ERJ Express. Published on March 22, 2012 as doi: 10.1183/09031936.00002512

Sarcoidosis associated fatigue

Prof. dr. Marjolein Drent, MD, PhD
Faculty of Health, Medicine and Life Science, UNS 40 room 4.550
University Maastricht,
PO Box 3100
6202 NC Maastricht
The Netherlands
phone: +31 43 3882087
fax: +31 842234007
email: m.drent@maastrichtuniversity.nl

Dr. Elyse E. Lower, MD
University of Cincinnati
Oncology Hematology Care, Inc.
Cincinnati, OH USA 45220
ELower@ohcmail.com

Prof. dr. Jolanda De Vries, PhD
CoRPS, Department of Medical Psychology, Room P510, Tilburg University,
PO Box 90153
5000 LE Tilburg
The Netherlands
phone +31 13 4662705,
fax: +31 13 4662067
email: j.devries@uvt.nl

MS ID: ERJ-00025-2012

Keywords:
Fatigue, fatigue assessment scale (FAS), quality of life, QOL, sarcoidosis

ABSTRACT

Sarcoidosis associated fatigue is globally recognized as a disabling symptom. Fatigue has been reported in up to 50-70% of sarcoidosis patients, causing impaired quality of life. The etiology of this troublesome problem remains elusive and is usually multifactorial. Fatigue can be a consequence of treatment itself, including the complications of corticosteroid therapy. The diagnosis of sarcoidosis associated fatigue requires an extensive evaluation to identify and treat potentially reversible causes. Granuloma formation and cytokine release may be involved in its etiology. However, despite adequate sarcoidosis treatment, many patients continue to experience fatigue. Co-morbidities associated with sarcoidosis, including depression, anxiety, hypothyroidism, and altered sleep patterns, may all contribute to fatigue. Despite an exhaustive search for treatable clinical causes of fatigue, most patients' complaints of fatigue are not correlated with clinical parameters of disease activity. Recent studies have demonstrated the effectiveness of various neurostimulants, including methylphenidate, for the treatment of sarcoidosis-associated fatigue. These and other agents may be useful adjuncts for the treatment of sarcoidosis associated fatigue. Obviously, there is a need for studies evaluating the causes and new therapeutics options of sarcoidosis-associated fatigue. Psychological interventions should also be examined.

Sarcoidosis is a disseminated granulomatous disease of unknown aetiology. The clinical manifestations are highly variable and often non-specific, depending on the intensity of the inflammation and the organ systems affected. Virtually every organ can be involved, but most patients present with pulmonary, ocular, or cutaneous involvement. Pulmonary sarcoidosis is the second most common respiratory disease in young adults (<40 years) after asthma [1-3]. Sarcoidosis patients may present with symptoms directly related to the organ(s) involved. Remission occurs for more than half of the patients within 3 years of diagnosis, and within a decade for two-thirds with few or no consequences [4]. Unfortunately, up to one-third of patients have persistent disease, leading to significant impairment of quality of life (QOL) [5]. Apart from lung-related symptoms (*e.g.*, coughing, breathlessness, and dyspnea on exertion), patients may suffer from a wide spectrum of rather non-specific disabling symptoms. These symptoms, like fatigue, fever, anorexia, arthralgia, muscle pain, general weakness, muscle weakness, exercise limitations, and cognitive failure, do not correspond with objective physical evidence of disease [5-9]. Several studies have reported that neither lung function test results nor chest radiographs correlate with these non-specific health complaints or with QOL [5, 10]. Sarcoidosis-related complaints, including fatigue, may become chronic and affect the patients' QOL even after all other signs of disease activity have disappeared [11-13]. There is a positive ~~negative~~ association between symptoms suspected of small fiber neuropathy (SFN) and fatigue as well as dyspnea and fatigue [11, 14, 15].

Hence, fatigue is a common complaint among sarcoidosis patients [6, 10, 16-18]. Sarcoidosis patients report higher fatigue scores compared with healthy controls [8, 10, 19, 20]. Furthermore,

compared with healthy controls sarcoidosis patients suffer more from fatigue even in the absence of other symptoms [14]. In general, tools currently accepted in clinical practice to detect and monitor fatigue are limited. This review provides an overview of the currently published data on the assessment, prevalence, etiology, and treatment of sarcoidosis associated fatigue as well as its impact on patients' QOL.

METHODS

A computerized search of the literature from 1971 until October 2011 was performed using the search terms "sarcoidosis" and "fatigue". Hits were identified in PubMed (144 hits), PsycINFO (5 hits), the Cochrane Library (4 hits), and Web of Science (107 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: 1) the study objective was to describe fatigue in sarcoidosis; 2) the study population consisted of only sarcoidosis patients or included an identifiable and separately analyzed subgroup of patients with sarcoidosis; 3) the article was a full report (no case report, editorial, poster text, letter, or review); 4) the study was published in English or Dutch; and 5) published in peer reviewed journal.

The described inclusion criteria [21, 22] were applied to the initial 260 hits, with 71 identified as duplicate. Based on titles, abstracts, and references, 30 articles met the inclusion criteria. Fourteen articles were excluded because they did not criterion 1 and 31 did not meet criterion 2. Criteria 3 and 4 were reasons for excluding 101 and 13 articles, respectively. One article was

found through reference list inspection. After full article inspection, 29 articles met our selection criteria and were included in this review [5-11, 15-20, 23-36]. Figure 1 reveals the flow chart of the study selection.

Results

Fatigue

Currently, no general agreement exists on the definition of fatigue. Fatigue can be seen and measured as a unidimenisonal or a multidimensional concept. The multidimensional concept of fatigue can be divided into at least two categories: physical and mental [14], or passive and active fatigue [15]. Several studies have reported that neither lung function tests nor chest radiographs correlate with non-specific health complaints including fatigue or QOL. Some sarcoidosis patients are debilitated by the symptoms of their disease and are unable to work. Others are underemployed and incapable of reaching their full potential due to health-related issues [21]. Individuals affected by the disease usually appear completely healthy, so their symptoms are often not taken seriously by family, friends, and health care professionals. Consequently, some patients lose their desire and ability to effectively socialize with others, causing relationships and family dynamics to ultimately suffer. These factors combined have an impact on individual's economic status, interpersonal relationships, and family dynamics; increase their stress levels; and, induce depression in patients [21].

Self-reported measures used to assess fatigue

As presented in Table 1, a variety of measures can be used to assess fatigue in sarcoidosis patients. Some instruments include only one general indirect fatigue question, such as the Borg

score, or only one specific fatigue question as in the Sarcoidosis Health Questionnaire (SHQ). Only one instrument, the Fatigue Assessment Scale (FAS), contains 10 specific fatigue questions which has been validated in sarcoidosis patients (see Table 2). Several studies have confirmed the reliability and validity of the FAS instrument in sarcoidosis [5, 7, 10, 16-18, 25, 27-29, 35]. In addition, the minimal clinical important difference (MCID) score was established and found to be a 4-point difference across time [37]. A change in FAS score of four points or more indicates a clinically significant change in fatigue. As this MCID was only available recently, till now, no studies are published in which the MCID of the FAS were used in analyzing the data. Therefore, only the mean scores were compared to evaluate whether there was a significant improvement of fatigue in the studied populations.

Fatigue and quality of life

Only seven of the fatigue studies reported the relationship between fatigue and QOL or health status (HS), as shown in Table 3 [5, 13, 14, 16, 20, 26, 31]. These studies all had a cross-sectional design. Regardless of the method of assessment for fatigue and QOL or HS, fatigue appeared to be negatively related to QOL and HS in sarcoidosis patients. However, fatigue levels, and not depressive symptoms, appeared to be the best predictor of patients' overall QOL. This indicates that although depression plays a role in the reporting of fatigue, the symptom fatigue itself has a more incremental effect on patients' overall QOL [38].

Fatigue and depressive symptoms

American and Dutch studies have emphasized the important role depression plays in sarcoidosis [18, 31, 39]. It has been determined that depressive symptoms are negatively associated with and affect patients' fatigue scores [11, 14, 15]. In addition, the relationship between fatigue and depressive symptoms parallels the findings of other chronic illness , such as diabetes, chronic obstructive lung disease, cardiac disease, and rheumatoid arthritis [40]. Research suggests that the relationship between depressive symptoms and severity of medical illness is bidirectional. Depression may indirectly lead to increased symptoms, because depressive symptoms are associated with poor self-care (diet, exercise, cessation of smoking, medication regimens) in patients with chronic diseases. However, physical symptoms and resulting functional impairment caused by complications of medical illness also are likely to pose a burden on the patient's life and provoke depression [40].

Fatigue: Role of inflammation and cytokine release

Symptoms like fatigue can be nonspecific and difficult to objectify. Moreover, absence of evidence does not mean evidence of absence [7, 12, 13, 15]. Assessment of inflammatory activity in sarcoidosis patients without lung functional or radiological deterioration but with unexplained persistent disabling symptoms is an important and often problematic issue. Historically, evaluation of the value of the various available tools for assessment of inflammatory activity is hampered by the lack of a gold standard. Serological markers used are C-reactive protein (CRP), serum angiotensin converting enzyme (ACE), soluble interleukin 2 receptor (sIL-2R) and neopterin [4, 15, 41-43].

In the past years, F18-FDG PET/CT (PET) has been shown to be a very sensitive technique to assess inflammatory activity in sarcoidosis by detecting and quantifying the degree of

inflammatory and granulomatous reactions that occur in the lungs and elsewhere in the body [4, 41, 44-48].

It becomes obvious that PET is more and more used in sarcoidosis and that hypermetabolism detected with a PET scan indicates activity in patients with no other indication of disease activity assessed by other available inflammatory parameters. Mostard et al. [41] showed that negative serological test results do not exclude the presence of inflammatory activity. Therefore, the surplus value of PET for assessment of inflammatory activity is situated in the group of symptomatic sarcoidosis patients without serological signs of inflammatory activity. Moreover, in the latter study the value of whole-body evaluation was demonstrated by the fact that 80% extrathoracic lesions were found. In this study, five patients with OSAS who were adequately treated still suffered from disabling symptoms, including fatigue [41]. Hypermetabolism detected with PET appeared to be present in all these latter patients supporting the assumption that inflammatory activity was still present probably explaining the persistent fatigue. In a case series described by Keijsers et al. 12 patients were treated by infliximab [47]. Nine of these patients also suffered from fatigue. All of them showed an improvement on the post infliximab PET, illustrated by an overall decrease in SUVmax, and a reported reduction of fatigue.
Currently, the most widely held view is that chronic inflammatory disorders, including sarcoidosis, cause changes in the central nervous system (CNS). Tumor necrosis factor alpha (TNF-α) is increased in the serum of sarcoidosis patients and related to disease severity. Moreover, TNF-α induces a range of neurological, hematological, metabolic, endocrinological changes and is probably involved in the regulation of sleep [49]. Studies in inflammatory

vascular disease suggest that increases in TNF-α, oxidative stress and inflammation-induced changes can alter neurotransmitter metabolism [50, 51] and lead to cognitive impairment. There is evidence that TNF-α regulates synaptic transmission in the brain and that this cytokine is involved in the spatial memory impairment in mice [52]. Neuroinflammation with overexpression of cytokines is a characteristic of the brain pathology present in Alzheimer's disease [53]. Recent evidence also suggests that TNF-α may induce the expression of inducible nitric oxide synthase (iNOS). Because overexpression of iNOS was found in the brain of some Alzheimer's disease patients, anti-oxidants may be recommended to decrease oxidative damage leading to disease progression [50, 54]. More recently, the TNF-α inhibitor thalidomide was effective in reducing the iNOS/peroxynitrite-related pathology by restraining TNF-α increases without harming the physiological function of iNOS [54]. Involvement of excess TNF-α in the pathogenesis of cognitive impairment and fatigue in patients with sarcoidosis would explain the favorable effect of anti-TNF-α drugs in some studies.

Fatigue and autonomic dysfunction are both dominant symptoms and risk factors for depression [55]. The symptoms may share several neurobiological abnormalities, for example an increase in TNF-α [55]. The relationship between depressive symptoms and fatigue may also be explained by a cytokine imbalance, initiated by an inflammatory immune response in sarcoidosis [9, 40]. The cytokine ~~im~~balance of patients suffering from depression also appears to be disturbed [56]. Sarcoidosis patients treated with immunomodulating drugs exhibited a relationship between fatigue and plasma IL-1β concentrations[8]. In addition, Heessen et al. showed that fatigue in multiple sclerosis patients was associated with activation of proinflammatory cytokines [57].

Fatigue in sarcoidosis: multifactorial causes

Fatigue is a global problem experienced by most sarcoidosis patients. Little data are currently available regarding the specific treatment of fatigue associated with sarcoidosis. Because the cause of this symptom is often multifactorial, treatment requires investigation into many reversible and irreversible causes. Initial "reversible" fatigue treatment strategies focus on four areas: metabolic abnormalities, psycho-social conditions, disease-related fatigue, and treatment induced fatigue. Proper identification and treatment of anemia, diabetes mellitus, and thyroid disorders can improve altered QOL secondary to fatigue. Depression, anxiety, and stress are closely intertwined with fatigue [27]. Careful assessment and treatment of these underlying triggers are necessary before seeking other fatigue treatment strategies. For many patients, this may include psychological treatment or therapeutic interventions specifically targeted to anxiety, stress, and depression.

Sleep disturbances

Secondary organ related fatigue can occur in many forms, including neurologic manifestations and sleep disturbances. The relationship between fatigue and sleep in sarcoidosis has been studied previously. Drent et al. [58] reported a case in which symptoms of fatigue disappeared after treating sleep apnea and sarcoidosis. Sleep issues including obstructive sleep apnea (OSA) and restless leg syndrome, commonly afflict sarcoidosis patients [59, 60]. These disorders are frequently reported in European as well as United States populations. Sleep apnea is six to eight times more common in the sarcoid population compared to the general population [60]. In addition, in a study of Verbraecken et al. [59] OSA, periodic leg movement or restless legs were found in more than half of the sarcoidosis patients. Moreover, sleep disturbances are often related to small fiber neuropathy and autonomic dysfunction, which may in part explain the

fatigue [59]. 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 [61]. In one prospective study of sleep apnea risk in sarcoidosis patients, increased OSA was identified in male patients along with patients with lupus pernio, upper airway involvement, and increased body mass index (BMI). Interestingly, this study revealed no increased risk for OSA in patients receiving corticosteroids, despite the fact that increased BMI often accompanies prednisone usage [60].

It is very important and clinical relevant to differentiate sleep disorders from fatigue symptoms, especially with regard to treatment options. Recognition and treatment of OSA ~~this disorder~~ can greatly improve symptoms of fatigue and lethargy. Follow-up studies aimed to identify the most appropriate treatment option(s) for fatigue will require more careful evaluation of sleeping disorders, including sleep questionnaires like the Epworth Sleepiness Scale (ESS), as fatigue appeared to be at least partially caused by sleep disturbances. 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.

Small fiber neuropathy

Small fiber neuropathy (SFN), a frequent bothersome symptom in a substantial number of sarcoidosis patients, can be linked to fatigue [11, 55]. Although small fiber neuropathy may be difficult to diagnose, its identification can lead to possible targeted treatments including anti-tumor necrosis factors (TNF) inhibitors [7, 62] or intravenous immune globulin [63].

Patients with high TNF levels have been characterized with increased fatigue and myalgias. For many patients, successful treatment of active sarcoidosis will also improve the symptoms of fatigue. Some studies suggest that reversal of sarcoid activity with anti-TNF-α inhibitors can be efficacious in eradicating fatigue [7, 62]. Others have demonstrated that some patients on anti-TNF-α therapy still suffer from persistent fatigue although some improvement has been reported [18, 64]. In a meta- analysis of fatigue in rheumatoid arthritis patients, the use of anti-TNF-α therapy was associated with only a small improvement in fatigue [65].

Finally, can the drugs used to treat the granulomatous reaction in sarcoidosis cause fatigue? This remains a controversial area. Systemic corticosteroids frequently cause weight gain, diabetes, hypertension, and sleep disturbances including OSA and insomnia. Although many patients report an initial euphoria with institution of corticosteroid therapy, prolonged usage may actually lead to depression and lethargy [66]. One epidemiologic study comparing fatigue in American versus European patients reported a negative correlation between fatigue and use of hydroxychloroquine [18]. It remains unclear if the drug hydroxychloroquine successfully treated the fatigue symptoms or whether it was acting as a surrogate marker for less severe disease. Patients receiving hydroxychloroquine tend to have less multiorgan disease which has been associated with less fatigue. The anti-inflammatory effects of this less toxic drug may more successfully treat fatigue.

Treatment options for sarcoidosis associated fatigue

Unfortunately, despite careful evaluation and treatment for the reversible metabolic, psycho-social, organ, and treatment related causes of fatigue, many patients continue to experience debilitating fatigue. Frequently, successful treatment of active sarcoidosis fails to eradicate the

disabling symptoms of continued fatigue [8, 35]. This persistent malady, sarcoidosis associated fatigue, may require non-targeted generalized fatigue strategies. Virtually all chronic diseases, including cancer, autoimmune disorders, or neurologic conditions, have been associated with fatigue. To date, the most frequently employed pharmacologic fatigue strategies have focused on the use of neurostimulants, neurostimulant like drugs and anti-TNF-α drugs (see also Table 4) [7, 47, 67, 68]. These studies are very small and were, therefore, not included in the earlier parts of this review.

Treatment of fatigue with neurostimulants

For treating sarcoidosis-associated fatigue, the original report consisted of an open label trial of five persistently fatigued chronic sarcoidosis patients treated with methylphenidate hydrochloride [69]. Four of the five patients self-reported improved fatigue for up to two years. However, this report utilized no objective measurements of fatigue.

The use of dexmethylphenidate (D-MPH) and methylphenylate have been reported efficacious for the treatment of fatigue and memory loss in some cancer patients with "chemotherapy brain" [68]. In a large double-blind placebo-controlled trial, it was concluded that D-MPH treated patients experienced significant fatigue improvement [70]. This effect was observed after four weeks of treatment and persisted throughout the eight weeks of intervention. For some patients, improved memory was also detected.

In a double-blind placebo-controlled trial of dexmethylphenidate for sarcoidosis, study participants received either D-MPH or placebo for eight weeks followed by a two-week washout period [35]. These patients were subsequently crossed-over to the opposite study arm for an additional eight weeks of therapy. Most of the ten chronic sarcoidosis patients on this trial had

multi-organ involvement, and all patients had persistent fatigue despite adequate sarcoidosis therapy. All patients were receiving concurrent therapy, including systemic corticosteroids in eight patients. By four weeks of therapy, significant improvement in fatigue was detected in the D-MPH treated group [35]. This statistically significant improvement in fatigue persisted through eight weeks of treatment. Based on the presented table, the approximated mean change scores on the FAS was 4.5 points, indicating a change in fatigue that exceeded the MCID of the FAS [37].

The exact mechanism for improved fatigue in this population remains unclear. These agents have been beneficial for sleep disturbances such as narcolepsy and airplane pilot fatigue disorders. Hence, neurostimulants may relieve fatigue by reversing sleep disorders, including daytime somnolence and sleep apnea [71-74].

Armodafinil, the R-isomer of modafinil, has been shown effective for daytime somnolence [75] and both modafinil and armodafinil have been used to treat fatigue [67, 73, 76]. To better evaluate this possible mechanism of action, a follow-up study was performed using the agent armodafinil in sarcoidosis associated fatigue patients [77]. In this trial, the underlying sleep disorders were evaluated in all patients with an initial sleep study. A normal sleep study, defined as an apnea hypopnea index less than six, was required for all patients prior to study enrollment. Subsequently, patients were randomized in double-blind, cross-over fashion to receive armodafinil or placebo. A significant improvement in fatigue was detected for those patients receiving armodafinil compared to placebo. Additionally compared to placebo, armodafinil was associated with an improved Mean Sleep Latency Time by approximately one minute. Although this suggests that the drug was associated with less daytime sleepiness, there was no difference in

drug efficacy. In fact, patients with a normal Mean Sleep Latency Time of greater than eight minutes reported significantly greater improvement in fatigue compared to those with excessive daytime sleepiness. Overall, the drug was associated with significant improvement in overall symptoms. These studies suggest that neurostimulant drugs can provide effective treatment for some cases of sarcoidosis associated fatigue. The mechanism of action seems independent of their effectiveness on sleepiness. This improvement in fatigue with armodafinil mirrors that reported for fatigue associated with other chronic disorders including multiple sclerosis and cancer associated fatigue.

Treatment of fatigue: anti-TNF-α drugs

In sarcoidosis, inflammation results in an increase in TNF-α [4, 78]. Small case series suggest that improvement in fatigue can occur with the administration of anti-TNF-α therapies. Keijsers et al. evaluated the effect of infliximab treatment by PET-scanning [47]. In addition to other clinical parameters, fatigue improved in all 12 studied patients. In a subsequent investigation by Elfferich et al. anti-TNF-α treatment also appeared beneficial in reducing disease activity, cognitive failure, as well as fatigue [7]. In this study, patients who received anti-TNF-α therapy with either infliximab 5 mg/kg every four weeks (n=31) or adalimumab 40 mg s.c. once a week (n=11) experienced substantial improvement in both subjective cognitive functioning and fatigue during the 6-month follow-up. The improvement in FAS scores was significantly higher compared to a reference group of untreated patients as well as patients who received prednisone with or without methotrexate. Based on the presented data, the approximated mean change scores on the FAS indicated a change in fatigue that exceeded the MCID of the FAS.

More recently, Erckens et al. demonstrated in 26 refractory chronic non-infectious posterior uveitis sarcoidosis patients that adalimumab successfully improved intraocular inflammation and fatigue [62]. Fatigue as assessed by FAS was identified in 21 of 26 (81%) patients prior to treatment. During treatment with adalimumab 14 of 21 (67%) of patients became less fatigued, four (19%) remained unchanged and three (14%) reported increase in fatigue. Eight out of these 14 cases reached the MCID (these data were not presented in the original paper).

The evaluation and treatment of sarcoidosis associated fatigue requires a stepwise evaluation as shown in Figure 2. Initial assessment must include identification of reversible causes of fatigue related to metabolic disorders of diabetes, anemia, or thyroid dysfunction, psychological conditions of depression or anxiety, and organ related conditions of small fiber neuropathy or sleep disturbances. Additional assessment should include optimal treatment for active inflammation as well as complications from therapeutic drugs such as corticosteroids. Too few interventions studies have been performed to examine the contribution of treatment to the reduction of fatigue scores in sarcoidosis patients. Even with appropriate identification and treatment of these reversible causes, many sarcoidosis patients may continue to experience persistent fatigue, i.e. sarcoidosis-associated fatigue. For these patients, neurostimulant therapy may be helpful. In addition to pharmaceutical treatments, rehabilitation and cognitive behavioral therapy should also be considered as treatment strategies for sarcoidosis-associated fatigue. Cognitive behavioral therapy and graded exercise programs have proven effective in treating fatigue in patients with Chronic Fatigue Syndrome [79].

In conclusion, sarcoidosis-associated fatigue has a great impact on patients' lives. Although a number of reversible causes of fatigue in sarcoidosis patients are known, the cause of sarcoidosis-associated fatigue is still unknown. Management should focus on appropriate treatment of sarcoidosis and the nature of sarcoidosis-associated fatigue. Successful treatment of active sarcoidosis fails to eradicate the disabling symptoms of continued fatigue. Obviously, longitudinal prospective studies to better define sarcoidosis fatigue, explore its impact on QOL, define aggravating or alleviating factors, and evaluate new potential treatment strategies are needed.

ACKNOWLEDGEMENTS

The authors wish to thank Petal Wijnen for helping to prepare the manuscript.

REFERENCES

1. Morgenthau AS, Iannuzzi MC. Recent advances in sarcoidosis. *Chest* 2011: 139: 174-182.

2. Hunninghake GW, Costabel U, Ando M, et al. ATS/ERS/WASOG statement on sarcoidosis. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders. *Sarcoidosis Vasc Diffuse Lung Dis* 1999: 16: 149-173.

3. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007: 357: 2153-2165.

4. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. *JAMA* 2011: 305: 391-399.

5. Michielsen HJ, Drent M, Peros-Golubicic T, et al. Fatigue is associated with quality of life in sarcoidosis patients. *Chest* 2006: 130: 989-994.

6. Wirnsberger RM, de Vries J, Wouters EF, et al. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med* 1998: 53: 53-60.

7. Elfferich MD, Nelemans PJ, Ponds RW, et al. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. *Respiration* 2010: 80: 212-219.

8. Baydur A, Alavy B, Nawathe A, et al. Fatigue and plasma cytokine concentrations at rest and during exercise in patients with sarcoidosis. *Clin Respir J* 2011: 5: 156-164.

9. Korenromp IH, Grutters JC, van den Bosch JM, et al. Reduced Th2 cytokine production by sarcoidosis patients in clinical remission with chronic fatigue. *Brain Behav Immun* 2011: 25: 1498-1502.

10. Marcellis RG, Lenssen AF, Elfferich MD, et al. Exercise capacity, muscle strength and fatigue in sarcoidosis. *Eur Respir J* 2011: 38: 628-634.

11. de Kleijn WP, Drent M, Vermunt JK, et al. Types of fatigue in sarcoidosis patients. *J Psychosom Res* 2011: 71: 416-422.

12. Sharma OP. Fatigue and sarcoidosis. *Eur Respir J* 1999: 13: 713-714.

13. Korenromp IH, Heijnen CJ, Vogels OJ, et al. Characterization of chronic fatigue in patients with sarcoidosis in clinical remission. *Chest* 2011: 140: 441-447.

14. Wirnsberger RM, de Vries J, Breteler MH, et al. Evaluation of quality of life in sarcoidosis patients. *Respir Med* 1998: 92: 750-756.

15. Drent M, Wirnsberger RM, de Vries J, et al. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999: 13: 718-722.

16. Baughman RP, Sparkman BK, Lower EE. Six-minute walk test and health status assessment in sarcoidosis. *Chest* 2007: 132: 207-213.

17. Hinz A, Fleischer M, Brahler E, et al. Fatigue in patients with sarcoidosis, compared with the general population. *Gen Hosp Psychiatry* 2011: 33: 462-468.

18. de Kleijn WP, Elfferich MD, De Vries J, et al. Fatigue in sarcoidosis: American versus Dutch patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2009: 26: 92-97.

19. Hoitsma E, De Vries J, van Santen-Hoeufft M, et al. Impact of pain in a Dutch sarcoidosis patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2003: 20: 33-39.

20. Spruit MA, Thomeer MJ, Gosselink R, et al. Skeletal muscle weakness in patients with sarcoidosis and its relationship with exercise intolerance and reduced health status. *Thorax* 2005: 60: 32-38.

21. De Vries J, Drent M. Quality of life and health status in sarcoidosis: a review of the literature. *Clin Chest Med* 2008: 29: 525-532, ix.

22. Den Oudsten BL, Van Heck GL, De Vries J. Quality of life and related concepts in Parkinson's disease: a systematic review. *Mov Disord* 2007: 22: 1528-1537.

23. Gvozdenovic BS, Mihailovic-Vucinic V, Ilic-Dudvarski A, et al. Differences in symptom severity and health status impairment between patients with pulmonary and pulmonary plus extrapulmonary sarcoidosis. *Respir Med* 2008: 102: 1636-1642.

24. Wirnsberger RM, Drent M, Hekelaar N, et al. Relationship between respiratory muscle function and quality of life in sarcoidosis. *Eur Respir J* 1997: 10: 1450-1455.

25. Michielsen HJ, De Vries J, Drent M, et al. Psychometric qualities of the Fatigue Assessment Scale in Croatian sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis* 2005: 22: 133-138.

26. Michielsen HJ, Peros-Golubicic T, Drent M, et al. Relationship between symptoms and quality of life in a sarcoidosis population. *Respiration* 2007: 74: 401-405.

27. De Vries J, Drent M. Relationship between perceived stress and sarcoidosis in a Dutch patient population. *Sarcoidosis Vasc Diffuse Lung Dis* 2004: 21: 57-63.

28. De Vries J, Michielsen H, Van Heck GL, et al. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004: 9: 279-291.

29. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, et al. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004: 21: 127-136.

30. De Vries J, Van Heck GL, Drent M. Gender differences in sarcoidosis: symptoms, quality of life, and medical consumption. *Womens Health* 1999: 30: 99-114.

31. Elfferich MD, De Vries J, Drent M. Type D or 'distressed' personality in sarcoidosis and idiopathic pulmonary fibrosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2011: 28: 65-71.

32. Drent M, Wirnsberger RM, Breteler MH, et al. Quality of life and depressive symptoms in patients suffering from sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998: 15: 59-66.

33. Wirnsberger RM, De Vries J, Jansen TL, et al. Impairment of quality of life: rheumatoid arthritis versus sarcoidosis. *Neth J Med* 1999: 54: 86-95.

34. Spruit MA, Thomeer MJ, Gosselink R, et al. Hypogonadism in male outpatients with sarcoidosis. *Respir Med* 2007: 101: 2502-2510.

35. Lower EE, Harman S, Baughman RP. Double-blind, randomized trial of dexmethylphenidate hydrochloride for the treatment of sarcoidosis-associated fatigue. *Chest* 2008: 133: 1189-1195.

36. Brancaleone P, Perez T, Robin S, et al. Clinical impact of inspiratory muscle impairment in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004: 21: 219-227.

37. de Kleijn WP, De Vries J, Wijnen PA, et al. Minimal (clinically) important differences for the Fatigue Assessment Scale in sarcoidosis. *Respir Med* 2011: 105: 1388-1395.

38. de Kleijn WP, De Vries J, Lower EE, et al. Fatigue in sarcoidosis: a systematic review. *Curr Opin Pulm Med* 2009: 15: 499-506.

39. Chang B, Steimel J, Moller DR, et al. Depression in sarcoidosis. *Am J Respir Crit Care Med* 2001: 163: 329-334.

40. Katon W, Lin EH, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007: 29: 147-155.

41. Mostard RL, Voo S, van Kroonenburgh MJ, et al. Inflammatory activity assessment by F18 FDG-PET/CT in persistent symptomatic sarcoidosis. *Respir Med* 2011: 105: 1917-1924.

42. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PG, et al. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. *Clin Chem* 2003: 49: 1510-1517.

43. Ziegenhagen MW, Rothe ME, Schlaak M, et al. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. *Eur Respir J* 2003: 21: 407-413.

44. Keijsers RG, Verzijlbergen FJ, Oyen WJ, et al. 18F-FDG PET, genotype-corrected ACE and sIL-2R in newly diagnosed sarcoidosis. *Eur J Nucl Med Mol Imaging* 2009: 36: 1131-1137.

45. Teirstein AS, Machac J, Almeida O, et al. Results of 188 whole-body fluorodeoxyglucose positron emission tomography scans in 137 patients with sarcoidosis. *Chest* 2007: 132: 1949-1953.

46. Braun JJ, Kessler R, Constantinesco A, et al. 18F-FDG PET/CT in sarcoidosis management: review and report of 20 cases. *Eur J Nucl Med Mol Imaging* 2008: 35: 1537-1543.

47. Keijsers RG, Verzijlbergen JF, van Diepen DM, et al. 18F-FDG PET in sarcoidosis: an observational study in 12 patients treated with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2008: 25: 143-149.

48. Keijsers RG, Verzijlbergen EJ, van den Bosch JM, et al. 18F-FDG PET as a predictor of pulmonary function in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2011: 28: 123-129.

49. Darko DF, Miller JC, Gallen C, et al. Sleep electroencephalogram delta-frequency amplitude, night plasma levels of tumor necrosis factor alpha, and human immunodeficiency virus infection. *Proc Natl Acad Sci U S A* 1995: 92: 12080-12084.

50. McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. *Neurosci Biobehav Rev* 2009: 33: 355-366.

51. Hoitsma E, Faber CG, Drent M, et al. Neurosarcoidosis: a clinical dilemma. *Lancet neurology* 2004: 3: 397-407.

52. Baune BT, Wiede F, Braun A, et al. Cognitive dysfunction in mice deficient for TNF- and its receptors. *Am J Med Genet B Neuropsychiatr Genet* 2008: 147B: 1056-1064.

53. Tobinick EL, Gross H. Rapid cognitive improvement in Alzheimer's disease following perispinal etanercept administration. *J Neuroinflammation* 2008: 5: 2.

54. Alkam T, Nitta A, Mizoguchi H, et al. Restraining tumor necrosis factor-alpha by thalidomide prevents the amyloid beta-induced impairment of recognition memory in mice. *Behav Brain Res* 2008: 189: 100-106.

55. Freeman R, Komaroff AL. Does the chronic fatigue syndrome involve the autonomic nervous system? *Am J Med* 1997: 102: 357-364.

56. Kim YK, Na KS, Shin KH, et al. Cytokine imbalance in the pathophysiology of major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry* 2007: 31: 1044-1053.

57. Heesen C, Nawrath L, Reich C, et al. Fatigue in multiple sclerosis: an example of cytokine mediated sickness behaviour? *J Neurol Neurosurg Psychiatry* 2006: 77: 34-39.

58. Drent M, Verbraecken J, van der Grinten C, et al. Fatigue associated with obstructive sleep apnea in a patient with sarcoidosis. *Respiration* 2000: 67: 337-340.

59. Verbraecken J, Hoitsma E, van der Grinten CP, et al. Sleep disturbances associated with periodic leg movements in chronic sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004: 21: 137-146.

60. Turner GA, Lower EE, Corser BC, et al. Sleep apnea in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1997: 14: 61-64.

61. Abad VC, Sarinas PS, Guilleminault C. Sleep and rheumatologic disorders. *Sleep Med Rev* 2008: 12: 211-228.

62. Erckens RJ, Mostard RL, Wijnen PA, et al. Adalimumab successful in sarcoidosis patients with refractory chronic non-infectious uveitis. *Graefes Arch Clin Exp Ophthalmol* 2011.

63. Parambil JG, Tavee JO, Zhou L, et al. Efficacy of intravenous immunoglobulin for small fiber neuropathy associated with sarcoidosis. *Respir Med* 2011: 105: 101-105.

64. Baughman RP, Lower EE. Six-minute walk test in managing and monitoring sarcoidosis patients. *Curr Opin Pulm Med* 2007: 13: 439-444.

65. Chauffier K, Salliot C, Berenbaum F, et al. Effect of biotherapies on fatigue in rheumatoid arthritis: a systematic review of the literature and meta-analysis. *Rheumatol* 2011.

66. Baughman RP, Iannuzzi MC, Lower EE, et al. Use of fluticasone in acute symptomatic pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002: 19: 198-204.

67. Brown JN, Howard CA, Kemp DW. Modafinil for the treatment of multiple sclerosis-related fatigue. *Ann Pharmacother* 2010: 44: 1098-1103.

68. Minton O, Richardson A, Sharpe M, et al. Drug therapy for the management of cancer-related fatigue. *Cochrane Database Syst Rev* 2010: CD006704.

69. Wagner MT, Marion SD, Judson MA. The effects of fatigue and treatment with methylphenidate on sustained attention in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2005: 22: 235.

70. Lower EE, Fleishman S, Cooper A, et al. Efficacy of dexmethylphenidate for the treatment of fatigue after cancer chemotherapy: a randomized clinical trial. *J Pain Symptom Manage* 2009: 38: 650-662.

71. Boulos MI, Murray BJ. Current evaluation and management of excessive daytime sleepiness. *Can J Neurol Sci* 2010: 37: 167-176.

72. Golicki D, Bala MM, Niewada M, et al. Modafinil for narcolepsy: systematic review and meta-analysis. *Med Sci Monit* 2010: 16: RA177-186.

73. Hirshkowitz M, Black JE, Wesnes K, et al. Adjunct armodafinil improves wakefulness and memory in obstructive sleep apnea/hypopnea syndrome. *Respir Med* 2007: 101: 616-627.

74. Roth T, Rippon GA, Arora S. Armodafinil improves wakefulness and long-term episodic memory in nCPAP-adherent patients with excessive sleepiness associated with obstructive sleep apnea. *Sleep Breath* 2008: 12: 53-62.

75. Bogan RK. Armodafinil in the treatment of excessive sleepiness. *Expert Opin Pharmacother* 2010: 11: 993-1002.

76. Czeisler CA, Walsh JK, Wesnes KA, et al. Armodafinil for treatment of excessive sleepiness associated with shift work disorder: a randomized controlled study. *Mayo Clin Proc* 2009: 84: 958-972.

77. Baughman RP, Malhorta A, Surdulescu V, et al. Armodafinil (R-modafinil) for fatigue in sarcoidosis: not just for treating hypersomnulence. *Chest* 2009: 136: 128s.

78. Baughman RP, Lower EE, Drent M. Inhibitors of tumor necrosis factor (TNF) in sarcoidosis: who, what, and how to use them. *Sarcoidosis Vasc Diffuse Lung Dis* 2008: 25: 76-89.

79. White PD, Goldsmith KA, Johnson AL, et al. Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. *Lancet* 2011: 377: 823-836.

80. Hoitsma E, Faber CG, van Santen-Hoeufft M, et al. Improvement of small fiber neuropathy in a sarcoidosis patient after treatment with infliximab. *Sarcoidosis Vasc Diffuse Lung Dis* 2006: 23: 73-77.

TABLE 1 Self-report fatigue measures used in existing sarcoidosis studies and the psychometric properties in sarcoidosis

Measures used to assess fatigue	Reliability in sarcoidosis*	Validity in sarcoidosis*	Studies using the measures
Borg score fatigue	-	-	[20]
CIS	-	Construct validity examined using one scale [13]	[9, 13]
CRDQ domain Fatigue	-	ig[20]● ● FACIT-F● -● -	[20]
FACIT-F	-	-	[35]
FAS	Cronbach's alpha is good [25, 28] Test-retest reliability is good [7, 28] Sensitivity to change appears good [7]	Content validity shows one underlying factor [25, 28] Construct validity is good [16, 17, 28]; MCID (4 points change) [37]; no floor and ceiling effects [25]; Discriminant validity is good [25]	[5, 7, 10, 16-18, 25, 27-29, 31, 35]
Fatigue Scale	-	-	[23]
Interview	-	-	[6, 15, 24, 33]
Multidimensional Fatigue Inventory	-	Construct validity (examined using a single item) seems good [17]	[8, 17]
SF-36 scale Vitality	-	Construct validity examined using one scale [13]	[13, 34, 36]
Symptom Inventory Questionnaire	-	-	[6, 15, 19, 26, 30]
WHOQOL-100 facet Energy and fatigue		Construct validity examined using one scale [19]	[14, 15, 19, 26, 28]

Note: CIS=Checklist Individual Strength; CRDQ = Chronic Respiratory Disease Questionnaire; FACIT – F = Functional Assessment of the Chronic Illness Therapy – Fatigue; FAS = Fatigue Assessment Scale; WHOQOL-100 = World Health Organization questionnaire of Quality of Life-100.

TABLE 2 Fatigue Assessment Scale (FAS) with instructions

	never*	sometimes*	regularly*	often*	always*
1. I am bothered by fatigue.	1	2	3	4	5
2. I get tired very quickly.	1	2	3	4	5
3. I don't do much during the day.	1	2	3	4	5
4. I have enough energy for everyday life.	1	2	3	4	5
5. Physically, I feel exhausted.	1	2	3	4	5
6. I have problems to start things.	1	2	3	4	5
7. I have problems to think clearly.	1	2	3	4	5
8. I feel no desire to do anything.	1	2	3	4	5
9. Mentally, I feel exhausted.	1	2	3	4	5
10. When I am doing something, I can concentrate quite well.	1	2	3	4	5

*The following ten statements refer to how well the person usually feels. Per statement one out of five answer categories can be chosen, from never to always. 1 = never, 2 = sometimes (think about monthly or less); 3 = regularly (think about a few times a month); 4 = often (think about weekly); 5 = always (think about every day). Per statement the person can choose one out of five answer categories, varying from never to always. An answer to each question has to be given; even the person does not have any complaints at the moment.
Scores on questions 4 and 10 should be recoded (1 = 5, 2 = 4, 3 = 3, 4 = 2, 5 = 1). Subsequently, the total FAS score can be calculated by summing the scores on all questions (the recoded scores for question 4 and 10). The sum of questions 3+6+7+8+9 indicates mental fatigue, and the sum of the questions 1+2+4+5+10 indicates physical fatigue. The minimal score is 10 the maximal score is 50. Based on large representative samples of the Dutch population, the cut-off score of the FAS is 21, *i.e.*, scores of ≥ 22 are considered to represent substantial fatigue. A change in the FAS score of 4 points is considered to be clinically relevant (MCID) [37].
The FAS has been validated in the Croatian, Danish, Dutch, English, French, German, Italian, Japanese, Norwegian, Romanian, Russian, Spanish language.
A PDF and digital version of the English FAS can be found at the website of the ild care foundation: http://www.ildcare.nl/index.php?id=100
More information can be provided by the corresponding author.

TABLE 3 The relationship between quality of life (QOL) or health status (HS) and fatigue

Study	Sample size	Study design	Questionnaires used	Results
[5]	145 patients	Cross-sectional	Fatigue: FAS QOL: WHOQOL-100	Fatigue was negatively related to all WHOQOL domains and the general facet. Furthermore, women more tired and worse QOL on all domains compared with men
[14]	64 patients and 64 matched controls	Cross-sectional	Fatigue: WHOQOL-100 QOL: WHOQOL-100	The facet Energy and fatigue was unrelated to the QOL domain Psychological health
[20]	22 patients and 21 matched controls	Cross-sectional	Fatigue: CRDQ- domain fatigue HS: SF-36	Fatigue correlated high with all HS scales
[16]	142 patients	Cross-sectional	Fatigue: FAS HS: SGRQ	Fatigue correlated high with all HS scales
[26]	150 patients	Cross-sectional	Fatigue: Symptom Inventory Questionnaire QOL: WHOQOL-100	Fatigue was a negative predictor of the QOL domains Physical health, Psychological health, and Level of independent
[31]	441 patients	Cross-sectional	Fatigue: FAS QOL: WHOQOL-Bref	Fatigue (together with depressive symptoms) predicted overall QOL ($p<0.001$)
[13]	75 patients	Cross-sectional	Fatigue: CIS HS: SF-36	Fatigued patients scored lower on all HS scales (all $p<0.001$)

TABLE 4 Pharmacologic treatment of sarcoidosis associated fatigue

Treatment Categories	Specific agents	Comments
Anti-inflammatory therapies for disease		
Anti-malarial agents	Hydroxychloroquine	Use of agent associated with less fatigue [18]
Anti-TNF monoclonal antibodies		
	Infliximab	Case report and series [7, 47, 80]
	Adalimumab	Case series [7, 62]
Neurostimulants		
	Methylphenidate	Case series [69]
	d-Methylphenidate	Double blind cross over trial [35]
	Armodafinil	Double blind cross over trial [77]

Figure Legends

FIGURE 1 Flow chart of included studies

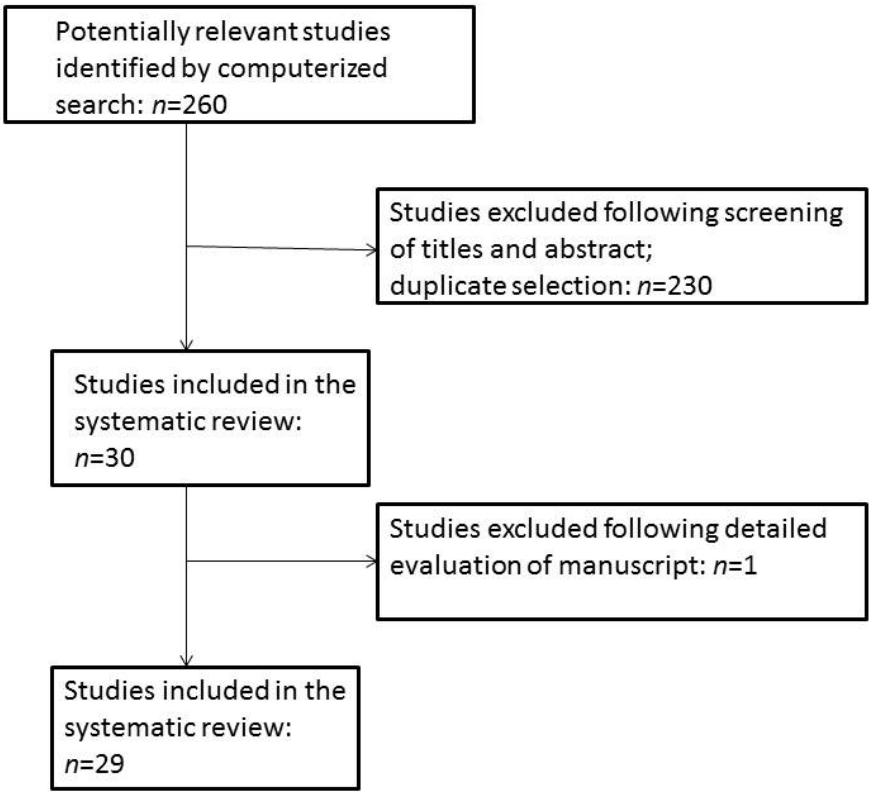

FIGURE 2 A step wise approach to the management of sarcoidosis associated fatigue