Chapter 2

Fatigue in sarcoidosis: a systematic review

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Abstract

Purpose of review
Several studies have investigated fatigue among sarcoidosis patients. The purpose of this review is to analyze published data on the assessment, prevalence, etiology, and treatment of sarcoidosis-associated fatigue.

Recent findings
Fatigue was identified as a prominent problem in sarcoidosis, and its presence was frequently associated with impaired quality of life, compared with patients without fatigue. Although the studies with good methodological fatigue assessment found no relationship between clinical parameters and fatigue in sarcoidosis patients, the remaining studies reported associations between fatigue and clinical and psychological parameters. No studies were designed to analyze the etiology of fatigue, but some studies showed that prednisone-treated patients reported more fatigue compared with untreated patients. In addition, only one study focused on a treatment for fatigue, dexmethylphenidate hydrochloride. Several instruments to measure fatigue were used, with the Fatigue Assessment Scale most frequently utilized.

Summary
This review illustrates the importance of fatigue as an under-recognized complication of sarcoidosis. It further emphasizes the need for longitudinal prospective studies to better define sarcoidosis-associated fatigue, explore its impact on quality of life, define aggravating or alleviating factors and evaluate new potential treatment strategies.

Introduction

Fatigue remains an underestimated and difficult problem in the management of sarcoidosis patients[1,2]. A study among Dutch sarcoidosis patients showed that fatigue was the most often reported symptom[3]. The etiology for this complaint remains unclear, as it is usually multifactorial. Although the granulomas and their released cytokines may be involved in the etiology of fatigue, the disease treatment along with comorbidities, including depression[4], weight gain, exercise intolerance, or altered sleep patterns[5], may be culprits too. Frequently, the disease itself is a direct cause of this troublesome symptom; however, in some patients the successful treatment of sarcoidosis with corticosteroids can worsen fatigue. Regardless of the etiology, fatigue was negatively related to the patients' quality of life[3].

Currently, no general agreement exists on the definition of fatigue. According to a number of researchers, fatigue can be divided into at least two categories: physical and mental[6], or passive and active fatigue[7]. However, a recent study claims that fatigue should be treated as a unidimensional concept[8].

As in other chronic diseases, fatigue needs to be objectively measured in sarcoidosis. Although various fatigue questionnaires exist, the Fatigue Assessment Scale (FAS) is the only one that has been validated for use in sarcoidosis patients[9]. Unfortunately, physical measurements of fatigue, such as exercise testing, fail to correlate with the patients' complaints of fatigue. This review focuses on published studies that are designed to assess the subjective aspects of fatigue experienced by sarcoidosis patients. Furthermore, the data on prevalence, etiology, and treatment of sarcoidosis-associated fatigue are analyzed.

Methods

A computerized search of the literature from 1997 until October 2008 was performed using the search terms 'sarcoidosis' and 'fatigue'. Hits were identified in PubMed (113 hits), PsycINFO (3 hits), the Cochrane Library (3 hits), and Web of Science (78 hits). Reference lists of relevant studies were checked to identify any additional published research not identified by computerized database searches.

Selection criteria

Studies included for evaluation met the following criteria: the study objective was to describe fatigue in sarcoidosis; the study population consisted of only sarcoidosis patients or included an identifiable and separately analyzed subgroup of patients with sarcoidosis; the article was a full report (no case report, editorial, poster text, letter, or review); the study was published in English; and published in a peer reviewed journal.

The described inclusion criteria[10,11] were applied to the initial 197 hits, with 55 identified as duplicate. On the basis of titles, abstracts, and references, 23 articles met

the inclusion criteria. After full article inspection, 20 articles met our selection criteria and were included in this review[3,5,9,12–26,27••,28••]. Figure 2.1 reveals the flow chart of the study selection.

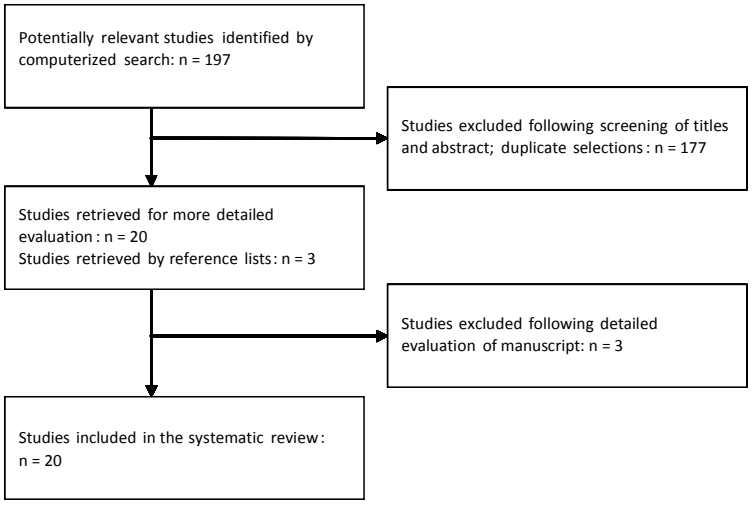

Figure 2.1 Study selection process

Assessment of methodological rank

The procedure of a systematic review was chosen, because we wanted to include as many studies into fatigue as possible. In order to conduct a meta-analysis it is necessary that studies employ the same questionnaire. As most studies used different questionnaires or methods to assess fatigue only a few studies would remain.

Using a standardized systematic review checklist of 17 predefined criteria, the methodological rank of the studies was independently assessed by three reviewers (DK, DO, and DV). The checklist was a modified version of an established criteria list for systematic reviews on quality of life[11,29]. Table 2.1 lists the criteria analyzed. One point was assigned to each item that met a criterion. If an item did not meet a particular criterion, it was described insufficiently, or not at all, no point was assigned. With the highest possible score 17, studies scoring 70% or more of the maximum attainable score (i.e., ≥12 points) were considered to be of 'high rank'. Studies scoring between 50% and 70% (9 or 10 points) were rated as 'moderate rank', whereas, studies scoring lower than 50% (≤8 points) were considered 'low rank'[11].

Table 2.1 Methodological rank of studies on fatigue among sarcoidosis patients[a]

Study	Criteria																	Points
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	
21	1	1	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	12
3	1	1	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	12
23	0	1	1	1	1	1	1	1	0	1	1	0	1	0	0	1	1	12
9	1	1	0	1	1	1	0	0	0	1	1	0	1	0	0	1	1	10
25	0	0	1	1	1	1	0	1	0	1	1	0	1	0	0	1	1	10
15	0	0	1	1	1	1	1	1	0	1	1	0	1	0	0	1	0	10
14	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	1	1	10
28••	0	0	1	1	1	1	1	0	0	0	1	0	1	0	1	1	1	10
27••	0	0	1	1	1	1	0	0	0	1	1	0	1	0	0	1	1	9
19	0	0	0	1	1	1	0	1	0	1	1	0	1	0	0	1	1	9
17	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	1	0	9
26	0	0	1	1	1	1	0	1	0	1	1	0	1	0	0	1	0	9
5	1	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	1	9
22	0	0	0	1	1	0	0	1	0	1	1	0	1	0	0	1	1	8
18	0	0	1	1	1	1	1	0	0	1	1	0	1	0	0	0	0	8
24	0	0	1	1	1	1	1	0	0	0	1	0	1	0	0	1	0	8
20	0	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	0	7
12	0	0	1	1	1	1	0	0	0	0	1	0	1	0	0	1	0	7
16	0	0	0	1	1	0	0	0	0	1	1	0	1	0	0	1	0	6
13	0	0	0	1	1	0	0	0	0	1	1	0	1	0	0	1	0	6
All	4	4	15	20	20	17	7	8	0	15	20	0	20	0	1	19	11	

A. A description is given of fatigue by describing the subjective experience of the patient;
B. A reason is given for choosing a certain questionnaire;
C. The diagnosis of sarcoidosis is according to the World Association of Sarcoidosis and Other Granulomatous Disorders criteria;
D. A description is included of at least two socio-demographic variables (e.g., age, sex, employment status, educational status);
E. A description is present of at least two clinical variables (e.g., duration of symptoms, use of medication, lung function tests);
F. Inclusion and/or exclusion criteria are provided;
G. Participation rates for patient groups are described and these rates are exceeding 75%;
H. The study describes potential prognostic factors by using multivariate analyses or structural equation modelling;
I. Characteristics of responders were compared with non-responders in order to give information about the representativeness of the responders (A patient who participates in a study is defined as a responder and a patient who refused to participate is defined as a non-responder);
J. The study size is consisting of at least 50 patients (arbitrarily chosen);
K. The collection of data is prospectively gathered;
L. The design is longitudinal (more than 1 year);
M. The process of data collection is described (e.g., interview or self-report);
N. The follow-up period is at least 6 months;
O. The loss to follow-up is no more than 20%;
P. The results are compared between two groups or more (e.g., healthy population, groups with different severity of sarcoidosis or age) and / or results are compared with at least two time points (e.g., longitudinally or pre- versus post-treatment);
Q. A psychometrically sound fatigue questionnaire is used.

[a] Studies scoring ≥12 points were considered to be of 'high rank' studies scoring 9 or 10 points were rated as 'moderate rank', and studies scoring 8 points or less were considered 'low rank' studies.

Results

Table 2.2 provides all study characteristics. Fatigue was the major study outcome in eight of the identified studies; whereas, it was a minor outcome in twelve studies. In six of these twelve studies, quality of life and/or health status were the main objectives, and three studies analyzed muscle function in relation to sarcoidosis-associated fatigue. The remaining three studies described fatigue in relationship to stress, pain, and the 6-minute walk distance (6MWD) during an exercise test. Sample sizes ranged from 10 to 1046, and patients mostly were treated with systemic corticosteroids medication for treatment of sarcoidosis.

Methodological rank

Table 2.1 summarizes the assessment of the methodological rank of the 20 studies. Initially an eight-percent discrepancy was reported among the three reviewers; however, these differences were resolved at a consensus meeting. The rank scores ranged from 6 (low rank) to 12 points (high rank) with the mean rank score 9. Three, ten, and seven studies were considered as high, medium, and low rank, respectively. All studies prospectively collected data (item K), described the data collection (item M), and included at least two socio-demographic (item D) and at least two clinical (item E) variables. Most studies provided inclusion and exclusion criteria (item F), evaluated more than 50 patients (item J), or compared their results between two or more groups (item P). Fifteen of the 20 studies defined patients with sarcoidosis using American Thoracic Society (ATS)/ World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) criteria[30]. As patients in the remaining five studies were self-reported members of the Dutch Sarcoidosis Society (DSS), no data from medical records were available for disease confirmation. Half of the studies used a psychometrically valid fatigue questionnaire (item Q). Eight studies used multivariate analyses or structural equation modeling to describe potential prognostic factors (item H), and seven trials reported a participation rate of more than 75% (item G). Only a few studies described the subjective experience of fatigue by the patient (item A) or provided a reason for choosing a certain questionnaire (item B). Only one double blinded trial[28••] compared two instruments of fatigue, and reported no patients lost after 8 weeks follow-up (item O). In addition, this study[28••] used a crossover design, which has a higher level of internal validity, compared with the cross-sectional designs in the remaining studies. However, none of the studies provided a longitudinal design (item L, N). This is a major shortcoming, because no conclusion can be drawn with respect to the causality of fatigue. Moreover, none of the studies described whether the nonresponders were comparable to the responders (item I).

Table 2.2 Characteristics of studies on fatigue among sarcoidosis patients[a]

Study	Major outcomes	Sample size (n)	Male/female (n)	Age (mean)	Medication (n)
21	Fatigue	60	31/29	41	Corticosteroids 26
3	Fatigue	145	52/93	44	Corticosteroids 73
23	Fatigue, psychometric qualities	150	54/96	44	
9	Fatigue	1046[d]	390/617	45-49[b]	Corticosteroids 282
		80[d]	36/44	41	Corticosteroids 21
25	Exercise, 6MWD	142	41/101	51	Corticosteroids 124
15	QOL, depression	64	37/27	43	Corticosteroids 21
14	QOL	64	37/27	43	
28••	Fatigue	10	2/8	52	Corticosteroids 9; hydroxylchloroquine 7; methotrexate 6; azathioprine 1; eflunomide 1.
27••	Fatigue	81	20/61	48	
19	Pain	821	305/508	46	Corticosteroids 469; NSAIDS: 259; analgesics: 268; psychological /neurological drugs 100
17	QOL	37	21/16	45	Corticosteroids 14
26	QOL, symptoms	150	54/96	44	Corticosteroids 74
5	Fatigue	38	22/16	40	
22	Stress	1046	390/617	45-49[b]	Corticosteroids 282
18	Development of HS	149[c]	48/101	44	Current therapy for sarcoidosis 105; corticosteroids 94
	questionnaire	111[c]	24/87	45	Current therapy for sarcoidosis 62; corticosteroids 55
24	Muscle weakness	22	14/8	42	Corticosteroids 11
20	Muscle weakness	34	18/16	45	Corticosteroids 9
12	Muscle weakness	18	11/7	43	Corticosteroids 7
16	QOL	975	358/617	47	Corticosteroids 559; heart medication 89; pain killers 328; psychological/neurological medication 119; NSAIDS 322; bronchodilators 291; eye drops 235.
13	Fatigue	1026	380/646	47	Corticosteroids 565

6MWD = 6-meter walking distance; HS = Health Status; NSAIDS = Non-steroidal Anti-Inflammatory Drugs; QOL = quality of life.

[a] Information about sarcoidosis patients is presented, no information about controls or other than patient groups is included; [b] Median age; [c] 149 patients of development study and 111 patients of validation study; [d] 1046 members of Dutch Sarcoidosis Society and 80 outpatients

Fatigue

International studies recognize that fatigue is a common problem for sarcoidosis patients[2,3]. Despite adequate treatment for other manifestations of sarcoidosis, a substantial number of sarcoidosis patients suffer from persistent fatigue[13,14]. According to initial Dutch studies, fatigue was the most frequently reported symptom in sarcoidosis patients[13–15]. Fatigue afflicted 80% of the members of the DSS, which consist mainly of chronic sarcoidosis patients[9]. Furthermore, in a study of sarcoidosis patients from Dutch hospitals[15], 73% of the symptomatic sarcoidosis patients reported fatigue. This self-reported fatigue approximates the incidence of fatigue reported by another group of chronic inflammatory disease patients, rheumatoid arthritis patients[17]. In addition, the sarcoidosis patients reported a lower level of energy compared with healthy controls[17]. Table 2.3 summarizes the incidence, assessment, and conclusion about fatigue reported in the selected studies.

Sex differences in fatigue are inconsistent. Although compared with male sarcoidosis patients, females from both the DSS[16], and Croatia[23] reported more symptoms of fatigue, a Dutch study of chronic outpatients showed higher scores for fatigue in men[9]. Furthermore, an additional Dutch study failed to reveal sex differences for fatigue[21].

Assessment of fatigue

The 20 analyzed studies utilized a variety of objective instruments to measure fatigue. As noted in Table 2.3, fatigue was usually measured with questionnaires, whereas other subjective tests, including interview and symptom inventories, were infrequently used.

The three high rank studies[3,21,23], three medium rank studies[9,25,28••] and one low rank study[22] employed the 10-item FAS to measure fatigue in sarcoidosis. The FAS is a well validated and reliable fatigue measure among sarcoidosis patients. Two studies reported that the content validity, construct validity and internal consistency of the FAS were good. The test–retest reliability was 0.89[9,23].

Five additional medium rank studies[5,9,14,19,26] measured fatigue using the facet Energy and Fatigue of the World Health Organization Quality of Life Assessment Instrument-100 (WHOQOL-100). This facet consists of four questions: ‘How easily do you get tired?’, ‘How much are you bothered by fatigue?’, ‘Do you have enough energy for everyday life?’, and ‘How satisfied are you with the energy you have?’ This tool appeared to be a sensitive instrument to measure fatigue[14]. In two medium rank studies, fatigue was measured with fatigue questionnaires that are not validated in sarcoidosis, that is, the Fatigue Scale[27••] and the Functional Assessment of the Chronic Illness Therapy–Fatigue (FACIT-F)[28••].

Table 2.3 Incidence, assessment, and conclusions about fatigue of studies among sarcoidosis patients[a]

Study	Incidence of fatigue n (%)	Assessment of fatigue	Conclusions about fatigue
21	44 (73%)	FAS	Clinical or serological parameters, except DLCO, did not predict fatigue.
3	83 (57%)	FAS, symptom inventory	Tired patients reported a worse QOL, and clinical parameters were unrelated to fatigue.
23	83 (55%)	FAS	The Croatian translation of the FAS is reliable and valid.
9	837 (80%)[b] 68 (85%)[b]	FAS, WHOQOL-100 facet Energy & Fatigue	The FAS is a promising measure to assess fatigue.
25	98 (69%)	FAS	Fatigue was related with 6MWD and with dyspnea.
15	27 (73%)[c]	Interview	Fatigue was a major complaint, and QOL was related to the perception of complaints.
14	28 (76%)[c]	WHOQOL-100, interview	WHOQOL-100 is a sensitive instrument to measure fatigue. The facet Energy & Fatigue was related to depression, but unrelated to the domain Psychological Health and lung function.
28••	10 (100%)[d]	FAS, FACIT-F	Treatment with d-MPH was associated with a significant improvement in fatigue
27••		Fatigue Scale	Patients with extrapulmonary involvement are more fatigued than patients with pulmonary involvement.
19	599 (73%)	WHOQOL-100, symptom inventory	Fatigue was related to pain.
17	28 (76%)	Interview	Sarcoidosis patients reported as much fatigue as patients with RA, and more than controls.
26	88 (60%)	WHOQOL-100, symptom inventory	Fatigue predicted QOL after controlling for demographics and clinical parameters.
5	25 (66%)	WHOQOL-100 facet Energy & Fatigue, symptom inventory	Fatigue was related to an acute phase response, but not to markers of disease activity. Tired patients suffered more frequently from dyspnea, exercise intolerance, muscle pain, eye problems and needed more sleep.
22		FAS	Fatigue was related to perceived stress, when the role of depression was partialed out.
18		SHQ	SHQ is appropriated to measure fatigue in sarcoidosis, including fatigue.
24	22 (100%)[d]	Domain fatigue of CRDQ, Borg score fatigue, 6MWD	Quadriceps peak torque was negatively associated with fatigue. Patients reported more fatigue than healthy controls.
20		Vitality subscale SF-36	Vitality was related to inspiratory muscle endurance.
12	6 (33%)[c]	Interview	Fatigued patients had lower maximum expiratory muscle pressures than those without fatigue.
16	720 (74%)	Symptom inventory	Women reported more fatigue, and women who used oral steroids reported more fatigue.
13	728 (71%)	Symptom inventory	The most frequently reported symptom was fatigue. Symptoms and corticosteroids were not related. Women suffered more frequently from fatigue.

6MWD = 6-meter walking distance; CRDQ = Chronic Respiratory Disease Questionnaire; DLCO = Diffusing Capacity of the lung for Carbon monoxide; d-MPH = dexmethylphenidate hydrochloride; FACIT-F = Functional Assessment of the Chronic Illness Therapy-Fatigue; FAS = Fatigue Assessment Scale; QOL = quality of life; RA = Rheumatoid Arthritis; SF-36 = Short Form 36; SHQ = Sarcoidosis Health Questionnaire; WHOQOL-100 = World Health Organization questionnaire of quality of life.

[a] Information about sarcoidosis patients is presented; no information about controls or other patient groups is included.

[b] 837 members of Dutch Sarcoidosis Society and 68 outpatients .

[c] Percentage among patients with current symptoms.

[d] Fatigue was an inclusion criterion

The 14 questions in the Fatigue Scale are designed to distinguish mental from physical fatigue. It is both reliable and valid in 100 consecutive patients in general medicine practice[27••]. The FACIT-F, which examines 41 items, is considered a reliable and valid measure of fatigue in cancer patients[31]. No difference was noted in the assessment of fatigue by the FAS or FACIT-F in one study[28••]. In three medium rank studies[14,15,17] and one low rank study[12], patients were interviewed about fatigue. Furthermore, patients completed a symptom questionnaire or inventory in three medium rank studies[5,19,26], in two low rank studies[13,16], and in one high rank study[3].

In the remaining low rank studies fatigue was measured using health status instruments, such as the Sarcoidosis Health Questionnaire (SHQ)[18], the subscale Vitality of the Short Form 36 (SF-36)[20], and the fatigue domain of the Chronic Respiratory Disease Questionnaire (CRDQ)[24]. Although the SHQ[18] is a reliable and validated instrument for assessing health status in sarcoidosis, the domain fatigue was queried in the SHQ with only one item: 'Daily Functioning-Felt you were full of energy'. Spruit et al.[24] also assessed fatigue utilizing a Borg fatigue score[32] after an incremental cycle exercise test. Regarding the SHQ, Vitality of the SF-36, CRDQ, and the Borg fatigue scale, no information is available of the validity and reliability of the fatigue measurement in sarcoidosis.

Causes of fatigue

Despite the complex and multifaceted etiology of fatigue, several investigators have attempted to elucidate the potential causes of fatigue in sarcoidosis. Most studies have evaluated clinical parameters with few studies postulating psychological factors as underlying mechanisms of fatigue.

Two high rank studies found no relationship between fatigue in sarcoidosis patients and clinical variables tested, including pulmonary function, metabolic measures, laboratory parameters of inflammation, or T-cell activation and granuloma formation[3,21]. Likewise, one medium rank study found no correlation between fatigue and lung function[14].

However, other medium rank studies reported associations between fatigue and acute phase response, 6MWD, dyspnea, pain, and extrapulmonary involvement. In a recent study[27••] sarcoidosis patients with pulmonary plus extrapulmonary involvement reported more fatigue than patients with pulmonary involvement only. In addition, Drent et al.[5] found that fatigue was related to an acute phase response, but unrelated to markers of disease activity. Moreover, fatigue was related to dyspnea, as measured with the Medical Research Council, and to the 6MWD during an exercise test[25]. Furthermore, a large study of sarcoidosis patients without comorbid conditions showed that fatigue was associated with specific types of pain, such as muscle pain, chest pain, arthralgia, abdominal pain, and headache[19].

With regard to the psychological factors stress and depression, fatigue was found to be related to depression[14]. Moreover, a Dutch study correlated high scores on perceived stress with more fatigue, even after depressive symptoms were excluded[22].

Some low rank studies have also sought to correlate fatigue with muscle weakness as quantified by expiratory muscle pressure, inspiratory muscle endurance, and quadriceps peak torque. Patients with fatigue experienced significantly lower maximum expiratory muscle pressures[12], a lower inspiratory muscle endurance than those without symptoms[20], a lower fat free mass over body weight ratio, and a lower quadriceps peak torque after an incremental exercise test[24]. Moreover, fatigued sarcoidosis patients compared with non-fatigued patients also reported more exercise intolerance and muscle pain[24]. These studies were limited by the small sample size.

Treatment and fatigue

Interestingly, treatment for symptomatic sarcoidosis may improve or worsen the fatigue experienced by sarcoidosis patients. Most of the twenty analyzed studies reported some treatment for their fatigued sarcoidosis patients. Although corticosteroids remain the mainstay of sarcoidosis treatment, some chronic patients also received a variety of steroid-sparing regimens. In a medium rank study[9], that examined fatigue in two groups of sarcoidosis patients, it appeared that DSS patients who used prednisone exhibited higher fatigue scores than patients not using prednisone. However, fatigue was unrelated to prednisone use in the outpatient group. One low rank study found that women who used oral steroids reported lower scores in the facet Energy and Fatigue[16].

Thus far, few data are available regarding specific treatment for fatigue-associated sarcoidosis. Only one treatment study was included in this 20-study analysis. In a recent small double-blinded, placebo-controlled cross over medium rank study, the stimulant dexmethylphenidate hydrochloride (d-MPH) was associated with a significant reduction in sarcoidosis-associated fatigue[28••].

Fatigue and quality of life

Fatigue is not synonymous with impaired quality of life (QOL). In a high rank study fatigued sarcoidosis patients reported a worse QOL in all domains[3]. In an additional medium rank study fatigue remained an important negative predictor for the QOL domains of physical and psychological health and level of independence, after controlling for demographics, disease stage and clinical parameters[26]. However, in another study, no correlation was found between the facet Energy and Fatigue and the domain Psychological Health of the WHOQOL-100[14].

Discussion

The purpose of this review was to focus on subjective fatigue among sarcoidosis patients in published studies. In addition to the methodological rank of the selected studies, we reviewed the assessment, potential causes, treatment, and QOL in sarcoidosis-associated fatigue. The mean methodological rank score is moderate, and

one major shortcoming of the current fatigue studies is the lack of longitudinal follow-up.

Regardless of the rank of study, all 20 published reports confirm that fatigue is a prominent symptom in sarcoidosis, because of the high prevalence, the aggravating influence on patients' life, and a lack of convincing evidence for the cause of fatigue. Despite no consistent definition, this symptom is reported in up to 85% of symptomatic sarcoidosis patients in multinational studies, and it frequently is associated with an impaired QOL. Furthermore, high rank studies found no potential causes for sarcoidosis-associated fatigue. Possibly, the inflammation and granuloma burden in sarcoidosis may be responsible for fatigue; however, little is known about phenotypic prognostic factors for fatigue such as specific organ involvement or disease chronicity. Likewise no data are available regarding genotypes and sarcoidosis-associated fatigue. Hence, the etiology of fatigue remains enigmatic and complex, which might reflect the interrelationships between mental and physical domains.

Although the definition of fatigue is not standardized and its etiology remains complex, validated questionnaire instruments help to measure fatigue. The FAS is the most widely used objective measurement for sarcoidosis-associated fatigue and available in several languages (http://www.ildcare.eu/pages/artsen_informatie_fasen.html, please contact the authors for further information). This reliable and validated instrument is short and lends itself to usage for both inpatients and outpatients. All three high rank studies and three of the medium rank studies utilized this tool. It is important to assess fatigue by means of a questionnaire validated in sarcoidosis patients, because fatigue might be expressed differently in sarcoidosis compared with a healthy controls or another disease population.

Regarding treatment strategies, only one recent medium rank study showed that treatment with d-MPH improved sarcoidosis-associated fatigue[28••]. Other studies suggest that prednisone usage can even be associated with more severe fatigue[9,16], although corticosteroids can successfully treat the symptoms of sarcoidosis. Unfortunately, these studies were not designed to ascertain if steroids represent cause or effect for fatigue. It is possible that corticosteroids represent a surrogate marker for more severe or chronic disease or the development of comorbid conditions of weight gain, diabetes, depression, inactivity, or altered mood states including sleep. In addition to medication, cognitive behavioral therapy should also be considered as treatment strategy, because cognitive behavioral therapy and graded exercise programs have been shown effective in treating fatigue in patients with chronic fatigue syndrome[33].

For future research we recommend improved study designs, that is, studies with longitudinal design and more patients, and to explore relationships between fatigue and associated factors such as sleeping disorders, cognitive problems, small fiber neuropathy (SFN), and treatment with anti-tumor necrosis factor-alpha (anti- TNF-α) drugs. Although the included studies that found relationships between fatigue and clinical or psychological variables were considered of medium to low rank, they often focused on aspects not examined in higher rank studies. In addition, many high rank

studies were conducted in referral centers whereas, for example the Dutch survey[9,13,16,22] involved unselected patients.

Although the high rank studies are methodologically more sound because they can provide much information about their participants, participants in studies such as the Dutch survey may be more representative of patients not seen in referral centers. The study on d-MPH[28••] was not an incidence study, because fatigue was an entry criterion for all patients. However, it provides information regarding reproducibility and placebo effect. Therefore, we recommend duplicating existing low and medium rank studies but this time using a more rigid methodological design, for example, regarding found relationships between fatigue and acute phase response, 6MWD, dyspnea, pain, organ involvement, muscle weakness, stress and depression.

Sleeping disorders[34] and cognitive problems (Elfferich M, De Vries J, Wijnen P et al., unpublished data) are factors that may interact with fatigue in sarcoidosis. Therefore, questions regarding sleeping disorders and neuropsychological assessment should be assessed in addition to the FAS.

SFN is frequently reported among patients with sarcoidosis and is associated with autonomic dysfunction[35]. Moreover, it has been found that autonomic dysfunction is frequently accompanied by chronic fatigue[36]. Therefore, it is interesting to explore the relation between SFN and fatigue in sarcoidosis.

Treatment with anti-TNF-α improves lung function[37] in sarcoidosis and appeared to be useful in treating chronic sarcoidosis[38]. Also, in Crohn's disease[39] and in rheumatoid arthritis[40] a positive effect on fatigue was demonstrated. Two case reports described a reduction in fatigue due to anti-TNF-α medication in sarcoidosis[41,42]. In addition, an observational study[43•] showed a reduction of fatigue and other symptoms after treatment with anti-TNF-α in 12 sarcoidosis patients. Moreover, changes depicted by the positron emission tomographic scan were correlated with these clinical improvements. Future studies should incorporate untreated as well as treated multinational sarcoidosis patients and they should be randomized and blinded in order to improve the evaluation of treatment in general, especially with biologicals, including anti-TNF-α drugs.

Conclusion

More research is needed to standardize the assessment of fatigue, identify prognostic factors for the development of fatigue, and explore treatment strategies to reduce fatigue and thereby improving patients' quality of life. Longitudinal studies will provide follow-up needed to better identify predictors of fatigue and new potential targets for therapy.

References

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
••of outstanding interest

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