al. [22]. In their study, Giordano et al. found no significant associations between the presence of either antiglycosphingolipid [24] or anti-ganglioside-GM1 antibodies and the development of PNs [24].

Hsu et al. showed that anti-β2glycoprotein-I antibody (aβ2GPI) and perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA)

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levels might carry a risk for the development of neuropathy in pSS patients [41].

In a retrospective cohort study, Jamilloux et al. demonstrated that cryoglobulinemia is a unique predictive factor for developing neurological manifestations, in particular sensorimotor neuropathies and mononeuritis multiplex [42]. Similarly, Sène et al. found a strong association between sensorimotor neuropathies and presence of mixed cryoglobulins [55], suggesting that vasculitis is a possible pathogenetic mechanism for pSS-related PN.

B-cell activity

In their studies, Sène et al. demonstrated an association between sensorimotor pSS-related neuropathy and higher prevalence of B-cell monoclonal proliferation markers as well as chronic B-cell activation [54, 55]. In contrast, presence of B-cell activation markers is lower in nonataxic sensory neuropathies (ANA, anti-SSA [Ro], anti-Sjogren's syndrome B [La], rheumatoid factor, hypergammaglobulinemia), indicating that these patients may belong to a subgroup of pSS with a peculiar peripheral sensory neurotropism [54].

Management of pSS-related neuropathy

Glucocorticoid monotherapy

Glucocorticoid therapy is the most tested intervention for the management of neuropathy attributable to pSS [19, 33, 42–44]. In a retrospective cohort study, Terrier et al. used oral glucocorticoids (prednisone, $n = 16$; pulse methylprednisolone, $n = 22$) as a first-line treatment and found that patients with vasculitis had a better response than those without at 6 months ($p < 0.001$) [43]. Similarly, Mori et al. assessed pSS patients who received prednisone (at a dose of 1 mg/kg/day) for the management of neuropathy ($n = 51$) and found that those suffering from mononeuritis multiplex had the greatest benefit, perhaps suggesting that these patients had pSS-related vasculitis of the PNS [19]. In a prospective cohort study, oral prednisone (at a dose of 0.5–1 mg/kg/day) was examined either as monotherapy or in combination with cyclophosphamide or intravenous immunoglobulin (IVIG) in patients with pure sensory neuropathy, resulting in a clinical stabilization or improvement in most cases for a mean follow-up period of 10 years [47]. In contrast, in their retrospective cohort study, Delalande et al. found no beneficial effect of steroids in patients with axonal polyneuropathy or ganglionopathy [44].

Immunosuppressive agents

Immunosuppressive agents have been investigated less in the management of pSS-related neuropathy. Cyclophosphamide combined with corticosteroids was assessed in a small group of pSS patients with multiple mononeuropathy ($n = 7$), leading to a partial recovery or stabilization in all patients [44]. In a retrospective cohort study, mycophenolate mofetil has been tested as an add-on to glucocorticoids in a small group of pSS patients with sensory ganglionopathy ($n = 7$), with good results [33].

Intravenous immunoglobulin

In a retrospective multicenter study, the efficacy and tolerance of IVIG was investigated in 19 patients with pSS-related neuropathy without necrotizing vasculitis [53]. All patients were initially treated with monthly IVIG, at a dose of 2 g/kg body weight over either 2 or 5 days. IVIG treatment was well tolerated, and half of the patients improved. Patients with sensorimotor neuropathies or nonataxic sensory neuropathy had the best response. In a cross-sectional study by Mori et al., 13 patients with pSS-related neuropathy were treated with IVIG at a dose of 2 g/kg body weight over 5 days [19]. Patients with polyradiculoneuropathy and painful sensory neuropathy showed the most favorable response, whereas patients with sensory ataxic neuropathy had a less favorable response. In a retrospective cohort study by Pereira et al., IVIG was administered in a small number of pSS patients with sensory ganglionopathy ($n = 6$), either as a monotherapy or as an add-on treatment, with poor results [33].

Pindi Sala et al. recently published their experience in the use of IVIG in a series of pSS patients with pure SFN ($n = 12$), reporting that in 75% of patients analgesics were discontinued and in the remaining 25% of patients the need of analgesics was reduced following IVIG treatment (median duration of treatment = 21 months, range = 2–51 months). Interestingly, even in patients who had completed the IVIG treatment the benefit remained for a mean follow-up of 25 months. This suggests a long-term benefit of immunoglobulin in patients with SFN; however, a large controlled trial is needed to determine the optimal doses of immunoglobulin in SFN for initial and maintenance therapy [64].

Prognosis: natural history

Skopouli et al. followed up 258 pSS patients with no evidence of PN at baseline for a mean period of 43 months (median = 36 months, interquartile range = 24–60 months) [52]. In their study, with a more prolonged follow-up period, Ter Borg and Kelder reported that of 129 pSS patients with no evidence of PN at baseline after a median period of 89 months (range = 0–368 months), 11% developed PN [60].

Descamps et al. followed up 10 pSS patients with pure SFN for a mean period of 37 months (range = 20–56 months), finding that one patient developed PN [49].

It has been demonstrated that the presence of vasculitis (necrotizing or lymphocytic), the mononeuritis multiplex subtype of neuropathy, acute onset, and high C-reactive protein levels are

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associated with a better prognosis in pSS-related neuropathy [43]. Font et al. suggested that the chronic and insidious course of neuropathic symptoms is linked to a poor response to the available treatments; however, the neuropathy is overall slowly progressive [47]. Compared to pSS patients without any signs of neuropathy, the survival of pSS patients with PN is reduced, particularly in those with mononeuropathy multiplex and axonal polyneuropathy [40].

DISCUSSION

Our work provides valuable information on the epidemiology of PNS involvement in patients with pSS in addition to clarifying the clinical phenotypes, the risk factors, the prognosis, and the response to various treatments. A key finding of this study is that PN is the most common neurological manifestation of pSS, affecting 15.0% (95% CI = 10.7%–20.7%) of this population. A strength of our meta-analysis is that we used very strict inclusion criteria and considered only studies reporting on patients with a pSS diagnosis that was based on established classification criteria [70, 71]. Moreover, we only considered studies where patients underwent electrophysiological studies to confirm the clinical diagnosis of PN.

Overall, the commonest type of PN is distal axonal polyneuropathy, accounting for 80% of patients with pSS-related neuropathy. It must be noted that this figure was calculated based only on studies clearly classifying PN by distal axonal (or length dependent) and by sensory ganglionopathy (or asymmetrical sensory and ataxic neuropathy).

Neuropathy may be the first manifestation of pSS, even in the absence of sicca symptoms. This initially is sensory but eventually can become sensorimotor. The second most frequent type, accounting for the remaining 20% of patients with pSS-related neuropathy, is sensory ganglionopathy. Notably, this finding might be underestimated and actually be higher, as often patients with pSS present with trigeminal neuropathy, which at least in part can be secondary to trigeminal ganglia involvement. The exact pathophysiological mechanisms remain unclear, although both vasculitic and immune mediated mechanisms have been implicated.

SFN also appears to be prevalent in pSS; however, a meaningful meta-analysis could not be performed, as not many relevant studies using similar methodology have been identified. Our literature search strategy revealed a few studies commenting on small fiber dysfunction, mainly using QST and skin biopsies, but it was not always clear whether the abnormalities were seen in patients with comorbid large fiber dysfunction. This is an interesting field for future research, including further research on the degree and nature of autonomic dysfunction that can be associated with autonomic small fiber involvement.

Several risks factors associated with PN in pSS patients were observed, including older age and the presence of various autoantibodies, in particular aβ2GP I, p-ANCA, and cryoglobulins. These intriguing findings need to be confirmed in larger cohorts.

Regarding treatment options, this systematic review demonstrated that available evidence to guide management decisions is limited. Treatment with glucocorticoids is the hallmark of managing PN, when associated with vasculitis, followed by the use of IVIG. Research into the use of immunosuppressive medication in nonvasculitic neuropathies in the context of pSS merits further consideration.

Our results should be interpreted with some caution, given the limitations of our study design. First, publication bias can occur in systematic reviews and may undermine the validity of the results. This is reflected in the significant heterogeneity among the studies assessing pSS-related PN. Second, there were no restrictions on the date of publication applied in this review. This was a deliberate decision made so as to review the full range of literature pertinent to the topic in question. However, a consequence of inclusion of older literature is more heterogeneity, as the clinical outcomes changed over time.

In conclusion, in this study, we found that distal axonal PN is the most common neurologic manifestation in the PNS among pSS patients, followed by sensory ganglionopathy and peripheral or cranial mononeuropathies, particularly carpal tunnel syndrome and trigeminal neuralgia, respectively. In addition, the presence of cryoglobulins, beta-2 glycoprotein antibodies, p-ANCA, and older age are risk factors associated with PN in pSS patients. Evidence on the management and long-term prognosis of PN in pSS is limited, and further research is needed.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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