

EDITORIAL

Fatigue and sarcoidosis

O.P. Sharma

*In the morning a man walks with his whole body
in the evening only with his legs*

(Emerson).

Fatigue is a common symptom. It is responsible for an estimated 10–15 million clinic or office visits annually in the USA. As an isolated symptom, fatigue is seldom a cause for concern. However, fatigue in association with a systemic illness can be ominous. Although interest in understanding the pathogenesis of fatigue is of relatively recent onset, the symptom has been with us forever. As Samuel Butler so elegantly stated "Life is one long process of getting tired" [1].

Fatigue may be transient or self-limiting and chronic or persistent. Transient fatigue is often associated with viral illness, overwork, stress, sleep deprivation, jet-leg and other temporary infirmities. Persistent or chronic fatigue may signify an associated serious, systemic illness including tuberculosis, cancer, diabetes mellitus, hypothyroidism, adrenal deficiency, anaemia or an autoimmune disorder. Sleep disorders constitute an important cause of fatigue. The occurrence of fatigue in sarcoidosis is well known, but the exact incidence has not been established and varies from 30–70% depending on age, sex, race and organ involvement by the granulomatous process [2, 3]. Four types of fatigue can be recognized in sarcoidosis. 1) Early-morning fatigue, where the patient either is not able to arise or arises with feelings of inadequate sleep. This type of fatigue is also seen in patients with autoimmune diseases and may reflect troublesome muscle or joint pains or sleep disorders including sleep apnoea syndrome [4]. 2) Intermittent fatigue, where the patient wakes up normally but after a few hours of activity, feels tired and exhausted. After a short rest of an hour or so, the patient is able to resume activity, only to be succumbed soon after by another episode of fatigue. The patient learns to pace his or her activities throughout the day with periods of rest alternating with periods of activity. Intermittent fatigue may last for days, weeks or months. 3) Afternoon fatigue, where the patient arises in the morning with adequate energy but "runs out of gas" or "feels washed up" in the early afternoon. These patients compare their fatigue to "having a flu-like syndrome". The feeling of exhaustion and sleepiness when not in bed and cannot get to bed is described by many of these patients as the "meanest feeling". Finally, the patient goes to bed early and stays there

until the next morning. 4) Post-sarcoidosis chronic fatigue syndrome. This occurs in about 5% of patients who seemingly have recovered from active sarcoidosis. The phenomenon has attracted many synonyms, including postviral fatigue syndrome, Royal Free disease, myalgic encephalomyelitis, fibromyalgia, neuromyasthenia, Iceland disease and chronic Epstein–Barr virus (EBV) syndrome. The persistent symptoms are widespread myalgia, incapacitating fatigue and depression. Physical signs are absent. The lack of any objective evidence confuses the patient and the physician alike as to the relationship of the syndrome with sarcoidosis and its existence [5].

For clinical purposes, the duration of fatigue can be divided into <3 months, 3–6 months and >6 months. In the absence of any obvious clinical signs or symptoms not related to sarcoidosis, patients with fatigue for <3 months do not require an extensive evaluation.

However, if fatigue persists beyond 3 months, then a thorough re-evaluation of abdominal, cardiovascular, musculoskeletal, haematological and neurological systems should be performed. Routine laboratory testing including a complete blood count, sedimentation rate, C-reactive protein (CRP), thyroid stimulating hormone (TSH), alkaline phosphatase and urinalysis should be performed. In patients with fatigue lasting for >6 months, anxiety disorders, family dysfunction, stress and depression should be considered.

In this issue of the Journal DRENT *et al.* [6] state that fatigue in sarcoidosis patients is associated with an acute phase response. They studied 38 biopsy-proven sarcoidosis patients. None of the patients had any other medical illness. All patients completed a quality-of-life (QoL) questionnaire and had resting energy expenditure (REE) measured by indirect calorimetry. Twenty-five (66%) patients had fatigue and 13 (34%) had no fatigue. Patients who had fatigue were more dyspnoeic and tired easily on exercise. They had lost weight and complained of muscle pains, eye irritation and loss of sleep. These patients had higher resting energy expenditure (REE). They also had increased serum CRP levels. Patients who had fatigue and those who did not complain of fatigue did not differ with respect to age, chest radiographic changes, serum angiotensin converting enzyme levels, lung function tests or serum calcium levels [6]. Cytokine levels in either the blood or bronchoalveolar lavage fluid were not measured. Some of the patients with fatigue had impaired $P_{L,max}$ levels. Although the reason for this abnormality is not clear it may be related either to poor test performance or to the muscle weakness and depression so frequently seen in such patients [7]. DRENT *et al.* [6] conclude that fatigue in sarcoidosis reflects a metabolic derangement that requires further studies.

Malaise, fever and weight loss occur in a wide variety of infectious and noninfectious granulomatous disorders [8]. LING *et al.* [9] demonstrated that both tumour necrosis factor (TNF) and interleukin (IL)-1 produce weight and net nitrogen loss and skeletal muscle catabolism in animals. TNF- α (Cachectin), produced mainly by macrophages, causes endothelial cell damage, fever and weight loss. 1,25-Di-hydroxy vitamin D and interferon (IFN)- γ enhance the ability of macrophages to release TNF [10]. GARCIA-MARTINEZ *et al.* [11] suggested that, along with TNF, IL-6 may play an important role in the development of cachexia and malaise. TNF- α also mediates insulin resistance in the obese, as increased TNF- α levels are associated with obesity [12]. LLOYD *et al.* [13] suggested that impaired immunoregulation may allow antigen stimulation to be followed by the release of excessive amounts of cytokines, causing fatigue. The question remains: what instigates this reaction? Many years ago MITCHELL and REES [14] and TAUB and SILTZBACH [15] suggested that sarcoidosis was caused by a transmissible agent. HIRSHAUT *et al.* [16] found significantly high serum titres of antibody to herpes-like virus (human immunodeficiency virus (HIV)) or (EBV) in 141 patients with sarcoidosis, the titres being highest in the chronic stage. HIV was then regarded as a passenger virus that possibly multiplied with proliferation of lymphocytes in which they were found. We have observed that sarcoidosis patients with fatigue have extremely high levels of EBV antibodies that decrease when fatigue subsides, either spontaneously or in response to therapy. The significance of this observation is unclear.

Management of the patient with fatigue requires more than prescribing drugs. It is important for the physician to listen to the patient; it is wise to believe what the patient says. I have found prednisone 10 mg *q.d* and hydroxychloroquine 200 mg *b.i.d.* or both very efficient in controlling fatigue. The tricyclic antidepressant agents amitriptyline (Elavil) or doxepin (Sinequan), 5–20 mg at bedtime, are effective. In addition, the patient should be encouraged to avoid physical or emotional stress and to pace their activities. Furthermore, the patients should be instructed to lead as active and involved a life as possible.

Thus, fatigue is an integral part of the clinical picture of sarcoidosis [17]. The mechanism of this debilitating phenomenon is unknown but studies such as that by DRENT *et al.* [6] have opened up the proverbial chink in the armour of fatigue associated with sarcoidosis. Further studies are needed to slay the dragon.

References

1. Butler S. Lord what is Man? Note Books 1912.
2. Gupta SK, Gupta S. Sarcoidosis in India: a review of 125

- bopsy proven cases from eastern India. *Sarcoidosis* 1990; 7: 50–57.
3. Edmondstone W, Wilson A. Sarcoidosis in Caucasians, Blacks and Asians in London. *Br J Dis Chest* 1985; 79: 27–36.
4. Turner G, Lower E, Corser B, Grunther K, Baughman R. Sleep apnea in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1997; 14: 61–64.
5. James DG. Complications of sarcoidosis. *Sarcoidosis* 1993; 10: 1–3.
6. Drent M, Wirnsberger R, de Vries J, van Diejen-Visser MD, Wouters EFM, Schols AMWJ. Association of fatigue with an acute phase response in sarcoidosis. *Eur Respir J* 1999; 13: 718–722.
7. Alsalek M, Farr S, Chang J, Sharma O. Respiratory muscle function impairment in sarcoidosis: clinical, physiological and radiological correlation. *Am J Respir Crit Care Med* 1998; 153: A813.
8. Friedland J, Weatherall D, Ledingham J. A chronic granulomatous syndrome of unknown origin. *Medicine (Baltimore)* 1990; 69: 325–333.
9. Ling P, Schwartz J, Bistran B. Mechanisms of host wasting induced by administration of cytokines in rats. *Am J Physiol* 1997; 272: E333–E339.
10. Foley N, Millar A, Maeger A, Johnson N, Rook G. Tumour necrosis factor production by alveolar macrophages in pulmonary sarcoidosis and tuberculosis. *Sarcoidosis* 1992; 9: 29–34.
11. Garcia-Martinez C, Costelli P, Lopez-Soriano FJ, Alijada A. Is TNF really involved in cachexia? *Cancer Invest* 1997; 15: 47–54.
12. Dandona P, Weinstock R, Thusu K, Abdel-Rahman E, Alijada A, Wadden T. Tumour necrosis factor-alpha in sera of obese patients: fall with weight loss. *J Clin Endocr Metab* 1998; 83: 2907–2910.
13. Lloyd A, Hekie I, Wakefield D, Boughton C, Dwyer J. A double-blind placebo controlled trial of intravenous immunoglobulin therapy in patients with chronic fatigue syndrome. *Am J Med* 1990; 89: 561–568.
14. Mitchell D, Rees R. A transmissible agent from sarcoid tissue. *Lancet* 1969; ii: 81–84.
15. Taub R, Siltzbach L. Induction of granulomas in mice by injection of human sarcoid and ileitis homogenates. In: Iwai K, Hosoda Y, eds. Proceedings of the IV International Conference on Sarcoidosis. Tokyo, Tokyo University, 1974; p. 20.
16. Hirshaut V, Glade P, Vierra L, Seltbach L. Sarcoidosis: another disease associated with serologic evidence of herpes like virus infection. *N Engl J Med* 1970; 283: 502.
17. Drent M, Wirnsberger R, Bretler M, Kock L, Wouters E. Quality of life and depressive symptoms in patients suffering from sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1998; 15: 59–66.