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Sarcoidosis-related small fiber neuropathy: Focus on fatigue, pain, restless legs syndrome, and cognitive function

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Abstract. *Background:* Of all sarcoidosis patients 60-90% suffer from fatigue, 40-80% experience small fiber neuropathy, 35% suffer from cognitive impairment and 16-52% experience restless legs syndrome (RLS). The prevalence, severity and association between fatigue, pain, RLS and cognitive impairment in patients with sarcoidosis and small fiber neuropathy (SFN) is unknown and will be investigated in this study. *Methods:* Healthy controls, patients with sarcoidosis with SFN and patients with sarcoidosis without SFN were compared. They completed multiple questionnaires (fatigue assessment scale (FAS), RLS rating scale, visual analogue scale (VAS) score for pain and cognitive failure questionnaire (CFQ), to estimate the prevalence, severity, and correlation of fatigue, RLS, pain, SFN and cognitive impairment. *Results:* Twenty healthy volunteers, 49 patients with sarcoidosis without SFN and 48 patients with sarcoidosis with SFN were included. Fatigue was the most prevalent symptom in patients with sarcoidosis with SFN (97%), followed by pain (85%), RLS (67%) and cognitive impairment (46%). Moreover, the severity of fatigue, pain, RLS and cognitive impairment was higher in patients with sarcoidosis with SFN compared with patients with sarcoidosis without SFN (resp. p=0.0006, p=0.003, p=0.02 and p=0.009). Finally, the FAS, RLS, VASmean, VASmax and CFQ showed a strong correlation with each other (R>0.5, p<0.05). *Conclusions:* Sarcoidosis patients with SFN showed an increased prevalence and higher severity of fatigue, pain, RLS and cognitive impairment compared to patients with sarcoidosis without SFN. Moreover, moderate to strong correlations were found between these symptoms.

Key words: quality of life, symptoms, prevalence, severity, small fiber neuropathy, sarcoidosis, fatigue, cognitive impairment, restless legs syndrome, chronic pain, symptom burden, patient reported outcome, quality of life, disease severity, neuropathic symptoms

Introduction

Sarcoidosis is a granulomatous and systemic disorder of unknown cause, mainly affecting lungs and lymph nodes (1). Symptoms can be either organ specific, such as dyspnea in pulmonary sarcoidosis or rhythm disturbances in cardiac sarcoidosis, or in non-organ specific such as fatigue, restless legs syndrome (RLS), pain or cognitive impairment, often resulting in a decreased quality of life (2). Because

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these symptoms are independent of granulomas or disease activity, they are difficult to quantify, monitor and treat (2). Fatigue is the most frequently reported symptom in patients with sarcoidosis. The estimated prevalence varies between 60-90%, and over 25% of patients even report extreme fatigue (2). The cause of fatigue is so far unknown and might be multifactorial. Fatigue may even persist despite adequate sarcoidosis treatment and in absence of disease activity (3). Pain is also commonly reported in patients with sarcoidosis and seems to be associated with small fiber neuropathy (SFN) (4). SFN is a disorder caused by damaged Aδ- and C-fibers nerve fibers (5) with a prevalence of SFN-related symptoms in sarcoidosis patients between 40-86% (6,7). Cognitive impairment is reported in around 35% of sarcoidosis patients, and is characterized by loss of memory, concentration problems and decreased perception (8,9). In patients with neurosarcoidosis, the prevalence of cognitive impairment is higher and estimated to be 55% (8). Fatigue and symptoms suggestive of SFN were predictors of cognitive impairment in previous studies (10). Data on prevalence of cognitive impairment in patients with sarcoidosis associated SFN is missing, but studies in patients with neurosarcoidosis and a case series of patients with Sjögren's syndrome and SFN reported increased cognitive failure (8,10). Sjögren's syndrome shares similar immunologic and histopathological features with sarcoidosis and is therefore of much interest (11). Restless legs syndrome (RLS) is a common movement disorder characterized by uncomfortable and sometimes painful sensations in the legs with a diurnal variation and a (partial) release with movement (12). RLS is a relative uniform disorder, and the severity of the basic symptoms is strongly related with the impact on quality of life (13). Data about RLS in sarcoidosis is limited with prevalence of RLS in sarcoidosis ranging from 0-50% (14,15). Although no data on RLS in patients with sarcoidosis with SFN is available, data suggesting an association between SFN and RLS is growing (16–19). It is unknown whether the presence of SFN in patients with sarcoidosis affects the prevalence and severity of fatigue, RLS, pain and cognitive impairment. Therefore, we investigated the prevalence and severity of these symptoms in healthy controls, patients with sarcoidosis without SFN and patients with sarcoidosis with SFN. Additionally, the association between these symptoms was investigated.

Methods

Design

This was a cross-sectional, prospective observational study between January 2021 – September 2022. Healthy controls were recruited from partners of patients with sarcoidosis and colleagues from our hospital. Furthermore, patients with sarcoidosis with and without symptoms of SFN between 18-75 years were approached at the outpatient clinic of the St. Antonius hospital, a tertiary referral center for sarcoidosis and other interstitial lung diseases (ILD) in the Netherland. Sarcoidosis was diagnosed based on the criteria of the American Thoracic Society/ European Respiratory Society (1). Exclusion criteria were vitamin B12 deficiency, glucose intolerance, diseases affecting sensory nerve function, signs of polyneuropathy, other diseases with a risk for developing (poly) neuropathy or SFN, pregnancy, mental health problems, language barrier, rheumatoid arthritis, and excessive alcohol intake as judged by the treating lung physician.

Neuropathy assessment

Neuropathy assessment was performed according to the updated Besta criteria (20), the most widely recognized and standardized criteria for diagnosing SFN. Symptoms and clinical signs matching with a diagnosis of SFN as described in the diagnostic criteria were established. Large fiber dysfunction was assessed with sensory and motor nerve conduction studies at the tibial and peroneal nerves. Nerve conduction velocity, compound muscle action potential and sensory nerve action potential were examined with surface recording electrodes with standard placement. A diagnosis of "probable SFN" was made during a consultation at the neurologist based on symptoms and clinical signs during physical examination, in combination with normal nerve conduction studies according to the current diagnostic criteria (20), Patients with sarcoidosis and a diagnosis of probable SFN are called patients with sarcoidosis with SFN in this article. The group of patients with "no SFN" consist of patients without symptoms of SFN and patients with symptoms suggesting SFN but without clinical signs of SFN (20).

Fatigue assessment scale

The fatigue assessment scale (FAS) is a questionnaire developed to assess fatigue (21). The questionnaire consists of 10 questions on a 5-point Likert scale. Consequently, the FAS-score can range between 10-50. FAS-scores below 22 indicate no fatigue, scores between 22-34 indicates mild-to-moderate fatigue and above 34 indicates severe fatigue (22). To simplify our results, we defined no fatigue (FAS<22) and fatigue (FAS≥22) for determining the prevalence. The median score per group was used to determine the severity of fatigue.

Visual analogue scale

The visual analogue scale (VAS) is the most valid method to assess subjective pain experience (23). It is an easy and quick method consisting of 2 horizontal lines of 100 mm, with the end points at "no pain" at the left and "worst imaginable pain" at the right. The first line is used to indicate the mean level of pain (VASmean) experienced in the past 7 days. The second line is used to indicate the maximal level of pain (VASmax) experienced in the past 7 days. No clear cutoff values are generally used for the VAS score to define groups. Therefore, we defined three groups based on a study on preoperative pain score as marker of postoperative drugs consumption (24), which established a minimal important difference of 30 points. Consequently, we defined "no pain" with a VAS-score below 30, "mild-to-moderate pain" with a VAS-score between 31-60 and "severe pain" with a VAS-score above 60. To simplify our results, we identified no pain (VAS<30) and pain (VAS≥30) for determining the prevalence. The median score of the mean pain per group was used to determine the severity of pain. The results of the mean pain are plotted in the figures, data on the maximum pain is written in text.

Restless legs syndrome rating scale

The RLS rating scale is an instrument to assess RLS severity (25), The rating scale consists of 10 questions with 5 multiple choice answers ranging from none (0 points) to severe (4 points). A score of 0 points means "no RLS", 1-10 means "mild RLS", 11-20 means "moderate RLS", 21-30 means "severe RLS" and a score between 31-40 means "extreme severe RLS". To simplify our results, we defined no RLS (RLS<11) and RLS (RLS≥11) for determining the prevalence. The median score per group was used to determine the severity of RLS.

Cognitive failure questionnaire

The cognitive failure questionnaire (CFQ) is a questionnaire assessing everyday failures in attention, perception, memory and motor function (26). The CFQ consists of 25 questions with 5 multiple choice answers ranging from "never" (0 points) to "very often" (4 points). An extreme low score is below 10, a low score ranges between 10-21, a normal score ranges between 21-43, increased cognitive impairment ranges between 44-54 and severe cognitive impairment is present when the CFQ-score is above 54 points (27). To simplify our results we defined no cognitive impairment (CFQ<44) and cognitive impairment (CFQ≥44) for determining the prevalence. The median score per group was used to determine the severity of cognitive failure.

Statistics

Chi-square test was used to calculate significant differences in prevalence between healthy controls and sarcoidosis patients with and without SFN. Kruskal Wallis was used to calculate significance between the severity of symptoms between the three groups. Spearman's rank correlation coefficient was used to determine the association between the four symptoms only in patients with sarcoidosis with SFN.

Results

Inclusion process

A flowchart from the inclusion process is displayed in Figure 1. In total, 117 participants are used for analysis of which 20 healthy controls, 49 patients with sarcoidosis are classified as sarcoidosis without SFN and 48 are classified as sarcoidosis with SFN according to the updated Besta criteria (20). Patient characteristics are displayed in Table 1. No significant differences between the three groups could be found, except for sex between patients with sarcoidosis

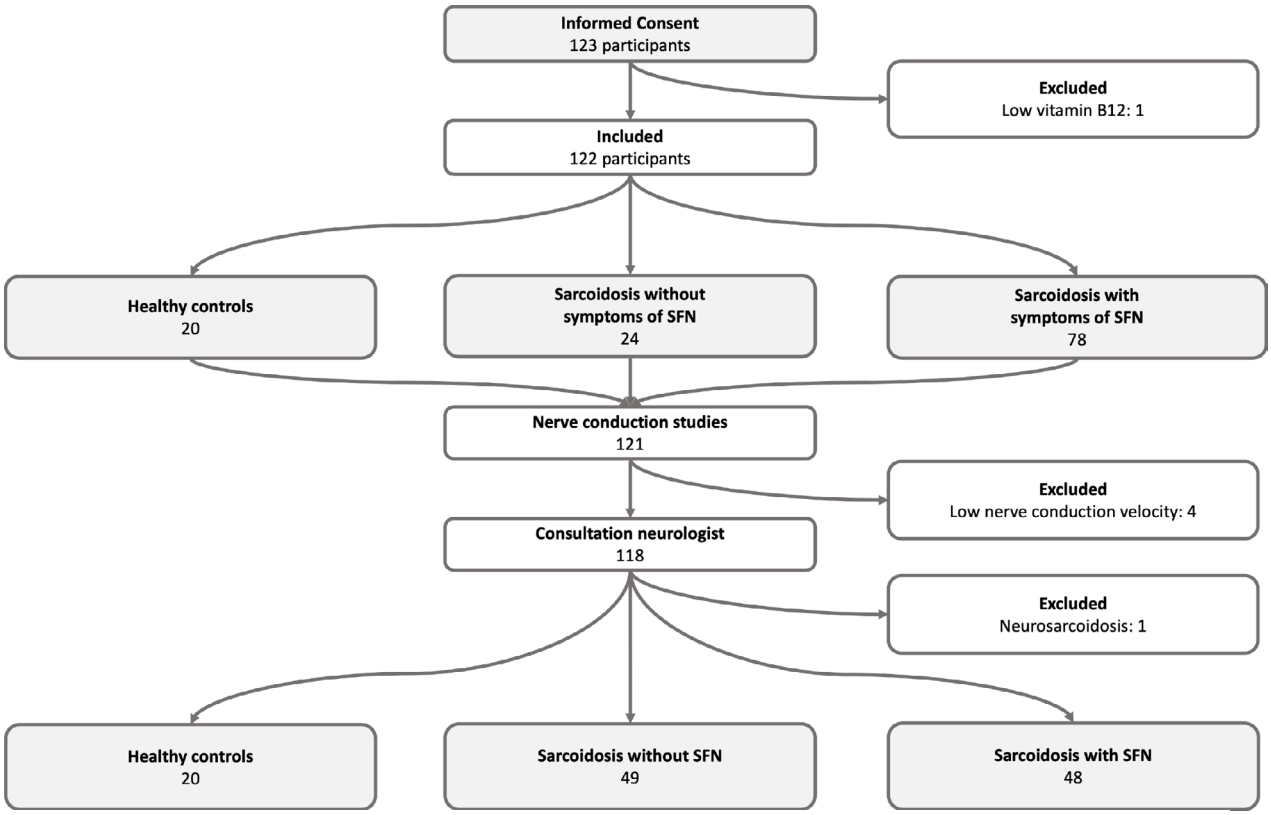

Figure 1. Overview of the inclusion process.

Table 1. Patient characteristics in healthy controls and patients with sarcoidosis. P-values were calculated with Kruskal-Wallis for continuous data and with Pearson chi-square for binary data.

Group	Healthy control	Sarcoidosis without SFN	Sarcoidosis with SFN	p-value Kruskall-Wallis	p-value HC-without SFN	p-value HC-with SFN	p-value without SFN-with SFN
n	20	49	48				
Age (mean yrs ± std)	48±12	52±11	52±9	0.5			
Sex Males (n (%))	10 (50%)	36 (73%)	21 (44%)		0.06	0.6	0.003
Height (mean cm ± std)	176±9	178±9	176±11	0.9			
BMI (mean ± std)	23±2	26±4	28±6	0.001	0.002	$8.5*10^{-5}$	0.3
Disease duration sarcoidosis (mean yrs ± std)		8±6	9±7	0.5			

Abbreviations: BMI = body mass index; SFN = small fiber neuropathy

without SFN were more likely to be male than patients with sarcoidosis and probable SFN (OR=3.6, p=0.003). In addition, patients with sarcoidosis, with and without SFN, showed significantly higher BMI than healthy controls. SFN symptoms occurred or were diagnosed at a mean of 6.4±5.3 years after the diagnosis of sarcoidosis.

Prevalence

Prevalence of fatigue in sarcoidosis patients without SFN is 84%, and in patients with sarcoidosis with SFN it is 96% (p=0.049). Particularly, extreme fatigue (FAS>34) is more prevalent in patients with sarcoidosis with SFN compared with patients

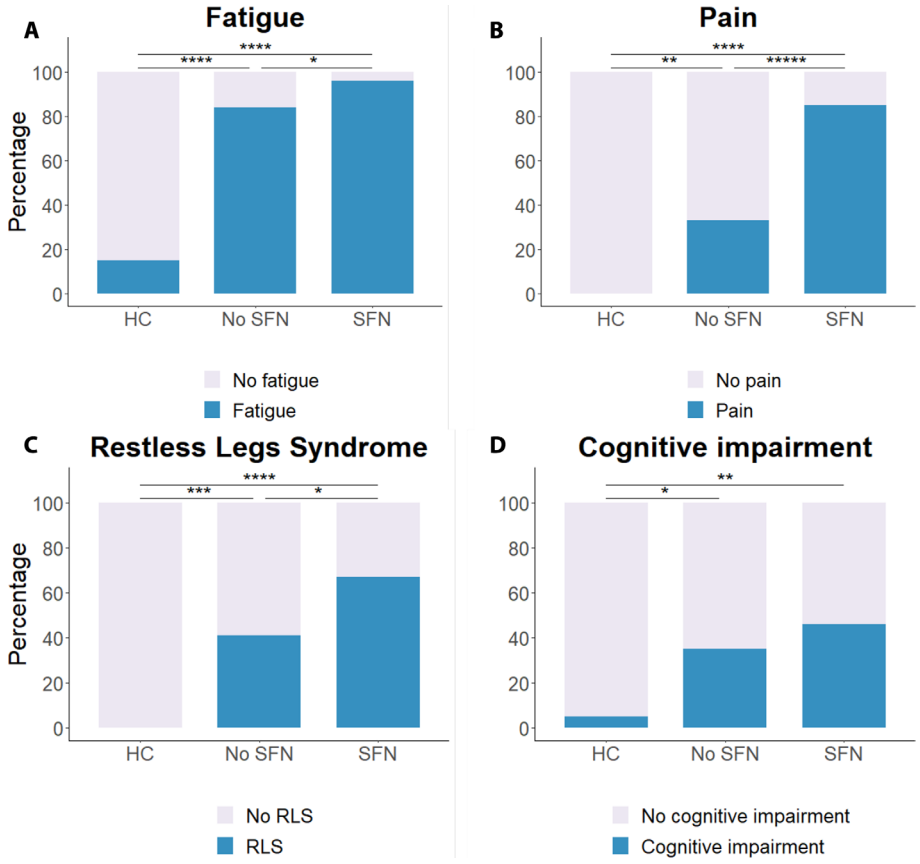

Figure 2. Prevalence of A) fatigue, B) pain, C) restless legs syndrome (RLS), and D) cognitive impairment. Distributions are displayed for three groups: healthy controls (HC), patients with sarcoidosis without small fiber neuropathy (No SFN) and patients with sarcoidosis with SFN. p-values were displayed as stars: *<0.05; **<0.01; ***<0.001; ****<0.0001.

with sarcoidosis without SFN, resp. 60% and 39% (p=0.03). Mean pain was reported in 33% of patients with sarcoidosis without SFN and up to 85% of patients with sarcoidosis with SFN ($p=1.3*10^{-7}$). Maximum pain was reported in 45% of patients with sarcoidosis without SFN and up to 92% of patients with sarcoidosis with SFN ($p=7.9*10^{-7}$). RLS was prevalent in 41% of sarcoidosis patients without SFN and 67% in sarcoidosis patients with SFN (p=0.01). The prevalence of a cognitive impairment was 35% in sarcoidosis patients without SFN and 46% in sarcoidosis patients with SFN (p=0.3), see Figure 2.

Severity

Overall, patients with sarcoidosis showed higher scores on the FAS, VASmean, VASmax (p=0.009 & $p=8.4*10^{-11}$ resp. for patients with sarcoidosis without and with SFN) for patients with sarcoidosis, RLS, and CFQ than healthy controls. Moreover, within the group of sarcoidosis patients, patients with SFN showed more fatigue, mean pain, max pain ($p=5.3*10^{-6}$) and RLS compared to patients without SFN (Figure 3).

Correlation

FAS, VASmean, VASmax, RLS and CFQ all show a significant correlation with each other in patients with sarcoidosis with SFN. The FAS shows a correlation above 0.5 with all questionnaires and therefore shows a strong correlation with RLS, VASmean, VASmax, CFQ and each other. Next to strong correlations with the FAS, VASmean and VASmax show a strong correlation with RLS and CFQ, see Figure 4.

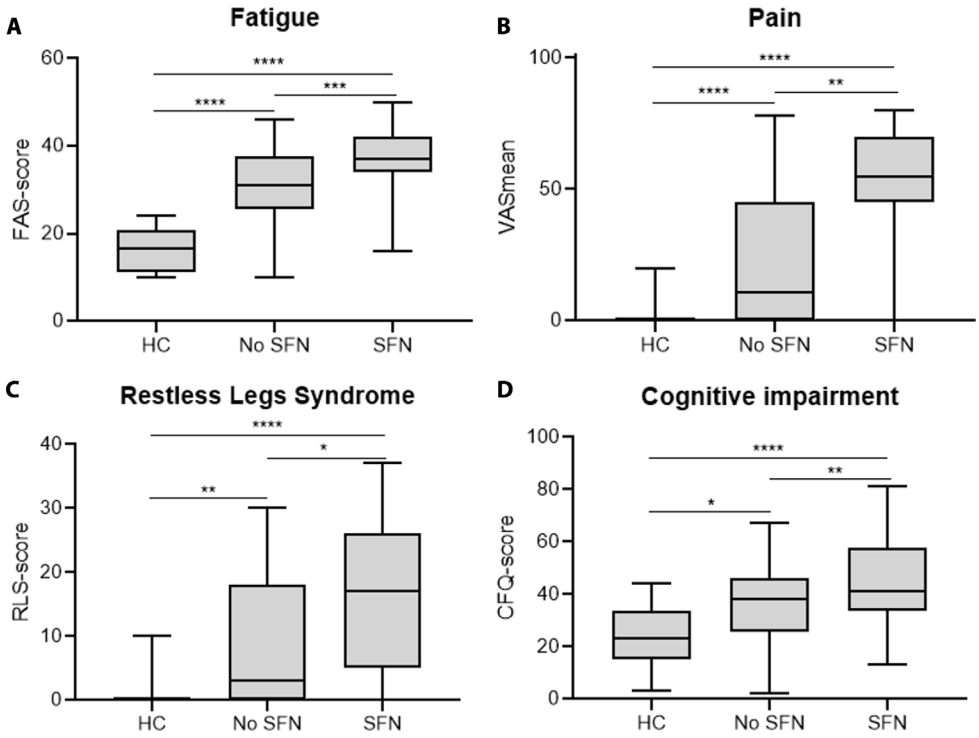

Figure 3. Boxplots with median, interquartile range and min-max values of questionnaire from the fatigue assessment scale (FAS), mean pain score on the visual analogue scale (VAS), restless legs rating scale (RLS) and the cognitive failure questionnaire (CFQ). Results are divided between healthy controls (HC), sarcoidosis patients without SFN (No SFN) and sarcoidosis patients with SFN (SFN). p-values were displayed as stars: *<0.05; **<0.01; ***<0.001; ****<0.0001.

Discussion

This study is the first to investigate a range of non-organ specific symptoms as fatigue, pain, RLS and cognitive impairment specifically related to the presence or absence of SFN in patients with sarcoidosis. We found that the prevalence of fatigue, pain and RLS is higher in patients with sarcoidosis with SFN compared to patients with sarcoidosis without SFN. No difference in prevalence is found for cognitive impairment between patients with sarcoidosis with and without SFN. However, the severity of cognitive impairment is significantly higher in patients with sarcoidosis with SFN compared to patients with sarcoidosis without SFN. Although our cohort of patients with sarcoidosis was dominated by male sex (58%), the group with SFN showed female predominance (56%), while the group without SFN showed male predominance (73%). Almost all autoimmune diseases disproportionately affect women. Several effects have been described on how x-linked genes and female sex hormones are important determinants of granuloma formation (28). The same processes may be involved in increasing the risk of developing sarcoidosis-associated SFN in female individuals. Furthermore, a female predominance of 67% was also observed in patients with idiopathic SFN (29). The bias towards male sex predominance in our cohort may have caused a lower female predominance than in the population with idiopathic SFN. In our cohort of patients with sarcoidosis fatigue is the most prevalent of the investigated symptoms, which is in line with previous studies (2). Interestingly, extreme fatigue defined by a FAS>34 is even more prevalent in patients with sarcoidosis with SFN compared with patients with sarcoidosis without SFN, a new finding further strengthening the previous suggested associations between SFN, pain and fatigue. Among the healthy controls, an elevated FAS-score was also most prevalent, occurring in 15% of this cohort. This is consistent with literature. The cutoff value for a score of up to 21 as normal was

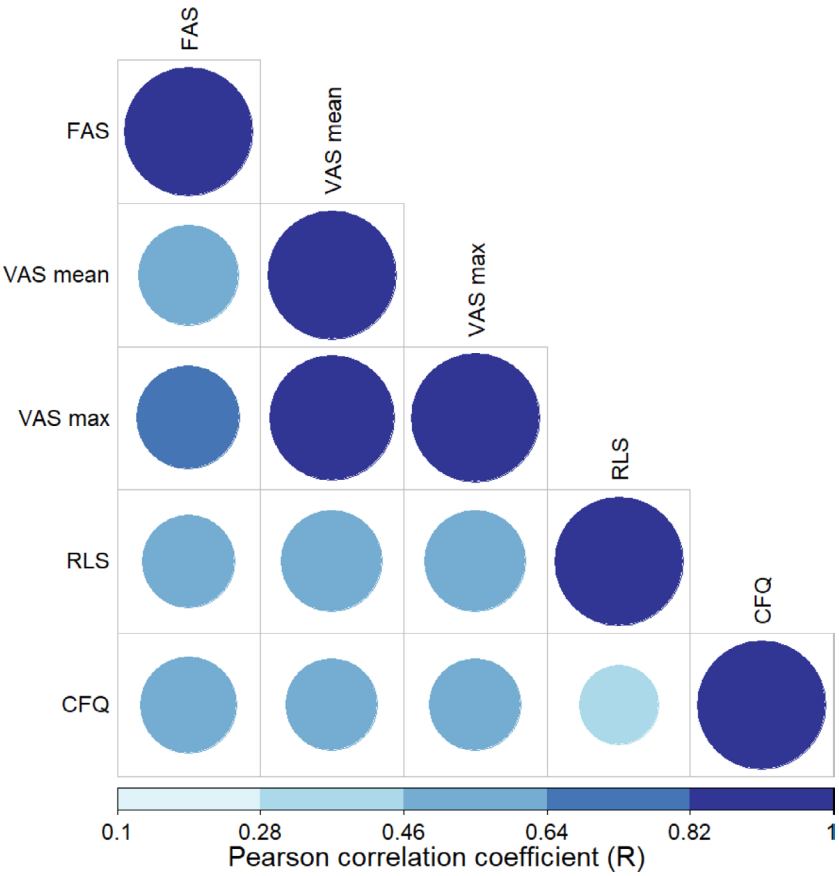

Figure 4. Correlation plot between fatigue assessment scale (FAS), mean and maximal (max) pain score on the visual analogue scale (VASmean, VAS max), restless legs syndrome (RLS) rating scale and cognitive failure questionnaire (CFQ). All displayed correlations are significant ($p<0.05$). The colors represent the Pearson correlation coefficient between -1 and 1, where 1 indicates the strongest possible correlation and 0 indicates no correlation.

previously established based on data from a healthy general population compared to sarcoidosis patients (30). This study showed that 80% of healthy individuals fall below a score of 22, meaning that 20% of healthy individuals are measured as abnormal. In our population, with 15% classified as abnormal, our findings fall within this range. In previous studies, the estimated prevalence of RLS in patients with sarcoidosis varies between 0-50% (14,15). Our data confirm these numbers and even show a higher prevalence of 67% in patients with sarcoidosis with SFN compared to patients with sarcoidosis without SFN (41%). The important clinical relevance of our finding is the fact that in daily clinical practice an association between SFN and RLS is not known or overlooked. Consequently, RLS will not be investigated or confused with SFN-associated symptoms, while treatment of RLS can be different (31). Therefore, knowledge about the high prevalence of RLS in patients with SFN could be useful in clinical management of patients with SFN. In our study, no difference is found in the prevalence of cognitive impairment in sarcoidosis patients with SFN and without SFN. The prevalence of respectively 46% and 32% is comparable with previous studies addressing cognitive impairment in patients with sarcoidosis (8,9). We did find, however, a significant higher severity of cognitive impairment measured by the CFQ in patients with SFN, comparable with our previous finding regarding extreme fatigue. Once again, this points out that particularly in patients with SFN, clinicians should be aware of the high prevalence and severity of fatigue, pain, RLS and cognitive impairment. Nonspecific health complaints

such as fatigue and cognitive impairment are associated with impaired QoL (32). Furthermore, all these aspects might contribute to the negative vicious circle of physical deconditioning and reduced quality of life (2). Among healthy controls, an elevated QFC-score was measured in one individual (5%). Although, pain and RLS were fully absent in healthy controls, fatigue and cognitive failure were present. The difference between those symptoms are that CFQ and fatigue measure subjective mental status while pain and RLS are more physically orientated. Cognitive functioning is a complex process and can be influenced by many factors. For example circadian typology, wakefulness, mood, stress, environment, activity, age, hormonal state and time of the day show respectively increased risk of cognitive failures (33). These results show that it is important to realize that healthy people also sometimes experience fatigue and reduced cognitive functioning. There is a huge clinical unmet need regarding better treatment options for these symptoms negatively impacting quality of life in patients with sarcoidosis. For example, overlooking a concomitant diagnosis of RLS in patients with sarcoidosis with SFN, might withhold these patients from accurate therapy for RLS. Current treatment of painful SFN mainly consists of pregabalin and gabapentin, which could also be beneficial in treatment of RLS, but pharmacological RLS therapy options are more extensive, with apart from alpha$_2$-delta calcium channel ligands, also dopamine (agonist) or (low-potency) opioids (31). In addition, it is important to state that antidepressants, which are frequently used in treatment of SFN, may induce or worsen pre-existing RLS (34). In addition to pharmacotherapeutical treatment, life style interventions regarding RLS have been studies. For instance, focus on mental alerting and trial of abstinence from caffeine and alcohol could be beneficial in some patients (31). Moreover, exercises, acupuncture pneumatic compression devices and near-infrared light showed significant effects on reducing RLS symptoms (35). Whole-body cryotherapy, transcutaneous stimulation and repetitive transcranial stimulation shows short-term positive effects on RLS. Lastly, general assessment for RLS also includes examination for iron deficiency, other sleeping disorders or medication which can induce RLS. When all symptoms in the legs are assumed to be due to SFN instead of RLS, there would be no attention for an appropriate RLS analysis. Specific medication for treatment of fatigue in sarcoidosis is lacking. Nevertheless some small RCTs suggest that neurostimulants, such as methylphenidate and armodafinil (36,37), or steroids such as dexamethasone (38), could have the potential to improve sarcoidosis-associated fatigue. More recently, interest in non-pharmacological therapy options for fatigue in sarcoidosis is growing. A recent study in patients with sarcoidosis showed improvements in fatigue after a 12-week online mindfulness-based cognitive therapy (39). A limitation of our study was the subjective nature of questionnaires. The results of questionnaires are patient reported, providing an adequate impression of subjective fatigue, pain, RLS symptoms and cognitive impairment. No quantitative methods for assessment of fatigue, pain and cognition are available. Diagnostic criteria for RLS do not rely on a diagnostic test (40), however, polysomnography could be a method to quantify periodic limb movements during sleep (15). In general, objective clinical parameters correlate poorly with the patients' subjective sense of well-being (22). For example, subjective cognitive impairment can be influenced by the discrepancy between everyday memory functioning and memory demands (9). However, the subjects' sense of well-being may influence the QoL (2), which justifies the importance of rather subjective results gathered with questionnaires. Another limitation is the lack of diagnosing SFN with skin biopsy and/or quantitative sensory testing (QST) according to the current diagnostic criteria for SFN (20,41,42). However, given the low sensitivity of skin biopsy, the subjective outcome of QST and the fact that in clinical practice many patients suffer from SFN-associated complaints, we chose to study patients with a diagnosis of probable SFN instead of established SFN. The strength of this study is a clear comparison of multiple non-organ related consequences of sarcoidosis, such as fatigue, pain, RLS, SFN and cognitive impairment in sarcoidosis patients, which are frequently neglected by their healthcare providers. Moreover, studies investigating these aspects in sarcoidosis patients with SFN are scarce.

Conclusion

In patients with sarcoidosis, particularly when diagnosed with SFN, the prevalence of fatigue, pain, RLS, and cognitive impairment is high. The majority of patients with sarcoidosis suffered from fatigue

and pain. More than half of sarcoidosis patients with SFN also suffered from RLS and cognitive impairment. Additionally, the severity of all those symptoms was higher in patients with SFN compared with sarcoidosis patients without SFN. Therefore, the prevalence as well as the associations between fatigue, pain, RLS and cognitive impairment should make clinicians aware of the fact that the focus should not only be on assessment of pain but also other symptoms that can negatively influence the quality of life of patients. Although most of these symptoms cannot be cured or adequately treated at the moment, some of them, such as RLS, might be. Finally, merely addressing and acknowledging these bothersome symptoms is of outmost importance for these patients.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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