



Fatigue in sarcoidosis: incompletely understood, inadequately treated

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INTRODUCTION

Fatigue is a common complaint. As an isolated symptom, fatigue seldom is a cause of concern. As Samuel Butler said, 'Life is one long process of getting tired' [1]. However, fatigue in association with a systemic illness can be ominous. Fatigue is a prominent feature of many diseases including anemia, viral infections, hypothyroidism, autoimmune diseases, and malignancy. In 1999, Drent *et al.* [2] studied 38 patients with sarcoidosis. All patients completed quality-of-life (QoL) questionnaires and had resting energy expenditure measured by calorimetry; 25 (66%) patients had fatigue. The authors concluded that fatigue reflected a metabolic derangement that required further studies. Michielsen *et al.* [3] observed that fatigue was the most common symptom of sarcoidosis. Neither chest radiography nor lung function tests reflect the extent or severity of fatigue. The best way of assessing fatigue in clinical practice is by using the Fatigue Assessment Scale (FAS) [4]. Although many fatigue instruments have been used, FAS is the only fatigue questionnaire validated in sarcoidosis patients. Hinz *et al.* [5] applied the FAS and the Multidimensional Fatigue Inventory (MFI) to 1197 German patients with sarcoidosis. The percentages of patients exceeding the fatigue cut-offs were 70 (FAS) and 68% (MFI), respectively. Female patients were more affected by fatigue than male patients and, compared with the general population, young sarcoidosis patients were especially affected by fatigue.

FOUR TYPES OF FATIGUE IN SARCOIDOSIS

- (1) Early morning fatigue: The sufferer wakes up feeling tired and has difficulty in getting out of bed because of joint stiffness or muscle pain. This type of fatigue is also seen in patients with autoimmune diseases.
- (2) 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. The patient wakes up feeling refreshed but after a few hours of activity feels tired and needs to rest.
- (3) Afternoon fatigue: Patient arises in the morning with adequate energy feeling refreshed, performs morning activities normally, but starts feeling tired in the early afternoon. These patients describe their fatigue as 'a flu like syndrome'. By the afternoon fatigue gradually overpowers them and the patients need to rest. They go to bed early and stay in bed till the next morning.
- (4) Chronic fatigue: Fatigue that persists even after the patient has been treated for sarcoidosis falls in this category. These patients have normal chest radiographs and have no clinical signs of active sarcoidosis. Serum markers of sarcoidosis activity are normal. Main symptoms are: diffuse muscle aches, unbearable fatigue, insomnia, and depression. The lack of any objective evidence frustrates the patient and puzzles the physician. About 5% of the patients with clinical and radiological inactive sarcoidosis have chronic fatigue [6,7].

WHAT CAUSES FATIGUE IN SARCOIDOSIS?

Systemic inflammation is a feature of sarcoidosis and many other chronic illnesses. The relation between proinflammatory mediators has not been systematically analyzed. Baydur *et al.* [8] assessed relationship of fatigue in sarcoidosis with plasma cytokine levels (PCLs) at rest and with cardiopulmonary exercise testing in 22 sarcoidosis patients and 22 controls. They found that sarcoidosis patients exhibited greater fatigue, reduced cardiorespiratory function, higher Medical Research Council (MRC)

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scores and higher plasma tumor necrosis factor (TNF)- α concentrations than controls at all times. Plasma interleukin (IL)-1 β levels did not differ between cohorts. Treated sarcoidosis patients exhibited a relationship between physical fatigue, reduced motivation, and total fatigue and preexercise plasma IL-1 β concentrations. Acute exercise did not increase PCLs. Whether the reduced MRC score and physical fatigue in treated patients were related to the therapy or to the underlying inflammatory process was difficult to determine. In many patients after the inflammatory phase of sarcoidosis has subsided, complaints of chronic fatigue may persist. Low-grade residual inflammatory activity may play a role in maintaining chronic fatigue. Korenromp *et al.* [9] compared in-vitro cytokine/chemokine production and plasma cytokine/chemokine levels in chronically fatigued patients and nonfatigued patients who were in clinical remission. They found that the 'Th2 cytokine' component which consisting mainly of IL-4, IL-5, and IL-10 was significantly negatively associated with chronic fatigue. They concluded that in chronic fatigue patients in clinical remission, a cytokine/chemokine profile suggestive of a less competent Th2 could contribute to chronic fatigue. The problem of postsarcoidosis fatigue as a frequent symptom can be compared with chronic fatigue syndrome (CFS) or idiopathic autonomic dysfunction. Psychological distress and reduced health status often accompany the fatigue in sarcoidosis and CFS patients. Significantly reduced physical activity and muscle weakness were also common in these patients [10].

TREATMENT OF FATIGUE

Anti-TNF- α agents can cause a dramatic reduction in fatigue. This kind of drug, however, cannot be given to patients who are suffering exclusively from fatigue without other evidence of disease activity [11]. Several clinical trials reported positive effects of the methylphenidate (MPH) dexmethylphenidate hydrochloride in treating patients with

sarcoidosis-associated fatigue. MPH is used for treating fatigue in patients with cancer, HIV infection, and CFS. The drug is effective for medically ill patients with depression, which is an essential part of the clinical picture in sarcoidosis and CFS patients with fatigue. As yet, there are no evidence-based guidelines for effective treatment of fatigue in sarcoidosis.

CONCLUSION

Fatigue in sarcoidosis remains a mystery. In order to assess severity of fatigue the use of health status measures and QoL measures is essential. More clinical studies are urgently needed to develop appropriate treatment.

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Conflicts of interest

There are no conflicts of interest.

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