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Types of fatigue in sarcoidosis patients

Willemien P.E. De Kleijn a,b, Marjolein Drent b,c, Jeroen K. Vermunt a,d, Hide Shigemitsu e, Jolanda De Vries a,b,f,*

a CoRPS, Department of Medical Psychology and Neuropsychology, Tilburg University, The Netherlands
b Sarcoïdis Management Center, Maastricht University Medical Centre, The Netherlands
c Department of Respiratory Medicine, Maastricht University Medical Centre, The Netherlands
d Department of Methodology and Statistics, Tilburg University, The Netherlands
e University of Southern California Keck School of Medicine, Division of Pulmonary and Critical Care Medicine, Los Angeles (CA), USA
f Department of Medical Psychology, St. Elisabeth Hospital, Tilburg, The Netherlands

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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, depressive symptoms, 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.

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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 multifactorial. 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.

Method

Study subjects

All sarcoidosis patients (n = 588) known at the outpatient clinic 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 Fig. 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 BAL fluid analysis results, no biopsy was obtained. This policy is consistent with the World Association of Sarcoidosis and Other Granulomatous diseases [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).

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 Screening 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

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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 above 40, 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 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 retest reliability of this instrument was found to be good [25].

The SIMP measures personality by means of 5 descriptions representing the poles of each of the Big Five factors: Extraversiveness, 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 Extraversiveness. 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/m²), 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 (FEV₁) 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 adding stage IV: the end stage of lung fibrosis.

Table 1

<table>
<thead>
<tr>
<th>Diagnostic criteria for the estimated latent class models.</th>
<th>Log-likelihood value (LL)</th>
<th>BIC (LL)</th>
<th>Number of parameters</th>
<th>df</th>
<th>Bootstrap p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Cluster</td>
<td>−2175</td>
<td>4429</td>
<td>13</td>
<td>421</td>
<td>~0.01</td>
</tr>
<tr>
<td>2-Clusters</td>
<td>−2101</td>
<td>4324</td>
<td>20</td>
<td>414</td>
<td>~0.01</td>
</tr>
<tr>
<td>3-Clusters</td>
<td>−2051</td>
<td>4267</td>
<td>27</td>
<td>407</td>
<td>0.05</td>
</tr>
<tr>
<td>4-Clusters</td>
<td>−2038</td>
<td>4283</td>
<td>34</td>
<td>400</td>
<td>0.14</td>
</tr>
<tr>
<td>5-Clusters</td>
<td>−2033</td>
<td>4314</td>
<td>41</td>
<td>393</td>
<td>0.23</td>
</tr>
</tbody>
</table>

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

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.

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Table 2

<table>
<thead>
<tr>
<th>Significance tests for indicators in 3-class model.</th>
<th>Wald</th>
<th>p</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Do you have difficulties when waking up in the morning?</td>
<td>23.1</td>
<td>&lt;0.01</td>
<td>0.27</td>
</tr>
<tr>
<td>2. Do you feel tired a few hours after waking up?</td>
<td>35.2</td>
<td>&lt;0.01</td>
<td>0.33</td>
</tr>
<tr>
<td>3. How do you feel in the early afternoon?</td>
<td>11.1</td>
<td>&lt;0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>4. Do you need more sleep?</td>
<td>16.3</td>
<td>&lt;0.01</td>
<td>0.32</td>
</tr>
<tr>
<td>5. Do you feel tired the whole day?</td>
<td>12.3</td>
<td>&lt;0.01</td>
<td>0.88</td>
</tr>
<tr>
<td>6. Do you take a nap during the daytime?</td>
<td>27.7</td>
<td>&lt;0.01</td>
<td>0.24</td>
</tr>
</tbody>
</table>
ADF All Day Fatigue IF Intermittent Fatigue MF Mild Fatigue.

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

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

<table>
<thead>
<tr>
<th>Indicators</th>
<th>MF</th>
<th>IF</th>
<th>ADF</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 130, 0.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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 |
| 2. Do you need more sleep?  
(1 6% 70% 50% | 4% | 0% | 97% |
| 3. Do you take a nap during the daytime?  
(1 13% 67% 60% | 4% | 0% | 97% |

ADF All Day Fatigue IF Intermittent Fatigue MF Mild Fatigue.

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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 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 relation 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 dissociation 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 derive the FAS, but they scored relatively low on all indicators used to derive

Data are expressed as means±standard deviation or in percentages. Comparisons between ADF, IF and MF: * Significant difference between the three types of fatigue; ** Significant difference between ADF versus IF and MF; *** 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; FEV1 Forced Expiratory Volume in one second; FVC Forced Vital Capacity IF Intermittent Fatigue; MF Mild Fatigue; SFN Small Fiber Neuropathy.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>ADF (n=84)</th>
<th>IF (n=220)</th>
<th>ADF (n=84)</th>
<th>All patients (n=434)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea*</td>
<td>9.6±1.0 (n=84)</td>
<td>12.6±1.3 (n=220)</td>
<td>9.3±1.0 (n=84)</td>
<td>12.6±1.3 (n=434)</td>
</tr>
<tr>
<td>Depressive symptoms*</td>
<td>15.8±3.9 (n=84)</td>
<td>19.4±4.1 (n=220)</td>
<td>15.8±3.9 (n=84)</td>
<td>19.4±4.1 (n=434)</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>2.0±1.1 (n=84)</td>
<td>2.6±1.2 (n=220)</td>
<td>2.0±1.1 (n=84)</td>
<td>2.6±1.2 (n=434)</td>
</tr>
<tr>
<td>Mental fatigue*</td>
<td>17.3±3.8 (n=84)</td>
<td>20.5±3.7 (n=220)</td>
<td>17.3±3.8 (n=84)</td>
<td>20.5±3.7 (n=434)</td>
</tr>
<tr>
<td>Physical fatigue*</td>
<td>12.8±4.0 (n=84)</td>
<td>17.3±3.8 (n=220)</td>
<td>12.8±4.0 (n=84)</td>
<td>17.3±3.8 (n=434)</td>
</tr>
</tbody>
</table>


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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 COPD 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 copings 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 correlating with the development of the various types of fatigue.

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.

Acknowledgments

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