

Medical University of Gdansk

Doctoral Thesis

Characteristics of peripheral neuropathy in primary Sjögren's disease based on the carpal tunnel syndrome cases

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I. LIST OF PUBLICATIONS

1. **Original paper**

Authors: Kościńska-Shukla Iga, Jaskólska Marta, Chylińska Magdalena, Jaskólski Dawid, Siemiński Mariusz, Chmielewski Michał

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IF 2,9 | MNiSW 70 pkt | Q2

2. **Review Article**

Authors: Kościńska-Shukla Iga, Jaskólska Marta Magdalena, Chmielewski Michał

Title: **Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications**

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3. **Original paper**

Kościńska-Shukla I, Szarmach A, Chylińska M, Jaskólski D, Chmielewski M, Dułak N, Rytlewska M, Olech M, Mikołajczak Z, Pociej A, Jaskólska M.

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IF 5,6 | MNiSW 140 pkt |Q1

II. ABBREVIATIONS

SjD – Sjögren's disease

pSjD – primary Sjögren's disease

CTS – carpal tunnel syndrome

PN – peripheral neuropathy

CYC – cyclophosphomide

RTX – rituximab

IVIG – intravenous immunoglobulins

USG – ultrasonography

ENG – electroneurography

EMG – electromyography

MRI – magnetic resonance imaging

EULAR – European League Against Rheumatism

ESSDAI – EULAR Sjögren's Syndrome Disease Activity Index

B2MG – β2-microglobulin

BCTQ – Boston Carpal Tunnel Questionnaire

FSS – Functional Status Scale

SSS – Symptom Severity Scale

BDI - Beck Depression Inventory

DASH – Disability of Arm, Shoulder and Hand

ESSPRI – EULAR Sjögren's Syndrome Patient Reported Index

SF-36 – 36-Item Short Form Health Survey

anti-SSA – anti-Sjögren's Syndrome A antibody

anti-SSB – anti-Sjögren's Syndrome B antibody

CI – confidence interval

CSA – cross sectional area

d – Cohen's d (effect size)

PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses

MHC - major histocompatibility complex

HLA - human leukocyte antigen

SLE – systemic lupus erythematosus

FM – fibromyalgia

RA – rheumatoid arthritis

SSc – systemic sclerosis

OA – osteoarthritis

QST - quantitative sensory testing

IgM – immunoglobulin M

CK – creatine kinase

CUN – centralny (ośrodkowy) układ nerwowy (central nervous system)

OUN – obwodowy układ nerwowy (peripheral nervous system)

ZCN - zespół cieśni nadgarstka (carpal tunnel syndrome)

Keywords in English: Sjögren syndrome, peripheral nervous system diseases, carpal tunnel syndrome, injections intra-articular, neurophysiology, central nervous system sensitization, inflammatory neuropathy

Słowa kluczowe w języku polskim: zespół Sjögrena, neuropatia obwodowa, zespół cieśni nadgarstka, iniekcje, ultrasonografia, neurofizjologia, centralna sensytyzacja, neuropatia zapalna

III. ABSTRACT

Sjögren's disease (SjD) is a chronic systemic autoimmune disorder characterised by lymphocytic infiltration of exocrine glands and a broad spectrum of extraglandular manifestations. Among these, nervous system involvement is one of the most disabling complications and may affect both the central (CNS) and peripheral nervous systems (PNS). Peripheral neuropathy (PN) in SjD remains insufficiently understood, frequently underdiagnosed, and often precedes the appearance of classical sicca symptoms, contributing to delays in diagnosis and treatment. Carpal tunnel syndrome (CTS), the most common entrapment neuropathy, has been reported more frequently in patients with rheumatic diseases, including SjD; however, its pathogenesis and optimal management in this population remain poorly defined.

The overall aim of this thesis was to investigate the relationship between SjD, PN, and CTS, with particular emphasis on the prevalence, clinical characteristics, treatment outcomes, and potential laboratory predictors of neurological involvement. The work presented in this thesis consists of a case-based review and two clinical studies conducted in patients with SjD.

The case-based review described two patients with SjD and atypical courses of CTS. Both cases demonstrated persistent or recurrent symptoms despite standard treatment, suggesting that CTS in SjD may represent a manifestation of more complex immune-mediated neurological involvement rather than an isolated entrapment neuropathy. These observations formed the basis for subsequent clinical investigations.

The first clinical study was a prospective observational cohort involving 50 patients with SjD and 50 age- and sex-matched controls with osteoarthritis (OA). All participants underwent rheumatological assessment, laboratory testing, neurological examination, and nerve conduction studies. CTS was diagnosed in 54% of patients with SjD compared with 8% of controls. Elevated β2-microglobulin (B2MG) concentrations were significantly more common among SjD patients with CTS than among those without CTS (85.2% vs. 56.5%, $p = 0.024$), whereas no associations were found with autoantibodies, complement levels, inflammatory markers, vitamin deficiencies, thyroid dysfunction, or articular involvement. These

findings suggested that CTS in SjD may be associated with systemic disease activity rather than local joint pathology alone.

The second study included 105 patients with established SjD who underwent comprehensive rheumatological, laboratory, neurophysiological, and ultrasonographic assessment. CTS was diagnosed in 51 patients by ultrasonography (USG) and in 43 patients by neurophysiological testing, indicating that USG may be more sensitive in detecting early structural changes of the median nerve. Neurophysiological examination revealed PN in 58% of participants, substantially exceeding prevalences commonly reported in the literature. Mononeuropathy and axonal sensorimotor polyneuropathy were among the most frequently observed neuropathic patterns.

Patients diagnosed with CTS were offered standard treatment, including ultrasound-guided corticosteroid injections. Twenty patients with SjD and 19 patients with idiopathic CTS consented to the procedure. Nineteen patients with SjD and eighteen patients with idiopathic CTS completed follow-up assessments. Significant reductions in median nerve measurements were observed in both groups, with a greater decrease in patients with SjD (0.46 mm^2 vs. 0.31 mm^2; $p = 0.006$). However, despite this favorable structural response, clinical improvement was significantly less pronounced in the SjD group. Improvements in the Boston Carpal Tunnel Questionnaire (BCTQ) Symptom Severity Scale (SSS) and Functional Status Scale (FSS) were greater in controls than in patients with SjD (SSS: −14.16 vs. −6.13, $p = 0.021$; FSS: −6.39 vs. −1.42, $p = 0.033$). Furthermore, patients with concomitant CTS and additional neuropathies experienced significantly poorer outcomes than patients with isolated CTS. No clinically meaningful associations were identified between treatment response and inflammatory markers, autoantibodies, or other laboratory parameters.

In conclusion, the findings presented in this thesis demonstrate that CTS and PN are highly prevalent among patients with SjD and may represent manifestations of a broader immune-mediated neurological process. Although standard CTS therapies effectively reduce structural nerve abnormalities, symptomatic and functional improvement is frequently limited, particularly in patients with concomitant neuropathies. These results support the hypothesis that CTS in SjD differs from idiopathic CTS and should be evaluated within the wider context of PNS

involvement. Comprehensive neurological assessment, including USG and neurophysiological testing, should be considered in patients with SjD presenting with neuropathic symptoms. Further studies are needed to clarify the underlying mechanisms of nerve injury and to develop more effective therapeutic strategies for neurological manifestations of SjD.

IV. ABSTRACT IN POLISH

Charakterystyka neuropatii obwodowej u pacjentów z chorobą Sjögrena na podstawie analizy przypadków zespołu cieśni nadgarstka

Choroba Sjögrena (SjD) jest przewlekłym układowym zaburzeniem autoimmunologicznym, charakteryzującym się naciekiem limfocytarnym w obrębie gruczołów wydzielania zewnętrznego oraz szerokim spektrum objawów pozagruczołowych. Wśród nich zajęcie układu nerwowego stanowi jedno z najbardziej uciążliwych dla pacjentów powikłań i może dotyczyć zarówno ośrodkowego (CUN), jak i obwodowego układu nerwowego (OUN). Neuropatia obwodowa w przebiegu SjD pozostaje niedostatecznie poznana, jest często niedodiagnozowana i nierzadko wyprzedza wystąpienie klasycznych objawów zespołu suchości, co przyczynia się do opóźnień w rozpoznaniu i leczeniu. Zespół cieśni nadgarstka (ZCN), będący najczęstszą neuropatią z uwięźnięcia, zgłaszany jest częściej u pacjentów z chorobami reumatycznymi, w tym z SjD; jednak jego patogeneza oraz optymalne postępowanie terapeutyczne w tej populacji pozostają słabo zdefiniowane.

Głównym celem niniejszej rozprawy doktorskiej było zbadanie zależności między SjD, neuropatią obwodową i ZCN, ze szczególnym uwzględnieniem częstości występowania, charakterystyki klinicznej, wyników leczenia oraz potencjalnych wskaźników laboratoryjnych zajęcia układu nerwowego. Praca zaprezentowana w tej rozprawie składa się z przeglądu opartego na opisach przypadków oraz dwóch badań klinicznych przeprowadzonych u pacjentów z SjD.

Przegląd oparty na opisach przypadków przedstawiał dwóch pacjentów z SjD i nietypowym przebiegiem ZCN. W obu przypadkach zaobserwowano utrzymywanie się lub nawracanie objawów pomimo zastosowania standardowego leczenia, co

sugeruje, że ZCN w przebiegu SjD może stanowić przejaw bardziej złożonego procesu neurologicznego o podłożu immunologicznym, a nie jedynie izolowaną neuropatię z uwięźnięcia. Obserwacje te stanowiły podstawę do kolejnych badań klinicznych.

Pierwsze badanie kliniczne stanowiła prospektywna, obserwacyjna analiza kohortowa, obejmująca 50 pacjentów z SjD oraz 50 osób z grupy kontrolnej z chorobą zwyrodnieniową stawów, dobranych pod względem wieku i płci. Wszyscy uczestnicy zostali poddani ocenie reumatologicznej, badaniom laboratoryjnym, badaniu neurologicznemu oraz badaniom przewodnictwa nerwowego. ZCN rozpoznano u 54% pacjentów z SjD w porównaniu z 8% osób z grupy kontrolnej. Podwyższone stężenia β2-mikroglobuliny (B2MG) występowały istotnie częściej u pacjentów z SjD i ZCN niż u tych bez ZCN (85,2% vs. 56,5%, p = 0,024), podczas gdy nie stwierdzono powiązań z obecnością autoprzeciwciał, stężeniem składników dopełniacza, markerami stanu zapalnego, niedoborami witamin, zaburzeniami czynności tarczycy ani zajęciem stawów. Wyniki te sugerują, że ZCN w przebiegu SjD może wiązać się z układową aktywnością choroby, a nie jedynie z lokalną patologią stawową.

Drugim badaniem objęto 105 pacjentów z ustalonym rozpoznaniem SjD, u których przeprowadzono kompleksową ocenę reumatologiczną, laboratoryjną, neurofizjologiczną oraz ultrasonograficzną. ZCN rozpoznano u 51 pacjentów na podstawie badania ultrasonograficznego oraz u 43 pacjentów na podstawie badania neurofizjologicznego, co wskazuje, że ultrasonografia może wykazywać wyższą czułość w wykrywaniu wczesnych zmian strukturalnych nerwu pośrodkowego. Badanie neurofizjologiczne wykazało obecność neuropatii obwodowej u 58% uczestników, co znacznie przewyższa częstość występowania powszechnie zgłaszaną w piśmiennictwie. Mononeuropatia oraz aksonalna polineuropatia czuciowo-ruchowa należały do najczęściej obserwowanych wzorców neuropatycznych.

Pacjentom z rozpoznanym ZCN zaoferowano standardowe leczenie, w tym iniekcje glikokortykosteroidów pod kontrolą ultrasonografii. Dwudziestu pacjentów z SjD oraz dziewiętnastu pacjentów z idiopatycznym ZCN wyraziło zgodę na zabieg. Wizyty kontrolne ukończyło odpowiednio dziewiętnastu i osiemnastu pacjentów. W obu grupach zaobserwowano istotne zmniejszenie wymiarów nerwu pośrodkowego,

przy czym większy spadek odnotowano u pacjentów z SjD (0,46 mm^2 vs. 0,31 mm^2; p = 0,006). Jednak mimo tej korzystnej odpowiedzi strukturalnej, poprawa kliniczna była znacznie mniej wyrażona w grupie z SjD. Poprawa w Skali Ciężkości Objawów (SSS) oraz Skali Stanu Funkcjonalnego (FSS) Kwestionariusza Zespołu Cieśni Nadgarstka Boston (BCTQ) była większa u osób z grupy kontrolnej niż u pacjentów z SjD (SSS: −14,16 vs. −6,13, p = 0,021; FSS: −6,39 vs. −1,42, p = 0,033). Ponadto u pacjentów z współwystępującym ZCN i dodatkowymi neuropatiami uzyskano istotnie gorsze wyniki leczenia w porównaniu z pacjentami z izolowanym ZCN. Nie zidentyfikowano istotnych klinicznie zależności między odpowiedzią na leczenie a markerami zapalnymi, autoprzeciwciałami czy innymi parametrami laboratoryjnymi.

Podsumowując, wyniki przedstawione w niniejszej rozprawie doktorskiej wskazują, że ZCN i neuropatie obwodowe występują z dużą częstością u pacjentów z SjD i mogą stanowić manifestację szerszego procesu neurologicznego uwarunkowanego immunologicznie. Choć standardowe metody leczenia ZCN skutecznie zmniejszają strukturalne nieprawidłowości nerwu, poprawa w zakresie objawów i funkcjonowania jest często ograniczona, szczególnie u pacjentów ze współistniejącymi neuropatiami. Rezultaty te wspierają hipotezę, iż ZCN w przebiegu SjD różni się od idiopatycznej postaci ZCN i powinien być oceniany w szerszym kontekście zajęcia OUN. U pacjentów z SjD zgłaszających objawy neuropatyczne należy rozważyć przeprowadzenie kompleksowej oceny neurologicznej, obejmującej badanie ultrasonograficzne i neurofizjologiczne. Dalsze badania są konieczne do wyjaśnienia mechanizmów leżących u podstaw uszkodzenia nerwów oraz do opracowania skuteczniejszych strategii terapeutycznych dla neurologicznych manifestacji SjD.

V. INTRODUCTION

Sjögren's Disease

Sjögren's disease (SjD) is a chronic systemic autoimmune disorder with a rich historical pedigree [1]. It was first described in the 1930s by the Swedish ophthalmologist Henrik Sjögren, who observed the coincidence of marked ocular and oral dryness with articular deformities in a young female patient — a constellation that has remained the clinical signature of the disease ever since [2]. The hallmark "sicca" symptoms — dryness of the eyes, oral cavity — arise from autoimmune injury of the exocrine glands, mediated by focal lymphocytic infiltration of the salivary and lacrimal apparatus and progressive glandular failure [1, 3, 4].

Contemporary understanding of SjD extends well beyond these initial clinical descriptions. The disease is now recognised as a multisystem disorder capable of involving pulmonary, gastrointestinal, renal, and, importantly, both the peripheral (PNS) and central nervous systems (CNS) [3, 5]. Diagnostic classification rests on a combination of objective criteria: the presence of disease-specific autoantibodies, a positive Schirmer test, a diminished unstimulated whole-saliva flow rate, and histopathological confirmation of focal lymphocytic infiltrates within minor salivary-gland biopsies [6–9]. Like most autoimmune diseases, SjD exhibits a striking female predominance, with a male-to-female ratio of approximately 1:9 and a typical onset between the fourth and sixth decades of life [2].

Epidemiologically, however, the true burden of SjD remains incompletely mapped. Reported prevalence estimates range from 0.02–0.77% in general-population studies to 0.2–1%, and 0.2–2% of the global adult population, depending on case ascertainment and the classification criteria applied [1, 2]. The heterogeneity of these figures is itself instructive: it reflects substantial diagnostic delays, the diverse spectrum of clinical presentations, and the frequent underestimation of disease burden when extraglandular features precede or overshadow classical sicca symptoms [10, 11].

Peripheral Neuropathy in Sjögren's Disease

Among the many extraglandular manifestations of SjD, nervous-system involvement is recognised as one of the most disabling — and one of the most poorly understood [12, 13]. Patients with SjD may experience both peripheral neuropathy (PN) and CNS involvement, the latter including epilepsy, dementia and even psychosis [14]. The prevalence of PN has been reported to reach up to 60% in selected SjD cohorts [10, 11, 15], a figure that substantially exceeds the 3–6% prevalence reported for the general population and stands alongside the very high rates observed in other connective-tissue diseases — up to 70% in systemic vasculitis and approximately 15% in systemic lupus erythematosus (SLE). Yet these values are widely regarded as underestimates, particularly when neurological symptoms precede the appearance of sicca complaints and the formal SjD diagnosis, leading to misdirected therapy, prolonged patient distress and compromised quality of life [16, 17].

The clinical spectrum of PN in SjD is exceptionally broad. Recognised patterns include sensory neuropathies, axonal sensorimotor polyneuropathy, mononeuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy, cranial neuropathy and autonomic neuropathy [12, 15–17]. This morphological heterogeneity, compounded by the inconsistent terminology used across published studies, materially impairs inter-study comparability and the pooling of evidence [10, 11]. Of particular clinical relevance is the observation that PNS involvement may precede sicca symptoms and the formal diagnosis of SjD, meaning that some patients initially present with atypical neuropathic complaints that subsequently resolve only under immunosuppressive therapy [16]. The pathophysiological substrate remains poorly characterised: over the years, multiple candidate mechanisms — complement activation, disease-specific autoantibodies, vitamin deficiencies [18], small-fiber injury — have been proposed, but none has been confirmed in adequately powered studies [3, 19].

Two further layers of clinical complexity merit emphasis. Firstly, patients with SjD exhibit a markedly elevated prevalence of psychiatric comorbidities, particularly depression and anxiety, as well as fibromyalgia (FM) — conditions that may amplify nociceptive processing, impair quality of life and adversely modify the response to both pharmacological and interventional pain management [20–25]. Second, the

most consistently effective disease-modifying options for SjD-associated PN remain intravenous immunoglobulins (IVIG), cyclophosphamide (CYC) and rituximab (RTX), with RTX reported to be particularly successful in the vasculitis-related PNS phenotypes encountered in SjD [13, 26–28].

Carpal Tunnel Syndrome

Carpal tunnel syndrome (CTS) is the single most common entrapment neuropathy in clinical practice, accounting for approximately 90% of all focal entrapment syndromes and affecting 3–6% of the adult population [29–31]. As with SjD, it predominantly affects females [32, 33], and although the classical textbook description emphasises median-nerve compression in the dominant hand related to repetitive motion (typing, vibration-induced occupational exposure, elite athletic overuse) [30, 31, 34], the clinical pattern is often broader than the canonical distribution in the thumb and ring finger. In previously described cohort of 159 patients with electrodiagnostically confirmed CTS, the symptom map extended well beyond the classical median-territory sensory loss: 21% reported forearm paraesthesia and pain, 13.8% elbow pain, 7.5% arm pain, 6.3% shoulder pain and 0.6% neck pain [35]. The pathophysiology rests on elevation of intracarpal pressure within an anatomically rigid compartment bounded by the carpal bones and the transverse carpal ligament, leading to perineurial oedema, impaired intraneural blood flow, and, in advanced disease, axonal-demyelinating injury of the median nerve [34, 36]. Patients typically experience nocturnal tingling and pain in the thumb and radial digits, with progressive thenar motor dysfunction in more severe cases [29].

Local corticosteroid injection around the median nerve is well established as the first-line short-term therapy for CTS, often employed as a bridge towards definitive surgery or as an adjunct to physiotherapy [37–39]. A clinical regimen of three injections spaced four weeks apart is widely recommended, with the four-week interval chosen to capture the peak anti-inflammatory and anti-oedematous effects while attenuating transient post-injection discomfort. Yet despite this generally favourable experience, clinicians managing patients with SjD frequently observe a less pronounced therapeutic response compared with individuals without autoimmune disease — a clinical impression that has, until recently, rested

almost exclusively on anecdotal observation.

Carpal Tunnel Syndrome in Rheumatic Diseases

The prevalence of CTS in patients with rheumatic diseases is consistently higher than in the general population [40, 41]. In SLE, rheumatoid arthritis (RA), and systemic sclerosis (SSc) — the conditions in which this association has been most extensively studied — both the occurrence and the symptomatic severity of CTS have historically been attributed to articular activity: synovial swelling and chronic joint deformity have been regarded as the primary culprits, narrowing the carpal tunnel from within [40, 42]. A similar mechanistic framework was, until recently, also proposed for SjD.

The three publications that constitute this thesis challenge this assumption directly. In the first prospective study of 50 patients with primary SjD (pSjD) compared with 50 sex- and age-matched individuals with osteoarthritis (OA), CTS was diagnosed in 27 of 50 (54%) pSjD patients but in only 8% of the control group. A subsequent study of 105 patients with established SjD, employing combined ultrasonographic (USG) and neurophysiological assessment, confirmed CTS in 51 patients on USG (29 bilaterally) and in 43 patients on electrodiagnostic testing (10 bilaterally), with neurophysiological examination revealing any form of peripheral neuropathy in 58% of the entire cohort — a figure that materially exceeds the prevalences commonly reported in the published literature [10, 11]. The pooled literature-derived estimate, drawn from 11 studies encompassing 733 patients with pSjD, reports an average CTS incidence of 12.8% (95% CI 7.2–21.8%, I^2 = 85%), underscoring both the heterogeneity of the underlying populations and the genuine excess of CTS in SjD [10, 40].

Critically, our findings argue strongly against a primarily articular mechanism. Within the 50-patient cohort, joint involvement was distributed evenly between the CTS and non-CTS subgroups (15 vs. 13; p = 0.945). Hypergammaglobulinemia, the canonical SjD autoantibody profile, complement levels and systemic inflammatory markers likewise failed to differentiate the two subgroups. What did discriminate them was an elevated serum concentration of β2-microglobulin (B2MG), defined as above 2.6 mg/l — the upper limit of normal in the institutional laboratory — which

was significantly more frequent in patients with CTS (23 vs. 13; p = 0.024), alongside self-reported paraesthesia and sleep disturbance. These observations support the hypothesis that CTS in SjD may be coupled to overall disease activity — operationalised through serum B2MG as a marker of B-cell and immune activation [18, 43]— rather than to local articular pathology alone, and that a neuropathic or amyloidogenic substrate may contribute to median-nerve compromise [44].

The discordance between structural and clinical outcomes further sharpens this picture. In the ultrasonographic cohort of 20 SjD patients and 19 idiopathic-CTS controls treated with USG-guided corticosteroid injection, the cross-sectional area (CSA) of the median nerve decreased more in SjD than in controls (mean reduction 0.46 vs. 0.31 mm^2; p = 0.006, Cohen's d = 0.96). Yet this favourable biological response was accompanied by significantly worse symptomatic recovery in the SjD group: reductions in the Boston Carpal Tunnel Questionnaire (BCTQ) Symptom Severity Scale (SSS) (−6.13 vs. −14.16; p = 0.021) and Functional Status Scale (FSS) (−1.42 vs. −6.39; p = 0.033) were markedly less pronounced in SjD [45]. The presence of concomitant peripheral neuropathies — identified in 58% of the cohort — further worsened symptomatic outcomes, with isolated CTS faring considerably better than CTS accompanied by another neuropathy (SSS: −12.94 vs. −4.98, p = 0.040; FSS: −5.95 vs. 0.43, p = 0.014). Bilateral involvement was likewise disproportionately common in SjD (75%) compared with controls (47%).

Carpal Tunnel Syndrome Treatment

Despite the substantial prevalence of CTS, formal clinical guidelines for its treatment remain limited. Standard care comprises USG-guided corticosteroid injection — most commonly as a temporary resolution of symptoms, used to bridge the interval to definitive surgical decompression (median-nerve release) or to facilitate concurrent physiotherapy [46–48] — followed by surgical release in refractory or advanced cases [49, 50]. In the general population, this regimen is effective even when provoking factors cannot be fully eliminated from daily activities [37–39].

The situation in SjD is conspicuously different. Surgical decompression, while initially able to relieve mechanical compression, is frequently followed by recurrent

symptoms and repeated presentations despite favourable imaging findings [51–53]. Moreover, surgical intervention in rheumatological patients — particularly those already on immunosuppressive therapy — carries an independent, elevated risk of infection, post-surgical complications and exacerbation of the underlying autoimmune disease [54]. This constellation of observations led our group to the working hypothesis that CTS in SjD should not be regarded as an isolated entrapment phenomenon amenable to standard release procedures but should instead be considered a manifestation of a broader, immune-mediated neurological involvement [10, 17]. In this reframing, the symptomatic component of CTS in SjD is more likely to respond to systemic immunosuppressive strategies — oral corticosteroids, IVIG and RTX — than to repeated surgical or local interventional measures alone. The principal aim of the work presented in this thesis was therefore to move this hypothesis from the clinic to the bench: to objectively evaluate, using a structured clinical and ultrasonographic protocol, the discordance between biological response and subjectively experienced improvement that constitutes the everyday clinical reality of CTS in SjD, and to identify clinical, laboratory and patient-reported predictors of unsuccessful treatment [13, 26, 28].

VI. AIMS

Objectives of the Thesis

This doctoral dissertation was conceived as an integrated, internally coherent research programme designed to address a central hypothesis: that CTS in SjD represents a peripheral-nerve manifestation of systemic immune activation requiring systemic disease control, rather than a focal mechanical entrapment phenomenon amenable to standard release procedures [10, 17].

To address this question, the thesis pursued three primary objectives across its constituent studies:

Objective 1: Epidemiological Quantification and Biomarker Identification

- **Primary Aim:** To establish the clinical scale of CTS within a SjD population and evaluate whether local articular pathology accounts for this excess prevalence [40].
- **Secondary Aim:** To identify serum biomarkers capable of facilitating early CTS detection in SjD [44, 55, 56].

Objective 2: Clinical Characterisation and Descriptive Summary

- **Primary Aim:** To thoroughly review existing literature regarding the incidence and clinical presentation of CTS in SjD patients [10, 11].
- **Secondary Aim:** To illustrate, through detailed case examples, the management challenges associated with treatment-refractory SjD-CTS—specifically highlighting patterns of surgical non-responsiveness and transient response to local corticosteroid administration to inform interdisciplinary care.

Objective 3: Mechanistic Evaluation of Structural vs. Functional Dissociation

- **Primary Aim:** To evaluate the prospective relationship between structural ultrasound decompression (CSA reduction) and subjective functional recovery following standardised corticosteroid injection in SjD-associated CTS compared to idiopathic controls [57, 58].

- **Secondary Aim:** To identify clinical, laboratory, and patient-reported predictors of suboptimal therapeutic response [45, 59]. (Note: While this study prospectively documents the marked discordance between biological and functional trajectories post-treatment, it intentionally avoids assuming or asserting a formal statistical correlation between these dimensions).

Methodological Framework

Taken in concert, these studies were structured as a deliberate research progression: moving from epidemiological quantification, through clinical-pattern recognition, to mechanistic dissection. The unifying goal of this thesis is to provide an empirical foundation to reframe CTS in SjD as an immunologically driven systemic manifestation, thereby supporting treatment strategies that prioritise systemic immunomodulation over repeated focal interventions.

VII. CONCLUSIONS

Collectively, the three investigations of this dissertation converge upon a single thesis-level paradigm: CTS in SjD cannot be adequately conceptualised through the traditional framework of focal mechanical compression alone [10, 17].

Epidemiological and Biomarker Insights

The initial prospective observational study provided the epidemiological anchor for this paradigm. Demonstrating a 54% prevalence of CTS in SjD patients—compared to 8% in age- and sex-matched OA controls and an established 3–5% baseline in the general population [29, 31, 32]—confirms that CTS is significantly over-represented in SjD. Furthermore, biomarker analysis revealed that articular involvement was distributed equivalently between CTS-positive and CTS-negative subgroups (15 vs. 13; $p = 0.945$). Conversely, elevated serum B2MG (> 2.6 mg/L) was observed in 23 versus 13 patients ($p = 0.024$), co-occurring with paraesthesia and sleep disruption. These findings argue strongly against a purely localised articular mechanism, pointing instead toward a neuropathic or amyloidogenic substrate driven by systemic immune activation [43, 44]. The proposed mechanistic link to B2MG deposition introduces a novel, testable histopathological hypothesis bridging SjD-associated CTS with systemic amyloid pathways [56, 60].

Clinical Translation and Neuropathic Heterogeneity

The narrative synthesis and case series contextualised these quantitative observations within clinical practice. The pooled CTS incidence of 12.8% (95% CI: 7.2–21.8%; $I^2 = 85\%$) underscores a substantial, albeit heterogeneous, clinical burden across cohorts [10, 11]. This observed heterogeneity reflects the diverse spectrum of PNS involvement in SjD, encompassing sensory, axonal sensorimotor, mononeuropathy, demyelinating polyradiculoneuropathy, cranial, and autonomic phenotypes [16, 17, 61]. Within this context, the presented treatment-refractory clinical examples illustrate the clinical discordance between technically successful

surgical decompression and durable symptomatic relief, highlighting the limitations of localised interventions in this population [51, 52].

Structural versus Functional Discordance

The prospective ultrasonographic study quantified this structural-functional dissociation longitudinally within a comparative framework. Despite exhibiting a significantly greater anatomical response to local corticosteroid administration than idiopathic controls (mean CSA reduction: 0.46mm^2 vs. 0.31^2; p = 0.006; Cohen's d = 0.96), SjD patients demonstrated significantly worse symptomatic and functional recovery (BCTQ SSS: p = 0.021; FSS: p = 0.033) [45]. Concomitant PN — present in 58% of the SjD cohort—further attenuated clinical outcomes, with isolated CTS showing markedly superior recovery compared to CTS accompanied by co-existing neuropathy (SSS change: -12.94 vs. -4.98, p = 0.040; FSS change: -5.95 vs. 0.43, p = 0.014). Bilateral median nerve involvement was likewise disproportionately prevalent in SjD (75% vs. 47% in controls).

It should be emphasized that, in accordance with formal statistical terminology, these observed divergences between anatomical regression and functional indices represent clinical discordance rather than an asserted or inferred statistical correlation.

Implications for Clinical Practice

Synthesising the evidence across these three studies yields a unified clinical paradigm: in SjD, the symptomatic manifestations of CTS are driven primarily by systemic immune pathways and are therefore more responsive to systemic immunomodulatory strategies (e.g., systemic corticosteroids, IVIG, CYC, or RTX in vasculitic neuropathy phenotypes) than to repeated local interventions [10, 13, 26, 28].

Furthermore, elective surgical decompression in autoimmune populations on active immunosuppressive regimens carries inherent risks, including increased susceptibility to surgical site infections, delayed wound healing, and potential disease flares [54]. From a diagnostic perspective, these findings highlight the need to consider

underlying systemic autoimmune diseases, particularly SjD, in patients presenting with atypical CTS or an unsatisfactory response to conventional treatment [40, 41].

Future Research Directions

To build upon the conclusions of this dissertation, three high-priority research directions are proposed:

1. **Histopathological Validation:** Direct molecular and histological examination of surgical transverse carpal ligament and flexor tenosynovial specimens from SjD patients to evaluate local B2MG and amyloid deposition [44, 56, 60, 62–64].

2. **Advanced Neuropathic Characterisation:** Prospective integration of skin biopsy for small-fibre density, quantitative sensory testing (QST), corneal confocal microscopy, and comprehensive neurophysiological profiling to delineate the relative contributions of small-fibre, large-fibre, and autonomic neuropathies in SjD-associated CTS [13, 65–67].

3. **Interventional Clinical Trials:** Comparative clinical trials evaluating early systemic immunosuppressive escalation versus conventional focal pathways (steroid injection/surgical decompression) as the primary therapeutic strategy for SjD-associated median nerve dysfunction [50, 52, 53, 68].

Final Conclusion

In conclusion, the research presented in this thesis establishes that CTS in SjD is best conceptualised not as a primary compressive lesion, but as a focal peripheral-nerve manifestation of systemic autoimmunity—a clinical sign rather than an isolated cause [10, 17]. Recognising this fundamental distinction has immediate, direct implications for refining multidisciplinary clinical decision-making and reorienting future translational research in rheumatology and peripheral nerve medicine [57, 58, 69, 70].

VIII. DISCUSSION OF PUBLICATIONS INCLUDING THE DOCTORAL DISSERTATION

Publication 1.

Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients

Article in Brief

Our prospective observational study investigated CTS, one of the relatively conspicuous yet insufficiently characterised neurological comorbidities of SjD. CTS was identified in more than half of the patients with SjD included in our cohort and, importantly, its occurrence was associated with an elevated serum concentration of B2MG, providing a potential link between immune activity and peripheral nerve entrapment in this population.

1. Introduction

SjD is a systemic connective-tissue disease characterised predominantly by lymphocytic infiltration of the exocrine glands, with an estimated prevalence of 0.2–1% in the general population and a marked female predominance (male-to-female ratio approximately 1:9) [1, 2].

The rationale for the study was based on the observation that CTS appears to occur more frequently among patients with SjD than would be expected from its reported prevalence of approximately 3–5% in the general population [29, 31, 32]. Despite this apparent association, the mechanisms underlying the increased frequency of CTS in SjD remain insufficiently understood, and no serum biomarker had previously been clearly linked to its occurrence in this patient population. The study therefore aimed to investigate the prevalence and clinical characteristics of CTS in SjD and to identify potential laboratory markers associated with its development.

2. Materials and Methods

A prospective, single-centre, case–control observational study was conducted. The study group consisted of 50 patients with a diagnosis of SjD, while the control group comprised 50 sex- and age-matched individuals with OA. All participants underwent a structured clinical assessment by a rheumatologist, routine laboratory investigations, and standardised electrophysiological evaluation.

Continuous variables were compared using either the Mann–Whitney U test or Student's *t*-test, according to data distribution, whereas categorical variables were analysed using the chi-squared test. Statistical significance was defined as $p \leq 0.05$. An a priori diagnostic work-up was performed in all patients, with elevated serum B2MG and included plasma-protein electrophoresis, assessment of immunoglobulin light chains, testing for monoclonal proteins, and, where clinically justified, bone-marrow biopsy. In cases raising suspicion of lymphoma, peripheral lymph-node USG and whole-body computed tomography were additionally performed. Depressive symptomatology was assessed using the Beck Depression Inventory (BDI). Sleep disturbance was assessed with the use of Athens Insomnia Scale.

3. Results

CTS was diagnosed in 27 of the 50 patients with SjD (54%), compared with 8% of individuals in the OA control group. Within the SjD cohort, the prevalence of joint involvement did not differ significantly between patients with and without CTS (15 vs. 13; $p = 0.945$). This finding argues against the assumption that articular inflammation alone accounts for the increased occurrence of CTS in SjD [40].

In contrast, an elevated serum concentration of B2MG, defined as >2.6 mg/L according to the upper limit of normal in the local laboratory, was significantly more frequent among patients with CTS than among those without CTS (23 vs. 13; $p = 0.024$). The same numerical difference was observed for self-reported paraesthesia (23 vs. 13; $p = 0.024$). Sleep disturbance was reported by 18 vs. 9 patients respectively ($p = 0.012$). By comparison, hypergammaglobulinaemia and the characteristic autoantibody profile of SjD, although commonly used as indicators of disease activity, did not significantly distinguish patients with CTS from those without CTS.

4. Discussion

The observed association between CTS and serum B2MG was considered in the context of the established biological properties of this protein. B2MG is a 100-amino-acid, 11,800-Da polypeptide encoded on chromosome 15 and constitutively expressed on the surface of nucleated cells as a component of the major histocompatibility complex (MHC) class I/ human leukocyte antigen (HLA) class I complex [44]. Under physiological conditions, it is predominantly eliminated through renal filtration, with serum concentrations generally ranging from approximately 1 to 3 µg/mL [44].

Markedly increased B2MG concentrations have been described in several pathological conditions, including multiple myeloma, lymphoma, hepatic disease, and, particularly, renal failure, in which serum concentrations may reach levels many times above the upper limit of normal [44, 64]. B2MG is also recognised as a marker of systemic immune activation in autoimmune rheumatic diseases, where elevated serum concentrations reflect chronic lymphocyte activation and increased MHC-I turnover [71–74]. The findings of the present study prompted consideration of a potential pathogenetic relationship between CTS in SjD and the mechanisms underlying dialysis-related B2MG amyloidosis [56, 60].

The historical development of this concept provides an important basis for this hypothesis. Although an association between end-stage kidney disease and CTS was reported as early as 1975 and was initially attributed to oedema associated with arteriovenous fistulas [60, 64], subsequent histopathological examination of surgical specimens demonstrated amyloid deposits within the tissues affected by CTS [44, 56]. Analysis of synovial amyloid subsequently identified B2MG as the precursor protein [60, 64]. Systemic deposition was later supported by autopsy studies demonstrating amyloid accumulation in the rectal mucosa of patients undergoing chronic haemodialysis [62].

The serum B2MG concentrations observed in SjD, however, are generally substantially lower than those encountered in end-stage kidney disease, unless renal failure or a haematological malignancy is present [44]. Furthermore, a definitive relationship between circulating B2MG concentrations and the risk of

amyloid deposition has not been established. Consequently, the findings do not permit direct attribution of CTS in SjD to B2MG amyloidosis.

Nevertheless, the results support a potential mechanistic hypothesis in which chronic immune activation characteristic of SjD, together with the presence of inflammatory proteins and autoantibodies, may facilitate local B2MG accumulation or deposition within osteoarticular tissues [63, 64]. Such a process could provide a plausible link between systemic immunological activity and local compression of the median nerve. This hypothesis remains tentative and requires confirmation through histopathological, biochemical, and longitudinal studies.

5. Conclusions

Our findings demonstrate a substantially higher prevalence of CTS among patients with SjD than in the OA control group and support an association between CTS and elevated serum B2MG concentrations [43, 75]. Importantly, the occurrence of CTS was not associated with the presence of joint involvement itself, suggesting that articular inflammation alone is unlikely to explain the increased prevalence of CTS observed in SjD.

These findings support consideration of CTS within the broader spectrum of peripheral neurological manifestations of SjD rather than exclusively as an isolated mechanical entrapment neuropathy [10, 17]. The observed association with B2MG also raises the possibility that amyloidogenic and immune-mediated mechanisms may contribute to median-nerve compression in SjD. Further investigation is warranted to determine whether B2MG represents a clinically useful biomarker of neurological involvement and to clarify the potential contribution of local amyloid deposition or other immune-mediated mechanisms to the pathogenesis of CTS in SjD.

Publication 2.

Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications

Article in Brief

Our narrative review, complemented by two case descriptions, examined CTS in SjD as a potentially distinct clinical entity from classical mechanical median-nerve entrapment. By integrating findings from the available literature with detailed clinical, ultrasonographic, and neurophysiological observations from two patients with SjD and CTS, we explored the possibility that inflammatory and immune-mediated mechanisms contribute to CTS in this population. The findings suggest that conventional surgical decompression may not provide durable symptom resolution in patients with SjD and support consideration of immunosuppressive treatment at an earlier stage of the therapeutic algorithm.

1. Introduction

The study was initiated from the established epidemiology of CTS, which represents the most common focal entrapment neuropathy and accounts for approximately 90% of all entrapment syndromes [29, 31]. CTS affects approximately 3–6% of the adult population [30]. PNS involvement is also well recognised across systemic autoimmune diseases, with reported frequencies of up to 70% in systemic vasculitis, approximately 15% in SLE, and up to 60% in SjD [10, 11].

SjD was historically described in the early 1930s by the ophthalmologist Henrik Sjögren, who recognised the characteristic combination of marked ocular and oral dryness in a patient with articular deformities [1, 2]. Within this broader clinical spectrum, neurological manifestations represent an important but heterogeneous component of the disease and may occur before the classical sicca symptoms or the formal diagnosis of SjD [10, 16].

2. Materials and Methods

A structured literature search was conducted using PubMed, Scopus, and Web of Science. The search strategy combined terms related to CTS and median-nerve compression with terms describing SjD and diagnostic modalities including nerve USG, nerve-conduction studies (ENG), and electromyography (EMG).

The literature-selection process was documented using a PRISMA-style flow. A total of 145 records were identified in PubMed, 180 in Scopus, and 105 in Web of Science. Following removal of 93 duplicate records, 337 publications were screened. Forty-three records were excluded during the screening stage, leaving 294 publications for retrieval. Of these, 92 could not be retrieved, while 202 were assessed for eligibility. Ultimately, 54 publications met the predefined inclusion criteria and were incorporated into the review.

The exclusion criteria comprised publication before 1985, non-peer-reviewed sources, publications in languages other than English, studies involving secondary Sjögren's syndrome or other autoimmune diseases, and basic-science investigations without direct clinical relevance.

Among the reviewed literature, one paper synthesised data across 11 distinct studies, including a total of 733 patients, showing that the mean reported prevalence of CTS was 12.8% (95% CI: 7.2–21.8%) [10, 11]. Substantial heterogeneity was observed between the studies (I^2 = 85%). The epidemiological characteristics of SjD were also considered, with the disease affecting approximately 0.2–2% of the global adult population, predominantly women, with a male-to-female ratio of approximately 1:9 and typical disease onset occurring between the fourth and sixth decades of life [1, 2].

3. Case Descriptions

Case 1

The first case involved a 62-year-old woman who was admitted to the Department of Rheumatology, Clinical Immunology, Geriatrics and Internal Medicine of the Medical University of Gdańsk in 2014 for diagnostic evaluation. The patient reported approximately one year of joint pain and neurological symptoms, including

subjective reduction in muscular strength affecting the left upper and lower extremities and impaired fine motor function of the hands.

The initial diagnostic evaluation demonstrated positive anti-*Borrelia* immunoglobulin M (IgM) antibodies, together with elevated aminotransferase and creatine kinase (CK) concentrations. EMG was unremarkable, and brain magnetic resonance imaging (MRI) did not reveal significant abnormalities. Despite treatment with doxycycline, the symptoms persisted, prompting further evaluation for systemic connective-tissue disease.

A diagnosis of SjD was subsequently established on the basis of positive anti-SSA and anti-SSB antibodies and histopathological examination of a minor salivary-gland biopsy demonstrating a focus score >1. In November 2014, ENG confirmed electrophysiological evidence of CTS. Surgical median-nerve release was subsequently performed and initially resulted in symptomatic improvement. Within several months, however, CTS symptoms recurred, and local corticosteroid injections were initiated.

A subsequent ultrasonographic examination demonstrated bilateral radiological features of CTS. These findings were confirmed by neurophysiological assessment, which demonstrated demyelinating changes on ENG. The clinical course therefore indicated recurrence or persistence of median-nerve dysfunction despite previous surgical decompression [51, 52].

Case 2

The second case involved a 52-year-old woman with an established diagnosis of SjD and CNS involvement. In March 2020, she presented to an orthopaedic outpatient clinic because of symptoms characteristic of CTS. Several courses of local corticosteroid injections had previously provided only temporary relief.

Because of recurrent symptoms, the patient was eventually referred for surgical management and underwent median-nerve release combined with flexor synovectomy of the right hand in December 2020. At the time of evaluation, no laboratory abnormalities capable of explaining the symptoms were identified. Thyroid function and electrolyte concentrations were normal, and no vitamin deficiencies were detected [18].

In March 2021, the patient reported recurrence of her symptoms. USG assessment did not demonstrate significant abnormalities beyond expected postoperative changes. Nevertheless, persistent swelling of the operated area and CTS-like symptoms continued, resulting in repeated medical consultations and further corticosteroid injections for symptomatic relief. Subsequent neurophysiological assessment demonstrated axonal-demyelinating changes. This case therefore demonstrated persistence of clinically and electrophysiologically evident neurological dysfunction despite management consistent with the conventional therapeutic approach to CTS [51, 52].

4. Discussion

The clinical observations were interpreted within a broader spectrum of PNS involvement in SjD. Neurological manifestations may be highly heterogeneous and include sensory neuropathies, axonal sensorimotor polyneuropathy, mononeuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy, cranial neuropathy, and autonomic neuropathy [12, 14, 16, 17].

An important limitation identified during the review was the considerable variation in terminology used to describe peripheral neurological manifestations of SjD. This heterogeneity may substantially limit comparisons between studies and complicate the interpretation of reported prevalence and treatment outcomes [10, 11].

The temporal relationship between neurological manifestations and the classical clinical features of SjD is also of particular importance. PNS involvement may precede the development of sicca symptoms or the formal diagnosis of SjD. Consequently, patients initially presenting with atypical CTS or other peripheral neurological symptoms may represent an early or incompletely recognised manifestation of systemic autoimmune disease [16]. In selected cases, neurological symptoms may subsequently improve following initiation of immunosuppressive treatment, further supporting the possibility of an immune-mediated component.

From a therapeutic perspective, systemic corticosteroids and IVIG have been reported as effective treatments for PN associated with autoimmune diseases, while

RTX has also demonstrated efficacy in selected cases of vasculitis-related PN in patients with SjD [13, 26, 28]. These observations support consideration of systemic immunomodulatory mechanisms when evaluating neurological symptoms in patients with SjD.

A clinically important observation emerging from both the reviewed literature and the two cases was the absence of a clear association between joint involvement in SjD and electrophysiologically confirmed CTS. This differs from the recognised relationship between CTS and articular disease in conditions such as RA and SLE [40, 42]. The findings therefore suggest that the pathophysiology of CTS in SjD may not be adequately explained by local joint inflammation or by the classical mechanical model of median-nerve compression.

The clinical courses described in our cases further raised concerns regarding the long-term effectiveness of surgical decompression in SjD. Although median-nerve release initially resulted in symptomatic improvement in the first case, symptoms subsequently recurred [51, 52]. In the second case, persistent symptoms and neurophysiological abnormalities were observed despite surgical decompression and flexor synovectomy. These observations suggest that mechanical decompression alone may not address the underlying pathological process when CTS occurs in the context of systemic autoimmune disease.

Surgical intervention must also be considered in the context of the additional risks associated with rheumatological disease and immunosuppressive treatment. These include an increased susceptibility to infection, postoperative complications, and potential exacerbation of underlying disease activity [54]. Consequently, the risk–benefit profile of surgery may differ between patients with autoimmune-associated CTS and those with conventional idiopathic or mechanically mediated CTS.

5. Clinical Implications

The findings of the review have several implications for the clinical assessment of patients presenting with CTS in the context of SjD. The potentially distinct pathophysiology of PN, including CTS, may influence both diagnostic reasoning and therapeutic decision-making in patients with an established diagnosis of SjD as

well as in those presenting with neurological symptoms before the autoimmune disease has been recognised.

The clinical presentation may be heterogeneous and may not conform to the classical pattern of isolated median-nerve entrapment. Multiple neurological complaints, proximal symptoms, recurrence following conventional treatment, or a discrepancy between clinical symptoms and postoperative imaging findings should therefore prompt consideration of an underlying systemic process [40, 41].

In patients with known or suspected SjD, particular attention should consequently be given to the possibility that CTS represents one component of broader PNS involvement. In such circumstances, assessment of systemic disease activity and consideration of immunomodulatory treatment may be warranted rather than relying exclusively on mechanical decompression [10, 13].

Our observations indicate that surgical release of the carpal tunnel may not provide durable symptom control in this patient population [51, 52]. The potential contribution of immune-mediated mechanisms should therefore be considered when determining the optimal therapeutic strategy, particularly in patients with multiple neurological manifestations or recurrence following conventional interventions.

6. Conclusions

Our review and case observations support the concept that CTS occurring in SjD may differ pathogenetically from classical mechanical median-nerve entrapment [10, 17]. This distinction has potentially important implications for both treatment selection and prognosis.

In patients presenting with multiple neurological complaints, atypical CTS symptoms, or persistent or recurrent symptoms despite conventional treatment, an underlying rheumatological disorder should be considered [40]. In the context of established or suspected SjD, peripheral neurological symptoms may represent an expression of systemic disease rather than an isolated local entrapment neuropathy.

The higher prevalence of CTS reported in patients with SjD, together with the clinical courses observed in our cases, warrants further investigation of the underlying mechanisms. A more comprehensive understanding of the relationship between systemic immune activity, peripheral nerve dysfunction, and median-nerve compression may ultimately support the development of a more unified, interdisciplinary, and patient-centred approach to diagnosis and treatment.

Publication 3.

Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease-Associated Carpal Tunnel Syndrome

Article in Brief

Our prospective observational study investigated the response to USG-guided corticosteroid injection in patients with CTS associated with SjD and compared treatment outcomes with those observed in patients with idiopathic CTS. The study addressed an important clinical problem: despite objective improvement in the structural features of median-nerve compression, patients with SjD may continue to experience substantial neurological symptoms and functional impairment [45].

The central focus of the study was the relationship between structural and clinical treatment outcomes. USG was used to assess changes in the CSA of the median nerve, while clinical response was evaluated using measures of symptom severity and hand function. By analysing these parameters together, the study investigated whether a reduction in local median-nerve swelling corresponded to meaningful symptomatic and functional improvement and whether additional PNS involvement influenced treatment response.

1. Aim of the Study

The aim of the study was to compare the efficacy of USG-guided corticosteroid injection in patients with SjD-associated CTS and patients with idiopathic CTS. Treatment response was assessed using both objective structural parameters and subjective clinical outcomes.

The objective assessment comprised ultrasonographic measurement of changes in the CSA of the median nerve [57, 58]. Clinical outcomes were evaluated using the DASH and BCTQ, including the SSS and FSS [45]. The study also examined whether concomitant peripheral neuropathy, bilateral CTS, or other clinical characteristics influenced the response to treatment.

2. Materials and Methods

The study included 20 patients with SjD-associated CTS and 19 with idiopathic CTS who consented to local injections. These recruitment numbers reflect patient preferences regarding therapeutic interventions previously documented by our team [76]. The latter group served as a comparison cohort representing CTS occurring in the absence of the systemic autoimmune background associated with SjD. The follow-up visits and evaluations were completed by 19 and 18 patients respectively.

All participants underwent USG-guided corticosteroid injection [46, 48]. Clinical and ultrasonographic assessments were performed before treatment and during follow-up. USG was used to measure the CSA of the median nerve as an objective indicator of local nerve swelling and the structural component of CTS [58, 77–80].

Clinical outcomes were assessed using the BCTQ, comprising the SSS and FSS. The presence of additional peripheral neuropathies and bilateral CTS was also evaluated, as these features could indicate more extensive peripheral nervous system involvement and potentially influence treatment response.

3. Results

USG-guided corticosteroid injection resulted in a significant reduction in the CSA of the median nerve in patients with SjD-associated CTS. The magnitude of this structural response was greater than that observed in patients with idiopathic CTS. The mean reduction in CSA was 0.46 mm^2 in the SjD group compared with 0.31 mm^2 in the idiopathic CTS group. This difference was statistically significant ($p = 0.006$; Cohen's $d = 0.96$).

Despite the greater structural response, patients with SjD did not experience a comparable degree of clinical improvement. The reduction in the BCTQ SSS was −6.13 in the SjD group compared with −14.16 in the idiopathic CTS group ($p = 0.021$). Similarly, the reduction in the FSS was −1.42 in the SjD group and −6.39 in the idiopathic CTS group ($p = 0.033$). Thus, patients with SjD demonstrated a greater reduction in median-nerve swelling but significantly less improvement in both symptom severity and hand function.

The presence of additional PN was associated with poorer clinical outcomes. PN was identified in 58% of the overall study cohort. Patients with isolated CTS demonstrated greater improvement than those with CTS accompanied by another PN. The reduction in the SSS was −12.94 among patients with isolated CTS compared with −4.98 among those with concomitant peripheral neuropathy (p = 0.040). Corresponding changes in the FSS were −5.95 and 0.43, respectively (p = 0.014).

Bilateral CTS was also more frequent among patients with SjD, occurring in 75% of this group compared with 47% of patients with idiopathic CTS. The higher frequency of bilateral involvement further supported the possibility of systemic factors contributing to the neurological manifestations observed in SjD [40].

4. Discussion

The principal finding of the study was the discordance between structural and clinical treatment outcomes [45]. Corticosteroid injection produced a greater reduction in median-nerve swelling in patients with SjD than in those with idiopathic CTS. Nevertheless, the SjD group demonstrated significantly less improvement in symptom severity and hand function.

This discrepancy suggests that the clinical manifestations of CTS in SjD cannot be explained exclusively by local mechanical compression of the median nerve [10, 17]. Although corticosteroid treatment reduced the local structural component of nerve compression, this improvement did not translate into a comparable degree of symptomatic recovery. The findings therefore support the involvement of additional pathological mechanisms affecting the PNS [65–67].

Concomitant PN appeared to be particularly relevant. The poorer clinical response observed in patients with additional neuropathy suggests that CTS may form part of a more extensive neurological phenotype in SjD [16, 61]. In these patients, local treatment directed at the carpal tunnel may reduce median-nerve swelling without adequately addressing the broader mechanisms contributing to pain, paraesthesia, sensory disturbances, and functional impairment.

The high frequency of bilateral CTS provides further support for the contribution of systemic factors. Bilateral involvement is less readily explained by an isolated local

abnormality and may instead reflect the effects of systemic autoimmune activity on the PNS [40]. This observation may also help explain differences in the clinical course and treatment response between SjD-associated CTS and idiopathic CTS.

Taken together, these findings strengthen the concept that CTS in SjD may represent more than a purely mechanical entrapment neuropathy. The local compression component remains therapeutically relevant, as demonstrated by the reduction in median-nerve CSA following corticosteroid injection; however, the limited clinical response indicates that additional immune-mediated or diffuse peripheral neurological mechanisms may contribute to the persistence of symptoms.

5. Clinical Implications

The findings have several implications for the assessment and management of CTS in patients with SjD. Firstly, a reduction in the USG CSA of the median nerve should not be interpreted as evidence of complete clinical recovery [45]. Structural improvement and symptomatic improvement appear to represent partially independent dimensions of treatment response and may not occur to the same extent.

Secondly, patients with persistent symptoms following corticosteroid injection should be evaluated for additional PN. Neurophysiological assessment may be particularly informative in patients with bilateral symptoms, manifestations extending beyond the classical median-nerve distribution, or clinical complaints that appear disproportionate to the local ultrasonographic findings [59, 70, 81].

Lastly, treatment planning should incorporate both local and systemic aspects of the disease. USG-guided corticosteroid injection can effectively reduce median-nerve swelling and therefore addresses an important local component of CTS [46–48]. However, its limited effect on symptoms and functional impairment in some patients indicates that local treatment alone may be insufficient when CTS occurs in the context of broader SjD-associated neurological involvement [10, 66, 67].

These findings also highlight the importance of integrating clinical, neurophysiological, and imaging assessments when evaluating treatment responses. Reliance on a single objective parameter, particularly ultrasonographic

reduction in nerve swelling, may overestimate the overall clinical benefit of treatment.

6. Conclusion

Our study demonstrated that USG-guided corticosteroid injection produces a significant structural response in patients with SjD-associated CTS, with a greater reduction in the CSA of the median nerve than that observed in patients with idiopathic CTS. However, this greater structural response was not accompanied by equivalent clinical improvement. Patients with SjD showed significantly less improvement in both symptom severity and hand function.

The observed discrepancy between ultrasonographic improvement and clinical recovery indicates that CTS in SjD cannot be considered solely a consequence of local mechanical median-nerve compression [10, 17]. Concomitant PN was associated with poorer treatment outcomes, while bilateral CTS was more frequently observed in patients with SjD, further supporting the contribution of systemic neurological mechanisms.

These findings support a broader interpretation of CTS in the context of SjD, in which local median-nerve compression is considered alongside the possibility of diffuse or immune-mediated peripheral nervous system involvement [12, 13]. Consequently, treatment response should be evaluated using a combination of structural, clinical, functional, and neurophysiological parameters rather than relying exclusively on ultrasonographic changes [57, 58, 70].

Overall, the study supports a more comprehensive approach to SjD-associated CTS, integrating local treatment of median-nerve compression with assessment for broader PN and systemic neurological involvement.

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X. PUBLICATIONS

1. Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients

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OBSERVATIONAL RESEARCH

Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome – a prospective observational study on 50 patients

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Abstract

Introduction Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by lymphocytic infiltrates in the exocrine glands. Carpal tunnel syndrome (CTS) is suggested to be more frequent among SS patients than in the general population. The aim of this study was to seek associations between the CTS and the laboratory and clinical findings of SS patients.

Methods Fifty patients diagnosed with primary SS (pSS) were examined. Clinical evaluation by a rheumatologist and electrophysiological studies were conducted. Data on laboratory tests results was collected. Control group consisted of 50 sex and age-matched individuals with osteoarthritis (OA).

Results Out of 50 patients in the study group 27 (54%) were diagnosed with CTS. The prevalence of CTS among 50 individuals in the control group was 8%. Among pSS patients with CTS the joint involvement was not more common than in those from the non-CTS group [15 vs. 13 ($p=0.945$)]. There was an expected difference in sleep disorders [18 vs. 9 ($p=0.012$)] and paresthesia [23 vs. 13 ($p=0.024$)]. The major finding was a significant difference in elevated beta2-microglobulin (B2MG) [23 vs. 13 ($p=0.024$)]. Other studied factors, suggested in the literature as significant in the pSS-related neuropathy, were not statistically different between the groups.

Conclusion Our study confirms that CTS is more prevalent among pSS patients than in the general population and suggests that a new approach is required towards the pathogenesis of this phenomenon. We hypothesize that CTS is more associated with an overall disease activity than joint involvement as such.

Keywords Beta 2-microglobulin · Carpal tunnel syndrome · Amyloid neuropathy · Connective tissue diseases · Sjögren's syndrome · Peripheral nervous system diseases

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Introduction

The Sjögren syndrome (SS) was first described in the early 30s of the 20th century by an ophthalmologist Henrik Sjögren, who observed remarkable dryness of the eyes and oral cavity in a patient with articular involvement [1]. This connective tissue disease, characterized by lymphocytic infiltrates in the exocrine glands affects 0.2–1% of the general population, more commonly females (male-to-female ratio being 1:9) [2]. The symptoms usually develop in the fourth to sixth decade of life. Despite the dryness of the oral cavity and eyes being the most widely recognized symptoms, SS may lead to other, extraglandular manifestations, involving respiratory, cardiovascular, gastrointestinal, musculoskeletal and urinary systems [3, 4]. A common, yet understudied and underdiagnosed, manifestation of SS is the nervous system involvement, which affects both central (CNS) and peripheral nervous system (PNS) with the incidence of 6–48% and 2–60% respectively [5–8]. The PNS involvement may present itself in a variety of ways including sensory neuropathies, axonal sensorimotor polyneuropathy, mononeuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy, cranial neuropathy, chronic inflammatory demyelinating polyneuropathy (CIPD), small fiber neuropathy and autonomic neuropathy [9, 10]. The pathophysiology behind the high incidence of PNS involvement is not yet known. The researchers refer to the potential importance of antinuclear antibodies (ANA), anti-SSA and anti-SSB antibodies and their affinity to different nervous fibers [11–13] as well as the role of rheumatoid factor (RF). It has been suggested that clinical features, such as longer course of the disease, history of vasculitis and Raynaud phenomenon could be the risk factors for development of PNS symptoms [14, 15]. Among the laboratory biomarkers factors such as lowered concentration of complement components, especially C3 and C4, hypergammaglobulinemia, vitamin D and vitamin B12 deficiencies are brought to attention [16–20].

The carpal tunnel is an anatomical region localized on the palmar area of the wrist. It is formed at the base by eight bones organized in two parallel rows (proximally scaphoid, lunate, triquetrum, and pisiform; distally trapezium, trapezoid, capitate, and hamate) and by a thick sheet of connective tissue (flexor retinaculum, otherwise known as transverse carpal ligament) at the top. Ten structures pass through the tunnel from the forearm to the hand - nine long flexor tendons (flexor pollicis longus, four tendons of flexor digitorum superficialis, and four tendons of flexor digitorum profundus) and the median nerve. A rigid surrounding, formed by bones and ligament, on one hand grants protection, on the other significantly limits the tolerance for an increase in the volume of any of the elements.

Carpal tunnel syndrome (CTS) is characterized by the presence of neurological signs and symptoms resulting from injury of the median nerve caused by compression within the carpal tunnel. Patients may experience paresthesia (tingling and numbness within the palm), sensory deficits, pain of the hand and forearm, weakness of the muscles of the hand. Neurologic signs and symptoms are accompanied by abnormalities in nerve conduction study of the median nerve [21].

Among patients diagnosed with rheumatic diseases, CTS is the most frequent among those with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [22]. This phenomenon is attributed in the literature to the joint abnormalities observed in the diseases – particularly with joint (including wrists) swelling in the periods of exacerbation [22], which leads to compression and consequently mechanical damage and ischemia of the median nerve. Until now, similar pathogenesis was suggested in the case of primary Sjögren Syndrome (pSS) due to commonly occurring arthritis [23]. However, our clinical observations do not support this hypothesis.

Based on the characteristics of CTS among pSS patients (frequently occurring bilaterally, poorly responding to local therapeutic procedures) we hypothesize that in fact CTS constitutes one of the presentations of PNS involvement. At the same time, it is common also among the general population, making it a good base for comparative analysis. The novelty and clinical significance of this study lies in the extensive data collected on the participants (laboratory findings, neurophysiological testing). The aim of this study is to determine potential risk factors, biomarkers and the pathomechanism of this peripheral neuropathy in patients diagnosed with pSS, allowing clinicians managing this group of patients in their daily practice to implement early diagnostic and therapeutic approaches.

Methods

We studied a group of fifty consecutive patients with pSS from a large university-based hospital. All patients met the diagnostic criteria for pSS of the American European Consensus Group from 2002 [24] or the criteria of Sjögren's International Collaborative Clinical Alliance from 2012 [25]. According to these, in case of absence of anti-SSA and/or anti-SSB with concomitant sicca symptoms, the patients underwent biopsy of labial salivary gland with evaluation of focus score, with a FS >= 1 (a cluster of >= 50 lymphocytes within a 4mm2 area) being indicative for the diagnosis. Patients with secondary SS were excluded from the study. Other exclusion criteria included: diagnosis of diabetes or other conditions leading to damage of nervous fibers,

such as degenerative disc disease, abuse of alcohol or other toxic substances, organ failure (particularly liver and kidney), severe vitamin deficiencies with focus on the vitamin B complex and vitamin D as well as other neurological disorders and chronic renal failure. All patients underwent clinical evaluation by a rheumatologist and data on the medical history was collected. The control group consisted of age and sex-matched adults with diagnosed osteoarthritis who were under the care of the orthopedic outpatient clinic of the hospital. Patients were included in the study following an exclusion of any rheumatological diseases during evaluation by a certified rheumatologist.

All the patients underwent neurological assessment and nerve conduction studies of nine peripheral nerves (peroneal, tibial, sural, median bilaterally and ulnar unilaterally). Studies were performed under the protocol recommended by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [26]. Medtronic's Dantec Keypoint G4 equipment was used in a standardized environment (temperature of 32-34oC). To establish the lower limits of normal values 50 age-matched healthy individuals were examined. Polyneuropathies were classified following the European Standardized Telematic Tool to Evaluate Electrodiagnostic Methods (ESTEEM) guidelines. Classification included axonal, demyelinating, or mixed polyneuropathies [27]. Based on the results, coupled with physical examination (both performed and interpreted by a certified neurologist) the patients were divided into two groups – with peripheral nervous system involvement (PNS+) and without peripheral nervous system involvement (PNS-). Inclusion in the PNS + group involved finding of at least one of the following signs on the clinical examination: sensory deficit (tactile or vibration) or paresthesia or neuropathic pain found in at least one anatomical area innervated by specific peripheral nerves or neural roots; flaccid paresis found in any of the limbs; reduction of at least two tendon reflexes in at least one limb; signs of demyelination or axonal injury found in NCS of at least two nerves, behind typical localization of entrapments.

Moreover, for this analysis patients were divided into two groups based on the results of neurophysiological tests of median nerves – presenting signs of carpal tunnel syndrome (CTS) and free from carpal tunnel syndrome signs (non-CTS). Carpal tunnel syndrome was diagnosed in patients presenting typical signs and symptoms of CTS (any sign or symptom from the list: tingling and numbness within palm, pain of the hand and the forearm, sensory loss within the hand, loss of strength in hand) with positive Tinel's sign or Phalen's sign [28] accompanied by abnormal neural conduction in the corresponding median nerve.

The diagnostic techniques used in the nerve conduction studies of CTS have been described collectively by Werner and Andary [29]. All the tests performed in this study followed the AANEM recommendations [30]. According to these, the standard diagnostic approach to CTS includes the sensory conduction studies of the median nerve measured across the wrist and if abnormal compared with another sensory nerve of the symptomatic limb as well as additional studies in case of normal electrophysiological test result when conduction distance is greater than 8 cm. Moreover, it is suggested to perform a motor conduction studies from the thenar muscle and one other nerve in the symptomatic limb as well as optionally electromyography of muscles innervated by the C5 to Th1 spinal roots and comparison of motor nerve distal latencies of the median and ulnar nerves.

Disease activity and functional outcomes were assessed using the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) [31]. The scale focuses on 12 domains: cutaneous, respiratory, renal, articular, muscular, PNS, CNS, hematological, glandular, constitutional, lymphadenopathic, and biological. Depending on the score, each of the domains is divided into 3–4 levels of activity. The definition of moderately active disease involves the ESSDAI$\geq$ 5.

The subjective perception of the disease activity was assessed by the patients using EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) [32]. This evaluation includes a questionnaire related to complaints such as: dryness, fatigue, and pain. Each of the components is measured with a 0–10 numerical scale, referring 0 as the lowest disease activity.

The study was approved by the Independent Bioethics Committee for Scientific Research of Medical University of Gdańsk, Poland (consent no. NKEBN/345/2011) and it met the ethical standards of the 1964 Helsinki declaration with successive amendments. All participants gave their written, informed consent.

The study was an observational study, performed on the results of patients under the care of our Department in the years 2012–2018.

Statistical analysis

The normality of the distribution was checked using the Shapiro-Wilk test. Depending on its result, the continuous variables were compared using the Mann–Whitney U test or the Student T-test. Categorical variables were compared with the use of the Chi-squared test. A p-value of 0.05 or less was considered significant.

Results

Our group consisted of 50 patients with a median age of 57.5 years (33–74). Of them 48 (96%) were female. The median age at pSS diagnosis was 53.5 years (23–69) with the median age of first symptoms of 46 years (18–66). The median disease duration since diagnosis in the group was 1.5 years, ranging from 1 to 15 years. The median time from the first symptoms to the diagnosis was 5 years (0–26). The median BMI of the participants was 25.1 (16.6–34.4).

Based on the neurophysiological examination 27 patients (54%) were classified into the CTS group and 23 into the non-CTS group. The prevalence of CTS among the control group was 8%, which corresponded with the epidemiologic data for the general population described in the literature.

There were no statistically significant differences between the groups in terms of age, BMI, age at the onset of symptoms, age at diagnosis, time elapsed from the first symptoms till the diagnosis or the disease duration. The detailed descriptives are presented in Table 1.

Among the laboratory findings, those involving the prevalence of antibodies, including SS specific anti-SSA and anti-SSB antibodies, rheumatoid factor (RF) and antineutrophil cytoplasmic antibodies (ANCA) did not differ between the groups. The classic meters of inflammation, such as elevated erythrocyte sedimentation rate (ESR), elevated concentrations of C-reactive protein (CRP) or fibrinogen were not significantly different between the groups. Decreased C3 and C4 component elements' concentrations were observed in only 4 and 3 patients respectively in each of the analyzed groups. Prevalence of vitamin D and B12 deficiencies was similar in both groups, as were the abnormalities in the total blood count, such as leukopenia, neutropenia, lymphopenia, anemia. Moreover, in terms of clinical features, including the history of vasculitis and thyroid insufficiency or presence of Raynaud phenomenon there was no statistically significant difference between the groups. Interestingly, CTS was more prevalent among patients reporting symptoms suggesting peripheral nervous system (PNS) involvement (24 vs. 16; $p=0.089$). The neurophysiological tests, however, excluding the cases of CTS, did not find signs of PNS involvement more commonly in that group of participants. Statistically significant differences were found between the groups in the following aspects: elevated B2MG concentration, defined as a concentration > 2.6 mg/l, which is the upper limit of normal in our laboratory, (23 vs. 13; $p=0.024$), reporting paresthesia (23 vs. 13 patients; $p=0.024$) and reporting sleep disorders (19 vs. 8; $p=0.012$). As a standard proceeding, in all the patients with elevated B2MG concentrations a full diagnostic process was performed, including the electrophoresis of plasma proteins, immunoglobulin light chains assessment and testing for presence of a monoclonal protein. In justified cases a bone marrow biopsy was performed. In case of lymphoma suspicion the patients underwent ultrasonography of the peripheral lymph nodes and in case of doubts also a full-body CT scan for detection of pathological lymph nodes. Detailed descriptions of the group are included in Table 2 below.

The patients underwent assessment in the direction of depressive disorders using Beck Depression Inventory [33]. Out of the whole group, 29 patients (58%) scored 10 or more points, suggestive of depressive episode, but no statistically significant difference was noted between the CTS and non-CTS groups (mean result 12.826 vs. 12.37 points; $p=0.639$). A history of previous psychiatric treatment (mainly due to depression, anxiety and sleep disorders) was more prevalent among CTS group but without statistical significance (13 vs. 9; $p=0.522$).

Discussion

The present study demonstrates a significant positive correlation between the elevated B2MG and the presence of CTS in pSS patients. There were no statistically significant differences among other laboratory findings and CTS, including elevated ESR and CRP as well as clinical characteristics of the patients, including history of vasculitis, thyroid insufficiency and presence of Raynaud phenomenon.

The values of CRP and ESR are commonly used in clinical practice as disease activity measures. For instance, in the case of RA their role has been so well described, that their values constitute a part of a popular clinical tool for the measurement of disease activity – Disease Activity Score (DAS 28) [34]. However, according to the literature, CRP and ESR do not constitute trustworthy measures of the disease activity in SS. Similar to ESR and CRP, other parameters recognized as activity measures in rheumatic diseases, such as decreased C3 and C4 or increased fibrinogen concentration did not correlate with the occurrence of CTS in

Table 1 Clinical characteristics of the CTS and the non-CTS patients' groups

	CTS ($n=27$)	Non-CTS ($n=23$)	p
Age (years)	61	56	0,072
BMI (kg/m^2)	26,17	23,14	0,350
Age at first symptoms (years)	49	44	0,173
Age at diagnosis (years)	57	50	0,084
Time till diagnosis (years)	7,7	6,65	0,799
Disease duration (years)	3	1	0,479

Table 2 Prevalence of laboratory test abnormalities and clinical features in groups of CTS and non-CTS patients diagnosed with pSS

	non-CTS ($n=23$)	CTS ($n=27$)	p
POSITIVE SSA ANTIBODIES	15 (65.22%)	19 (70.37%)	0.542
POSITIVE SSB ANTIBODIES	12 (52.17%)	11 (40.74%)	0.346
POSITIVE ANCA	0 (0%)	0 (0%)	0.106
POSITIVE RF	14 (60.87%)	16 (59.26%)	0.969
DECREASED C3	4 (17.39%)	4 (14.81%)	0.821
DECREASED C4	3 (13.04%)	3 (11.11%)	0.639
HYPERGAMMAGLOBULINEMIA	12 (52.17%)	16 (59.26%)	0.774
ELEVATED ESR	7 (30.43%)	11 (40.74%)	0.449
ELEVATED CRP	3 (13.04%)	7 (25.93%)	0.256
ELEVATED B2MG	**13 (56.52%)**	**23 (85.19%)**	**0.024**
VITAMIN B12 DEFICIENCY	0 (0%)	3 (11.11%)	0.166
VITAMIN D DEFICIENCY	9 (39.13%)	15 (55.56%)	0.467
ELEVATED FIBRINOGEN	10 (43.48%)	16 (59.26%)	0.266
LEUKOPENIA	7 (30.43%)	11 (40.74%)	0.449
NEUTROPENIA	4 (17.39%)	8 (29.63%)	0.313
LYMPHOPENIA	5 (21.74%)	9 (33.33%)	0.363
ANEMIA	7 (30.43%)	12 (44.44%)	0.309
RAYNAUD PHENOMENON	7 (30.43%)	9 (33.33%)	0.546
VASCULITIS	5 (21.74%)	6 (22.22%)	0.967
JOINT INVOLVEMENT	13 (56.52%)	15 (55.56%)	0.945
HYPOTHYROIDISM	3 (13.04%)	3 (11.11%)	0.834
PNS INVOLVEMENT SUBJECTIVE	16 (69.57%)	24 (88.89%)	0.089
PNS INVOLVEMENT OBJECTIVE (EXCLUDING CTS)	9 (39.13%)	14 (51.85%)	0.368
SLEEP DISORDERS	**8 (34.78%)**	**19 (70.37%)**	**0.012**
PARESTHESIA	**13 (56.52%)**	**23 (85.19%)**	**0.024**

the studied group. Moreover, patients develop compounding decreases in concentrations of the morphotic elements as the disease progresses, making cytopenia one of the clinically utilized meters of disease activity. Cytopenia can develop in the course of SS or even precede typical sicca symptoms and delay the diagnosis [35]. Considering this aspect, we performed the analysis of cytopenia prevalence among the patients. No statistically significant difference between CTS and non-CTS patients was found.

Vasculitis is a group of several diagnostic entities that share the inflammation and consequently necrosis of the blood vessels of different diameters. A specific subtype, described as *vasculitic neuropathy* constitutes one of the reasons for nervous system dysfunction in rheumatic diseases. Inflammatory changes at the level of vasa nervorum impair the blood supply to the nervous fibres, leading to their damage, with time – irreversible [36, 37]. Small vessel disease is usually associated with ANCA antibodies [38–40], therefore their presence has been suggested in the literature as a potential biomarker of susceptibility to PNS involvement. Among our patients none of those in the CTS nor non-CTS group tested positive for ANCA antibodies.

Hypothyroidism is most frequently caused by chronic autoimmune thyroiditis (Hashimoto disease), however there are several more potential reasons for this disorder [41]. The severity of symptoms varies from mild impairment to disability. Although both muscular and neurological symptoms are well recognized complications of untreated thyroid hormone deficiency, their prevalence is not coherently described. Based on the literature, neurological manifestations (mostly sensorimotor neuropathy) are present in 10 to 70% of patients [42]. Additionally, increased BMI is suggested as an independent risk factor for CTS among hypothyroidism patients [43]. In the case of our patients none of these factors proved significant to the development of CTS.

Although some researchers considered the anti-SSA and anti-SSB antibodies potential culprits in the PNS involvement, there is plenty of discrepancy among the studies. Some of them highlight the role of anti-SSA antibodies [11], others attributing nearly equal importance to both anti-SSA and anti-SSB antibodies [13]. In the case of our group there was no statistically significant difference in the prevalence of either of the antibodies, neither in the CTS and non-CTS groups, nor in the population of patients diagnosed with PNS involvement other than the CTS. Literature reports suggest though, that patients seropositive for both of the antibodies present higher levels of B2MG [44]. Therefore, considering the association between B2MG concentration and prevalence of CTS there might be an indirect relationship between the antibody type and susceptibility to CTS.

Connective tissue disorders often co-occur with mental health problems, particularly depression. Symptoms such as persistent pain, joint deformities, pulmonary or cardiac manifestations substantially lower the quality of life of

patients (QoL). Long-lasting, immunosuppressive treatment carries the risk of opportunistic infections and malignancies. Other aspects impairing daily functioning include among others: lack of support from family and friends, lack of understanding of patients' complaints and symptoms, costs generated by healthcare visits and medication, feeling of insecurity related to the future (source of income, disease complications, side effects of the therapy). According to data published in 2021, 3% of the Polish population experienced at least one depressive episode [45]. Meanwhile, among our study group 29 patients (58%) scored 10 or more points in the Beck depression scale and 22 patients (44%) had a history of psychiatric treatment (mainly due to depression, anxiety and sleep disorders). Long-lasting, lowering the QoL symptoms of CTS, including sleep disorders and paresthesia, coupled with higher prevalence of psychiatric disorders in pSS population, may lead to the development of depression requiring pharmacological treatment.

The role of beta2-microglobulin

B2MG is a naturally occurring polypeptide, encoded in chromosome 15, consisting of 100 amino acids, with a total molecular weight of 11 800 Da. Its binding with major histocompatibility complex II (MHC II) / human leukocyte antigen I (HLA I) is present on all nucleated cells [46]. Moreover, the complex created between the alpha chain of HLA I and B2MG is vital for antigen presentation [47, 48]. In healthy individuals, the majority of B2MG is excreted through renal filtration, maintaining a normal serum concentration at the level of 1–3 ug/ml [49]. Normal values may differ slightly depending on the laboratory. Elevated levels of B2MG are observed, among others, in myeloma, lymphoma, liver disease and renal failure. In case of renal failure, the B2MG concentrations are inversely correlated with the glomerular filtration rate and can reach levels even 60 times higher than normal [50, 51]. The significance of B2MG as a biomarker of other conditions has been overlooked for many years. Nowadays, however, there is evidence suggesting its importance in malignancies (including ovarian [52], prostate [53], breast [54], gallbladder [55] cancers and renal cell carcinoma [56]), systemic lupus erythematosus (SLE) and Still disease [57, 58] by corresponding B2MG concentrations with disease activity and survival. Based on literature, B2MG also plays a role in SS.

A big prospective study, conducted on 395 participants, showed that B2MG concentration, together with the free light chains of gamma-globulins best corresponded with the disease activity measured in ESSDAI [44]. In the case of our patients, hypergammaglobulinemia did not correlate with the presence of CTS diagnosis. However, the incidence of CTS correlated with the elevation of B2MG above 2.6 mg/l reaching a statistically significant difference, giving the basis to correlate the occurrence of CTS with the overall disease activity, rather than just the articular manifestation. Moreover, B2MG has a known potential for the formation of amyloid fibrils which tend to deposit in the osteoarticular system, leading among others to CTS symptoms. Such findings are well-described in end-stage kidney disease (ESKD) patients undergoing hemodialysis (HD) but the pathomechanism behind it has not been fully understood [59, 60].

The first reports of increased prevalence of CTS among ESKD come from 1975 paper by Warren and Otieno [61]. Initially this phenomenon was attributed to the kind of fistulas with coexisting upper limb oedema leading to compression of the median nerve. Histopathological findings of samples from CTS surgical specimens proved that theory wrong, revealing with Congo-red staining presence of amyloid [62]. Further investigations on synovial amyloid led to the discovery of B2MG [50]. The proof for systemic character of the B2MG deposition comes from autopsies of patients on chronic HD, specifically the rectal mucosa [63]. Currently CTS secondary to ESKD is a frequent clinical problem due to the increasing number of patients on chronic renal replacement therapy. However, the symptoms tend to appear later from the initiation of HD and are often more subtle due to improvement of dialysis technology, including an increased B2MG clearance [64].

In the case of ESKD patients the B2MG levels usually significantly exceed the normal range (as mentioned above reaching even 60-fold of the upper normal range). The concentrations observed in pSS do not reach such levels, unless in instances of concomitant hematological malignancy or kidney failure. Nevertheless, based on the literature there is no definite correlation between the serum levels of B2MG and risk of amyloidosis development [65]. Despite over 40 years of studies on the underlying cause of dialysis related amyloidosis (DRA) little is still understood. Researchers raise the matter of probable facilitating factors, but those have not been established yet. Therefore, some form of interaction between inflammatory proteins or antibodies occurring in pSS patients cannot be ruled out and requires further research in this area. A systemic involvement, like the one observed in DRA, might be a contributing factor to other extraglandular symptoms in pSS.

Our results allow us to suspect that the increased incidence of CTS in ESKD and SS patients may share a similar mechanism. To our knowledge, no such observation has been made until now. Undoubtedly, more research is required in this field, most probably involving histopathological examinations of samples obtained during surgical interventions of the carpal tunnel release. Should our hypothesis find its support in the results, it would constitute a substantial change in

the diagnostic and therapeutic approach to SS patients with symptoms suggestive of CTS and raise the importance of immunosuppressive medication and local steroid administration above the traditional, orthopedic interventions.

Limitations

The study was conducted in a tertiary care university hospital, potentially resulting in a bias in patient selection caused by referral.

Unequivocal contribution of neuropathy to the underlying systemic disease requires years of observation. Therefore, we are unable to state with all certainty that observed neuropathy does not result from other causes (except those identified as exclusion criteria). However, such distinction does not affect the presented results, significant for the essence of the study.

The main advantage of this study is a thorough neurological and rheumatological assessment performed by one certified specialist in each field. Much of the research in this topic and related topics was based on retrospective assessment. Additionally, only patients with pSS were included in the study, after excluding other significant diagnoses, which allows us to obtain the most precise information about a specific disease entity.

Conclusion

The analysis of data on 50 pSS patients conducted by our team suggests the need for reassessment of CTS pathophysiology among SS patients. We hypothesize that CTS is in fact more of a presentation of PNS abnormalities found in SS patients rather than isolated mononeuropathy, which might affect the therapeutic approach to this group of patients. Moreover, based on hitherto clinical observations we hypothesize that beta2-microglobulin (B2MG) plays a significant role in the pathogenesis of CTS in SS patients.

Our results suggest the need of extended screening for CTS among patients diagnosed with SS and elevated B2MG concentration who report upper limb paresthesia. CTS, if untreated, leads to unpleasant symptoms, severely impairing the quality of life of our patients. Therefore, there is a substantial demand for more research into the matter, particularly at the molecular level, in order to find the most efficient therapeutic strategies for our patients.

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Author contributions As the corresponding and first author of the article I take full responsibility for the accuracy and integrity of all aspects of the work by all authors.

Data availability Parts of the data, regarding prevalence of peripheral nervous system involvement in primary Sjögren Syndrome patients, were presented during poster session on EULAR 2019 congress: Ann Rheum Dis, volume 78, supplement 2, year 2019, page A1173. https://doi.org/10.1136/annrheumdis-2019-eular.4851.

Declarations

Conflict of interest None of the authors has any conflict of interest to disclose.

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2. Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications

Case-based review

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Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications

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Abstract

Carpal tunnel syndrome (CTS) is the most common entrapment syndrome, affecting 3–6% of the adult population. Its prevalence among patients with primary Sjögren's disease (pSJD) is much higher. Interestingly, clinical observations do not support the view that the incidence of CTS increases with joint involvement. Moreover, patients with pSJD oftentimes present worse outcomes of traditional therapeutic methods. Herein, we present two cases of patients with CTS in the course of pSJD. In one of them, there was rapid recurrence of symptoms after surgery, and in the other, delayed healing was observed. In this article, the authors highlight the diagnostic and therapeutic challenges encountered in daily practice, resulting from probable differences in the pathophysiology of nerve involvement in Sjögren's disease patients.

Key words: systemic disease, neuropathy, Sjögren's disease, entrapment syndromes.

Introduction

Carpal tunnel syndrome (CTS) is the most common entrapment syndrome, accounting for 90% of all focal entrapment neuropathies [1, 2] and affecting 3–6% of the adult population [3]. The symptoms include characteristic pain, numbness, and paraesthesia in the palmar and dorsal distribution of median nerve innervation. As the syndrome progresses, patients may experience motor dysfunction such as weakness and impaired fine motor skills, along with atrophy of the thenar muscles. Although the majority of reported cases remain idiopathic, some predisposing factors have been identified, including wrist trauma and repetitive flexion of the wrist (e.g., while operating machinery or a computer). Females are 3 times more likely to develop this neuropathy, attributed to their higher representation among high-risk professions (e.g., tailors, secretaries) and the anatomically smaller carpal tunnel, which facilitates the occurrence of increased pressure on the structures within it [4, 5]. Moreover, potential genetic factors have been suggested [6]. When evaluating potential risk factors, it is crucial not to overlook the role of rheumatological conditions of the patient, particularly systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's disease (SjD).

Sjögren disease, previously known as Sjögren syndrome, is an autoimmune disease characterised by lymphocytic infiltrates in the exocrine glands. However, as the disease progresses, multiple organs can be affected, sometimes leading to life-threatening complications. One of the frequent yet understudied manifestations of this disease is peripheral neuropathy. According to the literature and our clinical experience, the incidence of CTS in SjD patients significantly exceeds that observed in the general population. A review of 11 studies focusing on CTS in SjD patients revealed considerable discrepancies in the reported prevalence. An analysis of 733 patients showed an average incidence of 12.8% (95% CI: 7.2–21.8%), with high heterogeneity across studies (I^2 85%) [7]. This article aims to highlight the diagnostic and therapeutic challenges encountered in clinical practice due to potential differences in the pathophysiology of nerve involvement in SjD patients.

Material and methods

The literature search was conducted using PubMed, Scopus, and Web of Science. The search phrase was: ("Carpal Tunnel Syndrome" OR "CTS" OR "Median Nerve Compression" OR "Median Nerve Entrapment") AND ("Primary Sjögren's Syndrome" OR "Primary SD" OR "Sjögren's Syndrome") AND ("Ultrasonography" OR "Ultrasound" OR "Nerve Ultrasound") AND ("Neurophysiological Tests" OR "Nerve Conduction Studies" OR "Electromyography").

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Only articles published in English between 1985 and 2024 were considered. The search yielded 145 articles from PubMed, 180 from Scopus, and 105 from Web of Science, totalling 430 papers. Inclusion criteria were: focus on CTS in the context of primary SjD (pSjD), relevant data on the prevalence, diagnosis, or management of CTS, published in English between 1985 and 2024 in peer-reviewed sources (including case reports, clinical studies, cohort studies, and systematic reviews). Exclusion criteria included: publication prior to 1985, non-peer-reviewed sources (conference abstracts, opinion pieces), full texts published in languages other than English, involvement of patients with secondary SjD or other autoimmune diseases, and basic science investigations lacking clinical relevance. After initial screening and application of inclusion/exclusion criteria, 202 papers were evaluated by the authors for their relevance to the article question (Fig. 1).

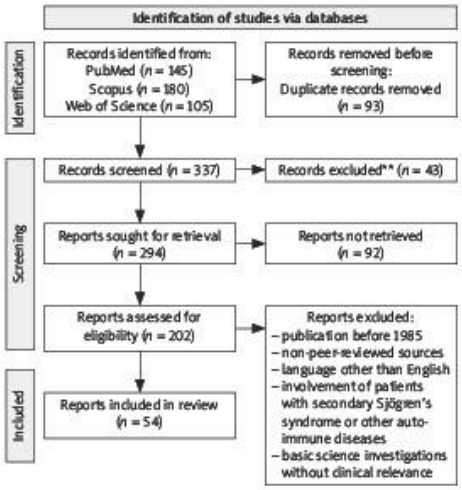


Fig. 1. PRISMA flow chart of literature screening.

Case descriptions

Case report 1

A 62-year-old female patient was first admitted to Department of Rheumatology, Clinical Immunology, Geriatrics and Internal Medicine of the Medical University of Gdansk in 2014 for diagnostic evaluation. The patient was reporting symptoms lasting approximately 1 year, including joint pain as well as multiple neurologic complaints, such as a subjective decrease of muscular strength in the left upper and lower extremity, and impaired fine hand movements. During the diagnostic workup, positive anti-*Borrelia* immunoglobulin M antibodies were detected, alongside elevated aminotransferases and creatinine kinase concentrations. Electromyography did not reveal any abnormalities, and magnetic resonance imaging of the brain was insignificant. Despite undergoing doxycycline therapy, the patient continued to experience persistent symptoms. Consequently, a comprehensive evaluation for systemic connective tissue disease was conducted. Based on positive anti-SSA and anti-SSB antibodies, a histopathological examination of minor salivary gland biopsy (focus score > 1) diagnosis of SjD was established. Given the absence of major structural abnormalities that could explain the patient's symptoms, and the observed improvement in the periods of intensified systemic treatment, the consulting neurologist raised a suspicion of nervous system involvement in the course of pSjD. In November 2014, a nerve conduction study confirmed signs of CTS. The patient underwent surgical treatment (median nerve release), which initially provided relief. However, after a few months, the patient presented again with recurrent CTS symptoms. Treatment with local steroid injections was initiated. A recent ultrasonographic (US) assessment revealed bilateral radiologic signs of CTS, which were later confirmed by neurophysiological studies (demyelinating changes in the electroneurography).

Case report 2

In March 2020, a 52-year-old female patient with a known diagnosis of SjD with central nervous system (CNS) involvement sought treatment at the orthopaedic outpatient clinic due to symptoms characteristic of CTS. Steroid injections had been performed on several occasions, providing only temporary relief. Due to recurrence of symptoms, the patient was eventually referred for surgical treatment and underwent a median nerve release with flexor synovectomy in the right hand in December 2020. The patient continued to be supervised by both orthopaedic and rheumatological outpatient clinics at our hospital. At the time of observation, there were no abnormalities in the laboratory tests, which could explain the complaints (normal thyroid function and electrolyte levels, no vitamin deficiencies). However, in March 2021, the patient reported a recurrence of symptoms. Ultrasonographic assessment revealed no significant abnormalities beyond expected post-surgical changes. Despite this, the patient continued to seek medical attention due to persistent swelling of the operated joint and required repeated steroid injections for symptom relief. The case presents an example of CTS symptoms persisting (as additionally confirmed by neurophysiological studies – axonal-demyelinating changes) despite the application of treatment according to the standard clinical practice.

The absence of ultrasonographic abnormalities suggests a different pathophysiology of CTS.

Discussion

Carpal tunnel syndrome – anatomy and pathophysiology

The carpal tunnel is an anatomical region located at the palmar aspect of the wrist. Its base is formed by 8 carpal bones arranged in 2 parallel rows: proximally, the scaphoid, lunate, triquetrum, and pisiform; distally, the trapezium, trapezoid, capitate, and hamate. The roof of the tunnel consists of a thick sheath of connective tissue, the flexor retinaculum, also known as the transverse carpal ligament. This ligament attaches to the tubercle of the scaphoid bone and the ridge of the trapezium on the radial side and to the pisiform bone and the hook of the hamate on the ulnar side. Ten structures pass through this region from the forearm to the hand – 9 long flexor tendons (the flexor pollicis longus, 4 tendons of the flexor digitorum superficialis, and 4 tendons of the flexor digitorum profundus) and the median nerve. While the bony and connective tissue structures provide support and protection, they also create a narrow space with minimal tolerance for volume increase. Nerve entrapment typically occurs at the proximal edge of the carpal tunnel and the hook of the hamate [8]. Repetitive wrist movements significantly elevate the intraarticular pressure by 10-fold on extension and 8-fold on flexion [9], simultaneously leading to oedema around the flexor tendons. In the course of diseases such as RA or SLE, notably in the periods of exacerbation, oedema can be observed in the connective tissue of the joints including wrists [10]. Prolonged compression of the median nerve results in mechanical injury as it traverses the carpal tunnel. Surgical observations from entrapment syndromes' release procedures describe nerve thinning at the site of compression with proximal swelling [9]. Chronic compression leads to ischaemia and consequently damage of the blood-nerve barrier with accumulation of inflammatory proteins and cells [11]. This condition may eventually mimic the compartment syndrome, where increased permeability facilitates the accumulation of endoneurial fluid, leading to intra-fascicular oedema [2].

Another factor contributing to CTS is anatomical variations, such as high division of the median nerve, proximal to the carpal tunnel, known as the bifid median nerve. Although a rare cause of CTS symptoms, it accounts for approximately 0.8% to 2.3% of cases. This variation increases the cross-sectional area of the nerve, predisposing it to compression in the carpal tunnel [12, 13].

Despite well-documented symptoms of CTS, the clinical presentation alone may be insufficient for a definitive diagnosis. In routine practice, nerve conduction studies (both motor and sensory) are employed to assess the median nerve function. The standard protocol is the one suggested by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [14–16]. Sensory fibres of the median nerve are examined using the orthodromic method, while compound muscle action potential is recorded from the abductor pollicis brevis muscle. Carpal tunnel syndrome is diagnosed when characteristic symptoms are accompanied by clinical abnormalities and signs of focal demyelination in the carpal tunnel. The potentials measured on the median nerve across the wrist should be compared to another nerve segment that is not topographically related to carpal tunnel (for instance, radial or ulnar). Other diagnostic modalities, such as vibrometry threshold testing, current perception testing, and Semmes-Weinstein monofilament testing, have not been proven as sensitive as traditional nerve conduction studies [9].

Increasing attention is being given to US as a diagnostic tool. With the growing availability of portable devices and improved physician proficiency in US examination, US constitutes a more patient-acceptable alternative to neurophysiological testing. Beyond diagnosis, based on the cross-sectional area of the median nerve, US allows for the evaluation of additional factors, such as potential causes of CTS occurrence (thickness of the transverse ligament), as well as performance of dynamic tests or elastography of the surrounding tissues [17]. Interestingly, studies suggest a correlation between US findings and the neurophysiological assessment of CTS severity [18]. Moreover, US may play a role in treatment, including corticosteroid injections and US-guided carpal tunnel release [19].

Patients typically present with pain, numbness, and paraesthesia in the palmar and dorsal distribution of median nerve innervation. However, the symptom presentation varies considerably, as described in a 1999 study by Stevens et al. [20]. In this study, which included 159 patients with electrodiagnostically confirmed CTS, symptom assessment via a questionnaire revealed that symptoms were more frequently reported in both the median and ulnar digits rather than the median digits only. Additionally, 21% of patients reported forearm paraesthesia and pain, 13.8% elbow pain, 7.5% arm pain, 6.3% shoulder pain, and 0.6% neck pain. These findings underscore the importance of comprehensive electrophysiological assessment in the diagnostic process.

Sjögren's disease

Sjögren's disease was first described in the early 1930s by the ophthalmologist Henrik Sjögren, who observed remarkable dryness of the eyes and oral cavity in

a patient with articular deformities [21]. Sjögren's syndrome can be classified as pSjD or secondary to other rheumatic diseases. This autoimmune disorder affects 0.2–2% [22] of the global adult population, with a female predominance (male-to-female ratio of 1 : 9). Disease onset typically occurs between the fourth and sixth decades of life [23]. The hallmark "sicca" symptoms result from lymphocytic infiltration of exocrine glands. Therefore, abnormalities found in patients include dryness of the eye, dryness of the oral cavity (which may lead to impaired consumption of solid foods), and parotid gland enlargement. Clinicians should bear in mind other, extraglandular manifestations of SjD, which patients may report as more significant, mimicking other conditions and delaying the diagnosis. Systems potentially affected include cardiovascular, musculoskeletal, gastrointestinal, respiratory, and urinary. Additionally, skin changes can be observed, particularly with vasculitis pattern [22, 24, 25]. The diagnosis is based on the 2016 European Alliance of Associations for Rheumatology/American College of Rheumatology diagnostic criteria [26].

Nervous system involvement in SjD is an understudied yet clinically significant aspect, affecting both the CNS and peripheral nervous system (PNS) in 6–48% and 2–60% of cases, respectively [27–31]. The high discrepancy regarding data on the prevalence of neuropathy results from the retrospective character of studies, particularly since patients are not routinely screened for nervous system involvement until symptoms become severe and significantly diminish the quality of life. Peripheral nervous system involvement can have diverse presentations: sensory neuropathies, axonal sensorimotor polyneuropathy, mononeuropathy, multiple mononeuropathy, demyelinating polyradiculoneuropathy, cranial neuropathy, and autonomic neuropathy [32]. Such diversity poses a notable difficulty mentioned by the authors of literature reviews – multiple scholars researching the subject tend to use diverse terminology, which may impair results sharing and comparison [7, 33]. Interestingly, nervous system involvement symptoms may precede typical dryness symptoms and the pSjD diagnosis [34]. This article presents collective data on peripheral neuropathy with a special focus on the information related to CTS.

Carpal tunnel syndrome as a peripheral neuropathy presentation among primary Sjögren's disease patients

Peripheral neuropathy has been well described in several systemic diseases, including systemic vasculitis (prevalence up to 70% of patients) [35], SLE (15% of patients) [36, 37], and SjD (up to 60% of patients) [38]. As of today, there are still limited data regarding the pathophysiology of this phenomenon. Naturally, various autoimmune factors are suspected. Some researchers indicate the potential influence of antinuclear antibodies, anti-SSA, and anti-SSB antibodies and their affinity to different nervous fibres as well as the role of rheumatoid factor [39, 40]. Others direct attention towards laboratory findings which could facilitate early detection of disease exacerbation and foresee probable development of neurological symptoms. Those factors include lowered concentration of complement components, especially C3 and C4, hypergammaglobulinemia, and vitamin D deficiency with its immunomodulatory action [41–45]. Our observations revealed a positive correlation between the concentration of β_2-microglobulin and the occurrence of CTS [46]. When analysing the history of patients with PNS involvement, factors such as a longer course of the disease, the presence of Raynaud's phenomenon and vasculitis have been noted [7, 47].

As mentioned above, a review of 11 studies focusing on CTS in SjD patients showed an average incidence of 12.8% (95% CI: 7.2–21.8%) with high heterogeneity across the studies (I^2 85%) [7]. Despite discrepancies among studies, likely due to a shortage of prospective studies, this result proves that CTS is more common among pSjD patients than in the general population (12.8% vs. 3–6%, respectively). According to some authors, the abovementioned autoimmune mechanisms are unlikely to cause mononeuropathies, due to their systemic nature (inherently affecting the nervous tissue in a widespread manner) [33]. As previously mentioned, PNS involvement may precede the occurrence of other, more typical symptoms of SjD and the definite diagnosis. It cannot be ruled out that some of the patients initially presented with symptoms of CTS (perhaps non-standard) which resolved in the course of immunosuppressive therapy. The highest efficacy of treatment for peripheral neuropathy in autoimmune diseases is attributed to orally administered steroids and intravenous immunoglobulins. There are also reports of successful rituximab usage for vasculitis-related peripheral neuropathy in pSjD patients [7, 47].

Clinical implications

The distinct pathophysiology of peripheral neuropathy in pSjD, including CTS, may significantly affect the therapeutic process, for both those with a known diagnosis and patients searching for medical help for the first time.

Typically, general practitioners refer patients with CTS symptoms to orthopaedic surgeons as the first-choice specialists, believing that surgical treatment is ultimately more effective than conservative therapy [48].

In-depth history taking at this point could facilitate the choice of therapeutic method [49]. If the patient reports any additional neurological symptoms, paraesthesia in other body regions, signs of ataxia, or sicca symptoms that cannot be attributed to any known chronic disease of the individual, such a person should be referred to a rheumatologist for diagnostics. When gathering the medical history, it is important to specifically name the symptoms which may be of interest. On the one hand, some of those suffering from chronic pain tend to under-report complaints, considering them insignificant and having become habitual to them or due to concerns of, for instance, a financial nature [50]. On the other hand, according to our previous studies, patients tend to over-report symptoms indicative of peripheral neuropathy, which do not comply with abnormalities found in diagnostic tests (80% of patients reporting symptoms vs. 46% of patients with established diagnosis of polyneuropathy) [41]. Practically, this may lead to a lengthy list of complaints from the patient that do not form any clinical pattern and may cloud the physician's judgment.

As described above, in terms of patients suffering from PNS complaints in the course of autoimmune diseases, the most effective therapeutic method proves to be immunosuppressive treatment. Our clinical observation shows that in the case of pSjD patients, there is no significant correlation between joint involvement in the course of the disease and electrophysiological diagnosis of CTS, unlike in the case of RA or SLE [46]. As a consequence, surgical intervention with the release of tension within the carpal tunnel may not bring desired long-term results. At the same time, any surgical intervention in rheumatological patients, especially those undergoing immunosuppressive treatment, carries an increased risk of infection, post-surgical complications, and exacerbation of the patient's initial disease activity [51].

Conclusions

The presented analysis of this topic based on literaure review and clinical picture in cases desriptions, highlighting the diversity of the pathogenesis of CTS and its further clinical implications. Physicians frequently encounter complaints related to the hand and wrist as they significantly affect the daily activities of the patients. Particularly in patients with multiple complaints and after unsuccessful therapeutic interventions, a rheumatic diagnosis should be considered. Moreover, the observations made by our team highlight the need for further research into the mechanisms behind the higher prevalence of CTS among SjD patients to enable a more unified, interdisciplinary, patient-focused treatment approach.

Disclosures

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3. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease-Associated Carpal Tunnel Syndrome

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Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease-Associated Carpal Tunnel Syndrome

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Abstract

Peripheral neuropathy constitutes a prevalent, albeit underrecognized, extraglandular manifestation of Sjögren's disease (SjD). Carpal tunnel syndrome (CTS) commonly coexists with SjD; however, the efficacy of standard CTS treatments in this population remains insufficiently characterized. This study evaluated the clinical and biological response to local corticosteroid injection in CTS patients with and without SjD and explored factors potentially associated with treatment outcomes. Twenty patients with SjD and CTS diagnosed based on typical clinical symptoms and supportive ultrasonographic findings and 19 control subjects with idiopathic CTS underwent ultrasound-guided corticosteroid injection. Median nerve cross-sectional area (CSA), the Boston Carpal Tunnel Questionnaire (BCTQ), and the Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire were assessed before treatment and 4 weeks after injection. Patients with SjD additionally underwent comprehensive clinical, laboratory, neurophysiological, and patient-reported outcome assessments. Patients with SjD appeared to demonstrate a significantly greater reduction in median nerve CSA following corticosteroid injection compared with controls (mean reduction: 0.46 vs. 0.31 mm^2; $p = 0.006$, Cohen's $d = 0.96$, CI90% [0.51, 1.49]). Despite this favorable biological response, clinical improvement was significantly smaller in the SjD group. Patients without SjD exhibited greater improvement in both the BCTQ Symptom Severity Scale ($p = 0.021$) and Functional Status Scale ($p = 0.033$), whereas changes in DASH scores did not differ significantly between groups. Patients with concomitant peripheral neuropathies experienced significantly poorer BCTQ improvement than those with isolated CTS, suggesting that neurological comorbidity may contribute to treatment resistance. No significant associations were identified between treatment response and fibromyalgia status or ESSPRI domains. Among quality-of-life measures, only the SF-36 General Health domain differed significantly between neuropathy types. Patients with SjD and CTS exhibit a dissociation between structural improvement of the median nerve and subjective symptom relief after corticosteroid injection. These findings suggest that mechanisms beyond local

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nerve compression, including coexisting peripheral neuropathy and potentially altered pain processing, may contribute to persistent symptoms. Comprehensive neurological assessment and multidimensional outcome evaluation may improve identification of SjD patients at risk of suboptimal response to conventional CTS therapies.

Keywords: Sjögren's disease; carpal tunnel syndrome; peripheral neuropathy; corticosteroid injection; ultrasonography; median nerve; chronic pain; patient-reported outcomes

1. Introduction

Sjögren's disease (SjD) may manifest as a primary systemic autoimmune disorder or develop secondary to other rheumatic conditions. It is classically characterized by sicca symptoms resulting from lymphocytic infiltration and dysfunction of the exocrine glands [1]. Consequently, patients commonly experience ocular, oral, and vaginal dryness. However, SjD extends far beyond glandular involvement, with manifestations affecting multiple organ systems, including the lungs, kidneys, and both the peripheral and central nervous systems. Peripheral neuropathies are among the most underrecognized extraglandular manifestations of SjD, although their underlying pathophysiological mechanisms appear to be not fully elucidated [2–4]. Furthermore, patients with SjD exhibit an increased prevalence of psychiatric comorbidities, particularly depression and anxiety [5], as well as fibromyalgia (FM) [6]. These conditions may amplify pain perception, impair quality of life, and adversely affect the response to both pharmacological and interventional pain management strategies. The epidemiology of SjD remains incompletely defined, with reported prevalence estimates varying widely between studies (0.02–0.77%), largely owing to differences in case ascertainment methods and classification criteria. The true prevalence of SjD may be underestimated because of substantial diagnostic delays and the diverse spectrum of clinical manifestations, especially when extraglandular features precede or overshadow sicca symptoms [7–9].

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy encountered in clinical practice [10] and is frequently observed in patients with rheumatic diseases [11]. While approximately 3–6% of the general population is affected [12], CTS is more commonly found in patients with rheumatic diseases, particularly rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and systemic sclerosis (SSc) [13–16]. The assessment of precise prevalence data within these cohorts appears elusive, primarily due to inherent discrepancies in study methodologies and the confounding influence of comorbidities [11]. Typically, the occurrence of entrapment neuropathy in rheumatic diseases is attributed to the articular manifestations, with either active inflammation leading to the narrowing of the carpal tunnel or irreversible deformations of the joints. In addition to splinting and physiotherapy, the administration of local corticosteroid injections around the median nerve is regarded as primary intervention for short-term improvement (for instance while awaiting surgery or before planned physiotherapy), which appears to demonstrate substantial efficacy in reducing symptoms and improving functional capacity [17]. Nevertheless, clinicians managing patients with SjD often observe a less pronounced therapeutic response compared with individuals without autoimmune disease. The mechanisms underlying these differences remain unclear but may be related to the coexistence of systemic inflammation, immunological mechanisms, peripheral neuropathy, chronic pain syndromes, and psychological comorbidities. These observations highlight the need for a better understanding of treatment outcomes in CTS patients with concomitant SjD.

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The primary objective of this investigation involves the evaluation of the efficacy of corticosteroid injections in patients with CTS associated with SjD and in patients with idiopathic CTS, with emphasis on both biological and functional outcomes. A structured literature search of MEDLINE, Embase, and Scopus up to July 2026 identified no previous study directly comparing local corticosteroid injection outcomes between SjD-associated and idiopathic CTS. Furthermore, this study sought to identify clinical, laboratory, and disease-related factors associated with a suboptimal therapeutic response and to determine potential predictors of treatment efficacy.

2. Results

Among patients with clinically suspected CTS, supportive ultrasonographic findings were observed in 51 patients (29 bilaterally), whereas neurophysiological abnormalities consistent with CTS were identified in 43 patients (10 bilaterally), reflecting the complementary nature and differing diagnostic sensitivity of imaging and electrodiagnostic modalities. Twenty-nine patients presented with features of CTS in both US and neurophysiological testing. All of those diagnosed with CTS were offered therapeutic procedures, but consent was obtained from 20 of them, which aligns with our findings on the patients' preferences regarding treatment strategies [18]. The study group comprised 20 patients with SjD and CTS diagnosed in the US, while the control group included 19 patients. A total of 35 corticosteroid injections were administered in the study group, with 15 patients receiving bilateral injections. In the control group, 28 injections were performed, including bilateral treatment in 9 patients. One patient from the control group did not return Boston Carpal Tunnel Questionnaire (BCTQ) and Disabilities of the Arm, Shoulder and Hand (DASH) results for post-injection. One patient from the study group did not attend the follow-up visit for the median nerve measurement (the patient lives abroad) and only completed the questionnaires. The complete-case analysis approach was implemented. Interestingly, one of the patients initially screened for the control group with bilateral CTS—upon rheumatological assessment presented symptoms of SjD (dryness of the eyes and oral cavity, peripheral neuropathy). Laboratory testing confirmed the presence of anti-SSA antibodies, and the patient was reclassified to the study group. The flow of patient inclusion is presented in Figure 1.

The mean age was 55.5 ± 12.9 years in the study group and 52.7 ± 13.4 years in the control group. Two participants were men (10.0%) in the study group and 3 participants (15.8%) in the control group. The sex distribution was comparable between groups and reflected the known female predominance of both SjD and CTS. The demographic data are presented in Tables 1 and 2.

Table 1. Age distribution of the study sample.

Group	*M*	*SD*	Min	Max
Database	55.56	13.89	23	82
SjD injections	55.47	12.93	37	78
SjD-free injections	52.65	13.41	27	73

Table 2. Sex composition of the study sample.

Group/Subgroup	N (%)		
	Database	SjD Injections	SjD-Free Injections
Total	125 (100)	20 (100)	19 (100)
Gender			
Male	11 (8.8)	2 (10)	3 (15.8)
Female	114 (91.2)	18 (90)	16 (84.2)

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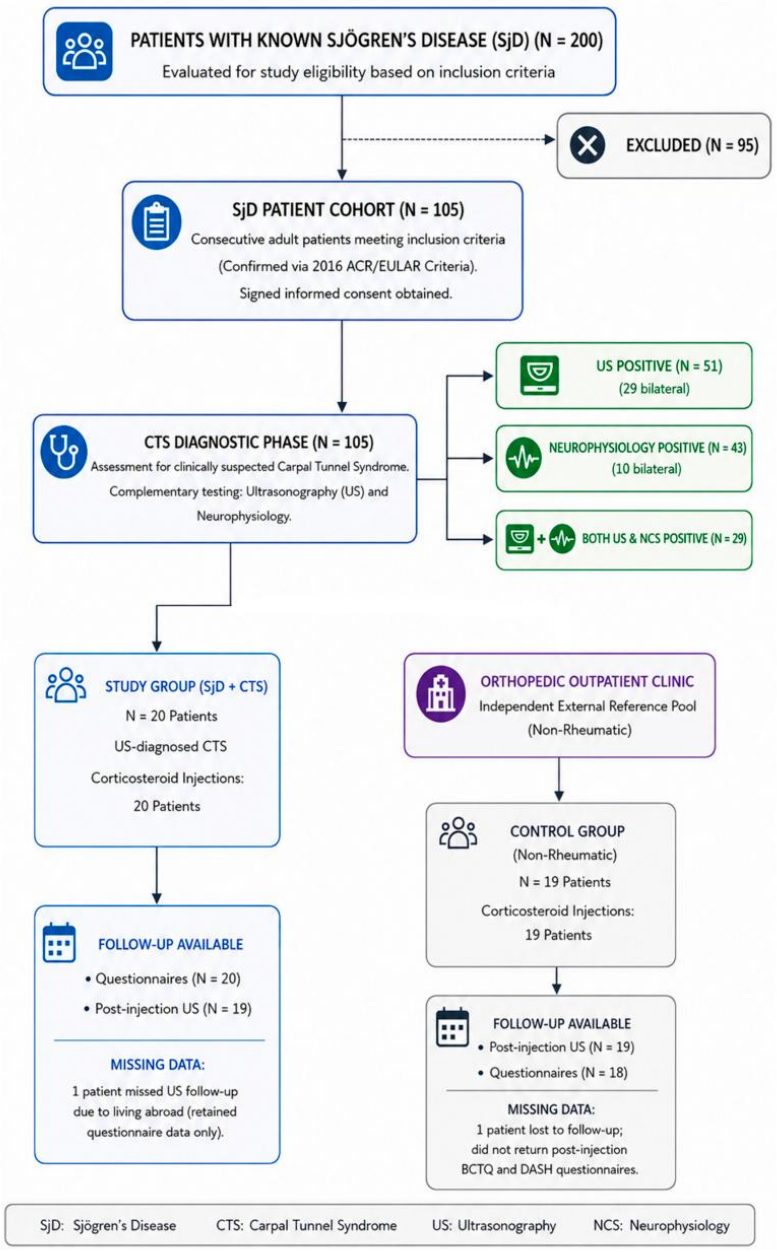


Figure 1. Flowchart of patient inclusion, diagnostic classification, and follow-up.

Overall, any form of peripheral nervous system involvement, including isolated CTS, CTS coexisting with other neuropathies, and non-CTS neuropathies, was identified in 69.5% (n = 73) of our cohort, substantially exceeding the prevalence reported in most previous studies and supporting the concept that neurological manifestations of SjD may

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be underrecognized. The high prevalence of neurological involvement observed in our cohort is consistent with our previous observations indicating that peripheral nervous system manifestations in SjD may be substantially underrecognized in routine clinical practice, particularly when comprehensive neurophysiological and ultrasonographic assessment is performed [19,20]. Among the patients diagnosed in the US with unilateral CTS 15 presented with at least one other form of polyneuropathy (PN) (68%) and among those with bilateral CTS nineteen suffered from other forms of PN (65%).

Comparison of treatment-related changes in median nerve measurements demonstrated a significant difference between patients with SjD and those without the disease. Levene's test confirmed homogeneity of variances ($p = 0.163$), and an independent-samples t-test revealed a significant between-group difference ($t(36) = -2.95$, $p = 0.006$). The effect size was large (Cohen's $d = -0.96$, CI90% [0.51, 1.49]). Patients with SjD exhibited a mean reduction in median nerve measurement of 0.46 mm^2, whereas patients without SjD showed a mean reduction of 0.31 mm^2. Detailed results are presented in Table 3 and Figure 2.

Table 3. Descriptive statistics for the difference in median nerve measurements [mm^2].

Group	*m*	*SD*	*skew*	*n*
Sjögren's disease	−0.46	0.18	−1.26	19
Without Sjögren's disease	−0.31	0.13	−0.33	19

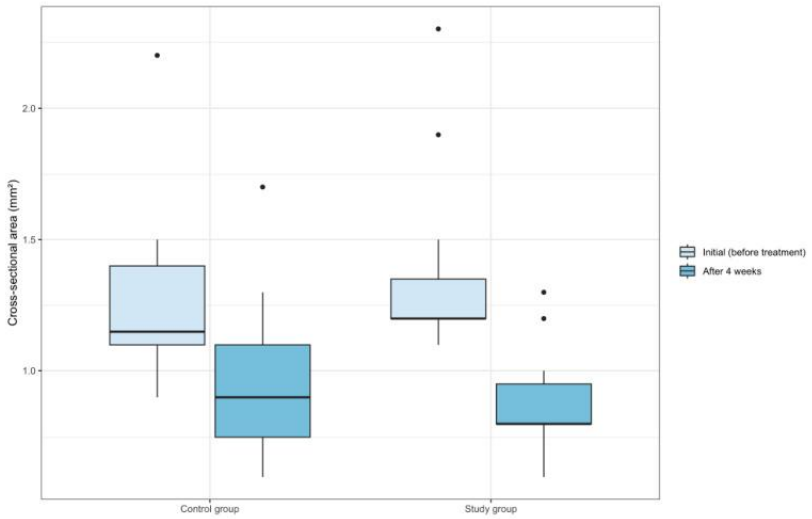


Figure 2. Cross-sectional area of the median nerve over time in the control and study groups.

Analysis of the BCTQ demonstrated significant group differences for both dimensions of the instrument. Homogeneity of variances was confirmed for the Symptom Severity Scale (SSS) and Functional Status Scale (FSS). Patients without SjD showed greater improvement in both BCTQ domains compared with patients with SjD. Significant differences were observed for the SSS ($t(35) = -2.42$, $p = 0.021$, Cohen's $d = -0.80$, CI90% [−1.50, −0.24]) and the FSS ($t(35) = -2.22$, $p = 0.033$, Cohen's $d = -0.73$, CI90% [−1.31, −0.22]), indicating moderate-to-large effect sizes. In contrast, the difference in DASH score improvement between groups did not reach statistical significance ($t(35) = -1.90$, $p = 0.066$). Results are presented in Table 4.

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Table 4. Descriptive statistics for changes in BCTQ dimension scores.

Dimension/Group	*M*	*SD*	*skew*	*n*
BCTQ SSS				
Sjögren's disease	−6.13	9.80	−0.82	19
without Sjögren's disease	−14.16	10.38	−0.46	18
BCTQ FSS				
Sjögren's disease	−1.42	5.86	1.27	19
without Sjögren's disease	−6.39	7.66	−0.36	18

Subsequent analyses compared BCTQ outcomes between patients with isolated CTS, and patients presenting with both CTS and another neuropathy. Significant differences were identified for both BCTQ dimensions between the subgroups. For the SSS, the comparison yielded $t(33) = 2.14$, $p = 0.040$, with a large effect size (Cohen's $d = 0.81$, CI90% [0.19, 1.58]). Similarly, the FSS demonstrated a significant difference ($t(33) = 2.60$, $p = 0.014$) and a large effect size (Cohen's $d = 0.97$, CI90% [0.52, 1.51]). Among the neuropathies CTS was mainly accompanied by mononeuropathy ($p = 0.023$) and axonal sensory-motor polyneuropathy ($p = 0.043$). Axonal-demyelinating polyneuropathy and radiculopathy approached statistical significance ($p = 0.057$ and 0.062 respectively). Details of this analysis are presented in Table 5.

Table 5. Descriptive statistics for the differences between BCTQ dimension scores.

Dimension/Group	*M*	*SD*	*skew*	*n*
BCTQ SSS				
CTS	−12.94	10.81	−0.35	24
CTS + other neuropathy	−4.98	8.7	−1.13	11
BCTQ FSS				
CTS	−5.95	6.98	−0.45	24
CTS + other neuropathy	0.43	6.15	1.52	11

To determine whether patients with CTS exhibited an increased likelihood of comorbid FM, a chi-square test was performed. This assessment, as well as subsequent analyses, was conducted across three cohorts: individuals with CTS, patients with both CTS and another neuropathy, and those presenting with another neuropathy exclusively. The findings suggest an absence of statistical significance ($p = 0.847$, $\chi^2 = 1.39$, $df = 4$).

A one-way ANOVA performed for the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) domains (dryness, fatigue, pain, joint pain, muscle pain, and neuropathic symptoms) showed no statistically significant differences among the analyzed groups (all $p > 0.05$). The detailed results are presented in Table 6.

Table 6. Results of the univariate analysis of variance (ANOVA) for ESSPRI scores.

Dependent Variable	F	df	df	*p*-Value
Dryness	1.36	2	63	0.265
Fatigue	0.83	2	63	0.443
Pain	0.84	2	63	0.436
Joint pain	1.93	2	62	0.154
Muscle pain	1.52	2	62	0.228
Neuropathic	1.01	2	62	0.370

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Analysis of SF-36 outcomes revealed a group effect on the edge of statistical significance only for the general health domain ($F(2) = 3.214$, $p = 0.047$) before the correction for multiple comparisons. No statistically significant differences were observed for the remaining SF-36 dimensions (presented in Table 7).

Table 7. One-way ANOVA results for SF-36 questionnaire scores.

Dependent Variable	F	df	df	*p*-Value
Vitality	1.75	2	59	0.183
Physical functioning	0.23	2	59	0.793
Bodily pain	1.46	2	59	0.242
General health	3.21	2	59	0.047
Role Limitations due to Physical Health	0.87	2	59	0.426
Role Limitations due to Emotional Problems	2.99	2	59	0.058
Social functioning	0.20	2	59	0.820
Mental health	0.41	2	59	0.665
Total	2.22	2	58	0.117

Among the hematological parameters, CRP levels differed significantly across groups ($F(2) = 3.81$, $p = 0.026$). Post hoc analysis demonstrated a significant difference in C-reactive protein (CRP) between patients with other neuropathies and those with concomitant CTS and another neuropathy (1.49 ± 2.71 vs. 3.64 ± 5.22 $p = 0.035$, Cohen's $d = -0.52$, CI90% $[-0.88, -0.15]$). No significant differences were detected between patients with CTS alone and those with CTS plus another neuropathy ($p = 0.983$), nor between patients with CTS and those with other neuropathies ($p = 0.073$). Nevertheless, in the study group CRP concentrations were within the normal ranges, suggesting that the clinical significance of this finding may be limited. Analysis was also performed for broader inflammatory markers, that is neutrophile to leukocyte rate (N/L), platelet to lymphocyte rate (P/L), and systemic immune inflammation index [(platelets x neutrophiles)/lymphocytes] (SII).

Notably, when comparing two groups of patients: CTS alone vs. CTS and other neuropathy + other neuropathy, a significant difference was noted in the beta2-microglobulin (B2MG) concentrations. However, this analysis is prone to error due to uneven distribution of patients (19 vs. 72 individuals). Nevertheless, consistent with the CRP observations, these values remained within physiological limits, suggesting that their clinical relevance may be limited. Results of laboratory findings analysis are presented in Table 8.

Table 8. Laboratory tests results.

Dependent Variable	CTS			CTS + Other Neuropathy			Other Neuropathy			F	df	df	*p*
	M	*SD*	*N*	*M*	*SD*	*N*	*M*	*SD*	*N*				
CRP [mg/L]	1.32	1.57	19	1.49	2.71	44	3.64	5.22	28	3.81	2	88	**0.026**
ESR [mm/h]	13.00	13.10	19	15.98	14.96	44	19.07	16.70	28	0.93	2	88	0.399
FBG [g/L]	3.25	0.58	19	3.42	0.65	44	3.46	0.67	28	0.68	2	87	0.508
Hgb [g/dL]	13.81	1.09	19	13.22	1.28	44	13.31	1.36	28	1.44	2	88	0.243
Fe [ug/dL]	101.79	34.17	19	99.55	33.26	44	88.38	38.20	28	1.14	2	88	0.326
Vit. B12 [pg/mL]	484.89	216.96	19	510.30	255.71	44	441.32	182.48	28	0.79	2	88	0.459
B2MG [mg/L]	1.94	0.52	19	2.17	1.09	44	2.61	1.45	28	2.20	2	88	0.117
N/L	1.65	0.71	19	2.57	2.13	44	2.36	1.23	28	2.04	2	88	0.136
P/L	140.46	48.26	19	191.24	104.35	44	179.67	87.14	28	2.12	2	88	0.126
SII	382.93	167.03	19	630.83	616.66	44	596.10	396.48	28	1.77	2	88	0.177

Abbreviations: CRP—C-reactive protein; ESR—erythrocyte sedimentation rate; FBG—fibrinogen; Hgb—hemoglobin; Fe—iron; vit. B12—vitamin B12; B2MG—beta2-microglobulin; N/L—neutrophiles to leukocytes; P/L—platelets to lymphocytes; SII—systemic immune inflammation index. Statistically significant results marked in bold.

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3. Discussion

The primary conclusion of this investigation resides in the discrepancy between the biological response of SjD patients to local steroid treatment (understood as decreased median nerve cross-sectional area (CSA)) and a comparatively limited self-reported amelioration in symptoms and function.

The symptoms resulting from CTS are mainly attributed to the compression of an enlarged nerve within the narrow space of the carpal tunnel [10]. This anatomical structure is limited by bones on one side and a thick layer of connective tissue (transverse ligament) on the other side. This mechanism constitutes the rationale for the therapeutic methods currently utilized—steroid injections, laser and extracorporeal shock waves as well as decompression surgeries. Initially, external compression leads to damage in the myelin sheath of the median nerve. If left untreated, the damage progresses into the deeper structures of the nerve, typically culminating in axonal-demyelinating CTS, which manifests as protracted, therapy-resistant complaints.

Steroid injections are considered a primary intervention for short-term relief of symptoms. The exact time span varies largely among the studies, with some reporting improvement as short as 6 weeks, others noting benefit even after 6 months [21–24]. In clinical practice, a series of 3 repeated injections every 4 weeks are recommended, which provided the rationale for the follow-up period established in this study. The period of 4 weeks is generally considered sufficient to both mitigate the post-injection adverse effects (e.g., transient exacerbation of symptoms and localized pain at the injection site) and sustain the beneficial outcomes of the procedure. The pathomechanism of steroid efficacy is based on three modes of action: anti-inflammatory, antifibrotic, and antiedematous [17]. Lack of initial symptom relief within 4 weeks strongly suggests therapeutic failure, as delayed significant improvement beyond this timeframe is uncommon. Conversely, evaluating outcomes at 1 month captures the peak anti-inflammatory and anti-edematous effects of the steroid, thereby providing indirect insight into the inflammatory component of the underlying pathophysiology. A greater biological response observed in SjD patients may reflect a larger contribution of local inflammatory or edema-related mechanisms within the median nerve. Although the laboratory findings of our participants did not reveal systemically elevated concentrations of inflammatory markers, their accumulation within the nervous tissue may remain plausible and would require histopathological examinations for confirmation.

In prior research, elevated B2MG concentrations were associated with the presence of CTS in patients with SjD [25]. B2MG is regarded as a marker of immune activation and B-cell activity in SjD and has been associated with higher EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) scores, autoantibody production, hypergammaglobulinemia and lymphoma risk [26,27]. Although this observation was not replicated in the present cohort, the overall lower B2MG levels may reflect improved disease control due to earlier diagnosis and more targeted treatment strategies. The persistence of symptoms despite low inflammatory marker levels suggests that factors other than ongoing immune activation may contribute substantially to symptom burden and treatment response in SjD.

To date, no consistent association has been established between the clinical severity of carpal tunnel syndrome symptoms and the CSA of the median nerve as measured by ultrasonography [28]. The rationale underlying the anticipated clinical improvement following CSA reduction is rooted in the established pathophysiology of CTS, in which symptoms are principally attributed to elevated intracarpal pressure and the consequent mechanical compression of the median nerve [29,30]. Accordingly, a CSA reduction of 0.46 mm^2—which, in the majority of cases, restores nerve dimensions to within the normal reference range—would be expected to result in complete symptomatic resolution through

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alleviation of perineurial oedema and restoration of adequate intraneural blood flow [31,32]. Nevertheless, in a proportion of cases, fibrotic alterations of the median nerve may prevail over the reversible inflammatory component, entailing protracted symptomatology despite demonstrable radiological improvement [33].

Despite a reduction in the CSA of the median nerve, the main mechanism responsible for alleviating the symptoms, our SjD patients reported worse symptomatic and functional results than their otherwise healthy counterparts. It is also noteworthy that 75% of the patients in the study group suffered from CTS bilaterally, as opposed to 47% in the control group. The groups did not differ in terms of professions, with office jobs being the most represented.

Our observation that symptom severity and median-nerve cross-sectional area do not exhibit a consistent cross-sectional association complements the longitudinal findings of Popescu et al. in the post-surgical setting [34]. In their prospective cohort of 100 patients treated with ultrasound-guided 5% dextrose hydrodissection, clinical outcomes and CSA improved in parallel across 6 and 12 months, yet electrodiagnostic recovery was distinctly more modest: only 28.7% of patients achieved improvement of $\geq$1 Bland category at 6 months despite 56.4% attaining a CSA reduction of $\geq$2 mm^2. The authors cautioned against interpreting CSA as a direct linear measure of clinical or electrodiagnostic severity, noting that greater baseline enlargement more likely reflects an underlying structural burden than symptom intensity [34]. Taken together, these data support a reorientation of CSA from a cross-sectional surrogate of symptom severity toward a trajectory marker of disease modification—a distinction that warrants particular consideration in pSjD-CTS, in which inflammatory and fibrotic mechanisms are expected to further uncouple nerve.

The management of patients with SjD is often complicated by the co-occurrence of FM and anxiety-depressive disorders. The prevalence of the former has been reported to range from 20% to 30% [6,35], although clinical observations suggest that this figure may reach 50% [36]. Existing literature suggests that such patients often report inferior self-assessment on the ESSPRI scales and manifest elevated disease activity. However, the pathogenesis of this phenomenon is still unclear. Although the current investigation failed to demonstrate a significant association between the BCTQ results and a concomitant FM diagnosis, the potential influence of this comorbidity cannot be definitely excluded, given the constraints of the participant sample size. Moreover, some of the study participants did not meet the diagnostic criteria for FM solely on the basis of symptom duration and with prolonged observation might require re-evaluation. Routine screening for FM may help identify patients who could benefit from dedicated pain management strategies. FM as well as depressive disorders, when left unmanaged, may lead to the development of central sensitization, an elusive condition, with unsatisfactory treatment strategies. A recent study [37] has demonstrated diminished function of hands in newly diagnosed SjD patients along with higher disease activity and anxiety levels. These findings corroborate established accounts and underscore the imperative for early screening and management of hand dysfunction, alongside comprehensive psychological evaluation in SjD.

Neuropathy is a broadly recognized complication of rheumatic conditions, and in case of diseases such as vasculitis, SLE, SSc, the pathogenesis has been quite well studied and verified. Conversely, the pathogenesis remains poorly elucidated in the context of SjD. Management of SjD-associated neuropathy remains challenging, and therapeutic responses to conventional immunomodulatory treatments are often incomplete [3,38]. Consequently, alternative pain-management strategies, including treatments used for neuropathic pain syndromes such as intravenous lidocaine or ketamine, have attracted increasing interest. However, evidence specific to SjD remains limited [39–44].

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A plausible interpretation of the observed dissociation between structural and symptomatic improvement is the presence of neuroimmune mechanisms that are not adequately addressed by local corticosteroid therapy. Peripheral nervous system involvement in SjD extends beyond large-fiber neuropathies and frequently includes small-fiber neuropathy (SFN), which may manifest as pain, dysesthesia, burning sensations, and sensory hypersensitivity despite normal conventional neurophysiological findings. Increasing evidence suggests that immune-mediated injury involving B-cell activation, pro-inflammatory cytokines, and autoantibody-associated neuronal dysfunction contributes to the development of neuropathic symptoms in SjD. Consequently, reduction in median nerve swelling following corticosteroid injection may improve the mechanical component of CTS while having limited influence on concurrent neuroimmune processes responsible for pain perception.

In addition, CTS in patients with SjD may occur in the context of a more generalized peripheral neuropathy rather than isolated focal entrapment syndrome. Polyneuropathy is among the most common neurological manifestations of SjD and may affect sensory, motor, or sensorimotor fibers through axonal or demyelinating mechanisms. In such cases, electrophysiological abnormalities and clinical symptoms may reflect diffuse nerve injury extending beyond the carpal tunnel. Structural improvement of the median nerve at the entrapment site may therefore not translate into proportional symptom relief if pathological processes simultaneously affect the nerve proximally or involve additional peripheral nerves. This premise is corroborated by observations including that patients with concomitant neuropathies experienced less favorable clinical outcomes despite demonstrating comparable reductions in median nerve cross-sectional area after treatment.

Although peripheral nervous system involvement is the most frequently recognized neurological manifestation of SjD, central nervous system (CNS) involvement has also been reported and may present with a broad spectrum of clinical manifestations [45–47]. The intricate relationship between CNS abnormalities, chronic pain, and central sensitization in SjD remains incompletely elucidated. Future studies integrating neurological, neuroimaging, and pain-processing assessments may help clarify the contribution of central mechanisms to persistent symptoms in this population.

A significant clinical inquiry concerns the identification of patients who may experience persistent symptoms despite objective improvement following CTS treatment. Although ESSPRI is the most used patient-reported outcome measure in SjD, none of its domains differentiated between neuropathy subgroups in our cohort. In contrast, the SF-36 General Health domain was associated with neurological status, suggesting that global health perception may better reflect the multidimensional impact of neuropathic symptoms. While these findings require confirmation in larger cohorts, they indicate that broader quality-of-life measures may be useful in identifying patients at risk of suboptimal treatment response.

The study's primary strength lies in the multidisciplinary assessment performed by specialists in rheumatology, neurology, radiology, and orthopedics, allowing comprehensive characterization of neurological involvement and exclusion of alternative diagnoses. Factors such as comorbidities and vitamin status were considered; furthermore, systemic treatment regimens remained invariant for all participants throughout the follow-up period, and the recruitment of all participants from a single tertiary university hospital may introduce potential referral bias. For the purpose of this study, data on the small fiber neuropathy was not considered. The relatively modest sample size of the intervention cohort and the abbreviated follow-up period may have limited the ability to evaluate long-term clinical outcomes.

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4. Materials and Methods

4.1. Study Group

A total of 105 consecutive patients with a confirmed diagnosis of SjD were enrolled in the study. Diagnosis was established based on the 2016 ACR/EULAR Classification Criteria [48]. Written informed consent was obtained from all participants prior to inclusion. Each patient underwent a comprehensive clinical, laboratory, and imaging assessment. The evaluation included ultrasonography of the upper limb nerves, neurophysiological examinations, measurement of inflammatory markers (CRP, B2MG, ESR, and fibrinogen), complete blood count, and autoimmune antibody profiling using immunoblot assays.

In addition, participants completed a standardized questionnaire comprising the Athens Insomnia Scale [49], ESSPRI [50], modified to separately assess neuropathic, articular, and muscular pain, the Short Form-36 Health Survey (SF-36) developed at RAND as part of the Medical Outcomes Study [51], and a questionnaire for the diagnosis of FM [52].

None of the patients included in the study group underwent changes in their systemic immunosuppressive treatment during the follow-up period.

The control group consisted of individuals without a previous diagnosis of rheumatic disease who were referred from the orthopedic outpatient clinic for the evaluation and treatment of CTS. All control participants underwent a rheumatological assessment performed by a board-certified rheumatologist and the principal investigator to exclude symptoms or signs suggestive of systemic rheumatic disease. Following clinical and laboratory screening, individuals in whom rheumatic disorders were excluded were included in the control group. For the assessment of treatment outcomes, control participants completed the BCTQ [53] and DASH [54] questionnaire at the same time points as the SjD cohort in relation to corticosteroid injection therapy. However, they did not undergo the extended patient-reported outcome assessment administered to patients with SjD.

4.2. Inclusion and Exclusion Criteria

4.2.1. Inclusion Criteria

- Age at least 18 years old;
- Informed consent;
- SjD diagnosis based on the ACR-EULAR 2016 Classification Criteria.

4.2.2. Exclusion Criteria

(1) Age below 18 years old;
(2) Lack of informed consent;
(3) SjD associated with another systemic autoimmune disease;
(4) Other systemic diseases, uncontrolled or in the periods of exacerbation, leading to impaired pain perception such as hypo/hyperthyroidism, diabetes mellitus, dyselectrolytemia, severe vitamin D and B12 deficiencies, anemia, active infections.

4.3. Neurophysiological Tests

All participants underwent neurophysiological assessment conducted by an experienced neurologist. Electrophysiological testing consisted of nerve conduction studies (NCS) performed using a Dantec Keypoint G4 EMG/NCS/EP Workstation (Natus) under standardized laboratory conditions, with skin temperatures maintained between 32 °C and 34 °C. All examinations followed the recommendations of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) [55].

Motor nerve conduction studies were carried out on the median, ulnar, radial, and peroneal nerves. Compound muscle action potentials (CMAPs) were recorded from the

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Abductor Pollicis Brevis, Abductor Digiti Minimi, Extensor Indicis Proprius, and Extensor Digitorum Brevis muscles, respectively.

Sensory nerve conduction studies included evaluation of the median and ulnar nerves using orthodromic techniques, and the radial and sural nerves using antidromic techniques. For the median nerve, sensory nerve action potentials (SNAPs) were elicited by stimulation of digits I and III with recording at the wrist. Ulnar nerve SNAPs were obtained following stimulation of digit V and recording at the wrist. Radial nerve studies involved forearm stimulation with recording at the anatomical snuffbox, whereas sural nerve responses were recorded at the lateral malleolus after stimulation along the lower leg.

A comprehensive overview of the examined nerves and the corresponding laboratory reference values is presented in Table 9. Polyneuropathies were classified according to the criteria proposed by the European Standardized Telematic Tool to Evaluate Electrodiagnostic Methods (ESTEEM) [56], and categorized as axonal, demyelinating, or mixed forms. Electrophysiological abnormalities were further classified into the following diagnostic categories: carpal tunnel syndrome (CTS); mononeuropathy; multiple mononeuropathy (motor, sensory, or sensorimotor); polyneuropathy (demyelinating, axonal sensory, axonal motor, axonal sensorimotor, or mixed axonal–demyelinating); and radiculopathy.

Table 9. Characteristics of the nerves included in the electrophysiological assessment and the corresponding laboratory reference ranges established for the SjD study population.

Nerve	Amplitude LLN	Distal Latency ULN [Distance]	Conduction Velocity LLN
Motor nerve conduction study			
Median (APB)	5 mV	4.2 ms [80 mm]	50 m/s
Radial (EIP)	3.5 mV	3.5 ms [120 mm]	51 m/s
Ulnar (ADM)	7 mV	3.2 ms [80 mm]	50 m/s
Peroneal (EDB)	3 mV	4.5 ms [80 mm]	40 m/s
Sensory nerve conduction study orthodromic			
Median dig I	10μV	3.5 ms [80 mm]	49 m/s
Median dig III	10 μV	3.4 ms [80 mm]	50 m/s
Ulnar dig. V	8 μV	3.5 ms [80 mm]	50 m/s
Sensory nerve conduction study antidromic			
Radial	10 μV	3.7 ms [100 mm]	51 m/s
Sural	9 μV	4.5 ms [100 mm]	40 m/s

Abbreviations: LLN, Lower Limit of Normal; ULN, Upper Limit of Normal; APB, Abductor Pollicis Brevis muscle; EIP, Extensor Indicis Proprius muscle, ADM, Abductor Digiti Minimi muscle, EDB, Extensor Digitorum Brevis muscle; dig, digit; mV, millivolt; ms, milliseconds; mm, millimeter; μV, microvolt; m/s, meters per second.

4.4. Ultrasonographic Examination

Ultrasound examination of the median nerve was performed using a high-frequency linear-array transducer (≥10 MHz). Patients were examined in a seated position with the forearm supinated, the wrist in a neutral position, and the fingers semi-extended. The median nerve was identified in the transverse plane at the level of the carpal tunnel inlet, corresponding to the pisiform bone and scaphoid tubercle. The CSA of the median nerve was measured by direct tracing of the inner border of the hyperechoic epineurium using the continuous-trace method. Three consecutive measurements were obtained, and the mean value was used for analysis. Care was taken to avoid excessive transducer pressure that could artificially reduce nerve dimensions. In addition to CSA measurement, qualitative assessment of nerve morphology, including nerve swelling, hypoechogenicity, and flattening

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within the carpal tunnel, was performed when applicable. CTS was diagnosed on the basis of characteristic clinical symptoms together with supportive findings on ultrasonography (a median nerve CSA exceeding 10 mm^2 at the carpal tunnel inlet), nerve conduction studies, or both. This approach was chosen to reflect routine clinical practice, where CTS diagnosis relies on the integration of clinical presentation and complementary diagnostic modalities rather than on a single test alone.

4.5. Intervention

The patients diagnosed with CTS were offered steroid injection. The measurement of the median nerve was confirmed by two independent researchers. Carpal tunnel injections were performed under ultrasound guidance by the same experienced physician. Procedure was done under aseptic conditions with the patient in a supine position and the wrist slightly extended. After skin disinfection, a corticosteroid (7 mg of betamethasone) preparation, without a local anesthetic according to institutional practice, was injected into the carpal tunnel adjacent to the median nerve. The needle was introduced at the level of the proximal wrist crease, typically just ulnar to the palmaris longus tendon (or along an alternative anatomical landmark in its absence), and advanced into the carpal tunnel while avoiding direct contact with the median nerve and surrounding vascular structures. Following a negative aspiration, the injectate was administered slowly. Patients were observed for immediate complications and advised to limit strenuous hand activities for the subsequent 24 to 48 h.

At baseline, prior to corticosteroid injection, patients completed the BCTQ and DASH questionnaires to assess CTS-related symptom severity and upper-extremity disability. BCTQ scores were analyzed separately for the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS).

Symptom severity and functional impairment related to CTS were assessed using the BCTQ, a validated disease-specific patient-reported outcome measure. The BCTQ consists of two subscales: the SSS, comprising 11 items evaluating the intensity and frequency of symptoms, and the FSS, comprising 8 items assessing difficulties in performing daily activities. Each item is scored on a 5-point Likert scale, with higher scores indicating greater symptom burden and functional disability. Mean scores for each subscale were calculated according to the original scoring guidelines. Upper-extremity disability and functional limitations were additionally evaluated using the DASH questionnaire. The DASH is a validated 30-item self-administered instrument designed to assess physical function and symptoms associated with musculoskeletal disorders of the upper limb. Scores range from 0 to 100, with higher scores reflecting greater disability and poorer upper-extremity function.

A follow-up examination was scheduled four weeks following the corticosteroid injections, given the literature-derived consensus regarding the peak efficacy interval for CTS management. Upon the visit, a total of six measurements of the median nerve were performed by two independent researchers. Moreover, the patients were asked to complete the same set of files, including BCTQ and DASH scales.

Biological effectiveness of injection was measured as a difference between the CSA of the median nerve after and before injection. For both instruments, assessments were performed before the intervention and during follow-up after corticosteroid injection. Changes in questionnaire scores were calculated as the difference between post-intervention and baseline values and were used for subsequent statistical analyses.

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4.6. Statistical Analysis

Statistical analyses were performed using the R programming language and the RStudio 2024.09.0+375 (2024.09.0+375) integrated development environment. All data analyses were conducted in R using several packages (including their dependencies), namely psych 2.4.3 [57], lavaan 0.6-17 [58], and tidyverse 2.0.0 [59].

Statistical analyses were performed to compare treatment-related changes between study groups and to evaluate differences in clinical, patient-reported, and laboratory outcomes. For continuous variables, change scores were calculated as the difference between post-injection and pre-injection measurements. Prior to group comparisons, homogeneity of variances was assessed using Levene's test. When the assumption of equal variances was met, independent-samples Student's *t*-tests were used to compare mean changes between groups. Effect sizes were estimated using Cohen's *d* and interpreted according to conventional thresholds.

Changes in median nerve cross-sectional measurements, BCTQ SSS and FSS scores, as well as DASH scores were analyzed using independent-samples *t*-tests. Additional comparisons of BCTQ outcomes were performed between patients with CTS, patients with other neuropathies, and patients presenting with both CTS and another neuropathy. Because BCTQ and DASH data were available only for a subset of participants, analyses were conducted on complete cases. Because all participants received an injection in the right wrist while only a minority underwent bilateral procedures, statistical evaluations were strictly conducted on the right wrist to ensure a consistent patient-level unit of analysis.

To assess differences in ESSPRI domains (dryness, fatigue, pain, joint pain, muscle pain, and neuropathic symptoms), Short Form-36 (SF-36) dimensions, and hematological laboratory parameters among the three clinical groups, one-way analysis of variance (ANOVA) was applied. For variables demonstrating significant overall group effects, post hoc pairwise comparisons were performed to identify specific between-group differences. Statistical significance was defined as a two-sided p value < 0.05.

4.7. Ethics Approval and Consent to Participate

The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Bioethics Committee of Medical University of Gdańsk (approval no. KB/438/2024, approved on 13 September 2024). Written informed consent was obtained from all participants prior to enrollment in the study.

5. Conclusions

Local corticosteroid injection appears to constitute an effective intervention for the attenuation of median nerve swelling in patients with CTS associated with SjD. However, despite the demonstration of a greater biological response—as reflected by a more substantial reduction in median nerve CSA—patients with SjD experienced significantly less amelioration in CTS-related symptomatology and hand function than individuals with idiopathic CTS. This discrepancy suggests that the symptom burden in SjD may not be explained exclusively by local nerve compression. Concomitant peripheral neuropathies, chronic pain mechanisms, central sensitization, and disease-related alterations in pain perception may substantially influence therapeutic outcomes. From a clinical perspective, structural improvement as documented via imaging may not necessarily constitute a reliable surrogate for patient-perceived benefit in SjD. Routine screening for PN, FM, and psychological comorbidities may facilitate a more individualized therapeutic approach and help identify patients at risk of persistent symptoms despite a technically successful intervention. The present findings suggest that CTS in SjD may represent a multifactorial disorder in which mechanical nerve compression interacts with systemic neuroimmune

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mechanisms. Larger prospective studies incorporating neurophysiological, immunological, and molecular biomarkers are warranted to clarify the pathways responsible for the observed dissociation between biological and clinical treatment responses and to identify predictors of therapeutic efficacy.

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XI. STATEMENTS OF CO-AUTHORS

1. Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients

Gdańsk, dnia 19.08.2026

lek. Iga Kościńska-Shukla
.....
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

Mój udział w przygotowaniu tej publikacji polegał na zaplanowaniu projektu, zgromadzeniu i analizie danych, przeglądzie literatury i analizie uzyskanych wyników w kontekście wiedzy medycznej, opracowanie ostatecznej wersji manuskryptu.

Kościńska - Shukla
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Gdańsk, dnia 18.08.2016

dr n. med. Marta Magdalena Jaskólska
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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

Mój udział w przygotowaniu tej publikacji polegał na nadzorze nad przygotowaniem planu badania, wsparciu w procesie rekrutacji pacjentów, gromadzeniu danych, nadzorze merytorycznym.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

Mój udział w przygotowaniu tej publikacji polegał na zgromadzeniu danych, wykonaniu badań przewodnictwa nerwowego i elektromiografii, nadzorem nad przygotowaniem manuskryptu – w szczególności fragmentów dot. w/w badań.

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Gdańsk, dnia 18.08.2016

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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

Mój udział w przygotowaniu tej publikacji polegał na wsparciu w procesie rekrutacji pacjentów, rekrutacji grupy kontrolnej, nadzorze merytorycznym.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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(podpis współautora)

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

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Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Prof. dr hab. n. med. Mariusz Siemiński
Specjalista neurologii
Specjalista medycyny ratunkowej
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(podpis współautora)

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prof. dr hab. Michał Chmielewski
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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Elevated concentration of beta2-microglobulin among patients with carpal tunnel syndrome in the course of primary Sjögren syndrome - a prospective observational study on 50 patients**

Mój udział w przygotowaniu tej publikacji polegał na nadzorze merytorycznym.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

.....
(podpis współautora)

2. Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications

Gdańsk, dnia 19.08.2026

lek. Iga Kościńska-Shukla

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications**

Mój udział w przygotowaniu tej publikacji polegał na przeglądzie literatury, analizie danych dot. opisanych przypadków klinicznych, stworzeniu manuskryptu.

Kościńska-Shukla

(podpis współautora)

Gdańsk, dnia 18.08.2026

dr n. med. Marta Magdalena Jaskólska

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications**

Mój udział w przygotowaniu tej publikacji polegał na nadzorowaniu przygotowania manuskryptu, merytorycznego nadzoru nad opisem przypadków klinicznych, krytycznej analizie procesu przeglądu literatury, współuczestnictwie w tymże procesie.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Jaskólska Marta

(podpis współautora)

Gdańsk, dnia 18.08.2026

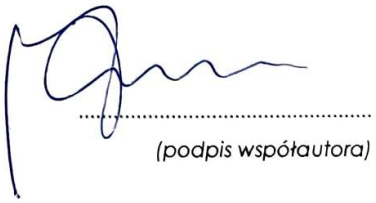
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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. **Distinct characteristics of carpal tunnel syndrome among Sjögren's disease patients and their clinical implications**

Mój udział w przygotowaniu tej publikacji polegał na nadzorowaniu procesu analizy dostępnej literatury pod względem merytorycznym, nadzorze nad tworzeniem manuskryptu.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.



.....
(podpis współautora)

3. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease-Associated Carpal Tunnel Syndrome

Gdańsk, dnia 19.08.2026

lek. Iga Kościńska-Shukla

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na stworzeniu projektu badania, uzyskaniu zgody Komisji Bioetycznej oraz Dyrekcji UCK w Gdańsku na przeprowadzenie badania, rekrutacji pacjentów, gromadzeniu danych, analizie danych, opracowaniu ostatecznej wersji manuskryptu.

Kościńska - Shukla

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Gdańsk, dnia 18.08.2026

dr hab. Arkadiusz Szarmach
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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome
Mój udział w przygotowaniu tej publikacji polegał na gromadzeniu danych, wykonaniu badań ultrasonograficznych, nadzorze merytorycznym nad przygotowaniem manuskryptu – w szczególności w zakresie w/w badań.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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dr n. med. Magdalena Chylińska
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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na zgromadzeniu danych, wykonaniu badań przewodnictwa nerwowego i elektromiografii, nadzorem nad przygotowaniem manuskryptu – w szczególności fragmentów dot. w/w badań.

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Gdańsk, dnia 18.05.2016

dr n. med. Dawid Jaskólski

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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na wsparciu w procesie rekrutacji pacjentów, nadzorze merytorycznym.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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(podpis współautora)

Gdańsk, dnia 18.08.2026

prof dr. hab. Michał Chmielewski
.....
(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome
Mój udział w przygotowaniu tej publikacji polegał na nadzorze merytorycznym, wsparciu w prowadzeniu projektu.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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(podpis współautora)

Natalia Natalia Dułak Lekarz 3805180
lek. Aleksandra Dułak

(tytuł zawodowy, imię i nazwisko)

Gdańsk, dnia 18.08.2026

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na udziale w procesie rekrutacji pacjentów, gromadzeniu danych (zwłaszcza w zakresie wyników badań neurofizjologicznych).

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Natalia Dułak

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Gdańsk, dnia 18.02.26.....

lek. Magdalena Rytlewska

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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na udziale w procesie rekrutacji pacjentów, gromadzeniu danych

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(podpis współautora)

Gdańsk, dnia 13.08.2026

dr Michał Olech

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome
Mój udział w przygotowaniu tej publikacji polegał na wykonaniu analiz statystycznych na podstawie dostarczonych danych, nadzorze merytorycznym nad manuskryptem w zakresie analiz statystycznych.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

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(podpis współautora)

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Gdańsk, dnia 19.08.2026

Zofia Mikołajczak

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OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

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(podpis współautora)

Gdańsk, dnia 19.08.2026

lek. Aleksandra Pociej

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na organizacyjno-logistycznym nadzorze nad projektem (dbanie o harmonogram wizyt, terminowość wypełniania ankiet) oraz gromadzenie części wyników w bazie danych.

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Aleksandra Pociej

(podpis współautora)

Gdańsk, dnia 18.08.2016

dr n. med. Marta Magdalena Jaskólska

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(tytuł zawodowy, imię i nazwisko)

OŚWIADCZENIE

W związku z ubieganiem się lek. Igi Kościńskiej-Shukla o stopień doktora w dyscyplinie nauki medyczne oświadczam, że jestem współautorem publikacji pt. Discordance Between Ultrasonographic and Clinical Outcomes After Corticosteroid Injection in Sjögren's Disease–Associated Carpal Tunnel Syndrome

Mój udział w przygotowaniu tej publikacji polegał na nadzorze nad procesem rekrutacji pacjentów, wykonywaniu procedur diagnostycznych i terapeutycznych, weryfikacji procesu realizacji projektu, nadzorze merytorycznym (w tym w zakresie przygotowania manuskryptu).

Jednocześnie wyrażam zgodę na przedłożenie w/w publikacji jako część rozprawy doktorskiej w formie spójnego tematycznie zbioru artykułów opublikowanych w czasopismach naukowych.

Jaskólska Marta

(podpis współautora)