

# Fatigue in Sarcoidosis: Detection and Treatment

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## SUMMARY

Fatigue is a prominent symptom in a large number of medical conditions, malignant and infectious diseases. Fatigue is also a prominent symptom of sarcoidosis. The occurrence of fatigue in sarcoidosis is well known but exact incidence has not been established and varies from 30-70% of patients depending on age, sex and organ involvement by the granulomatous process. The exact definition of fatigue varies broadly. It can be both physical and mental. The patients describe their sensation of fatigue qualitatively different from that fatigue they experienced before they became sick. Fatigue has a major impact on the quality of life in sarcoidosis. Establishing the extent of fatigue in sarcoidosis provides relevant insight regarding the patient's quality of life. Unfortunately there is no objective parameter for assessing fatigue in sarcoidosis. Generally, fatigue is detected by means of questionnaires. Regarding the therapy, there is no effective treatment for fatigue in sarcoidosis.

**Keywords:** sarcoidosis; fatigue; detection

## INTRODUCTION

Ever since the crucial description by Jonathan Hutchinson in 1877 and Caesar Boeck in 1899, sarcoidosis has fascinated the medical fraternity with its protean manifestations and unknown aetiology. The „Statement on Sarcoidosis”, issued jointly by the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG), has a descriptive definition that spans four paragraphs. A definition as lengthy as this reflects the stark reality that till today the cause of this disease still eludes us [1, 2].

Sarcoidosis is the disease that causes immense curiosity and anxiety, both among sufferers and their care providers. In more than 90% of patients, lungs are involved, therefore chest physicians are those who see the patients first and guide them through diagnostic procedures [3]. However, sarcoidosis is a complex multiorgan disease with multiple non-specific symptoms. Sometimes these symptoms go beyond the usual experience of chest physicians. Fatigue is an integral part of the clinical picture of sarcoidosis [4].

published, but no one cited a proper definition [5-8]. „Fatigue is a common symptom and the symptom that has been with us forever...”, as started by Dr. Om Sharma [9] his editorial article on fatigue in sarcoidosis written for the European Respiratory Journal in 1999. As Samuel Butler stated years ago, life is a long process of getting tired [9].

What is the definition of fatigue? There are many synonyms in a dictionary like: exhaustion, tiredness, weariness, low energy, weakness. But not a single one satisfies the proper meaning of fatigue in the terms of this topic. Fatigue (also called exhaustion, languidness, languor, lassitude, or listlessness) is a weariness caused by exertion. It describes a range of afflictions, varying from a general state of lethargy to a specific work-induced burning sensation of muscles. It can be both physical and mental. Physical fatigue is inability to continue functioning at the level of normal abilities. Mental fatigue, on the other hand, rather manifests in somnolence [10]. Fatigue may also be defined as a reduction in the maximal force-generating capacity of a muscle [11, 12].

The word *fatigue* originates from the experience in healthy individuals, but interview based studies have revealed that even though patients label their sensation as fatigue, they often find it qualitatively very different from the fatigue they experienced before they became sick [13]. These findings indicate that the story of fatigue needs a continual multidimensional approach with the analyses involving its physical, cognitive, emotional and functional parts [6].

## DEFINITION OF FATIGUE

It is quite difficult to find a proper definition on fatigue in general, or fatigue in sarcoidosis. In the last five years approximately 30 articles dealing with fatigue in sarcoidosis patients were

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Before proceeding with the topic, it is very important to emphasize the difference of the two terms and two different, although equally bothersome, unpleasant conditions: chronic fatigue syndrome (CFS) and chronic fatigue. Fatigue is a common symptom in many illnesses, but CFS is a multi-systemic disease and is relatively rare by comparison. CFS is one of several names given to a poorly understood, variably debilitating disorder of uncertain cause/causes. Most diagnostic criteria require that symptoms must be present for at least six months and all state the symptoms must not be caused by other medical conditions. It is extremely important to distinguish the two topics [14, 15].

## FATIGUE IN SARCOIDOSIS

Fatigue is a common symptom in a large number of medical conditions such as rheumatoid arthritis, malignant diseases and infectious diseases. However, several studies in the past decades have shown that fatigue is a prominent symptom of sarcoidosis [16-20]. The occurrence of fatigue in sarcoidosis is well known, but exact incidence has not been established and varies from 30-70% of patients depending on age, sex, race and organ involvement by the granulomatous process [21, 22].

There are many different approaches to the cause of fatigue in sarcoidosis. In Table 1 the most important factors related to fatigue in sarcoidosis are presented [8, 23-27].

There are four types of fatigue that can be recognized in sarcoidosis (Table 2) [9, 28]. For clinical purposes the duration of fatigue can be divided into less than 3 months, 3-6 months and longer than 6 months. In patients with fatigue persisting for more than 3 months the evaluation of other organs and systems should be performed. In patients with fatigue lasting beyond 6 months anxiety disorders, stress and depression should be considered [9].

Sarcoidosis predominantly affects the patients of young age, thus it may be more difficult to cope with this symptomatic multi-organ disease of unknown origin and unpredictable course than at older age. A chronic disease like sarcoidosis at young age may result in social problems, especially when the patient looks healthy, but suffers from serious loss of working capacity. Unfortunately, there is no objective method for establishing the degree of disabling fatigue and the long lasting loss of working ability.

## DETECTION OF SARCOIDOSIS ASSOCIATED FATIGUE

### How to detect fatigue in sarcoidosis?

There is no objective parameter either for asserting fatigue in general or in sarcoidosis. Generally, fatigue is detected by means of questionnaires.

The authors of a bibliographic study of fatigue measurements scales found in the last thirty years (1975-2004) searching Medline and Psych/INFO a total number of 2285 papers reporting the measures of fatigue in somatic and

**Table 1.** Possible causes of fatigue in sarcoidosis [7, 23-27]

Basic causes	General inflammation and metabolic dysfunction
	Myopathy (caused either by granulomatous inflammation or therapy, for example steroid myopathy)
	Sleeping disorders (obstructive sleep apnea syndrome, restless legs syndrome)
	Pain (specific types of pain: chest pain, arthralgia, headache, etc.)
	Lack of exercise can be a cause of fatigue in sarcoidosis
Causes related to psychological factors	Psychological factors (considerable number of sarcoidosis patients are diagnosed with depression the major symptom of which is fatigue)
	Perceived stress related to fatigue
	Development of fatigue and depressive symptoms may be attributed CNS involvement
	Small fibre neuropathy (SFN) is common among sarcoidosis patients. Sarcoidosis patients with SFN are reported with higher fatigue scores (FAS) than those without SFN.

**Table 2.** Clinical manifestations of sarcoidosis associated fatigue [9, 28]

Early morning fatigue	Patients wake-up unrested because of joint stiffness or muscle pain. This type of fatigue is also seen in patients with autoimmune diseases.
Intermittent fatigue	Patients wake-up feeling normal but after few hours of activity feel tired and exhausted. Throughout the day they need periods of rest.
Afternoon fatigue	Patient wake-up in the morning feeling energetic but become tired in the early afternoon. These patients evaluate their fatigue as a „flue-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 history of sarcoidosis, (normal chest radiograph and markers of disease activity). Main symptoms: widespread myalgia, unbearable fatigue and depression. Physical signs during examination are absent. Lack of any objective evidence confuses both the patients and physicians.

psychiatric diseases that were published between 1975 and 2004. An exponential increase in the number of fatigue studies was observed, and it was noticed that 80% of the studies were published during the last 10 years of that period. They defined no less than 252 different methods to assess fatigue, of which 150 were used only once. In 670 fatigue studies, fatigue was measured by one of 157 multi-symptom scales as one of several domains, like the generic questionnaire Short Form 36-item Health Survey (SF-36) or Cancer Specific EORTC QLQ-C30 [29, 30]. The majority of fatigue studies used fatigue scales with a multidimensional approach typically divided into a cognitive and mental part, where the latter could be divided into the cognitive and emotional part [5]. According to Dittner et al. [6], different manifestations and a wide range of mechanisms possibly causing fatigue makes it unlikely that any fatigue scale will ever be appropriate for measuring fatigue in all disease groups. Nevertheless, since fatigue is an unspecific symptom there is no need for developing disease specific fatigue scales for each individual disease [5].

Fatigue has a major impact on the quality of life (QOL) in sarcoidosis. Establishing the extent of fatigue will provide important insight regarding patients' QOL.

**Table 3.** The variety of quality of life (QOL) and health status (HS) questionnaires used in patients with different interstitial lung diseases and sarcoidosis [31]

CRQ*	Chronic Respiratory Questionnaire (HS questionnaire)
SF-36*	Short Form 36- item Health Survey (HS questionnaire)
SGRQ	St George's Respiratory Questionnaire (HS questionnaire)
SHQ	Sarcoidosis Health Questionnaire (HS questionnaire and the only disease specific questionnaire for patients with sarcoidosis)
SIP*	Sickness Impact Profile (HS questionnaire)
WHOQOL-100	100-item World Health Organization Quality of Life Instrument (QOL questionnaire)

\* validated in interstitial lung disease patients including patients with sarcoidosis [9]

It is however, important to emphasize two different but equally important items: QOL and health status (HS). QOL is defined as the individual's overall satisfaction with life and functional status. However, HS refers to the impact of disease on patients' physical, psychological and social functioning. QOL refers to patients' perception or evaluation of their functioning. Both QOL and HS refer to as a health-related quality of life (HRQOL) is increasingly recognized as important measures of disease impact and therapeutic outcome [31]. Both concepts consist of physical, psychological and social domain.

Using the right type of questionnaire for achieving the desired aim is of the highest importance, since QOL and HS measures may even yield opposing results. The choice of QOL or HS measure depends on the aim. In general, if information is required about what patients can or cannot do (physical functioning sphere) the HS measure should be used. However if the interest is in how patients' experience regarding different aspects of their lives, the QOL measure is indicated [31]. The variety of QOL and HS questionnaires has been used in patients with different interstitial lung diseases and sarcoidosis (Table 3) [31].

### Quality of life and health status questionnaires used in measuring fatigue associated with sarcoidosis

#### World Health Organization Quality of Life assessment instrument (WHOQOL-100)

Until now the WHOQOL-100 questionnaire is the only QOL general instrument that has been used in sarcoidosis. The WHOQOL-100 is a cross culturally developed generic multidimensional QOL measure that has been simultaneously developed in 15 centres worldwide (France, Russia, USA, Japan, and Thailand) [32]. The WHOQOL-group has defined QOL as an individual perception of his/her position in life in the context of culture and value systems in which he/she lives and in relation to their goals, expectations, standards and concerns.

The WHOQOL-100 consists of 100 items assessing 24 facets of QOL within six domains: physical health, psycho-

logical health, level of independence, social relationships, environment and spirituality, religion, personal beliefs and a general evaluative facet – overall QOL and general health. Each facet is represented by four items. The response scale is a five-point Likert scale, ranging from 1 (never) to 5 (always), with higher scores showing a better QOL for the facet or domain [31, 32].

#### Fatigue Assessment Scale (FAS)

The FAS is a fatigue questionnaire consisting of 10 items; five questions reflecting physical fatigue and five questions for mental fatigue. The response scale is a 5-point scale ranging from 1 (never) to 5 (always). Scores on the FAS can range from 10-50; cut off 22 [33].

#### Daily Activity List (DAL)

The degree of limitation in activities of daily living was evaluated with the List of Daily Activities (DAL), a scale that was originally designed by Stewart et al. The scale has been used in several studies in patients with chronic pulmonary diseases and sarcoidosis [34, 35].

The DAL contains 11 items that are related to the usual activities which persons in good health can perform without particular effort. The number of positive responses comprises the DAL score and indicates the degree of impairment.

#### Mental-psychological functioning and fatigue

The association between psychological factors and disease gained its scientific support in the beginning of the 20<sup>th</sup> century, and was initiated by researches working in a wide variety of fields. Early research suggesting that physical illness has a psychosomatic component was strongly dominated by psychoanalytical theory, an extension of the Freudian idea that symptoms are a symbolic expression of unconscious conflicts and repressed desires.

The relationship between fatigue and emotional stability is another important issue for the clarification of the concept of fatigue in sarcoidosis [34]. Although Klonoff and Kleinhenz [20] suggested that sarcoidosis patients as a group did not meet criteria for clinical depression, awareness of bodily sensations, however, was found to be associated with more depressive symptoms and escaping activities when alone [37-39]. Quite a few psychological functioning scales have been used in the assessment of emotional and mental functioning in interstitial lung diseases including sarcoidosis [39-43]. Magnusson et al. [44] found that emotional stability was the main predictors of fatigue. According to these authors, neurotic individuals may be more fatigue prone, given their general tendency to stress symptoms [44].

### How to Detect Depression Associated with Fatigue?

Quite a few scales measuring depression have been used in patients with different pulmonary diseases but mostly chronic obstructive pulmonary disease (COPD).

#### *Centre for Epidemiologic Studies Depression Scale (CES-D)*

The scale originated from the Centre for Epidemiologic Studies in Oxford, and has been successfully used in investigations on the QOL in patients with interstitial lung diseases, among them a group of sarcoidosis patients as well [41]. The full CES-D is a 20-item self-report scale designed to measure the presence and the degree of depression symptomatology in a broad-based survey research populations. The rating scale ranges from 1 (seldom or never) to 4 (almost always). A score of 16 or higher indicates depression.

### DYSPNEA AS THE POSSIBLE CAUSE OF FATIGUE IN SARCOIDOSIS

The most common symptom of patients with cardio-respiratory diseases is dyspnea. Dyspnea has been defined as a term used to characterize a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interactions among multiple physiological, psychological, social and environmental factors, and may induce secondary physiological and behavioural responses. Nevertheless, there is no clear relationship between the qualitative descriptors of dyspnea and the quantitative intensity among the patient groups; different diseases may be distinguished by quality, but not intensity of the sensation. However, dyspnea is a common symptom in patients with sarcoidosis [45, 46].

In our own experience dyspnea, as a symptom possibly related to HRQOL and fatigue, was determined by the Baseline Dyspnea Index (BDI) and the Modified Medical Research Council (MRC) [34].

The BDI divides dyspnea into three components: the degree of the functional impairment, the level of the activity, and the level of effort required to develop dyspnea. Each component is graded on a five-point rating scale from 0 (extreme impairment) to 4 (without impairment); therefore the total BDI score can range from 0 to 12 [34].

The MRC classifies subjects into one of five categories according to their degree of dyspnea when performing certain activities. Scores range from 0 to 4; higher scores indicate more severe dyspnea [34].

### PATIENT HEALTH STATUS AND FATIGUE

Two standardized questionnaires have been used among Serbian population of sarcoidosis patients to measure

health status: a generic measure, the fifteen-dimensional (15D) measure instrument of HRQOL and a respiratory-specific measure, the St George's Respiratory Questionnaire (SGRQ) [34].

The fifteen-dimensional (15D) is a multi-attributive instrument for the measurement of HRQOL [34]. It was originally developed and validated on a large Finnish population. The 15D was used in different diseases in many different countries. The Serbian version of 15D was previously used in patients with asthma where it demonstrated good psychometric measurement properties [34]. The 15D includes 15 different and mutually exclusive health dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality, and sexual activity, each represented by one item. The total questionnaire score ranges between 0 and 1, where 1 signifies the highest level of health status.

The Saint George's Respiratory Questionnaire (SGRQ) is an instrument that was originally designed to measure the health status of COPD patients. Its validity, reliability, and responsiveness were also shown in other pulmonary diseases. The questionnaire consists of 50 items with 76 responses, and encompasses three domains of health status: [1] symptoms, focusing on distress because of respiratory symptoms, [2] activities, measuring decreased mobility or physical activity and [3] impacts, measuring the psychosocial influence of disease on the everyday life and patients' well being. The scores of these domains, as well as the total score, are scaled from 0 to 100, where higher scores represent a poorer quality of life [47].

In a study of Gvozdenovic et al. [34], the severity of fatigue was measured using the health status measurement in two groups of sarcoidosis patients, with and without extra pulmonary disease. The results showed that those with pulmonary plus extra pulmonary sarcoidosis had statistically and clinically worse health status in terms of SGRQ scores than those with isolated pulmonary sarcoidosis. This is an interesting finding since the SGRQ is a respiratory-specific questionnaire. A possible explanation for this is that several items of the questionnaire relate to physical activities and the impact of disease on the patients' level of functioning, as well as fatigue. It is possible that extrapulmonary manifestations of sarcoidosis had a negative impact on these items. The same was confirmed in studies of Cox et al. [8].

In the same study, the 15D, a generic measure of health status did not show a statistically significant difference between the isolated pulmonary and pulmonary plus extrapulmonary groups, although the mean score reflected a poorer health status in the latter group. In the same study, Gvozdenovic et al. [34] showed that the dyspnea level was worse in patients with pulmonary and extra pulmonary sarcoidosis. This was demonstrated using the BDI measure but not the MRC.

The MRC addresses only the level of activities that leads to dyspnea without consideration of the associated effort necessary for the performance of particular activity, which is essential for patients with fatigue [34]. However, the BDI

assesses the degree of the functional impairment, which represents an important outcome of dyspnea. Since the patient's perception of dyspnea depends on the physical activities and the required effort, patients with extra pulmonary involvement may feel breathlessness because of their functional limitations.

Although our patients feeling fatigued had significant dyspnea, they perceived limitations in their physical activities, and had a poor health status, but with normal pulmonary function. This confirms reports by previous studies demonstrating that pulmonary function testing cannot function as a substitute for all these other parameters and cannot be used to assess the overall health of sarcoidosis patients [34].

### THERAPY OF SARCOIDOSIS ASSOCIATED FATIGUE

There are studies suggesting that patients using prednisone exhibited higher fatigue scores than patients who did not use prednisolone [33]. Several case reports of sarcoidosis patients treated with antitumour necrosis factor TNF- $\alpha$  showed a dramatic reduction in fatigue. This kind of drug however, cannot be administered to patients suffering exclusively from fatigue without other evidence of disease activity [31, 33].

There is no effective treatment for fatigue in sarcoidosis. There have been several clinical trials of d MPH dexamethylphenidate hydrochloride in treating patients with sarcoidosis associated fatigue [48]. Methylphenidate has been already used in the treatment of fatigue in patients with cancer, HIV infection and CFS. The drug has also

been reported to be effective for patients with confirmed depression, which is an essential part of clinical features in patients with fatigue [48].

### CONCLUSION

Even though fatigue is a well-known symptom of sarcoidosis, the problem of fatigue in this multisystem disease has not been taken seriously enough in clinical practice. Objective test results (chest X-ray, laboratory findings and inflammatory parameters) are not always in correlation with the objective well-being from the patient's perspective. There is no sufficient therapy available up-to-now. It is very important to instruct clinicians and other physicians involved in the follow-up of patients with sarcoidosis that the lack of objective parameters is not always a guarantee of the person's healthy condition.

### NOTE

The first author presented this literature review at the American Colleague of Chest Physicians (CHEST) conference in Philadelphia, USA, on October 29, 2008.

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## Замор у саркоидози: откривање и лечење

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### КРАТАК САДРЖАЈ

Замор је значајан симптом који прати велики број медицинских стања и малигних и инфективних обољења. Он је такође истакнути симптом саркоидозе. Иако је појава замора у саркоидози веома добро позната, његова учесталост у овој болести још није тачно утврђена. Претпоставља се да је између 30% и 70%, у зависности од старости болесника, пола и захваћености појединих органа процесом грануломатозе. Тачна дефиниција замора такође се веома разликује. Постоје физичка и ментална компонента замора. Болесници описују свој осећај замора квалитативно различито

у односу на замор који су имали пре него што су постали болесни. Замор има велики утицај на квалитет живота особа оболелих од саркоидозе. Одређивање степена изражености замора у саркоидози пружа значајан увид у процену погоршања квалитета живота болесника. Нажалост, не постоји објективан параметар за процену замора у саркоидози. Обично се степен тежине замора одређује здравственим упитницима. Засад не постоји ефикасно лечење особа са саркоидозом од замора.

**Кључне речи:** саркоидоза; замор; откривање