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Use of fatigue assessment scale and small fiber neuropathy screening list in Japanese patients with sarcoidosis

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Abstract. *Background:* The Fatigue Assessment Scale (FAS) and Small Fiber Neuropathy Screening List (SFNSL) are widely used in Western countries to investigate symptoms associated with fatigue and small fiber neuropathy (SFN). However, few studies have used these patient-reported outcome measures (PROMs) in Japan. *Methods:* This was a cross-sectional and longitudinal study at an outpatient clinic in a community teaching hospital in Japan. Participants completed the FAS, SFNSL, and Short Form-36. Clinical parameters, including angiotensin-converting enzyme (ACE) and soluble interleukin-2 receptor (sIL2R), were derived from the medical records of the patients. *Results:* The study population included 55 patients (29 males; 26 females; mean age: 59±15 years; median disease duration: 5.0 years). Eleven patients received a systemic corticosteroid. The mean FAS score was 22.7±8.2; 27 patients (49.1%) and five patients (9.1%) indicated fatigue (score: ≥22) and extreme fatigue (score: ≥35), respectively. The mean SFNSL score was 13.8±14.3; 23 patients (41.8%) and two patients (3.6%) indicated probable/highly probable SFN (score: 11–48) and SFN (score: ≥49), respectively. The FAS score exhibited strong correlations with physical function, vitality, and mental health of Short Form-36. The SFNSL score exhibited strong correlations with bodily pain and vitality. Of the 55 patients, 45 completed the 1-year follow-up. There were no significant changes noted in the FAS score (mean: 0.04, 95% confidence interval: –1.29–1.38) and SFNSL score (mean: 0.31, 95% confidence interval: –2.12–2.74) during the follow-up. Within-subject changes in FAS and SFNSL scores showed moderate correlations with those of physical function and general health, respectively. There was no significant relationship between FAS or SFNSL score and ACE or sIL2R values at baseline and within-subject changes in these parameters during the follow-up. *Conclusions:* Approximately half of the patients suffered from fatigue or SFN. These nonspecific symptoms have a great effect on quality of life.

Key words: fatigue assessment scale, small fiber neuropathy, SF-36, health-related quality of life, sarcoidosis

Introduction

Sarcoidosis is a systemic granulomatous disease with unknown cause, which primarily affects the lungs, eyes, and skin. In Japan, the prevalence of sarcoidosis in these organs is 86.9%, 50.4%, and 32.0%, respectively, based on a large survey using data from a digital registration system (1). Typically, patients with sarcoidosis experience organ-specific symptoms. Nevertheless, they may also develop a wide spectrum of nonspecific symptoms, such as fatigue (2,3), as well as symptoms associated with small fiber neuropathy (SFN), including pain (4-7), which can impose a significant burden. The European Respiratory Society established new guidelines for treating sarcoidosis (8). These guidelines utilize eight clinical

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questions based on the PICO (Patients, Intervention, Comparison, Outcomes) framework to reach specific evidence-based treatment recommendations. Two of those eight PICO questions have addressed such nonspecific symptoms, namely sarcoidosis-associated fatigue and SFN. This highlights the importance of such non-organ related symptoms.

Patient-reported outcome measures (PROMs) allow patients to directly self-assess their health without the involvement of a physician (9). Symptoms of fatigue and SFN are well established (2,6,10). At present, two PROMs are widely used in Western countries to assess fatigue and SFN, i.e., Fatigue Assessment Scale (FAS) (11,12) and Small Fiber Neuropathy Screening List (SFNSL) (13). However, thus far, few studies have used these PROMs in Japan. The clinical phenotype of sarcoidosis varies between different areas and ethnic groups. Therefore, we conducted a prospective observational study to assess fatigue and symptoms associated with SFN in Japanese patients with sarcoidosis using the FAS and SFNSL. The purposes of this investigation were to: 1) evaluate the frequency of fatigue and symptoms associated with SFN in Japanese patients with sarcoidosis; 2) test the *a priori* hypothesis that such nonspecific symptoms correlate with health-related quality of life (HRQoL); 3) examine longitudinal changes in fatigue and symptoms associated with SFN; and 4) test the *a priori* hypothesis that there is a correlation between changes in FAS and SFNSL scores, and those of HRQoL and clinical parameters.

Methods

Study population

In this study, we prospectively recruited all consecutive patients with sarcoidosis who presented to the Kobe City Medical Center West Hospital (Kobe, Japan) outpatient clinic between July 2018 and June 2024. Patients who had an active neoplasm and those unable to complete the questionnaires due to cognitive and/or reading impairment were excluded. The Japan Society of Sarcoidosis and Other Granulomatous Disorders (JSSOG) diagnostic standard and guideline for sarcoidosis-2015 (JSSOG 2015 criteria) was used to diagnose sarcoidosis and assess organ involvement (14). All patients provided written informed consent for their participation in this study.

Study design

We used a cross-sectional and longitudinal design to assess fatigue and symptoms associated with SFN. The attending physician enrolled patients at the time of their regularly scheduled clinic visit. The following data were collected at baseline: clinical and laboratory data, including sarcoidosis activity parameters, angiotensin-converting enzyme (ACE) levels and soluble interleukin-2 receptor (sIL2R) levels, pulmonary staging of patients using the method of Scadding (15), organ involvement, and concomitant therapy. We also employed the modified Medical Research Council general dyspnea scale for patient self-assessment of dyspnea based on a score ranging from 0 (absent) to 4 (dyspnea when dressing/undressing) (16). Follow-up data were collected 1 year after the baseline. This investigation was carried out in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Kobe City Medical Center West Hospital (approval number: 18-004, approval date: May 14, 2018).

Questionnaires

The FAS (a 10-item self-report fatigue questionnaire) is currently the only validated self-reporting instrument used to classify fatigue in patients with sarcoidosis. Fatigue is determined using a five-point scale ranging from 1 (never) to 5 (always), yielding a FAS score between 10 and 50 (higher scores indicate worse fatigue). Scores >21 and >34 denote fatigue and extreme fatigue, respectively (11,12). Moreover, the minimal clinical important difference (MCID) for FAS in patients with sarcoidosis was established as a four-point difference over time (17), and the percentage based on the MCID in the FAS is –10% (18). In previous research, the FAS demonstrated good reliability and validity in patients with sarcoidosis (12,19). The SFNSL was developed and validated in a sarcoidosis population, exhibiting good reliability and validity (13). This 21-item self-administered questionnaire is utilized for the identification of symptoms associated with SFN. This tool involves a five-point scale ranging from 0 (never) to 4 (always), yielding a score between 0 and 84. Of note, scores <11, 11–48, and >48 indicate no/few symptoms linked to SFN, probable/highly probable SFN, and SFN, respectively (13). This questionnaire

can recognize SFN and detect changes in SFN over time during follow-up and management (MCID: 3.5 points) (13,20). In this analysis, we used the FAS and SFNSL Japanese test version (21). Generic HRQoL was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) Japanese test version (i.e., SF-36v2®) (22). This 36-item questionnaire covers physical health (physical function, role-physical, bodily pain, general health) and mental health (vitality, social functioning, role-emotional, and mental health). The individuals scores of these eight components were processed to yield a score ranging 0–100, with higher scores denoting QoL associated with better health. These eight components are also aggregated into three summary measures, namely physical component summary, mental component summary, and role/social component summary scores (23). The physical component summary, which includes six subscales (i.e., physical functioning, bodily pain, general health, physical role, social functioning, and vitality), represents physical QoL. The mental component summary, which includes six subscales (i.e., bodily pain, general health, social functioning, emotional role, vitality, and mental health), represents mental QoL. The role/social component summary, which includes five subscales (i.e., bodily pain, general health, physical role, social functioning, and emotional role), represents role/social QoL. Higher and lower scores of these summary measures denote better and worse HRQoL, respectively. The SF-36 has been validated in patients with sarcoidosis among others and is widely used (24). In the present study, these questionnaires were self-administered according to the typical procedure.

Statistical analysis

JMP software package version 13 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses. Baseline characteristics and the clinical course were expressed as mean ± standard deviation, medians (interquartile ranges), and percentages. Chi-squared and Fisher's exact tests were used to compare categorical variables. Unpaired *t*- and Mann–Whitney U tests were employed to compare continuous variables. Correlations between FAS score, SFNSL score, and the transformed subscales, and summary measures of the SF-36 and clinical parameters were examined using Spearman's rank correlation. Changes were defined as absolute values from the value obtained at follow-up minus the initial value. A paired *t*-test or the Wilcoxon signed-rank test was used to analyze changes in FAS and SFNSL scores. Subsequently, correlations between within-subject changes in FAS and SFNSL scores, and those of the transformed subscales and summary measures of the SF-36 and clinical parameters were examined using Spearman's rank correlation. Coefficients ≤0.30, 0.30–0.60, and >0.60 denoted weak, moderate, and strong correlations, respectively.

Results

Cross-sectional study

The baseline characteristics of the patients are shown in Table 1. The study population included 55 Japanese patients (29 males and 26 females; mean age: 59.1±14.9 years; median duration of disease: 5.0 years). At the time of the initial study, 11 patients (20.0%) were treated with an oral corticosteroid (OCS) (prednisolone: 1–30 mg/day, median dosage: 5 mg/day) and four patients (7.3%) were treated with an inhaled corticosteroid (ICS) (budesonide: 320, 640, 800 μg/day and fluticasone: 500 μg/day). Among the patients, 10, 13, 23, 9, and 0 had radiographic stages 0, I, II, III, and IV, respectively. Extrathoracic manifestations included eye (n=26), skin (n=13), neurologic (n=5), spleen (n=5), liver (n=4), muscle (n=4), heart (n=3), and bone, testis, kidney (n=1, respectively). Table 2 shows results of the questionnaire in this cross-sectional study. The mean FAS score was 22.7±8.2; 27 (49.1%) and five (9.1%) patients had fatigue (score: ≥22) and extreme fatigue (score: ≥35), respectively. The mean SFNSL score was 13.8±14.3; 23 (41.8%) and two (3.6%) patients had probable/highly probable SFN (score 11–48) and SFN (score: ≥49), respectively. Regarding the effects of sex on these values, there were no significant differences noted in the FAS or SFNSL scores (mean FAS score: 21.7±8.6 and 23.8±7.7 in males and females, respectively [p=0.350]; mean SFNSL score: 12.1±14.1 and 15.7±14.5 in males and females, respectively [p=0.361]). The correlation between FAS and SFNSL scores at baseline is presented in Figure 1a, showing strong relationship (ρ=0.710). Table 3 shows Spearman's rank correlation between each FAS score and SFNSL score, and the transformed subscales and summary measures of the SF-36 and clinical parameters measured at baseline. The FAS

Table 1. Baseline characteristics of the study participants

Characteristics	Cross-sectional study	Longitudinal study	
		Available (n=45)	Not available (n=10)
Age, years	59.1±14.9	59.7±15.3	56.5±13.6
Sex			
Male	29 (52.7)	23 (51.1)	6 (60.0)
Female	26 (47.3)	22 (48.9)	4 (40.0)
Never smoked	17 (30.9)	14 (31.1)	3 (30.0)
Sarcoidosis diagnosis with biopsy	42 (76.4)	37 (82.2)	5 (50.0)
Duration of sarcoidosis, years	5.0 (1.2–10.0)	4.4 (0.9–9.9)	7.4 (2.0–13.9)
Scadding stage: 0/I/II/III/IV	10/13/23/9/0	9/11/18/7/0	1/2/5/2/0
Organ involved*			
Eyes	26 (47.3)	21 (46.7)	5 (50.0)
Skin	13 (23.6)	11 (24.4)	2 (20.0)
Neurologic	5 (9.1)	4 (8.9)	1 (10.0)
Heart	3 (5.5)	3 (6.7)	0 (0.0)
mMRC grade: 0/1/2/3/4	26/23/5/1/0	22/18/5/0/0	4/5/0/1/0
Current oral corticosteroid use	11 (20.0)	9 (20.0)	2 (20.0)
Current inhaled corticosteroid use	4 (7.3)	4 (8.9)	0 (0.0)
ACE, U/L (normal: ≤29.4 U/L)	21.1±10.0	21.6±10.4	18.8±8.4
>29.4 U/L	9 (16.4)	8 (17.8)	1 (10.0)
sIL2R, U/mL (normal: ≤613 U/mL)	726.5±512.3	758.2±521.0	583.7±469.0
>613 U/mL	25 (45.5)	22 (48.9)	3 (30.0)

Categorical and continuous data are presented as number (%) and the mean ± standard deviation or medians (interquartile range), respectively, unless stated otherwise. *Abbreviations:* ACE, angiotensin-converting enzyme; mMRC, modified Medical Research Council; sIL2R, soluble interleukin-2-receptor. *Other extrapulmonary disease: spleen (n=5), liver (n=4), muscle (n=4), bone, testis, kidney (n=1, respectively).

score exhibited significant correlations with all eight domains of the SF-36. In particular, the FAS score showed strong correlations with physical function (ρ=−0.648), vitality (ρ=−0.748), and mental health (ρ=−0.641). The SFNSL score was also significantly correlated with all eight domains of the SF-36. Of note, relationships between the SFNSL score and bodily pain (ρ=−0.623) and vitality (ρ=−0.649) were strong. Concerning summary measures, both FAS and SFNSL scores showed moderate correlations with each component summary. However, the FAS and SFNSL scores did not correlate with any clinical parameters, including ACE and sIL2R levels and OCS or ICS use.

Longitudinal study

Of the 55 patients, 45 patients (23 males) completed the follow-up study. Data were unavailable for the remaining 10 patients for the following reasons: death due to respiratory failure (n=1); lost to follow-up (n=3); and observation period from the initial study <1 year (n=6). Regarding treatment during the follow-up period, among 11 patients who received OCS at baseline, one patient who received prednisolone of 1 mg/day discontinued OCS early in the follow-up; in two patients, the dose of prednisolone was decreased from 13 mg/day to 11 mg/day, and from 30 mg/day to 5 mg/day, respectively. There was no change in the treatment of the remaining eight and four patients treated with ICS at baseline. Among 30 patients who did not receive corticosteroid therapy at baseline, one patient initiated corticosteroid of 35 mg/day for multi-organ sarcoidosis, which was gradually tapered to 7 mg/day at 1-year follow-up; another patient initiated corticosteroid of 35 mg/day for cardiac sarcoidosis, which was gradually tapered to 10 mg/day at 1-year follow-up. Therefore, among

Table 2. Questionnaire results at baseline and 1-year follow-up

	Cross-sectional study (n=55)	Longitudinal study (n=45)	
Variables	**Baseline**	**Baseline**	**1-year follow-up**
FAS score	22.7±8.2	23.2±8.0	23.2±8.3
Fatigue (≥22)	27 (49.1)	24 (53.3)	22 (48.9)
Extreme fatigue (≥35)	5 (9.1)	4 (8.9)	4 (8.9)
SFNSL score	13.8±14.3	14.6±13.6	15.0±13.6
(Highly) probable SFN (11–48)	23 (41.8)	22 (48.9)	22 (48.9)
SFN (≥49)	2 (3.6)	1 (2.2)	1 (2.2)
SF-36			
Physical functioning	79.5±21.3	79.9±19.6	81.1±19.9
Role-physical	75.0±27.9	75.6±26.3	76.8±27.9
Bodily pain	68.0±28.2	68.1±28.3	68.7±27.0
General health	53.2±22.1	50.7±20.3	51.8±21.5
Vitality	54.6±26.3	52.3±26.0	55.4±25.2
Social functioning	84.3±20.7	83.3±21.3	73.9±26.4
Role-emotional	77.4±27.6	77.0±25.8	74.6±30.0
Mental health	66.1±21.4	64.7±20.9	66.6±21.4
Physical component summary	43.4±16.1	43.7±13.7	45.7±12.5
Mental component summary	48.9±11.7	47.4±11.4	48.3±11.3
Role/social component summary	46.4±15.2	46.6±14.9	44.1±14.9

Categorical and continuous data are presented as number (%) and the mean ± standard deviation, respectively. *Abbreviations:* FAS, Fatigue Assessment Scale; SF-36, 36-Item Short-Form Health Survey; SFN, small fiber neuropathy; SFNSL; Small Fiber Neuropathy Screening List.

the 45 patients who completed the longitudinal study, 14 patients used OSC or ICS. During the follow-up, the patients did not receive treatment with corticosteroid-sparing medications or antifibrotics. Concerning any interventions other than pharmacological treatment, only one patient received acupuncture at an outside acupuncture clinic in addition to corticosteroid of 8 mg/day during the 1-year follow-up. The patients included in this study did not receive physiotherapy or supplemental oxygen therapy. Table 2 also shows results of the questionnaire in the longitudinal study. In patients who completed the longitudinal study, there were strong correlations between FAS and SFNSL scores both at baseline (ρ=0.667) (Figure 1b) and follow-up (ρ=0.667) (Figure 1c).

Table 4 shows changes in FAS and SFNSL scores and separately according to OCS or ICS use during the 1-year follow-up. There were no significant changes in FAS score (ΔFAS score, mean: 0.04, 95% confidence interval [CI]: –1.29–1.38) and SFNSL score (ΔSFNSL score, mean: 0.31, 95% CI: –2.12–2.74) during the 1-year follow-up. Using the MCID score of 4 for FAS, nine patients (20.0%), respectively, improved and deteriorated, while 27 patients (60.0%) were stable. Using the MCID score of 3.5 for SFNSL, 13 patients (28.9%) improved, 11 patients (24.4%) deteriorated, and 21 patients (46.7%) remained stable. There were no significant changes in these scores both in treated (n=14) and untreated patients (n=31). Changes in FAS and SFNSL scores in these patients during the 1-year follow-up are shown in Figures 2 and 3, respectively. The patient who received acupuncture in addition to OCS therapy showed an apparent decrease in the SFNSL score (i.e., from 54 to 28), with no change noted in the FAS score (i.e., 35).

Table 5 shows the correlation between within-subject changes in FAS and SFNSL scores, and those of the transformed subscales and summary scores of the SF-36 and clinical parameters. Within-subject changes in FAS score showed moderate correlations

Table 3. Spearman's rank correlation coefficients (ρ) between Fatigue Assessment Scale (FAS) score, Small Fiber Neuropathy Screening List (SFNSL) score, and clinical variables at baseline

Variables	FAS score	SFNSL score
Age	0.137	0.057
Disease duration	0.006	−0.070
Scadding stage	−0.103	−0.115
mMRC	0.255	0.195
ACE	0.075	0.048
sIL2R	0.136	0.051
Oral or inhaled corticosteroid use	0.018	0.012
SF-36		
Physical functioning	−0.648‡	−0.453†
Role-physical	−0.594‡	−0.536‡
Bodily pain	−0.559‡	−0.623‡
General health	−0.597‡	−0.507‡
Vitality	−0.748‡	−0.649‡
Social functioning	−0.452†	−0.566‡
Role-emotional	−0.508‡	−0.480†
Mental health	−0.641‡	−0.519‡
Physical component summary	−0.462†	−0.355†
Mental component summary	−0.563‡	−0.533‡
Role/social component summary	−0.324*	−0.331*

*p<0.05; †p<0.01; ‡p<0.0001. *Abbreviations:* ACE, angiotensin-converting enzyme; mMRC; modified Medical Research Council; SF-36, 36-Item Short-Form Health Survey; sIL2R, soluble interleukin-2 receptor

with those in physical functioning (ρ=−0.407) and physical component summary (ρ=−0.327). Within-subject changes in SFNSL score showed moderate correlations with those in general health (ρ=−0.384). There was no significant relationship observed between within-subject changes in FAS or SFNSL score and those in ACE or sIL2R values during the 1-year follow-up.

Discussion

In this prospective observational study, approximately half of the patients with sarcoidosis demonstrated fatigue as assessed by the FAS and symptoms of SFN assessed by the SFNSL. Both FAS or SFNSL scores were significantly correlated with all of the HRQoL domains assessed by the SF-36. In addition, changes in these scores were correlated with those in some domains of HRQoL. Based on our literature review, this is the first investigation evaluating the relationship between these two non-specific, non-organ related symptoms and HRQoL in Japanese patients with sarcoidosis.

Fatigue has been described as a 'core symptom' of sarcoidosis and is present in 38.6–84% of patients (18,25-29). However, few data on fatigue in Japanese patients with sarcoidosis are available. An epidemiological survey conducted between 2002 and 2011 in Japan (1) did not address such nonspecific, non-organ related symptoms, including fatigue and symptoms associated with SFN. A Japanese national epidemiological survey analyzed pathologically confirmed cases of sarcoidosis which were newly diagnosed in 2004 (30). According to the findings, only 66 of 1,001 cases (6.6%) had fatigue as one of the subjective symptoms. Importantly, the survey was performed using questionnaires; the attending physicians were requested to provide clinical data to a central database of the Ministry of Health, Labour and Welfare in Japan. Therefore, fatigue was assessed by attending physicians rather than patients. Consequently, these data do not reflect patient perspectives. Thus far, clinicians responsible for the follow-up of sarcoidosis patients in Japan have not actively evaluated fatigue. The present study using PROMs to assess fatigue showed higher frequency of fatigue (i.e., 49.1% and 9.1% of patients reported fatigue and extreme fatigue, respectively). This difference highlights the importance of documenting patient perspectives through the use of validated tools, such as FAS or SFNSL. Previous research on sarcoidosis has revealed that physician assessment correlates poorly with patient self-assessment (24). Fatigue has a major impact on the QoL of patients with sarcoidosis (31,32). Furthermore, it has been shown that fatigue is poorly correlated with clinically relevant measures in patients with sarcoidosis (2,26,33-35). The data derived from the present study are consistent with these findings, showing that the FAS score was significantly correlated with the SF-36 score and did not correlate with any clinical parameters (including ACE and sIL2R) cross-sectionally and longitudinally. Up to 70% of patients with sarcoidosis experience chronic pain with signs of SFN (6,36,37). A cross-sectional web-based survey conducted in Denmark, Germany, and the Netherlands revealed high prevalence (86%) of symptoms associated with SFN (38). The aforementioned national epidemiological survey

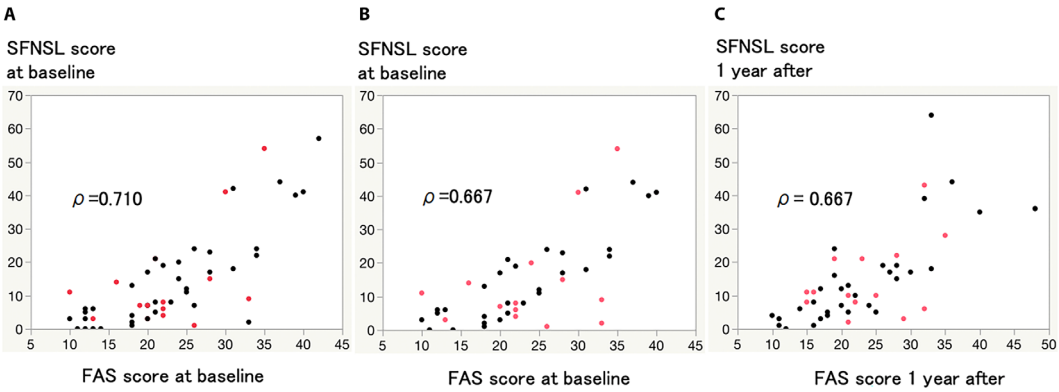

Figure 1. The association between Fatigue Assessment Scale (FAS) score and Small Fiber Neuropathy Screening List (SFNSL) score at baseline (n=55) (a), and in patients who completed the longitudinal study (n=45) at baseline (b) and at follow-up (at 1 year) (c), showing strong correlation (ρ=0.710, 0.667, and 0.667, respectively). Red mark represents patients who were treated with oral or inhaled corticosteroid at baseline or at follow-up (at 1 year).

Table 4. Changes in Fatigue Assessment Scale (FAS) score and Small Fiber Neuropathy Screening List (SFNSL) score according to oral or inhaled corticosteroid use during the 1-year follow-up

Variables		Oral or inhaled corticosteroid use	
		Yes (n=14)	No (n=31)
FAS score			
ΔFAS score	0.04 (−1.29–1.38)	−0.07 (−2.36–2.22)	0.10 (−1.62–1.82)
Improved	9 (20.0)	4 (28.6)	5 (16.1)
Stable	27 (60.0)	8 (57.1)	19 (61.3)
Deteriorated	9 (20.0)	2 (14.3)	7 (22.6)
SFNSL score			
ΔSFNSL score	0.31 (−2.12–2.74)	0.64 (−4.21–5.49)	0.16 (−2.80–3.12)
Improved	13 (28.9)	1 (7.1)	12 (38.7)
Stable	21 (46.7)	9 (64.3)	12 (38.7)
Deteriorated	11 (24.4)	4 (28.6)	7 (22.6)

Data are presented as number (%) or the mean (95% confidence interval).

performed in 2004 in Japan showed that 41 of 1,001 patients (4.1%) had chest pain as one of the subjective symptoms (30). Nevertheless, that study did not investigate symptoms associated with SFN in Japanese patients with sarcoidosis. The present study showed that 41.8% and 3.6% of the patients had probable/highly probable SFN and SFN, respectively. Although SFN is reportedly more prevalent in Caucasians than other ethnic groups (39), it is important to interpret these findings with caution. Additional epidemiological studies are warranted to confirm differences in the prevalence of SFN between ethnic groups or whether the observed disparity is due to differences in healthcare access and diagnostic recognition. SFN markedly impairs QoL (40). The present study showed that the SFNSL score was significantly correlated with the SF-36 score and did not correlate with any clinical parameters (including ACE and sIL2R) cross-sectionally and longitudinally. We also showed strong correlation between the FAS and SFNSL scores at baseline (ρ=0.710) and follow-up (ρ=0.667). This finding is in accordance with those of previous studies carried out in Western countries (38,41). Fatigue is also recognized as a general symptom of SFN-related symptoms (10), which might partly explain the strong association between the

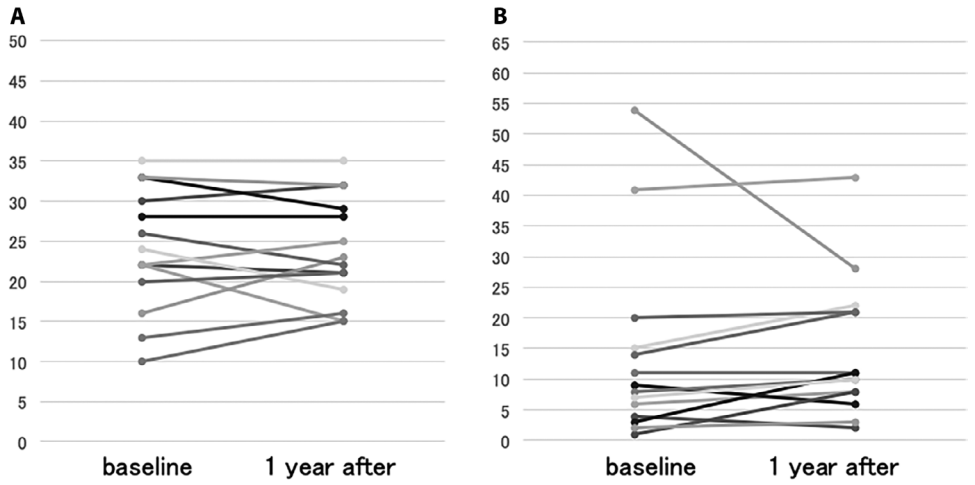

Figure 2. Changes in Fatigue Assessment Scale (FAS) score (a) and Small Fiber Neuropathy Screening List (SFNSL) score (b) in patients treated with oral or inhaled corticosteroid during the 1-year follow-up (n=14). There were no significant changes in the FAS score (ΔFAS score mean: −0.07, 95% confidence interval [CI]: −2.36–2.22) and SFNSL score (ΔSFNSL score mean: 0.64, 95% CI: −4.21–5.49) during the 1-year follow-up.

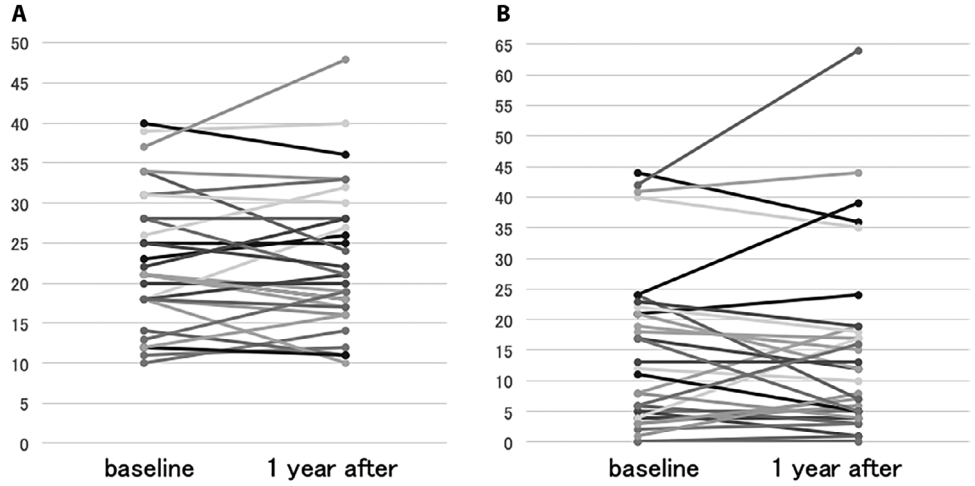

Figure 3. Changes in Fatigue Assessment Scale (FAS) score (a) and Small Fiber Neuropathy Screening List (SFNSL) score (b) in patients not treated with oral or inhaled corticosteroid during the 1-year follow-up (n=31). There were no significant changes in the FAS score (ΔFAS score mean: 0.10, 95% confidence interval [CI]: −1.62–1.82) and SFNSL score (ΔSFNSL score mean: 0.16, 95% CI: −2.80–3.12) during the 1-year follow-up.

FAS and SFNSL scores. The underlying pathophysiology linking fatigue with SFN remains unknown. Nonetheless, a previously unrecognized psychobiological connection between sarcoidosis-induced fatigue and circulating mitochondrial DNA (42) is interesting from the viewpoint of the association of SFN with the presence of single mitochondrial DNA deletion (43). These biological effects connected with the psychosocial aspects of the disease may lead to the development of novel therapeutic strategies for this patient population. A recent randomized controlled trial showed that the use of low-dose OCS alleviates sarcoidosis-associated fatigue, especially in the context of ongoing inflammation (44); however,

Table 5. Spearman's rank correlation coefficients (ρ) between within-subject changes in Fatigue Assessment Scale (FAS) score, Small Fiber Neuropathy Screening List (SFNSL) score, and changes in selected variables (n=45)

Variables	ΔFAS score	ΔSFNSL score
ΔACE	−0.007	−0.084
ΔsIL2R	0.025	0.006
SF-36		
ΔPhysical functioning	−0.407†	−0.212
ΔRole-physical	−0.283	−0.173
ΔBodily pain	−0.209	−0.246
ΔGeneral health	−0.237	−0.384†
ΔVitality	−0.289	−0.243
ΔSocial functioning	−0.077	−0.002
ΔRole-emotional	−0.244	−0.049
ΔMental health	−0.067	0.095
ΔPhysical component summary	−0.327*	−0.267
ΔMental component summary	−0.099	−0.083
ΔRole/social component summary	−0.188	0.037

*p<0.05; †p<0.01. *Abbreviations:* ACE, angiotensin-converting enzyme; SF-36, 36-Item Short-Form Health Survey; sIL2R, soluble interleukin-2 receptor.

we did not confirm the effects of corticosteroid therapy on these symptoms. Both fatigue and SFN complaints are difficult to manage due to the lack of a curative treatment. Furthermore, there is insufficient evidence to make a recommendation regarding low-dose OCS for sarcoidosis-associated fatigue (8). Anti-TNF alpha treatment may also represent a potential therapeutic option. Although previous studies primarily focused on fatigue and SFN as secondary outcomes, they demonstrated preliminary promising results in terms of reducing fatigue or alleviating SFN-associated symptoms (45,46). Moreover, additional research is required to evaluate whether acupuncture could serve as an adjunctive therapeutic option for the management of SFN, particularly in alleviating its symptoms such as pain (47). These two nonspecific, non-organ related symptoms are associated with each other and have a major impact on the HRQoL of patients with sarcoidosis. A survey involving patients with sarcoidosis revealed that QoL is the most important outcome for patients with sarcoidosis, followed by functionality (48). The European Respiratory Society guidelines for treating sarcoidosis (8) have stated that decisions depend on the risk of death or organ failure and impairment of QoL. Therefore, clinicians must appreciate fatigue and symptoms associated with SFN based on the perspective of the patient with sarcoidosis to provide the best care possible. This investigation had certain limitations. Firstly, this was a single-center study with a small sample size, which limits the generalizability of the results and affects the robustness of the statistical analysis and conclusions. Secondly, the diagnosis of sarcoidosis and assessment of organ involvement was conducted using the JSSOG 2015 criteria (14). These criteria (14) include "clinically proven diagnosis" (involvement of at least two of three systems confirmed solely through clinical assessment) due to the frequency of sarcoidosis with ocular, cardiac, and respiratory involvement in Japan and the challenge in collecting specimens. Nonetheless, the diagnostic approach has recently been updated (49), addressing clinical features and related relative probabilities supporting a diagnosis of sarcoidosis. Thirdly, we used only a generic questionnaire for HRQoL (i.e., SF-36) in this study. Consequently, although the cross-sectional study indicated strong correlations between some domains of the SF-36 and the FAS and SFNSL scores, within-subject changes among those showed only moderate correlations. Two sarcoidosis-specific QoL tools, Sarcoidosis Assessment Tool (50) and King's Sarcoidosis Questionnaire (51), were recently developed. It is expected that these instruments will be more sensitive in detecting changes in the HRQoL of patients with sarcoidosis. Fourthly, in the longitudinal study, the management of patients varied. Thus, we were unable to examine the impact of management on fatigue and symptoms associated with SFN.

In conclusion, in this study, approximately half of the Japanese patients with sarcoidosis demonstrated fatigue (assessed by the FAS) and symptoms of SFN (assessed by the SFNSL). Consistent with evidence from Western countries, the findings indicate that these two symptoms have a substantial influence on the HRQoL of patients in Japan. The present results highlight that nonspecific, non-organ related symptoms, as well as measures reflecting the patient perspectives, should be considered in the management of sarcoidosis. In the future, larger, multi-center studies using sarcoidosis-specific HRQoL tools, such as the King's Sarcoidosis Questionnaire, are needed to improve our understanding of such nonspecific, non-organ related symptoms in sarcoidosis.

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