ISSN: 2572-3243

Mihai et al. J Musculoskelet Disord Treat 2022, 8:115
DOI: 10.23937/2572-3243.1510115
Volume 8 | Issue 3
Open Access

Journal of
Musculoskeletal Disorders and Treatment

ORIGINAL ARTICLE

Decreased Protein Levels and Vitamin B12 Plasma Concentration in Primary Sjögren Syndrome are Associated with Peripheral Neuropathy: A Case-Control Study

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Abstract

Background: Prognostic factors for peripheral nervous system (PNS) manifestations in primary Sjögren Syndrome (pSS) are essential for predicting and preventing disease-related disability. Given the established relationship between vitamin B12 deficiency and pSS, we aimed to investigate the predictive value of low B12 concentration for Sjögren's induced peripheral neuropathy (PN).

Methods: We conducted a case-control study which included 96 patients with pSS, 13 of which were diagnosed with PN. We measured multiple nutrition-related biomarkers, including total protein levels, vitamin B12, folic acid, and iron concentrations.

Results: Total protein serum concentration was lower in PN diagnosed patients compared to the control group (7.15 vs. 7.64 g/dL, $p < 0.05$). In addition, the mean concentration of plasma B12 was decreased in the PN group with regard to control (431.92 vs. 588.43 ng/L, $p < 0.05$). However, a significant predictive pattern was not established for either of the biomarkers.

Conclusions: Peripheral neuropathy in pSS is associated with reduced serum protein and vitamin B12 levels. Although a predictive correlation was not demonstrated, the screening for early deficit is justified and recommended.

Keywords

Primary Sjogren syndrome, Peripheral neuropathy, Serum protein, Vitamin B12

Introduction

Primary Sjögren syndrome (pSS) is an autoimmune disease, determined by glandular tissue replacement with infiltrated lymphoid cells. The salivary and lachrymal glands are typically affected, with the most common clinical presentation being the sicca syndrome. However, approximately 30% of patients present with systemic extra-glandular manifestations, including cutaneous, articular, pulmonary and neurological symptoms, usually generating a delay in diagnosis from the onset of the disease [1,2]. According to different study cohorts, up to 45% of the pSS patients develop neurological complications, predominantly regarding the peripheral nervous system (PNS) [3]. The true prevalence of PNS involvement is challenging to estimate, as neurological diagnosis algorithms vary from pure clinical examination to nerve conduction

Citation: Mihai A, Chitimus DM, Casian M, Plesa CF, Dima A, et al. (2022) Decreased Protein Levels and Vitamin B12 Plasma Concentration in Primary Sjögren Syndrome are Associated with Peripheral Neuropathy: A Case-Control Study. J Musculoskelet Disord Treat 8:115. doi.org/10.23937/2572-3243.1510115

Accepted: September 28, 2022: **Published:** September 30, 2022

studies and cutaneous sensory nerve biopsy. Moreover, the majority of study groups includes patients with concomitant afflictions that may contribute to peripheral nerves impairment. An illustrative example is vitamin B12 deficiency, which is highly associated with pSS. A recent study demonstrated low vitamin B12 serum levels in 42.9% pSS patients, with no history of significant comorbidities, compared to 11.4% in the control group [4]. Given that nearly 80% of vitamin B12 deficiency patients display PNS impairment, it is crucial to identify this subset of pSS patients [5]. Although both pSS and B12 deficiency inflict damage on the peripheral nerves, the pathophysiological mechanisms are to some extent different, mainly with regard to the type of nerve fibers involved. Large nerve fibers suffer axonal and demyelinating injury in vitamin B12 deficiency, which reflects clinically in either sensory or sensory-motor peripheral neuropathy. According to recent published data, axonal impairment prevails in both nerve conduction studies and sural nerve biopsies [5,6]. On the other hand, in primary Sjögren's syndrome, painful small-fiber neuropathy (SFN) and dorsal root ganglionopathy (DRG) represent particular patterns of peripheral nerve involvement, alongside pure sensory neuropathies (PSN) and sensorimotor neuropathies (SMN) [3]. Distinguishing between the two etiologies can be daunting as the disease progresses, especially if the clinical presentation of both conditions is similar.

Throughout time, vitamin B12 deficiency has been widely documented, it's most investigated cause being pernicious anemia. Recently, the number one etiology has been declared food-bound cobalamin malabsorption (FBCM), a condition that implies the inability to release vitamin B12 from its transport proteins [7]. Besides malabsorption, low dietary intake of animal proteins leads to low levels of cobalamin, unless appropriate vitamin supplements are administered [8].

Vitamin B12 deficit has also been documented in 10 to 15% of the elder population, due to dysfunctional release of cobalamin from food proteins [9]. Given that the mean onset age for pSS patients is reported to be between the 4th and 5th decade of life and that the published data reported significant increased risk of low blood cobalamin in people over the age of 60-years-old, there is an association of predisposing risk for B12 deficit [9,10]. In addition to aging, xerostomia, an essential component of the sicca syndrome, has an important nutritional impact, as it affects key steps in digestion such as chewing and swallowing, leading to multiple vitamin deficiencies [11].

In order to understand the role that vitamin B12 plasmatic concentration plays in pSS patients diagnosed with peripheral neuropathy, we decided to investigate its predictive value for PNS impairment in a cross-sectional case-controlled study. Due to the close relationship between vitamin B12 and protein-based dietary intake, we decided to include total serum protein levels in our analysis, in order to investigate a possible nutritional pattern that influences the risk of developing peripheral neuropathy for pSS patients.

Methods

Study population

The study included 96 patients, who were admitted in our department, either as in or outpatients, in the period of April 2015 and March 2021. PSS diagnosis was decided according to the 2016 American - European Consensus Group classification criteria [12]. We excluded from the study all other comorbidities that cause peripheral neuropathy. Hence, patients that presented concurrent pathologies such as diabetes mellitus, alcoholism, paraneoplastic syndromes, virus C hepatitis, celiac disease, vitamin B12 or folic acid deficiency, paraproteinemia, cumulative trauma disorders (CTDs), and other autoimmune diseases (e.g. rheumatoid arthritis, systemic lupus erythematosus) were not included. Ongoing and previous medication included oral glucocorticoids (methylprednisolone), hydroxychloroquine and immunosuppressive agents (methotrexate).

Subjects that displayed PNS symptoms were examined by a neurologist and further investigated with nerve conduction studies and electrochemical skin conductance (SUDOSCAN) when necessary. The severity of neuropathy was clinically assessed by using a modified version of the Total Neuropathy Score (TNSr), previously documented in published studies on pSS peripheral neuropathy [13]. Prior to peripheral neuropathy diagnosis, patients were not under supplemental treatment with B vitamin complexes or antioxidant agents such as alpha-lipoic acid.

Data collection

Plasma B12 levels were determined by Chemiluminescent Microparticle Immunoassay (CIMA) and analyzed by ORGENTEC Alegria 2 analyzer (ORGENTEC Diagnostika GmbH, Mainz, Germany). Total protein serum concentrations and iron level were determined by spectrometry using Beckman Coulter AU5812 analyzer (Beckman Coulter, Inc., Brea, CA, USA). Patients with vitamin B12 deficiency, defined by a total plasma B12 < 200 ng/L, and protein deficiency, defined as a total serum level below 6.0 g/dL, were excluded.

Serological markers such as anti-Ro/SSA, anti-La/SSB antibodies were measured in order to confirm the pSS diagnosis, whilst seronegative patients were confirmed by minor salivary glands biopsy. An extensive panel of biomarkers were also performed in order to exclude the aforementioned conditions that generate neurological involvement. Only 1 patient diagnosed with peripheral neuropathy had cryoglobulinemia in the context of pSS. We also measured total iron levels, folate concentration

and vitamin D blood concentration in order to grasp a better understanding of the population nutrients status. Patients with folic acid levels that were out of our laboratory range (3.00-17.00 ng/mL) were excluded, given the particular relationship between vitamin B12 and folic acid, with the latter being able to mask vitamin B12 deficits when increased [14].

Regarding the investigation of PNS impairment, previous studies used the TNSr score for clinical evaluation of peripheral neuropathy in pSS, hence we chose the modified version in order to illustrate the clinical examination component. TNSr scale includes the assessment of sensory, motor and autonomic symptoms, strength evaluation, pin sensibility, vibration sensibility and tendon reflexes [13].

Nerve conduction studies included sensory nerve action potential (SNAP), compound muscle action potential (CMAP), nerve conduction velocities and F-wave and were performed in median, ulnar, peroneal, tibial and sural nerves using Nihon Kochden electromyography machine. The results were further classified as primarily axonal, primarily demyelinating, or mixed axonal and demyelinating. Needle electromyogram was also performed in order to exclude muscle pathologies [15]. Patients with symptoms indicating small fiber neuropathy (paresthesia, pain, loss of temperature detection) were evaluated using electrochemical skin conductance for sudomotor function with SUDOSCAN (Impeto Medical, Paris, France) [16,17].

Statistical analysis

The patients were divided in two groups, pSS with peripheral neuropathy (PSS + PN) which were compared with the pSS patients without peripheral neuropathy (PSS-PN), also considered the control group. The data was analyzed using Mann-Whitney test and one-way analysis of variance (ANOVA). Ulterior to results obtained in univariate analyses, variables were assessed using Binary Logistics Regression to evaluate independent associations. A p value < 0.05 was considered statistically significant. The statistical analysis was performed using IBM SPSS23.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and the design and methodology were approved by the Ethics Committee of the "Carol Davila" University of Medicine and Pharmacy, Bucharest (NO. 365/11.02.2020). All the patients gave informed consent.

Results

The study included 96 patients, the majority of (97.9%) females, with a median (range interval) age of 52.4 (19, 83). Vitamin B12 plasma levels were measured in 69 patients, while total protein serum concentration was measured in 81 patients. Anti-Ro/SSA antibodies and Anti-La/SSB antibodies were measured in the entire study population, yielding a higher percentage of seropositivity in the control group, without statistical significance. The prevalence of peripheral neuropathy was 13.5% (13/96), which is consistent with cited numbers in previous studies [18]. Characteristics of the study population are displayed in Table 1.

The median iron blood concentration was slightly higher in the PSS + PN group (73.42 ± 26.69 vs. 71.70 ± 29.09 µg/dL), while folic acid was decreased compared to the control group (8.75 ± 3.44 vs. 9.55 ± 4.47 ng/mL).

Table 1: Demographic, clinical and serological features of the study population.

Parameter	pSS patients with PN No = 13	pSS patients without PN No = 83
Age- Mean (min, max)	49 (34, 61)	53 (19, 83)
Sex- Women	13 (100%)	81 (97.5%)
Xerophthalmia	10 (76.9%)	71 (85.5%)
Xerostomia	9 (69.2%)	65 (78.3%)
ANA positivity, n (%)	11 (84.6%)	68 (81.9%)
Anti-Ro/SSA antibodies, n (%)	9 (69.2%)	70 (84.3%)
Anti-La/SSB antibodies, n (%)	6 (46.1%)	50 (60.2%)
Rheumatoid factor positivity, n (%)	3 (23.1%)	65 (78.3%)
Iron level (µg/dL)*	73.42 ± 26.69	71.70 ± 29.09
Folic acid level (ng/mL)*	8.75 ± 3.44	9.55 ± 4.47
25(OH) Vitamin D level (ng/mL)*	24.92 ± 12.03	27.01 ± 13.48
Pure sensory neuropathy	8 (61.5%)	-
Sensorimotor neuropathy	2 (15.3%)	-
Small fiber neuropathy	5 (38.4%)	-

PN: Peripheral Neuropathy; Pss: Primary Sjögren Syndrome

*Mean ± standard deviation

Table 2: Detailed description of the patients diagnosed with peripheral neuropathy.

Patient No.	TNSr[a]	NCS (Large Fiber Impairment)	SUDOSCAN (Sudomotor Function)[b]
Patient #1	12	Axonal PSN	N/A
Patient #2	17	N/A	N/A
Patient #3	12	Axonal PSN	No dysfunction
Patient #4	12	N/A	N/A
Patient #5	21	Mixed SMN	No dysfunction
Patient #6	15	Mixed PSN	No dysfunction
Patient #7	12	Axonal PSN	N/A
Patient #8	10	N/A	Severe dysfunction
Patient #9	11	Mixed PSN	Moderate dysfunction
Patient #10	20	Mixed SMN	Moderate dysfunction
Patient #11	18	Axonal PSN	No dysfunction
Patient #12	13	Axonal PSN	Severe dysfunction
Patient #13	17	Axonal PSN	Moderate dysfunction

PSN: Pure Sensory Neuropathy (N/A = Not Available); NCS: Nerve Conduction Studies; SMN: Sensory Motor Neuropathy; Tnsr: Total Neuropathy Score Reduced

[a]Score 0 indicates no PN, scores 1-9 indicate moderate PN, score > 20 corresponds to severe PN.

[b]Skin conductance is measured microSiemens (μS). Normal sudomotor function corresponds to an interval of 60-100 μS, moderately reduced sudomotor function: 40-60 μS and severely reduced sudomotor function: 0-40 μS.

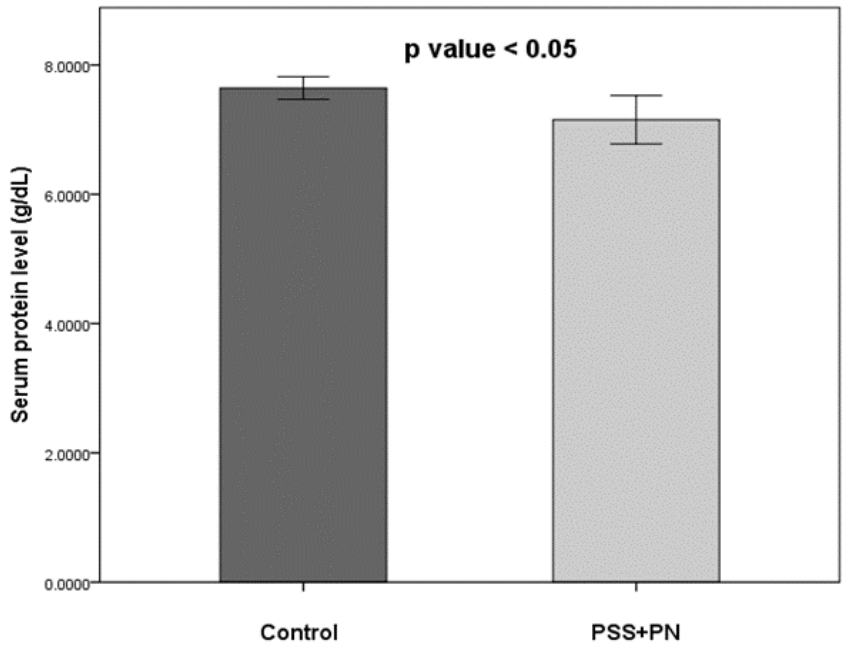

Figure 1: Serum protein level (g/dL) is represented as median with 95% CI intervals. PSS + PN patients exhibited significant lower concentrations compared the control group; 7.15 vs. 7.64 g/dL, 95% CI: [-0.94792; -0.003229], p = 0.036.

We noticed a slightly lower mean level of 25(OH) Vitamin D in PSS + PN group compared to the control group (24.92 ± 12.03 vs. 27.01 ± 13.48). These differences were not statistically relevant.

Clinical documentation of peripheral neuropathy was evaluated using TNSr as described in Table 2. Further testing of clinically diagnosed peripheral neuropathy patients revealed that the majority of the test group had sensory neuropathy (8/13, 61%), while a small proportion qualified as both sensory and motor neuropathy (2/13, 15.3%). It is also worth mentioning that primary axonal neuropathy was more prevalent, compared to mixed (axonal and demyelinating) peripheral neuropathy (46.1% vs. 30.7%). Small fiber neuropathy was described in 5 subjects (38.4%) and according to SUDOSCAN measurements they displayed moderate to severe sudomotor dysfunction. Four patients displayed both large nerve fibers impairment and small fiber damage described as moderate or severe (4/13, 30.7%), while the same percentage had only large fiber involvement, without SFN damage.

Total protein serum concentration was lower in the PSS + PN patients compared to the control group (7.15 vs. 7.64 g/dL, 95% CI: [-0.94792; -0.003229], p = 0.036) as illustrated in Figure 1. In addition, reduced vitamin B12 levels in the PSS + PN patients were significant compared to the control group (431.92 vs. 588.43 ng/L, 95% CI: [-310.93; -2.07], p = 0.047) as illustrated in Figure 2. Independent-samples Mann Whitney U test confirmed Asymptotic Significance (2-sided) < 0.03 for both Vitamin B12 and total protein.

Performing binary logistics regression, we observed a trend in low protein concentration as a predictor for PN, showing no significant statistical results (OR = 2.5, p value = 0.09).

Discussion

Nutritional deficiencies have previously been associated with pSS, predominantly vitamin B12 , vitamin A and iron deficits [4,19,20]. Our research focused on the possible benefits of identifying early patterns of vitamin B12 and protein blood concentrations in order to predict later onset of peripheral neuropathy.

Various studies examined possible prognostic factors in pSS related peripheral neuropathy. Cafaro, et al. have recently shown that pSS patients that develop mainly axonal SMN, exhibit a more active disease profile and those susceptible to poor evolution have serological markers such as leukopenia, low complement and cryoglobulinemia [21]. Furthermore, cryoglobulinemia was demonstrated to be an independent predictive factor for sensorimotor neuropathy and mononeuritis multiplex. Raynaud's phenomenon, cutaneous vasculitis and renal involvement were also associated with SMN, while seronegative patients (without anti-Ro/SSA antibodies) displayed pure sensory neuropathy [22]. Conversely, smaller cohorts studies proved significantly increased positivity for anti-Ro/SSA and anti-La/SSB antibodies in pSS patients diagnosed with peripheral neuropathy [23,24]. B-cell proliferation markers were generally higher in PN patients as reported by multiple authors, with a consistent higher incidence of hypergammaglobulinemia in non-PN patients [21,25]. Sene, et al. justified this particular finding with the significant increased frequency of Non Hodgkin lymphoma in Sjögren patients with peripheral nervous system involvement [25]. Dysproteinemia can manifest in a variety of ways, with high total protein levels due to hypergammaglobulinemia, or low albumin levels, which can be secondary to a protein-losing gastroenteropathy, renal or liver involvement [26,27]. Polyclonal hypergammaglobulinemia is a characteristic finding in pSS, as a result of lymphocytes hyperactivity, which is a hallmark for disease activity. Furthermore, hypergammaglobulinemia has been associated with a wide array of extra-glandular manifestations and is considered to be the most important predictor for B-cell lymphoma [28]. This is an important factor when monitoring pSS patients, as careful protein profiling might reveal early prognostic cues. Although protein electrophoresis has been intensively studied in Sjögren's, a conclusive analysis regarding the total protein serum concentration has not been published up to date.

Although subjects with protein concentrations below the laboratory range were not included, the trend showed that PNS involvement is associated with lower blood protein. This finding might seem contradictory with respect to the previous published data that relates conditions such as hypergammaglobulinemia to peripheral neuropathy in pSS [25].

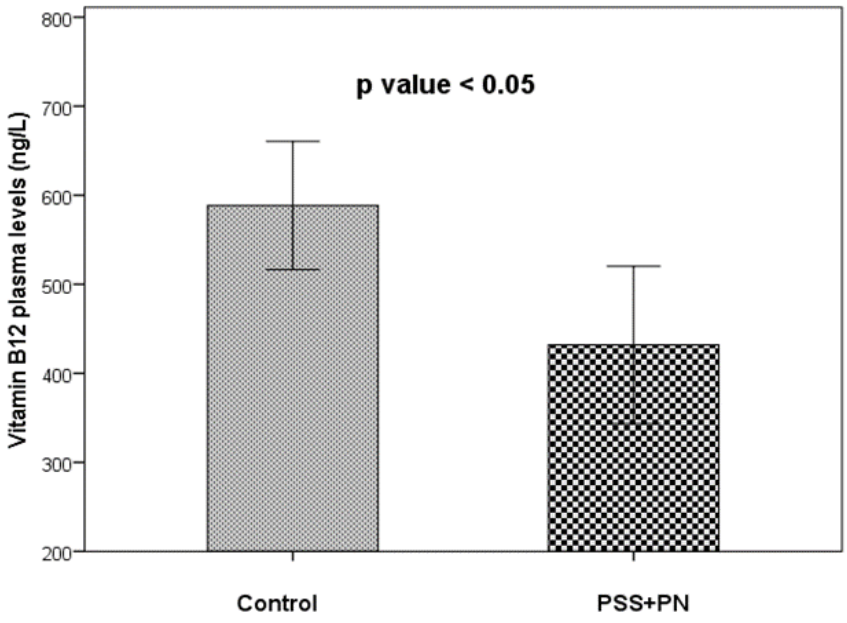

Figure 2: Vitamin B12 concentration (ng/L) is represented as median with 95% CI intervals. PSS + PN patients exhibited significant lower concentrations compared the control group; 431.92 vs. 588.43 ng/L, 95% CI: [-310.93; -2.07], p = 0.04.

While pSS patients with established vitamin B12 deficit are subject to developing PNS symptoms due to metabolic dysfunction in large nerve fibers, the borderline group displaying in range levels of B12, but adjacent to the lower limit might also be prone to develop peripheral nervous system complications. Whether the pathophysiological etiology is determined by decreased B12 levels or by accentuated peripheral nerve damage through DRG affection or vasa nervorum vasculitis it remains unclear [29,30].

A somewhat different perspective includes a correlation between decreased protein levels and vitamin B12 reduced concentration. Laboratory test for circulating B12 include a fraction of vitamin that is bind to transcobalamin proteins. Whether or not low levels of serum proteins can impact the measured fraction of blood, vitamin B12 remains to be questioned.

With regard to our study group, a particular feature is the high percentage of women 97.9%, compared to a mean of 80%, reported in previous published literature [31]. Moreover, all the subjects in the PN group were females. Although it is an acknowledged fact that pSS affects primarily women, population-based female to male ratio is 14:1, which is slightly lower than in our pSS cohort. A possible explanation for reduced vitamin B12 levels might stem in the proven preference of women for vegan/vegetarian diets compared to men (in the absence of vitamin supplementation), even though studies have not yet reached a consensus regarding the impact of meat-restrictive diets on circulating proteins and B12 levels [32,33]. It is also important to mention the possible adherence of these patients to special diets that have been confirmed of lowering the disease activity. Mediterranean diet has been associated with lower risk of developing pSS, while high-fat and high-protein Western diets showed an increased risk of autoimmune disease [34,35]. Intermittent fasting has also been demonstrated beneficial for various autoimmune diseases, with previously reported data on decreased protein synthesis in extreme restriction diets [36].

The patterns of peripheral nerve damage in pSS are controversial in many articles, as there has not been reached a consensus regarding the type of predominating neuropathy i.e. demyelinating, axonal, sensory, ataxic, motor or sensorimotor, and whether the PNS involvement is strictly an autoimmune manifestation of pSS. Sensory peripheral neuropathies are the most common, manifesting in different manners due to different sites involvement (nerve axons, DRG or small, unmyelinated nerve fibers) [37]. Small fiber neuropathy is reportedly underestimated in pSS patients, mainly due to its diagnostic methodology [18]. Although an universal approach on diagnosis criteria is not yet available, skin biopsy investigating reduced autonomic sudomotor sweat gland nerve fiber density (SGNFD) and sensory epidermal nerve fiber density (ENFD) is considered highly specific [38]. Electrochemical skin conductance, measure with SUDOSCAN technology or quantitative sensory testing (QST) are apparently less specific than skin biopsy [38,39]. With regard to sensorimotor peripheral neuropathy, recent studies stated that its frequency is comparable with that of PSN, however its prevalence remains debatable [18,21]. The study results are consistent with the aforementioned data, with 61.5% of the PN cohort displaying pure sensory neuropathy and 38.4% being diagnosed with small fiber neuropathy. The sensorimotor neuropathy had a slightly lower frequency in the PSS + PN group, although not all patients had nerve conduction studies performed. A quite interesting finding was the increased number of mixed peripheral neuropathy, meaning that a demyelinating mechanism was associated with axonal damage, which is consistent with previously published data [40]. Myelin sheath damage is documented in pSS in the context of both vasa nervorum inflammation and autoimmune mediated mechanisms [41,42]. Only one study had priorly identified a majority of demyelinating pattern in Sjögren's peripheral neuropathy, reporting subclinical demyelination in 24% of the patients [43].

The limitations of our study prevented us from obtaining a stronger predictive data for the role of vitamin B12 in pSS patients and especially for the PSS + PN group. As a future intention, assessing dietary preferences in pSS patients is of high priority, especially in the light of our findings. Although diagnosed vitamin B12 deficiency based on the plasma levels was excluded, we did not measure plasma homocysteine and plasma methylmalonic acid in order to confirm the absence of deficiency [44]. Careful assessment of protein electrophoresis is also desirable for future clarifications. A different aspect involves the lack of nerve conduction studies for all patients and sudomotor assessment. Given that we insisted on PNS assessment before vitamin B12 and antioxidant supplements administration, part of our patients did not have nerve conduction studies performed prior to supplementation, hence, we were forced to note it as not available. To further investigate the status of animal protein intake in patients, iron and ferritin levels should be analyzed simultaneously.

Conclusions

Our findings suggest a significant association between decreased level of serum proteins and vitamin B12 with peripheral neuropathy involvement in primary Sjögren syndrome patients. Although a predictive correlation was not significant, the results proved there is a strong association between low blood concentration of these nutrients and pSS related peripheral neuropathy. This justifies early screening and treating B12 deficiency in pSS patients.

Author Contributions

A.M., D.M., C.J. and R.I. Data curation and statistics:

A.M., D.M., M.C., C.P., A.D. and C.J., Original draft preparation: A.M., D.C. and R.I. Draft revision: R.I. Supervision: R.I.; Project administration: R.I. All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and the design and methodology were approved by the Ethics Committee of the "Carol Davila" University of Medicine and Pharmacy, Bucharest (NO. 365/11.02.2020). All the patients gave informed consent.

Conflicts of Interest

The authors declare no conflict of interest.

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