CLINICAL FOCUS SERIES

Lesions of Sarcoidosis

A Problem Solving Approach



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CHAPTER

3 Fatigue in Sarcoidosis

INTRODUCTION

Fatigue is a common complaint in general population and also a common symptom in many diseases, such as viral or other infections, hypothyreosis, rheumatoid arthritis, malignant diseases, and anemia.[1-4] Numbers of studies up-to-date have shown fatigue to be one of the most commonly reported complaints of patients suffering from sarcoidosis.[5-8]

The general intent of this chapter is not to solve the problems of fatigue in sarcoidosis, neither to define it as it should be, not even to suggest how to measure it, but to review the possible causes of fatigue observed in the current literature and to illuminate the important problems that the feeling of fatigue is bringing into patients' lives.

HISTORICAL ACCOUNT

Searching the PubMed for "fatigue in sarcoidosis", as many as 46 articles were found. The first published article on the topic fatigue in sarcoidosis was published 40 years ago (1972) in the *Chest* Journal by Sharma[9] and the latest one in July 2011 by Efferich et al.[10] The number of papers, however, increased remarkably during the last decade of this century suggesting that the clinicians treating sarcoidosis patients are aware of the serious problems fatigue can cause.

CLINICAL IMPLICATIONS

Regardless of the published papers, there is still no available definition of fatigue, the most common clinical complaint, in the terms of the clinical practice. There are many synonyms for the word "fatigue" like exhaustion, tiredness, low energy, and weakness. However, all the synonyms describe the sensation of fatigue of a healthy person. The word fatigue indeed originates from the experience of a healthy individual; however, these persons find the same sensation qualitatively completely different once they become sick (Table 3-1).[11]

For clinicians, the duration of fatigue can be divided into: less than 3 months, 3–6 months, and longer than 6 months. In patients with the duration of fatigue longer than 3 months, abdominal, cardiac, musculoskeletal, hematological, and

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Table 3-1 Clinical Types of Fatigue in Sarcoidosis[12,13]

Possible clinical manifestations of fatigue in sarcoidosis	
Early morning fatigue	Patients awakes with a feeling of unrest because of joint stuffiness' or muscle pain. This type of fatigue is also seen in patients with auto-immune diseases
Intermittent fatigue	Patients wake-up normally but after a few hours of activity feel tired and exhausted. Throughout the day they need periods of rest
Afternoon fatigue	Patient arises in the morning with adequate energy but feels tired in the early afternoon. These patients evaluate their fatigue as "a flu-like syndrome". They go to bed early and stay in bed until next morning
Post-sarcoidosis chronic fatigue syndrome	Presence of fatigue in persons with the history of sarcoidosis (with the normal chest radiograph and the markers of the disease activity). Main symptoms are widespread myalgia, unbearable fatigue, and depression. Physical signs during the examination are absent. The lack of any objective evidence confuses both the patients and the physicians

neurological system investigations should be performed. In patients with fatigue lasting for more than 6 months, anxiety, family dysfunction, stress, and depression should be considered.[12,13]

POSSIBLE CAUSES OF FATIGUE IN SARCOIDOSIS

General Inflammation and Metabolic (Endocrine) Derangements

Increased inflammation (both systemic and the airways inflammation) has been reported in sarcoidosis.[4] Although increased inflammatory status has also been reported in many chronic illness,[14-16] the relation of proinflammatory mediators (i.e., interleukin-2) and involuntary weight loss and thus the correlation with the sensation of fatigue in sarcoidosis patients has never been analyzed.[17] However, a few case reports with severe weight loss have been reported in sarcoidosis.[18]

On the contrary, patients with high body mass index (overweight) have been described in sarcoidosis with lower fat-free mass over body weight ratio.[19,20]

Male patients with sarcoidosis have been described to have reduced circulating testosterone serum levels related with the sensation of fatigue in many chronic illnesses.[21-23] It has also been described that oxidative stress factors are in correlation with the sensation of fatigue and that antioxidative therapy might be useful in the treatment of fatigue in sarcoidosis.[24,25]

Myopathy

Respiratory Muscle Weakness in Relation to Fatigue in Sarcoidosis

Respiratory muscle weakness has been described in patients with sarcoidosis compared with healthy controls.[4,20,26,27] Reduced inspiratory muscle pressure may be due to granulomatous involvement of the main inspiratory muscle-diaphragm.[28]

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The biopsy might be of an important diagnostic value to elucidate the mechanism of respiratory muscle involvement in sarcoidosis, however, not a study on this topic has been performed or published. Although magnetic stimulation of the phrenic nerve might also be helpful in possible explanation of the diaphragmal involvement, it has never been performed in sarcoidosis patients.[29]

The granulomatous involvement of the respiratory muscles should be considered in sarcoidosis patients with complaint of fatigue and dyspnea when the severity of dyspnea does not correlate with the degree of lung function impairments.

Baydur et al. found that forced vital capacity and transfer factor for carbon monoxide were significantly lower in sarcoidosis patients compared to healthy controls, but they did not correlate with the degree of perceived dyspnea. However, low respiratory muscles strength was in correlation with worse dyspnea score on the modified Medical Research Council scale, frequently used as a measure of dyspnea.[26]

It is quite possible that the reduction in respiratory muscles strength, significantly contributed to the feelings of dyspnea and fatigue during usual daily activities in a group of sarcoidosis patients, investigated using daily activity list in a study by Gvozdenovic.[30]

Skeletal Muscle Weakness

Skeletal muscle weakness is assumed to be a part of the granulomatous process in patients with sarcoidosis. Spruit et al.[4] found a significant difference in quadriceps peak torque and handgrip force between patients with sarcoidosis and healthy controls. All patients from this study reported fatigue.

Steroid Induced Myopathy

As already has been described in patients with chronic obstructive pulmonary disease, steroid therapy may also affect respiratory muscles in sarcoidosis patients.[31] Corticosteroid therapy has a significant influence on improvement of granulomatous inflammation in sarcoidosis. However, steroid therapy may also have harmful effects on skeletal muscles force.[32]

In a study of Spruit et al., significant negative correlation was found between quadriceps peak torque and the daily steroid dose in patients who were treated with oral steroid therapy for a period of 6 months prior to the test. Skeletal muscle force, however, did not differ between patients with and without steroid therapy prior to the testing.[4]

Improved skeletal muscle function was reported after the therapy with high doses of oral steroids in patients with sarcoidosis.[33,34]

It seems that the effects of steroid therapy on skeletal muscle function are influenced by the presence of granulomatous inflammation in the muscles.[34]

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Sleeping Disorders (Obstructive Sleep Apnea, Restless Legs Syndrome, and Small Fibre Neuropathy)

Sleeping disorders may be a part of the clinical picture of fatigue.[35] Restless leg syndrome (RLS) is probably the most frequent complaint associated with sleep disturbances in sarcoidosis.[36] However, nowadays, it is easily detected by transcranial ultrasound.

The majority of patients with RLS have normal neurological findings on clinical examination and routine neuroimaging.[37,38] Two trascranial ultrasound studies reported a reduction in substantia nigra (SN) echogenicity in 82% of patients with idiopathic RLS and 40% with the secondary RLS. The detectable area of SN was less than 0.1 cm^2. In both groups, the same pathological mechanism was suggested—iron homeostasis disorder in the brain.[39,40]

Pain

Chest pain see the chapter 6 of the possible causes of the chest pain, headache–see chapter 21)

Pain appears to be a substantial problem in sarcoidosis. In a study of Spruit et al.,[4] sarcoidosis patients who complained to be fatigued had positive correlation between quadriceps muscle weakness and Medical Short Form-36 (Section "PAIN"). The lack of energy and feeling of tiredness can possibly explain the variety of pain sensations in sarcoidosis. Therapeutic approach with pain coping regime and rehabilitation program is, therefore, suggested in these patients.[41]

Lack of Exercise

Exercise intolerance has been described in patients with sarcoidosis.[4,42,43] Quadriceps muscle weakness was found to correlate 6-minute walk distance in patients with sarcoidosis who complained of fatigue.[4]

Psychological Factors (Depression)

Although Klonoff and Kleinhenz suggested that sarcoidosis patients as a group does not meet the criteria for clinical depression, awareness of bodily sensations however, was found to be associated with more depressive symptoms and escaping of activities when alone. In relation to psychological factors, fatigue in sarcoidosis may also be related to a perceived stress.[44]

HOW TO MEASURE FATIGUE IN SARCOIDOSIS?

Unfortunately, there is no reliable instrument for measuring fatigue. The sensation of fatigue does not correlate with the objective clinical tests used in everyday practice (chest X-ray, lung function parameters, and routine laboratory tests). Although fatigue has a major influence on the quality of life, from the patients' perspective, doctors seem to be poor adjudicators of this mysterious symptom.

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POST-SARCOIDOSIS FATIGUE SYNDROME

To add some more to the confusion called " fatigue in sarcoidosis", doctors treating sarcoidosis patients often notice that the patients frequently complain of fatigue, even when sarcoidosis has come into the clinical remission. Group of Dutch authors[45] in a recent study emphasizes the problem of post-sarcoidosis fatigue as a frequent symptom which can be characterized as a severe long-lasting problem, symptomatically similar to chronic fatigue syndrome (CFS).

Psychological distress and reduced health status are associated with that type of fatigue. Significantly reduced physical activity and muscle weakness were also observed in this group of fatigued patients.

THERAPY

Several case reports of sarcoidosis patients treated with antitumor necrosis factor-α demonstrated a dramatic reduction in fatigue. This kind of drug, however, cannot be given to patients who are suffering exclusively from fatigue without any other evidence of disease activity.[46] Several clinical trials reported positive effects of dexmethylphenidate hydrochloride in treating patients with sarcoidosis associated fatigue. Methylphenidate has already been used in the treatment of fatigue in patients with cancer, HIV infection, and CFS. The drug has also been reported to be effective for medically ill patients with depression, which is an essential part of the clinical picture in patients with fatigue.[47] However, up to date, there are no guidelines for effective treatment of fatigue in sarcoidosis.

CONCLUSION

At the end of this chapter, the "fatigue problems" still remain. It is unclear if muscle weakness is the cause or the consequence of fatigue in some patients. What is the first trigger in the magic circle of granulomatous inflammation and fatigue?

The assessment of fatigue is not an easy task. For clinical studies in sarcoidosis patients, as for the daily practice, the use of health status measures and quality of life measures seems to be essential in order to evaluate patients' subjective well-being.

As a constitutional symptom, fatigue is not reflected in lung function test results or other clinical parameters, but working in daily practice with sarcoidosis patients, it is important to take this symptom seriously. One way of assessing fatigue in the clinical practice may be completion of the fatigue assessment scale (FAS) in regular terms (Table 3-2). Although many of fatigue scales have been used, FAS is the only fatigue questionnaire validated in sarcoidosis patients. This measure might provide physicians with complete information about the nature and extent of the patient's fatigue and the influence of fatigue on their general well-being. This can also bring into focus the sensation of fatigue, and even open the discussion between physicians and patients. Regardless of the insufficient therapy for fatigue, the patients at least can feel that their fatigue problems are taken truthfully.

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Table 3-2 The Fatigue Assessment Scale

FAS is a fatigue questionnaire consisting of 10 items: 5 questions reflecting physical fatigue and 5 questions for mental fatigue. The response scale is a 5-point scale (1 never to 5 always). Scores on FAS can range from 10–50, cut-off 22, scores beyond represent fatigue. The following 10 statements refer to how you usually feel. Per statement, you can choose 1 out of 5 answer categories, varying from never to always: 1 = never, 2 = sometimes, 3 = regularly, 4 = often, and 5 = always. Items 4 and 10 require reversed scoring. The scale score is calculated by summing all item scores

Statements	*Never*	*Sometimes*	*Regularly*	*Often*	*Always*
I am bothered by fatigue	1	2	3	4	5
I get tired very quickly	1	2	3	4	5
I don't do much during the day	1	2	3	4	5
I have enough energy for everyday life	1	2	3	4	5
Physically I feel exhausted	1	2	3	4	5
I have problems getting started	1	2	3	4	5
I have problems thinking clearly	1	2	3	4	5
I feel no desire to do anything	1	2	3	4	5
Mentally I feel exhausted	1	2	3	4	5
When I am doing something I can concentrate quite well	1	2	3	4	5

FAS, fatigue assessment scale.
The FAS is also available online in the e-version; fatigue scores (mental, physical, and total fatigue score) can be calculated immediately at www.ildcare.eu/.

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