Chapter 4

Types of fatigue in sarcoidosis patients

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Abstract

Objective
Fatigue is frequently reported in sarcoidosis and appears to differ between patients. Three types of fatigue (Early Morning Fatigue, Intermittent Fatigue, and Afternoon Fatigue) are described in the literature for sarcoidosis, but have not been validated. Therefore, the aim of this study was to examine whether these types of fatigue can be identified in sarcoidosis.

Methods
Outpatients (n = 434) from Maastricht University Medical Centre participated in this study. Data were obtained from medical records. Patients also completed questionnaires regarding depressive symptoms, fatigue, quality of life, restless legs, dyspnea, personality, anxiety, sleeping problems, symptoms indicative for small fiber neuropathy, and employment.

Results
Latent cluster analysis revealed three clusters: 1) Mild Fatigue: patients with mild or no complaints of fatigue, 2) Intermittent Fatigue: patients with complaints of fatigue that varied during the day, and 3) All Day Fatigue: patients who felt tired the whole day. The three patient clusters differed regarding clinical, psychological, and demographical characteristics, with All Day Fatigue patients reporting the most complaints.

Conclusion
Intermittent fatigue was validated and two other types were found. Careful consideration to categorize patients with sarcoidosis in the three types of fatigue will help healthcare providers to understand the challenges these patients encounter. The usefulness of psychological counseling should be evaluated in future research in order to improve the wellbeing of the patients, especially for those with All Day Fatigue.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin in which practically every organ can be involved. Lungs are the most commonly affected organ, however involvement of other organ systems such as lymph nodes, skin, eyes, muscles, heart, and joints are frequently observed. Symptoms can vary considerably depending on the specific organs involved and the severity of the granulomatous inflammation[1]. In addition to various symptoms related with the affected organs, patients often suffer from fatigue[2].

The etiology of fatigue associated with sarcoidosis is usually multifaceted. These include the release of cytokines from the granulomas[3-5] as a function of the disease itself and/or depression[6], weight gain, exercise intolerance, or altered sleep patterns as a result of disease related problems. Although to date no accepted definition of fatigue exists, several researchers have proposed to divide fatigue into at least two categories: physical and mental fatigue[7], or passive and active fatigue[8]. However, another study considers fatigue as a one-dimensional concept[9]. In this latter study, fatigue is regarded as a subjective experience, as measured by the Fatigue Assessment Scale (FAS).

Fatigue is the most frequently (71%) reported symptom in the sarcoidosis population in the Netherlands[2]. Moreover, fatigue appeared to be related with worse quality of life (QOL)[10], cognitive failure[11], and depressive symptoms[12]. Since there are no medications available for patients with fatigue, it is important to educate these patients to successfully cope with their fatigue. However, patients appear to experience variations in the type of fatigue[13], making it difficult to apply one universal coping strategy to all patients. Therefore, it is important in clinical practice to identify the possible types of fatigue which will ultimately enable healthcare providers to tailor the intervention appropriately to individual patients.

Sharma[13] described four types of fatigue in sarcoidosis: 1) Early-morning fatigue, where the patient arises with feelings of inadequate sleep; 2) Intermittent fatigue, where the patient wakes up normally but feels tired after a few hours of activity. After a short rest, the patient is able to resume activity, succeeded by another period of fatigue; 3) Afternoon fatigue, where the patient arises in the morning with adequate energy but feels exhausted in the early afternoon. As a result, the patient goes to bed early and stays in bed until the next morning; 4) Post-sarcoidosis chronic fatigue syndrome. This was recently identified[14] and occurs in about 5% of patients who seemingly have recovered from active sarcoidosis. In this condition, the patients complain of fatigue despite the absence of physical signs of sarcoidosis[13]. In our study, it was not possible to examine the post-sarcoidosis fatigue, because most of the participating patients had chronic sarcoidosis. Studies examining empirical evidence for the remaining three types of fatigue in sarcoidosis patients are needed to understand the challenges these patients encounter. However, this evidence is currently lacking in sarcoidosis.

Types of fatigue have been described in patients other than sarcoidosis such as with chronic heart failure[15], and were provided with empirical evidence by means of

latent cluster analysis (LCA)[16]. The purpose of LCA is to find the minimal number of clusters that best describe the associations between the observed indicators, such that individuals belonging to the same cluster are similar to one another, but differ from individuals in other clusters[17]. However, the classifications in fatigue found for chronic heart failure cannot be applied to sarcoidosis as the disease process is different from chronic heart failure which may influence the results.

The aims of this study were 1) to examine whether fatigue in sarcoidosis can be subdivided in types of fatigue: Early-morning fatigue, Intermittent fatigue, and Afternoon fatigue as previously described by Sharma[13] by means of LCA and 2) to describe the demographic, psychological, and clinical characteristics of the resulting clusters.

Methods

Study subjects

All sarcoidosis patients (n = 588) known at the outpatient clinic of ild care center of the Department of Respiratory Medicine of the Maastricht University Medical Centre, a referral centre for sarcoidosis in the Netherlands, were asked to participate in this study. Of these patients, 434 (74%) participated in this study (see Figure 4.1 for the patients selection). Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchial alveolar lavage fluid analysis results. The diagnosis was based on a positive biopsy in 71% of the cases. In patients with typical features of Löfgren's syndrome and characteristic features of bronchoalveolar lavage (BAL) fluid analysis results, no biopsy was obtained. This policy is consistent with the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) guidelines[18]. Comorbidity was defined as any medical problem not related to sarcoidosis. Disorders or conditions considered as comorbidity included cardiovascular disease, thyroid disease, diabetes, anemia, cancer, muscle weakness and immobility due to musculo-skeletal disorders. Extrapulmonary localizations of sarcoidosis were not considered as comorbidity but as sarcoidosis-related. The exclusion criteria were poor expression in the Dutch language (n = 3), relevant comorbidity, such as malignancy (n = 7), dementia (n = 1), and a history of psychiatric illness (n = 2). The institutional internal review board approved the study protocol, and written informed consent was obtained from all participants.

Methods

The following questions were used as indicators to identify the types of fatigue: 1) ‘Do you have difficulties when waking up in the morning?’ (1 *no difficulties at all* to 5 *very much*), 2) ‘Do you feel tired a few hours after waking up?’ (*no*; *yes*), 3) ‘How do you feel in the early afternoon ?’ (1 *not tired at all* to 5 *exhausted*), 4) ‘Do you need more

sleep?' (*no* ; *yes*), 5) 'Do you feel tired the whole day?' (*no*; *yes*), 6) 'Do you take a nap during the daytime?'(*no*; *yes*).

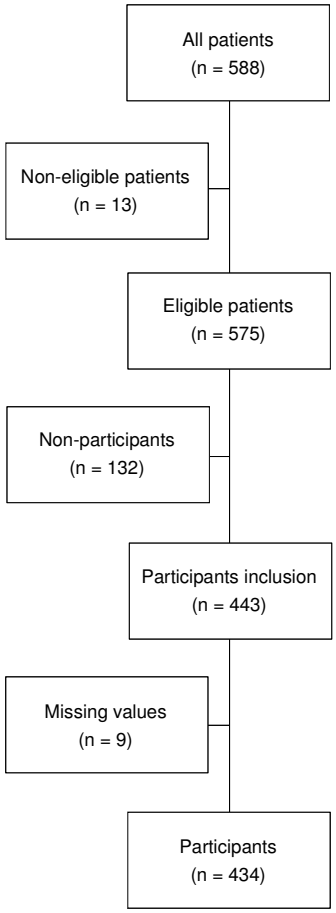

Figure 4.1 Flow chart of the patient selection.

The patients completed the Fatigue Assessment Scale (FAS)[19], the Center for Epidemiological Studies-Depression Scale (CES-D)[20], the State and Trait Anxiety Inventory (STAI)[21], the Small Fiber Neuropathy Screenings List (SFNSL)[22], the World Health Organization Quality of Life assessment instrument Bref (WHOQOL-BREF)[23], and the Single-Item Measures of Personality (SIMP)[24]. In addition, patients were asked to rate the Borg dyspnea index[25] and whether they suffered from restless legs (*yes* or *no*), pain (1 *no* to 5 *very*), woke up more often during the night (*yes* or *no*), or had difficulties fallen asleep (*yes* or *no*). Moreover, patients were asked whether they

were employed (*yes* or *no*), declared to be unfit to work (*yes* or *no*), and whether they worked on irregular hours (*yes* or *no*).

The FAS is a 10-item questionnaire to assess self-reported fatigue. Besides a total fatigue score, the FAS can be divided into a mental fatigue score as well as a physical fatigue score. The reliability and validity of the FAS appeared to be good in sarcoidosis patients[19,26]. Cronbach's alpha in this sample was 0.90. The CES-D is a 20-item scale that measures the presence and degree of depressive symptoms. Reliability and criterion validity appear to be good[27]. Cronbach's alpha in the current sample was 0.89. The STAI measures trait and state anxiety, and only trait anxiety was incorporated in this study. Trait anxiety concerns differences in individuals in the disposition to respond to stressful situations with varying amounts of stress. The trait scale consists of 20 statements and asks people to describe how they generally feel. The psychometric characteristics of the Dutch version of this questionnaire are well established and considered good. Cronbach's alpha in the current sample was 0.93. High trait anxiety was defined as a score of 40 or above, based on Dutch norm scores[21]. The SFNSL is a 21-item self-administered measure of symptomatology related to Small Fiber Neuropathy. The reliability and the validity of the SFNSL are good[22]. Cronbach's alpha in the current sample was 0.91. A higher score on the FAS, CES-D, STAI and SFNSL indicates more complaints. The WHOQOL-Bref instrument was derived from the WHOQOL-100 to measure QOL. QOL has been defined by the World Health Organization Quality of Life group as 'an individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and in relation to their goals, expectations, standards, and concerns'. The WHOQOL-Bref consists of the following broad dimensions: Physical Health (7 items), Psychological Health (6 items), Social Relationships (3 items), Environment (8 items) and the Overall Facet (2 items). Scoring of each domain ranges from 4 to 20, and scoring of the Overall Facet ranges between 2 and 10[23]. It is concluded that the content validity, construct validity, and the reliability of the WHOQOL-Bref are good[28]. Cronbach's alpha in the current sample was 0.92. A higher score indicates a better QOL. The Borg Dyspnea Index is a self-rated scale for dyspnea and scored from 0 (no impairment) to 10 (severe impairment). Test re-test reliability of this instrument was found to be good[25]. The SIMP measures personality by means of five descriptions representing the poles of each of the Big Five factors: Extraversion, Agreeableness, Conscientiousness, Emotional Stability and Openness[24]. The items are self-rated from 1 to 9 and a higher score indicates a higher Emotional Stability, more Agreeableness, more Openness, less Conscientiousness, or less Extraversion. The SIMP is a short valid and reliable measure[24].

Demographics and relevant clinical data, such as time since diagnosis, lung function measurements, Body Mass Index (kg/m^2), multisystemic involvement, treatment with corticosteroids, and chest radiographs were derived from the patients' medical files. Lung function measurements, including forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), were measured with a pneumotachograph. Diffusing capacity of the lung for carbon monoxide (DLCO) was measured by the single breathe method. Values were expressed as a percentage of

those predicted. Chest radiographs were graded according to the radiographic staging of DeRemee (0 to III), adding stage IV: the end stage of lung fibrosis.

Analysis

Types of fatigue were identified by means of latent class analysis (LCA), based on six indicators. Patients with missing values in all six indicators (n = 9) were excluded from the analyses, though patients with partially missing information were retained in the analyses. The two indicators with five ordered categories—'Do you have difficulties when waking up in the morning?' (1 *no difficulties at all* to 5 *very much*), and 'How do you feel in the early afternoon?' (1 *not tired at all* to 5 *exhausted*)—were treated as ordinal. Treating them as nominal did not result in a better fit.

Latent class modeling aims to obtain the smallest number of clusters that accounts for all the associations[17]. Initially, we fitted 1- to 5-class models and compared their Bayesian Information Criteria (BIC)[29]. Because the two ordinal indicators turned out to be more strongly related than could be explained by standard latent class models, we allowed these variables to be associated within classes (to be locally dependent). The preferred model is the one with the lowest BIC and a non-significant (bootstrap) p-value, for the goodness-of-fit chi-square test. The latter indicates that there is no need to reject the model concerned in favor of a more complex model[17]. Using the latent class model, each respondent was assigned to the most likely cluster (i.e., the one with highest posterior class membership probability).

For comparison of psychological, demographical and clinical characteristics between the encountered latent classes we used the chi-square tests for categorical and F tests for continuous variables. In line with De Vries et al.[19] we also divided the FAS into two groups: FAS scores 10 to 21 (not tired) and FAS scores 22 to 50 (tired). Percentages of tired patients were computed for each defined cluster.

The LCA was performed with Latent GOLD 4.5[30,31], and for the other data analyses we used Statistical Package Social Science 17.0[32]. A p-value < 0.05 was considered statistically significant.

Results

Table 4.1 provides the information for model selection. As shown, a solution with three clusters resulted in the lowest BIC value. Moreover, its p-value for the goodness-of-fit test indicated that there was no need to reject this model in favor of a more complex model.

The Wald tests reported in Table 4.2 show that all indicators were significantly related to the three clusters ($p < 0.01$ for all six indicators).

Table 4.1 Diagnostic criteria for the estimated Latent class models.

	Log-likelihood value (LL)	BIC (LL)	Number of parameters	df	Bootstrap p-value
1-Cluster	-2175	4429	13	421	<0.01
2-Clusters	-2101	4324	20	414	<0.01
3-Clusters	**-2051**	**4267**	**27**	**407**	**0.05**
4-Clusters	-2038	4283	34	400	0.14
5-Clusters	-2033	4314	41	393	0.23

BIC(LL) = Bayesian Information Criterion, computed using the log-likelihood value; the preferred model (in bold) is the one with the lowest BIC value.

Table 4.2 Significance tests for indicators in 3-class model.

Indicators	*Wald*	*p*	R^2
1. Do you have difficulties when waking up in the morning?	23.1	<0.01	0.27
2. Do you feel tired a few hours after waking up?	35.2	<0.01	0.33
3. How do you feel in the early afternoon?	11.1	<0.01	0.14
4. Do you need more sleep?	16.3	<0.01	0.32
5. Do you feel tired the whole day?	12.3	<0.01	0.88
6. Do you take a nap during the daytime?	27.7	<0.01	0.24

The cluster-specific means and percentages on the six indicators are enumerated in Table 4.3a. The first group, called Mild Fatigue (MF); n = 130, contained patients who scored relatively low on all six indicators. Cluster two contained patients who were likely to need more sleep (indicator 4), who most often took a nap (indicator 6), and did not feel tired all day (indicator 5), but a few hours after waking up (indicator 2). This group (n = 220) was called Intermittent Fatigue (IF). The third group (n = 84), called All Day Fatigue (ADF), consisted of patients who indicated that they felt very tired the whole day and also during the early afternoon (indicator 3). These patients needed slightly less sleep and naps and had more difficulties with waking up (indicator 1) compared to the patients with IF.

Table 4.3a Class proportion and class-specific means and percentages for the six indicators in the 3-class model.

Indicators	MF (n = 130, 0.31)	IF (n = 220, 0.49)	ADF (n = 84, 0.19)
1. Do you have difficulties when waking up in the morning? (1 *no difficulties at all* to 5 *very much*)	1.7	2.6	3.4
3. How do you feel in the early afternoon? (1 *not tired at all* to 5 *exhausted*)	2.0	3.0	3.7
2. Do you feel tired a few hours after waking up?[a]	4%	31%	0%
4. Do you need more sleep?[a]	6%	70%	50%
5. Do you feel tired the whole day?[a]	4%	0%	97%
6. Do you take a nap during the daytime?[a]	13%	67%	60%

[a] Percentage of patients who answered 'yes' to the question. ADF = All Day Fatigue; IF = Intermittent Fatigue; MF = Mild Fatigue

Because the BIC value of the fourth-cluster solution came close to the BIC value of the three-cluster solution, both solutions are shown in Tables 4.3a and 4.3b. The fourth cluster displays a similar pattern to IF patients, except that patients in this fourth cluster often needed more sleep and less often took a nap, compared to the IF patients (see Table 4.3b).

Table 4.3b Class proportion and class-specific means and percentages for the six indicators in the 4-class model.

Indicators	MF (n = 130, 0.31)	IF (n = 110, 0.23)	4th cluster (n = 110, 0.23)	ADF (n = 84, 0.19)
1. Do you have difficulties when waking up in the morning? (1 *no difficulties at all* to 5 *very much*)	1.8	2.6	2.7	3.4
3. How do you feel in the early afternoon? (1 *not tired at all* to 5 *exhausted*)	2.1	3.5	2.5	3.7
2. Do you feel tired a few hours after waking up?[a]	7%	41%	22%	0%
4. Do you need more sleep?[a]	0%	60%	98%	52%
5. Do you feel tired the whole day?[a]	1%	0%	0%	95%
6. Do you take a nap during the daytime?[a]	17%	87%	49%	60%

[a] Percentage of patients who answered 'yes' to the question. ADF = All Day Fatigue; IF = Intermittent Fatigue; MF = Mild Fatigue

According to the FAS score, 52% of the MF patients were tired, and 48% were not tired. In the IF group 91% of the patients were tired, and 9% were not tired. Approximately every ADF patient (99%) was tired and 1% of the patients were not tired.

Demographical and clinical characteristics for all patients, and stratified according to the three clusters, are summarized in Table 4.4. All groups differed regarding fatigue ($F(2, 427) = 121.1$, $p < 0.01$), mental fatigue, ($F(2, 427) = 76.9$, $p < 0.01$), physical fatigue, ($F(2, 427) = 120.8$, $p < 0.01$), depressive symptoms ($F(2, 421) = 35.1$, $p < 0.01$), trait anxiety ($F(2, 422) = 29.4$, $p < 0.01$, the QOL domains Psychological Health ($F(2, 426) = 28.6$, $p < 0.01$), Physical Health ($F(2, 425) = 84.4$, $p < 0.01$), and the Overall Facet ($F(2, 428) = 60.2$, $p < 0.01$, employment (χ^2 (2, 428) = 30.1, $p < 0.01$) and being unfit to work (χ^2 (2, 409) = 39.0, $p < 0.01$). ADF patients were more often declared to be unfit to work and unemployed, compared to the IF and MF patients (p's < 0.01). Likewise, IF patients were more often declared to be unfit to work and unemployed than the MF patients (p's < 0.01). The ADF patients also scored higher on fatigue, mental fatigue, physical fatigue, depressive symptoms, trait anxiety, and lower on the Overall Facet of Quality of Life and the QOL domains Physical and Psychological Health, compared with the other groups (p's < 0.05). Similarly, the IF patients reported more depressive symptoms, fatigue, mental fatigue, physical fatigue, trait anxiety, and scored lower on the Overall Facet and Physical and Psychological Health in comparison with the MF patients (p's < 0.05).

Table 4.4 Symptoms, demographical, clinical, and sleep related characteristics, stratified by type of fatigue in sarcoidosis.

		MF (n = 130)	IF (n = 220)	ADF (n = 84)	All patients (n = 434)
Demographics	Age in years	48.0 ± 11.2 (n =130)	47.7 ± 10.9 (n =220)	48.2 ± 11.1 (n = 84)	47.9 ± 11.0 (n = 434)
	Female [d]	35% (n = 130)	50% (n = 220)	52% (n = 84)	46% (n = 434)
Clinical	Radiographic stage: 0 / I / II / III / IV	35/7/25/15/18% (n = 129)	42/11/25/11/11% (n = 219)	40/7/23/13/17% (n = 84)	35/7/25/15/18% (n = 432)
	Use of corticosteroids	35% (n = 130)	34% (n = 216)	41% (n = 84)	35% (n = 430)
	Multisystemic involvement	45% (n = 130)	48% (n = 217)	48% (n = 83)	47% (n = 430)
	BMI (kg/m^2)	26.6 ± 4.6 (n = 124)	27.7 ± 5.4 (n = 198)	27.8 ± 6.8 (n = 82)	27.4 ± 5.5 (n = 404)
	Time since diagnosis in years	8.3 ± 9.6 (n = 130)	7.2 ± 6.5 (n = 219)	8.0 ± 8.0 (n = 84)	7.7 ± 7.8 (n = 433)
	FEV_1 [b]	87.6 ± 23.5 (n = 129)	91.9 ± 21.0 (n = 212)	84.4 ± 22.8 (n = 83)	89.1 ± 22.3 (n = 424)
	FVC [b]	97.5 ± 21.3 (n = 129)	101.1 ± 18.7 (n = 212)	93.4 ± 18.9 (n = 83)	98.5 ± 19.7 (n = 422)
	DLCO [b]	80.4 ± 19.6 (n = 129)	83.9 ± 15.3 (n = 212)	76.7 ± 17.8 (n = 83)	81.4 ± 17.5 (n = 424)
Symptoms	SFN-associated symptoms [d]	14.8 ± 12.8 (n = 120)	26.7 ± 13.8 (n = 191)	31.0 ± 17.5 (n = 79)	23.9 ± 15.6 (n = 390)
	Dyspnea [c]	2.0 ± 1.7 (n = 120)	2.6 ± 1.8 (n = 204)	3.8 ± 2.5 (n = 80)	2.6 ± 2.0 (n = 404)
	Depressive symptoms [a]	9.3 ± 8.0 (n = 125)	15.4 ± 8.9 (n = 215)	19.6 ± 10.6 (n = 84)	14.4 ± 9.7 (n = 424)
	Pain [d]	1.8 ± 0.9 (n = 128)	2.7 ± 1.1 (n = 217)	2.9 ± 1.2 (n = 83)	2.4 ± 1.2 (n = 428)
	Fatigue [a]	22.2 ± 6.8 (n = 128)	31.0 ± 6.9 (n = 218)	36.2 ± 6.3 (n = 84)	29.4 ± 8.5 (n = 430)
	Mental Fatigue [a]	9.4 ± 3.4 (n = 127)	13.4 ± 3.8 (n = 218)	15.7 ± 4.5 (n = 83)	12.7 ± 4.5 (n = 428)
	Physical Fatigue [a]	12.8 ± 4.0 (n = 127)	17.6 ± 3.8 (n = 218)	20.5 ± 2.7 (n = 83)	16.7 ± 4.6 (n = 428)
Sleep	Fallen asleep is difficult [c]	1.8 ± 1.1 (n = 130)	1.9 ± 1.0 (n = 219)	2.6 ± 1.4 (n = 84)	2.0 ± 1.2 (n = 433)
	Restless legs [d]	22% (n = 126)	44% (n = 218)	45% (n = 84)	38% (n = 428)
	Wakes up more often during night	44% (n = 126)	50% (n = 218)	55% (n = 84)	49% (n = 428)
	Sleep quality [a]	3.3 ± 1.1 (n = 127)	2.9 ± 1.0 (n = 219)	2.5 ± 1.1 (n = 84)	2.9 ± 1.1 (n = 430)
Psychological	Trait anxiety [a]	34.9 ± 10.1 (n = 125)	41.5 ± 9.7 (n = 216)	45.0 ± 10.0 (n = 84)	40.3 ± 10.5 (n = 425)
	Openness	5.9 ± 1.9 (n = 124)	6.0 ± 1.9 (n = 208)	6.2 ± 1.9 (n = 82)	6.0 ± 1.9 (n = 414)
	Conscientiousness	4.9 ± 2.1 (n = 124)	4.9 ± 2.1 (n = 207)	5.0 ± 2.1 (n = 82)	4.8 ± 2.0 (n = 413)
	Extraversion	5.0 ± 2.1 (n = 124)	5.2 ± 2.1 (n = 210)	5.6 ± 2.4 (n = 83)	5.2 ± 2.2 (n = 417)
	Agreeableness	5.2 ± 2.2 (n = 124)	5.7 ± 2.3 (n = 208)	5.8 ± 2.2 (n = 82)	5.5 ± 2.3 (n = 414)
	Emotional stability [d]	4.8 ± 2.2 (n = 124)	4.0 ± 2.0 (n = 208)	3.8 ± 2.2 (n = 83)	4.2 ± 2.1 (n = 415)
	Overall Facet [a]	6.9 ± 1.4 (n = 129)	5.8 ± 1.4 (n = 218)	4.8 ± 1.3 (n = 84)	6.0 ± 1.6 (n = 431)
	Physical Health [a]	14.9 ± 2.9 (n = 128)	12.0 ± 2.6 (n = 216)	10.3 ± 2.4 (n = 84)	12.5 ± 3.1 (n = 428)
	Psychological Health [a]	15.0 ± 2.5 (n = 128)	13.6 ± 2.2 (n = 218)	12.7 ± 2.4 (n = 83)	13.8 ± 2.5 (n = 429)
	Social Relationships [d]	15.3 ± 2.7 (n = 128)	14.3 ± 3.0 (n = 216)	13.9 ± 3.0 (n = 84)	14.5 ± 2.9 (n = 428)
	Environment [d]	16.3 ± 2.5 (n = 128)	15.1 ± 2.3 (n = 218)	14.5 ± 2.7 (n = 84)	15.4 ± 2.5 (n = 430)
Employment	Employment [a]	73% (n = 125)	56% (n = 219)	35% (n = 84)	54% (n = 428)
	Working on irregular hours	30% (n = 90)	31% (n = 119)	15% (n = 26)	29% (n = 235)
	Unfit to work [a]	12% (n = 121)	30% (n = 207)	53% (n = 81)	29% (n = 409)

Data are expressed as means ± standard deviation or in percentages. Comparisons between ADF, IF and MF: [a] Significant difference between the three types of fatigue; [b] Significant difference between ADF versus IF; [c] Significant difference between ADF versus IF and MF; [d] Significant difference between MF versus IF and ADF. ADF All Day Fatigue; BMI = Body Mass Index; DLCO = Diffuse capacity of the lung for carbon monoxide; FEV_1 = Forced Expiratory Volume in one second; FVC = Forced Vital Capacity IF = Intermittent Fatigue; MF = Mild Fatigue; SFN = Small Fiber Neuropathy.

The following question of the WHOQOL-Bref 'How satisfied are you with your sleep?' was examined separately. All groups differed regarding sleep quality ($F(2, 427) = 13.0$, $p < 0.01$). ADF patients were less satisfied with their sleep quality, compared to IF patients and MF patients ($p < 0.05$), and IF patients were less satisfied, compared to MF patients ($p < 0.01$).

Significant differences were found between ADF and IF regarding lung function tests: DLCO: $F(2, 421) = 5.6$, $p < 0.01$; FEV_1: $F(2, 421) = 3.9$, $p = 0.02$; and FVC: $F(2, 419) = 5.0$, $p < 0.01$. ADF patients had lower scores on lung function tests (DLCO: $p < 0.01$; FEV_1, $p = 0.03$; FVC: $p < 0.01$), compared with the IF patients. MF patients did not differ with respect to clinical characteristics in comparison to the other groups. ADF patients had more difficulties with falling asleep, compared with the other patients ($F(2, 430) = 13.9$, p's < 0.01), and complained more of dyspnea $F(2, 401) = 20.6$, p's < 0.01).

Finally, significant differences were found between MF patients and the other groups, regarding restless legs (χ^2 (2, 428) = 18.1, $p < 0.01$), pain ($F(2, 425) = 35.9$, $p < 0.01$), Emotional Stability ($F(2, 412) = 7.3$, $p < 0.01$), sex (χ^2 (2, 434) = 9.6, $p < 0.01$), the QOL domains Social Relationships ($F(2, 425) = 8.0$, $p < 0.01$) and Environment ($F(2, 427) = 15.4$, $p < 0.01$), and SFN-associated symptoms ($F(2, 387) = 37.7$, $p < 0.01$). The MF patients less often reported restless legs, and scored lower on trait anxiety, pain, and SFN-associated symptoms, compared with both fatigued groups (p's < 0.01). MF patients had a higher mean score on Emotional Stability, compared to ADF patients and IF patients (p's < 0.01). Furthermore, they were more often male, and scored higher on the QOL domains Social Relationships and Environment (p's < 0.05), compared with the other groups. No significant differences were found between the groups in the other characteristics.

Discussion

The aims of this study were 1) to examine whether fatigue in sarcoidosis can be subdivided in types of fatigue: Early-morning fatigue, Intermittent fatigue, and Afternoon fatigue as previously described by Sharma[13] by means of LCA and 2) to describe the demographic, psychological, and clinical characteristics of the resulting clusters.

LCA revealed three clusters: a subgroup with mild or no complaints of fatigue (MF patients), a subgroup with complaints of fatigue that varied during the day (IF patients), and a subgroup of patients who felt tired the whole day (ADF patients). Importantly, the ADF patients reported more psychological problems and clinical symptoms, in comparison to the other groups. In addition, they were most frequently unable to work.

It should be noted that the BIC value for the four-cluster solution was only slightly higher than the value for the three-cluster solution, indicating that the two models are equally good according to this criterion. The four-cluster solution is, however, clearly less preferred when looking at other criteria. First, the p-values for the

goodness-of-fit test indicated that there was no need to retain the more complex four-cluster model in favor of the simpler three-cluster model. Second, the proportion of classification errors was higher in the four-cluster model compared to the three-cluster solution, indicating stronger overlap between clusters. Third, the interpretation of the four-cluster solution had no substantial contribution from a theoretical perspective: the fourth cluster turned out to be very similar to the IF type. Therefore, we decided to keep the three-cluster solution as our final model.

In keeping with the findings described by Sharma[13], three types of fatigue were identified in this study when leaving the Post-sarcoidosis chronic fatigue syndrome aside. However, not every type of fatigue as described by Sharma has been validated in this study. For example, the Intermittent Fatigue type as described by Sharma was confirmed in our study. However, we did not identify an Afternoon Fatigue type, because we were not able to find a group of patients who specifically complained of fatigue in the afternoon. Instead, a group of patients was found whose complaints of fatigue were mild and not associated with a specific moment of the day. Based on these findings, Sharma's Early Morning Fatigue (EMF) type should be relabeled to ADF. Both EMF and ADF share the common feature that the patients have difficulties with starting up, but the present results showed a prolonged fatigue which lasted all day, instead of only fatigue in the morning.

Although the three groups appeared to differ in symptom severity, It is unlikely that the three types of fatigue can be explained in the context of the clinical stages that evolve chronically. Neither the chest X-ray stage nor the time since diagnosis had an impact on the extent of fatigue. This was in line with the results of a study by Marcellis et al.[33] who found no relationship between fatigue and the chest X-ray stage or time since diagnosis. In addition, the patients with ADF had lower lung function test scores than the patients with IF, but not significant differently from the MF group. It was expected that the MF patients would score significantly higher on the lung function tests, compared to the other groups. This was expected because lung function is a measure of disease severity in sarcoidosis and MF patients reported only mild symptoms. The disassociation between lung function and symptoms of fatigue confirms the results of previous research[34]. Thus it is plausible that regularly used clinical measurements such as lung function tests, are not appropriate to measure fatigue.

An alternative explanation is that an unknown underlying physical mechanism decreased the lung function test results of the MF patients. Also, the MF group may be better able to cope with their fatigue and other disease-related symptoms, compared to the other patients. Half of the MF patients had complaints of fatigue, as measured with the FAS, but they scored relatively low on all indicators used to define the types of fatigue (See Tables 4.3a and 4.3b). Possible explanations to why MF patients did not experience their fatigue as problematic may include: 1) They may have psychologically adapted to their fatigue; and/or: 2) they may have a more emotionally stable personality, compared to the other patients. We found that MF patients had a higher score on Emotional Stability, as measured with the SIMP[24], compared to ADF patients, and IF patients. In addition, MF patients had the lowest scores on trait anxiety, in comparison to the other groups. Studies in other chronic

diseases, such as breast cancer, show that trait anxiety is an important predictor of fatigue[35]. Which of the before mentioned explanations for the decreased lung function in MF patients are most important in sarcoidosis, needs to be explored in future research.

Regarding the psychological variables, the comparison between the groups showed a consistent pattern. ADF patients had the worst scores, followed by the IF and MF patients. Similar patterns were found in the frequencies of patients having an employment and in the number of patients who have been declared to be unfit to work. The clear relationship between psychological distress and type of fatigue indicates that psychological counseling is important in patient care. Vercoulen et al.[36] described that psychological factors could be involved in the development, but particularly in the maintainability of chronic fatigue. The nature of patients' attributions, avoidance of physical activity, and depressive symptoms also play a role. Given the high rate of depressive symptoms found in patients with chronic fatigue, it is likely that depressive symptoms are involved in the development and/or maintainability of fatigue. This relationship between depressive symptoms and chronic fatigue is complex, because both somatic and psychological factors are involved. In addition, avoidance of physical activity may lead to maintainability of fatigue. Recently, Esteban et al.[37] showed that low physical activity was significantly related to high levels of fatigue in chronic obstructive pulmonary disease patients. These results may be explained by avoidance of physical activity. It is assumed that patients "learn" that physical exertion increases fatigue and muscle aches, therefore patients try to evade these problems by avoiding physical activity. The physical condition of these inactive patients will deteriorate further and a vicious cycle between inactivity and fatigue arises. Finally, attributions of the symptoms of physical factors can also lead to maintainability of fatigue. For instance, denial of the influence of psychological factors coincides with difficulties coping with fatigue. The results of this study showed that ADF patients less often indicated that they needed more sleep, while they reported more symptoms of fatigue, in comparison to the IF patients. Therefore, it is possible that they have difficulties coping with fatigue and demand too much from themselves.

Treatment of depressive symptoms and anxiety may lead to an improvement in energy level. Especially ADF patients may benefit from psychological treatment, because these patients suffer the most from psychological problems. In fact, 69% of ADF patients had an anxiety score indicative of high trait anxiety and 57% had a score indicative for depression.

It is important to keep the causality problem in mind as to which came first: fatigue or disease-related symptoms? Sleeping problems and depressive symptoms can cause and maintain fatigue, but fatigue may also cause these symptoms[38]. Our results suggest that in ADF patients sleep disorders may be at least partly responsible for the fatigue complaints.

Several limitations of our study are noteworthy of mention. Firstly, because of the cross-sectional design of our study, it is not possible to comment on 1) cause and effect of fatigue and 2) the stability of the types of fatigue. Future research in a longitudinal prospective manner to elucidate the development of fatigue symptoms in

patients diagnosed with sarcoidosis is needed. Moreover, it will be important to identify clinical predictors correlative with the development of the various types of fatigue. In addition, it is important to acknowledge that all patients were recruited in a tertiary referral centre, which may diminish the generalizability of the results of this study. Secondly, our study used self-reported measures to assess fatigue and psychological symptoms. Gold standards to measure fatigue and psychological symptoms objectively are currently lacking[34], therefore subjective assessment remains a highly valuable method to understand the symptoms especially from the patient's perspective. Thirdly, the restricted number of questions regarding sleep may not have allowed a clear distinction between symptoms related to sleep disorders. There may be great clinical implications to differentiate sleep disorders from fatigue symptoms especially with regard to treatment options. However, the aim of this study was to examine the different presentations of fatigue and the focus was not on treatment options; sleep disorders were not specifically excluded. Follow-up study aimed to identify the most appropriate treatment option(s) will require more careful evaluation of sleeping disorders that may include sleep questionnaires as fatigue appeared to be related with sleep disturbances. Recently, Fortier-Brochu et al.[39] showed that severe fatigue was found in individuals with both severe and mild sleep disturbances. In addition, Bailes et al.[40] showed that fatigue was associated with obstructive sleep apnea. The relationship between fatigue and sleep in sarcoidosis has been studied previously and sleep disorders appeared to be a frequent phenomenon in sarcoidosis[41–43]. Turner et al.[41] found a higher prevalence of sleep apnea in patients with sarcoidosis, compared to control patients. In addition, in a study of Verbraecken et al.[42] obstructive sleep apnea, periodic leg movement or restless legs were found in more than half of the sarcoidosis patients. Drent[43] demonstrated that symptoms of fatigue disappeared after treating sleep apnea and sarcoidosis. Moreover, sleep disturbances are often related to small fiber neuropathy and autonomic dysfunction[41] which may in part explain the fatigue. However, sleep problems may be caused by anatomical dysfunction as well. For instance, involvement of the tongue, tonsils, infiltration of the upper airway, and larynx can provoke sleep apnea[44]. Because fatigue and sleep disorders frequently occur in patients with sarcoidosis, future studies should focus on the relationship between autonomic dysfunction, sleep disorders and fatigue in sarcoidosis to include in the management of sarcoidosis appropriate treatment strategies.

Strengths of this study are the large number of participants and the clustering method used[45].

In conclusion, three types of fatigue were found in this study. ADF patients reported the most clinical and psychological symptoms, followed by IF and MF patients. Appropriate classification of patients with sarcoidosis in the three types of fatigue identified in this study will further our understanding of the challenges these patients encounter. Furthermore, this classification may provide potential targets for the management of sarcoidosis. Especially patients who are suffering from ADF may benefit from the usefulness of psychological interventions. These interventions may be considered in the multidisciplinary management of sarcoidosis to improve the well-being of the patients.

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