CHAPTER 21

Sarcoidosis-Associated Disability

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INTRODUCTION

Sarcoidosis is complex and highly variable, with protean clinical manifestations and a wide array of consequences for patients. The course is likewise unpredictable, leading to the moniker "sarcoidoses" to connote that sarcoidosis may be a syndrome rather than a single disease.[1] The clinical manifestation, natural history, and prognosis of sarcoidosis are highly variable, and its course is often unpredictable, depending on the duration of the illness, the organs involved, and fluctuating granulomatous activity.[2] Patients report disabling impairments, especially when they become chronic.[3,4] As a consequence, the interpretation of the severity of sarcoidosis can be complicated by its heterogeneity.[2] Several major concerns of sarcoidosis patients include symptoms that cannot be explained by granulomatous involvement of a particular organ.[3] Apart from pulmonary symptoms (e.g., coughing, breathlessness, and dyspnea on exertion), patients may suffer from a wide range of rather nonspecific disabling symptoms. These symptoms, such as fatigue, fever, anorexia, arthralgia, muscle pain, general and muscle weakness, exercise limitation, and cognitive failure, often do not correspond with objective physical evidence of disease activity.[3] Several studies have reported that neither lung function tests nor chest radiograph abnormalities correlate with nonspecific health complaints, including fatigue or quality of life (QoL). Sarcoidosis-related symptoms may become chronic and affect patients' QoL even after all of the clinically measurable signs of disease activity have disappeared.[5,6] Sarcoidosis-associated chronic fatigue is often troubling to clinicians because it does not relate directly to physiologic abnormalities and is a challenge to treat. Moreover, absence of evidence does not mean evidence of absence.[3,7] It can be argued that when a disease is not overtly dangerous, decisions on treatment of morbidity should be patient-driven because the impact of symptoms on overall QoL is something that can never be fully grasped by anyone other than the patient and immediate family. However, when there is danger from disease (consisting of a higher risk either of mortality or disability due to major organ involvement), the management strategy should ideally be based on medical expertise.[8]

Assessment of Symptom Burden and Disability

Sarcoidosis consists of several overlapping clinical syndromes ('the sarcoidoses'), each with its own specific pathogenesis.[1,2] Physicians generally assess disease activity, severity, and progression in sarcoidosis on the basis of clinical tests, such as serological tests, pulmonary function tests, chest radiographs, and more recently positron emission tomography scans (https://www.ncbi.nlm.nih.gov/pubmed/23018903—comments).[2,9–11] However, these objective clinical parameters correlate poorly with the patients' subjective sense of well-being.[3,12] Moreover, the field of sarcoidosis is rapidly expanding from being solely the bailiwick of chest physicians to intense focus by other specialties, especially cardiology, rheumatology, ophthalmology, and neurology. A phenotyping system centered on the lung is increasingly less relevant.[1] Delineating distinct subgroups, "phenotypes", has been an attempt to simplify prediction about individual patients. Sarcoidosis phenotypes have been used most often to predict prognosis or to cluster patients with similar outcomes.[1,13] A complete evaluation of sarcoidosis could make use of novel phenotypes that are more powerful for prognosis, severity, treatment response, and other clinical characteristics. As these new phenotypes are developed, they must be interpreted and validated within the context of the sarcoidosis clinic and the patient's experience to be acceptable and useful.[1,13] Phenotyping could also be used primarily to stratify patients by clinical features such as extent of organ involvement or by perceived severity. Phenotypic organ-based clusters should assess the severity of sarcoidosis in each organ, which is defined as the degree of organ damage sustained from sarcoidosis. This damage can be estimated subjectively by the intensity of specific organ-related symptoms or objectively by critical localization of lesions, physiologic abnormalities, and the percentage decline from normal capacity. Membership in a given cluster entails higher odds for certain other clinical features, such as

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acute versus subacute onset, symptoms, and need for therapy.[1,13] Obviously, the interpretation, qualification, and quantification of the severity of sarcoidosis can be complicated by its heterogeneity.[1,6,14] The question whether the burden or localization of the disease contributes to fatigue levels and low energy is highly interesting. It has been shown that patients with both pulmonary and extrapulmonary sarcoidosis report higher fatigue levels than those in whom only the lungs are affected. This suggests a possible additive effect for the troublesome symptom of fatigue.

Fatigue

Although less recognized than exertional dyspnea, fatigue is a very common and frustrating physical symptom. Fatigue is the most frequently described and devastating symptom in sarcoidosis and is globally recognized as a disabling symptom. The reported prevalence varies from 60% to 90% of sarcoidosis patients.[15] Up to 25% of fatigued sarcoidosis patients report extreme fatigue. Several types of fatigue have been described in sarcoidosis.[16,17] One of these types is early morning fatigue, where the patient arises with feelings of inadequate sleep. Another type is 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, followed by another period of fatigue. Patients bothered by all-day fatigue have reported the highest level of clinical and psychological problems.[17] About 5% of the patients who appear to be recovered from active sarcoidosis suffer from the so-called postsarcoidosis chronic fatigue syndrome (CFS), first described by James.[7] These sarcoidosis patients may suffer from substantial fatigue even in the absence of other symptoms or disease-related abnormalities.

Cause, risk factors, and diagnosis of fatigue

Fatigue can be nonspecific and hard to objectify and quantify. So far, no organic substrate has been found for sarcoidosis-associated fatigue. The etiology of this fatigue is poorly understood, and there is evidence that it is multifactorial. Active inflammation, cytokine release, depression, altered sleep patterns, overweight, and/or small fiber neuropathy (SFN) all appear to contribute to fatigue.[15,16,18,19] Fatigue can also be a consequence of treatment itself, e.g., as a complication of corticosteroid therapy.

The diagnosis of sarcoidosis-associated fatigue requires an extensive evaluation to identify and treat potentially reversible causes. Despite an exhaustive search for treatable clinical causes of fatigue, however, most patients' complaints of fatigue do not correlate with clinical parameters of disease activity. This means that patients may experience substantial fatigue even without respiratory functional impairment, chest radiograph abnormalities, or markers of diseases activity.[20] Moreover, many patients continue to experience fatigue, causing limitations, even when effective treatment of the sarcoidosis activity is provided.

Predictors of sarcoidosis-associated fatigue

It is important to examine the potential factors that predict and sustain fatigue in sarcoidosis. This may be accomplished by understanding clinical, psychological, and social predictors of fatigue in these patients. The knowledge concerning correlates of the development of fatigue and possible interrelationships is still incomplete. Significant predictors of fatigue include everyday cognitive failure, depressive symptoms, symptoms suggestive of SFN, and, to a lesser extent, dyspnea.[21] Symptoms of fatigue and dyspnea induce exercise limitation, and fatigue may also lead to physical inactivity. Strookappe et al. showed that exercise capacity is also one of the predictors of patients' fatigue.[22] In their study, fatigue was not explained by lung function test results, inflammatory markers, or other clinical parameters. Fatigue, low energy, and exercise limitations affect patients' social life and physical as well as psychological capacities. Decreased physical activity can induce general deconditioning, which in turn contributes to increased perceived physical fatigue and a sense of dyspnea, lack of energy, or exhaustion.

Treatment options of fatigue

Treatment of sarcoidosis obviously is the first option. Often sarcoidosis-associated fatigue is not influenced by the sarcoidosis treatment. Besides, when there is no strict indication to treat sarcoidosis, fatigue can be very devastating for the patient. Some alternative options can be considered. Cognitive behavioral training is an effective behavioral intervention for the CFS, which combines a rehabilitative approach of a graded increase in physical activity with a psychological approach that addresses thoughts and beliefs about CFS which may impair recovery. In line with this, McBride et al. demonstrated subjective and objective performance improvements and suggest that a computerized, home-based cognitive training program may be an effective intervention for patients with CFS.[23] Studies are warranting to evaluate whether this works in sarcoidosis as well. Recent studies have demonstrated the effectiveness of various neurostimulants, including methylphenidate, for the treatment of sarcoidosis-associated fatigue, and these and other agents may be useful adjuncts in its treatment.[24]

Assessment of fatigue

The assessment of sarcoidosis-associated fatigue requires extensive evaluation to identify and treat potentially reversible causes. The severity of fatigue experienced by a patient can be assessed using the Fatigue Assessment Scale (FAS), a 10-item self-report fatigue questionnaire (Table 21.1). The minimum score is 10, and the maximum score is 50. Based on large representative samples of the Dutch population, the cutoff score of the FAS is 21, i.e., scores of >21 are considered to represent fatigue, and a score of ≥35 represents substantial fatigue.[15] A change in the FAS score of four points is considered to be clinically relevant (minimal clinically important difference).[25] The reliability and validity of the FAS appear to be good in sarcoidosis patients. The FAS has been validated in many languages and for various disorders. A PDF and digital version of a translation of the FAS in 20 languages, including an English version, can be found on the website of the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG; www.wasog.org).[26]

Everyday Cognitive Failure

Consequences of cognitive failure for the patient can be discomfort, such as memory problems and problems of attention and concentration, and may affect self-management.[23,27] Giving patients with sarcoidosis insight into their cognitive functioning is of great importance to optimize their self-management skills. Indeed, cognitive deficits may lead to difficulties in managing their disease and negatively affect their treatment. Everyday cognitive failure and depressive symptoms have been found to be the most important predictors of high levels of fatigue,[21] whereas background variables (time since diagnosis, sex, and age) and social support appeared not to predict fatigue. Patients with high levels of cognitive failure also reported higher levels of fatigue than those with lower levels of cognitive failure.[27] Currently, however, no data are available on the extent of cognitive underperformance among sarcoidosis patients. Research among patients with multiple sclerosis found that memory complaints were not associated with memory performance but were associated with fatigue complaints.[28] It is hypothesized that functional cognitive impairment, if present, may lead to increased fatigue and low compliance with medical treatment. An alternative hypothesis is that patients who experience more cognitive failures are continuously putting extra cognitive effort into daily tasks (compensation) and consequently become more tired. It is tempting to speculate that this may also be the case in sarcoidosis patients. Although treatment should first focus on treating sarcoidosis and its activity, alternatives could be considered if this is not effective.[27] Elfferich et al. found that antitumor necrosis factor alpha (TNF-α) therapy had a positive effect on cognition, fatigue, and other symptoms of sarcoidosis.[27] Modafinil has been shown to have beneficial effects on cognitive function. Recently, Kaser et al. found that modafinil may have potential as a therapeutic agent to help remitted depressed patients with persistent cognitive difficulties by improving episodic memory and working memory performance.[29]

Depressive Symptoms and Anxiety

Depressive symptoms and anxiety in sarcoidosis are at least partly an expression of exhaustion owing to the ongoing disease, and these psychological symptoms indeed play an important role in sarcoidosis.[30] They have been reported in 17%–66% of patients with sarcoidosis. Bosse-Henck et al. found that depression and anxiety were predictors of the development of severe fatigue.[31] Depressive symptoms were negatively associated with patients' fatigue scores. In addition, the relationship between fatigue and depressive symptoms parallels the findings for other chronic illnesses, such as diabetes, chronic obstructive pulmonary disease, cardiac disease, and rheumatoid arthritis. Stepanski et al. examined fatigue in patients with cancer.[32] They also showed that depressive symptoms were related to fatigue. Moreover, anxiety and depressive and SFN-related symptoms in sarcoidosis are moderated by the severity and nature of fatigue. Fatigue and autonomic dysfunction are both dominant symptoms and risk factors for depression. Anxiety consists of physical or hyperarousal symptoms, such as increased heart rate, perspiration, and dizziness, which are inherent to the reaction of the sympathetic nervous system. In addition to a physical component, anxiety also has a cognitive component, that is, a thought (or chain of thoughts) that determines the emotion experienced. Anxiety is a major problem in sarcoidosis patients. Because fatigue is a symptom that is known to co-occur with anxiety, it is not surprising that anxiety in general and trait anxiety in particular were found to be related to fatigue. Trait anxiety predicted fatigue at follow-up.[21]

Neurobiological Abnormalities

The nature of fatigue moderates the relationships between fatigue and everyday cognitive failure, depressive symptoms, and anxiety in sarcoidosis. The symptoms may share several neurobiological abnormalities, such as an increase in TNF-α. The relationship between

TABLE 21.1
Fatigue Assessment Scale (FAS)

		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

For each statement, one out of five answer categories can be chosen, from never to always—1: never; 2: sometimes (about monthly or less); 3: regularly (about a few times a month); 4: often (about weekly); and 5: always (about every day). An answer to each question has to be given, even if 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 questions 4 and 10). The sum of questions three and six to nine indicates mental fatigue, and the sum of questions 1, 2, 4, 5, and 10 indicates physical fatigue. Published with permission of the ild care foundation (www.ildcare.nl).

depressive symptoms and fatigue in sarcoidosis may also be based on a cytokine imbalance, induced by an inflammatory immune response. The cytokine balance of patients suffering from depression also appears to be disturbed. However, understanding the nature of the relationships between fatigue, depressive symptoms, and anxiety remains difficult. Recently, extrapyramidal signs in neurosarcoidosis have been associated with specific inflammatory pathways and specifically TNF-α.[33] To date, some studies demonstrated positive effect of anti–TNF-α treatment in pulmonary as well as extrapulmonary manifestations including fatigue and cognitive failure.[27,34,35]

SFN-Associated Symptoms

SFN was recognized as a symptom of sarcoidosis in 2002.[36] It is a disabling generalized sensory nerve disorder with a widespread spectrum of symptoms. The reported prevalence of SFN varies from 40% to 60% of patients with sarcoidosis and has been associated with poorer cognitive performance in a general sarcoidosis population.[27,37,38] Symptoms of SFN are disabling for patients and probably underrecognized.[3,39] Patients often feel misunderstood and are limited in their daily activities by the symptoms, which are moreover often difficult to treat.[40] Damage to or loss of small somatic nerve fibers results in pain, burning or tingling sensations, or numbness, typically affecting the limbs in a distal to proximal gradient. When autonomic fibers are affected, patients may experience restless legs, dry eyes, dry mouth, orthostatic dizziness, constipation, bladder incontinence, sexual dysfunction, and/or symptoms relating to autonomic cardiac dysfunction. Symptoms suggestive of SFN as assessed by the SFN Screening List were found to be related to fatigue.[41] Regarding the effect of the restless legs syndrome, the disturbance of sleep quality, i.e., sleep stages and sleep fragmentation, leads to daytime somnolence and fatigue. This may offer a partial explanation for the great burden of fatigue in patients with this syndrome.

Overall Impact on QoL

The impact of any disease depends on the way the patient perceives and experiences the disease and modifies his or her activities of daily living. Living with a long-term disease such as sarcoidosis significantly affects QoL, with negative consequences for general health and social and psychosocial well-being.[42,43] QoL is an important outcome measure of treatment, especially with regard to chronic diseases, including sarcoidosis (Fig. 21.1). It is a concept that concerns patients' evaluation of their functioning in a wide

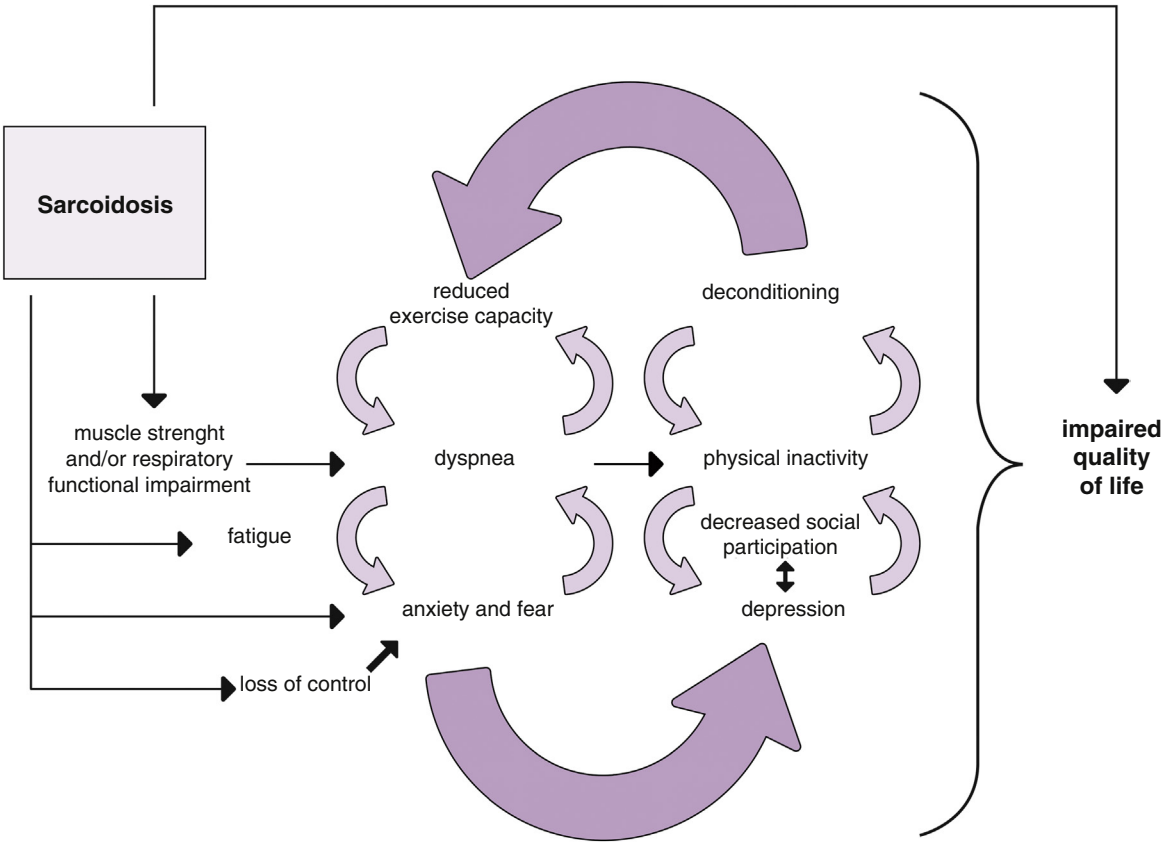

FIG. 21.1 Negative vicious circle of physical deconditioning. Disabling symptoms in sarcoidosis can reduce daily physical activities, resulting in general deconditioning and a reduced quality of life. (Adapted from Swigris JJ, Brown KK, Make BJ, et al. Pulmonary rehabilitation in idiopathic pulmonary fibrosis: a call for continued investigation. *Respir Med.* 2008;102(12):1675–1680. Published before in: Marcellis RG, Lenssen AF, De Vries J, et al. Reduced muscle strength, exercise intolerance and disabling symptoms in sarcoidosis. *Curr Opin Pulm Med.* 2013;19(5):528 and Drent M, Strookappe B, Hoitsma E, De Vries J. Consequences of sarcoidosis. *Clin Chest Med.* 2015;36:731.)

range of domains, but always including the physical, psychological, and social domains.[42] The assessment covering only these three domains is known as an assessment of health-related QoL.[42,43] QoL is often confused with health status, which concerns patients' physical, psychological, and social functioning.[42] QoL is influenced by psychological factors, such as burnout, emotional distress, and work-related social support.[44] Social support has been described as a buffer against pain and disability and also as being associated with greater activity levels among individuals with pain.[44,45] Support positively predicts return to work, and lack of social support at work is a well-known risk factor for developing pain.[46]

In sarcoidosis, there is poor agreement between physicians and patients with regard to the perceived symptoms attributable to the disease, with a particular failure of clinicians to recognize the impact of non–organ-specific features. For instance, pulmonary function test results do not always reflect changes in the severity of pulmonary sarcoidosis, which illustrates that the assessment of sarcoid activity and its clinical relevance remains an enigma. Assessment of inflammatory activity in sarcoidosis patients without deteriorating lung function or radiological deterioration, but with unexplained persistent disabling symptoms, is an important and often problematic issue. It has been proposed that assessment of QoL of sarcoidosis patients

would help to bridge this gap, aiding communication and treatment and complementing existing clinical assessments.[47,48]

Disability Due to Sarcoidosis

Many sarcoidosis patients have to face disability due to disease-associated symptoms and are therefore unable to work or underemployed and incapable of achieving their full potential due to health-related issues.[49] Individuals affected by sarcoidosis usually appear completely healthy, so their symptoms are often not taken seriously by family, friends, health-care professionals, and employers. Consequently, some patients lose their desire and ability to effectively socialize with others, causing relationships and family dynamics to ultimately suffer. These combined factors have an impact on an individual's economic status, interpersonal relationships, and family dynamics, increase their stress levels, and induce depression.[3]

We are living in a world where people are increasingly expected to 'participate', for instance, at work and in managing their own care processes. In fact, everyone is now expected by society to 'take part' at all levels. But, is this a realistic expectation for sarcoidosis patients, considering the huge impact that sarcoidosis can have on their QoL, physical and mental capacities, and social life? Although sarcoidosis often causes severe fatigue and reduced exercise tolerance, other people usually do not notice this. Patients encounter problems due to their sarcoidosis, in their job, with their employer, and/or with various authorities, such as occupational health and safety services or benefits authorities. Moreover, sarcoidosis imposes a significant economic burden and health-care costs.[49]

In general, sarcoidosis patients are disabled by functional impairments due to sarcoidosis-associated symptoms. Functional impairments are defined as limitations in, or inability to perform, certain physical activities, such as walking and lifting, or mental activities such as concentrating and conflict handling.[50] Hence, functional impairments can be distinguished from symptoms (such as pain and fatigue), activity limitations (such as self-care tasks and gardening), and participation restrictions (such as leisure time activities and work). Usually, however, the course of sarcoidosis is only monitored using pulmonary function test results and imaging.

The most promising approach would appear to be to gather information using instruments such as questionnaires, performance tests, or interviews, interpreted and assessed by physicians.[51] This needs to be followed by a multidisciplinary meeting in which the patients themselves participate to achieve optimal shared decision-making.[52] There is an urgent need for more information and guidelines to assess the physical and mental capacities of patients with sarcoidosis, to ensure that lung function is not the only aspect taken into account. Obviously, because sarcoidosis requires a multidisciplinary approach in view of its wide range of symptoms, communication among the various health-care workers involved and the patients is of great importance.

Role of Self-Management?

The presence of depressive symptoms is a mediator of the relationship between trait anxiety and fatigue. Depressive symptoms may indirectly lead to increased symptoms as such symptoms are associated with poor self-care (diet, exercise, giving up smoking, medication regimens) in patients with chronic diseases.[21,30] However, physical symptoms, the resulting functional impairments and stress caused by complications of the medical illness, are also likely to impose a burden on the patient's life and to provoke depression.[20]

From this perspective, various researchers have rightly suggested that sarcoidosis patients may benefit from psychological interventions focusing on coping and appraisal, such as stress-reduction therapy.[53,54] In any case, the basis for the interventions should be a type of cognitive behavioral therapy. Successfully adapting to an illness enables people to work or to participate in social activities and accept their limitations.[55] This has been shown in evaluations of the Stanford chronic disease self-management program, in which extensively monitored patients with chronic illnesses, who learned to manage their life better and to cope with their disease, reported improved self-rated health, less distress, less fatigue, more energy, and fewer perceived disabilities and limitations in social activities after the training program. Even health-care costs fell.[56–58] It is interesting to speculate that this concept could also work in sarcoidosis, but this needs to be explored.

CONCLUSION/SUMMARY

In addition to specific organ-related symptoms with functional impairments, sarcoidosis patients tend to be disabled by less specific symptoms, including fatigue, everyday cognitive failure, symptoms suggestive of SFN, pain, and physical impairments. Therefore, the management of sarcoidosis patients should focus not only on organ-related symptoms but also on the increased burden of concomitant symptoms. Multidisciplinary care programs should focus on this burden and also

teach patients how to cope with their disease. Because fatigue usually has a multifactorial cause, risk factors should also be examined and treated in combination. Future research involving more comprehensive neuropsychological batteries is warranted to investigate psychological functioning, SFN, and fatigue in sarcoidosis. A guideline to assess disability in sarcoidosis is also very much warranted.

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Conflict of interest

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