Chapter 1

General introduction

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Sarcoidosis

Sarcoidosis is a multisystemic disease of unknown cause characterized by cellular immunity activity with formation of noncaseating granuloma in various organ systems.[1,2] Although sarcoidosis can affect people of all ages, it commonly starts in young and middle-aged adults. The peak incidence occurs between twenty and forty years of age in both sexes. The disease appears to be more common in women than in men.[3,4] Sarcoidosis is prevalent throughout the world, but the incidence and phenotype differs according to specific regions and race. Löfgren's syndrome is the most frequent type of presentation in the Scandinavian countries and is defined by the presence of acute onset symptoms with fever, arthralgias, erythema nodosum, and bilateral hilar lymphadenopathy. In Japan, cardiac involvement and uveitis are more common.[5]

Clinical presentation

The clinical presentation is highly variable and unpredictable. The disease primarily affects the lungs (90%)[5] and the lymphatic system, but it may also affect the skin, eye, heart, liver, nervous and musculoskeletal system. Virtually every organ system can be involved.[2] Patients may suffer from a wide spectrum of organ specific symptoms, in relation to the organ system involved. In addition to symptoms related to the specific organ involvement (dyspnea on exertion, breathlessness and cough accompanying lung involvement e.g.) patients often have non-specific complaints such as exercise intolerance[6], arthralgia, depressive symptoms, cognitive failure[7], muscle weakness and fatigue.[6,8]

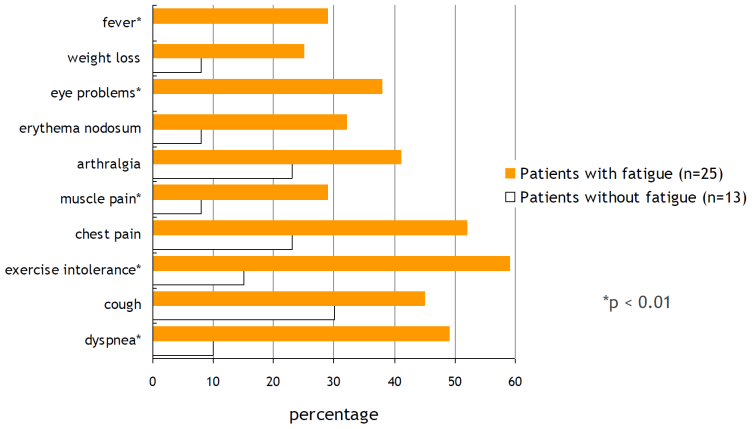

Figure 1.1 Most relevant reported symptoms in sarcoidosis. Group I (n=13): patients without fatigue, and group II (n=25): patients suffering from fatigue. *: p<0.05 group I versus group II.

The impact of the symptoms on patients' lives depends on the specific organ involvement, disease activity, duration and severity of the illness.[9] The most common symptoms include fatigue, respiratory symptoms like coughing or dyspnea, and symptoms related to extrapulmonary involvement.[5]

Since any organ may be affected, a multidisciplinary approach is needed in the majority of the patients.[10]

Pulmonary involvement

Involvement of the pulmonary parenchyma and mediastinal lymphadenopathy is present in approximately 90% of the sarcoidosis patients; hence the pulmonologist is often the prominent physician in the management of the disease. Deterioration of lung function is regarded as an indicator of disease activity in sarcoidosis.[11] A wide spectrum of lung function abnormalities can be present, including an obstructive pattern, restriction, a mixed obstructive and restrictive ventilatory effect, and a decreased diffusion capacity of the lungs for carbon monoxide (DLCO).[12] Abnormal lung function tests, especially forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and DLCO are traditionally used as an indication for treatment.[11] Baseline lung function tests are not related to the probability of disease progression and cannot distinguish between reversible granulomatous lesions and irreversible fibrotic changes.[11] In 80% of sarcoidosis patients presenting with abnormal spirometric findings, values return normal within two years.[13] No obvious correlation between lung function test results and chest X-ray (CXR) findings exists, although prominent lung restriction occurs especially in patients with CXR stages III-IV (this staging system is described below).[11,12] Due to the wide-ranging variety of possible lung function abnormalities in sarcoidosis, depicting a single lung function test as primary measure of change is difficult.

Chest X-ray stages

Between 85 and 95% of sarcoidosis patients have abnormalities on chest radiographs. According to the Scadding radiographic staging system, five stages of radiographic abnormality can be recognized: stage 0 (normal CXR), stage I (bilateral hilar lymphadenopathy (BHL)), stage II (BHL and parenchymal abnormalities), stage III (parenchymal abnormalities without BHL) and stage IV (advanced lung fibrosis with evidence of honeycombing, hilar retraction, bullae, cysts and/or emphysema) (Figure 1.2).[2,14,15] Patients initially present with CXR stage 0 in 5-15%, stage I in 45-65%, stage II in 30-40%, stage III in 10-15% and stage IV in 15-25%, respectively. As mentioned before, there is no strong relationship between CXR stages and lung function test results. However, in general, patients with a lower radiographic stage are more likely to experience resolution of symptoms and CXR abnormalities.[12]

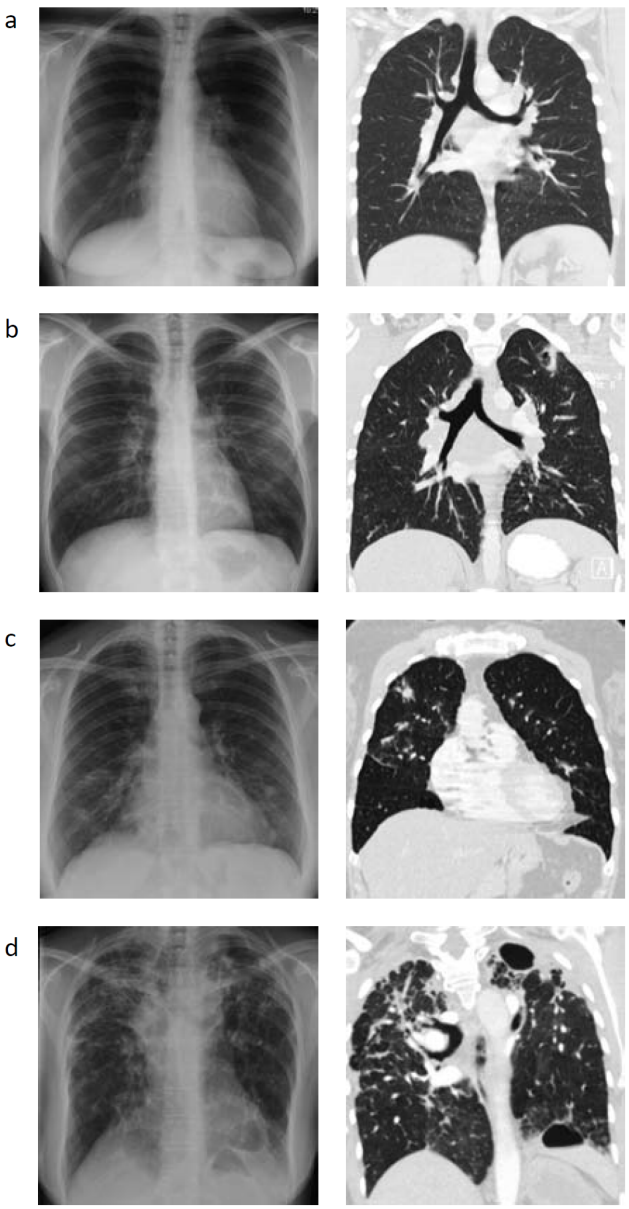

Figure 1.2 Chest radiographic staging system in sarcoidosis. a. Stage I : CXR (left) and coronal high-resolution computed tomography scan (HRCT; right) showing bilateral hilar lymphadenopathy, without parenchymal abnormalities. b. Stage II: CXR (left) and coronal HRCT image (right) showing both lymphadenopathy and parenchymal abnormalities (nodular and reticulonodular opacities). c. Stage III: CXR (left) and coronal HRCT image (right) showing parenchymal abnormalities without hilar lymphadenopathy. d. Stage IV: CXR (left) and coronal HRCT image (right) showing signs of lung fibrosis with hilar retraction and architectural distortion of the pulmonary parenchyma.

Fatigue

Despite the fact that fatigue is a common problem and a clear hallmark in sarcoidosis patients that affects quality of life (QOL), it still remains underestimated and poorly understood.[16] The reported prevalence varies from 60 to 90% of sarcoidosis patients, and up to 25% of the fatigued patients report extreme fatigue.[8,17,18] Sarcoidosis patients may suffer from substantial fatigue even in the absence of other symptoms or disease-related abnormalities. For example, fatigue and general weakness may persist even after routine clinical test results have returned to normal.[8] De Vries et al. found no relationship between fatigue in sarcoidosis patients and a number of clinical variables, including lung function, metabolic variables, laboratory parameters of inflammation and T-cell activation and granuloma formation.[19] A recent study showed that, although exercise intolerance and muscle weakness are frequent problems in sarcoidosis, fatigue was not predicted by the presence of these and other clinical characteristics.[20] In a study by Fleischer et al. extrapulmonary involvement in addition to pulmonary manifestation correlates with a higher fatigue level.[18] The fatigue assessment scale (FAS) has been shown to be an easy, reliable and valid scale for assessing fatigue in sarcoidosis patients.[21] When evaluating sarcoidosis patients suffering from fatigue, it is important to exclude disorders that may interact with fatigue in sarcoidosis, i.e. obstructive sleep apnea syndrome, hypothyroidism and depression.[19,22]

Multifactorial etiology of fatigue

Fatigue is the most frequently described and devastating symptom in sarcoidosis. The etiology of fatigue remains elusive and is usually multifactorial. Disease treatment (corticosteroid therapy), the disease itself (granuloma formation and cytokine release), comorbidities (depression, anxiety, hypothyroidism e.g.) may all contribute to fatigue.[8,18,19,23] The diagnosis of sarcoidosis-associated fatigue requires an extensive evaluation to identify and treat potentially reversible causes. Besides pharmacological treatment, non-pharmacological interventions should also be considered.[8]

Muscle involvement

As mentioned before sarcoidosis may affect any organ system, this also includes the skeletal muscles. In a retrospective study, Cremers et al. found muscle involvement in only 12% of the PET (positron emission tomography) positive cases (n=118).[24] This number is probably underestimated, as it only gives information about PET-positive cases. Asymptomatic myopathy is present in 50-80% of patients with sarcoidosis, whereas clinical symptoms are present in less than 5%.[25]

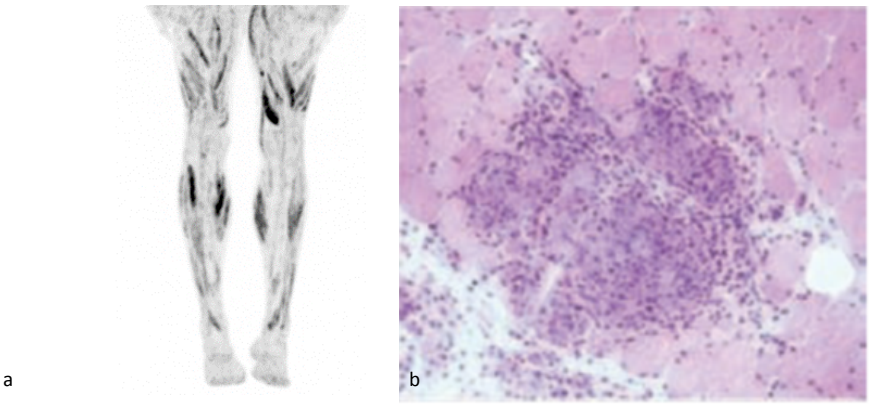

Figure 1.3 a. Fluorine-18 fluorodexyglocose position emission tomography (18F-FDG PET) metabolic activity in the muscles of the lower limbs of a patient with sarcoidosis. b. Biopsy from the left quadriceps muscle of the patient with sarcoidosis showing noncaseating granuloma (with courtesy of Dr. Ruth Keijsers).

Muscle function testing appeared to have additional value in the management of other chronic diseases.[26] Several tests and instruments can be applied to assess skeletal muscle functions. Some examples evaluating skeletal muscle functions are the Jamar (hand grip strength), hand-held dynamometer, and Biodex System.

Exercise capacity

A substantial number of patients with symptomatic sarcoidosis display exercise intolerance (45%), as well as muscle weakness (prevalence rates of 12–27%). Patients with impaired peripheral muscle strength are more fatigued and demonstrate impaired lung function test results, six-min walk distance (6MWD), and QOL compared with patients without reduced peripheral muscle strength.[20] Another cause of exercise intolerance can be the presence of pulmonary hypertension, which occurs in 6-23% of patients at rest and in more than 40% of patients during exercise.[27] Pulmonary hypertension complicates pulmonary sarcoidosis more frequently in advanced parenchymal disease and significantly worsens prognosis.[28]

In clinical practice, several tests are used to evaluate the concept exercise capacity. Exercise tests can be subdivided in maximal exercise tests and submaximal exercise tests. The ‘gold standard’ in determining exercise capacity is the cardiopulmonary exercise test (CPET, measuring maximal oxygen uptake).[29] The most used submaximal exercise test used in pulmonary diseases is the six-minute walking test (6MWT), assessing the submaximal level of functional capacity.[30] Despite the fact that maximal and submaximal exercise tests are very different in nature and assess different aspect of the general construct exercise capacity, exercise responses show similarities in patients with interstitial lung disease (ILD).[31]

Fatigue, muscle strength and physical activity

The relationship between decreased muscle strength, exercise limitation and fatigue is not studied extensively. Fatigue may be explained by skeletal muscle weakness and exercise intolerance, and both may be caused by multiple factors, such as sarcoidosis located in the skeletal muscle, negative vicious circle of physical deconditioning, decreased pulmonary function and corticosteroid-induced myopathy.[20,32] Several studies found decreased muscle strength in sarcoidosis patients[20,32-34], with prevalence rate between 12-27%.[20]

Marcellis et al. and Spruit et al. found a correlation between skeletal muscle strength and exercise capacity and fatigue.[20,32] However, muscle strength only appears to account for a small proportion of the variance regarding fatigue in sarcoidosis patients.[20] Exercise intolerance and muscle weakness are present in both fatigued and non-fatigued patients.[20,22] However, patients with impaired skeletal muscle strength were more fatigued and demonstrated impaired pulmonary function test results, exercise capacity and quality of life compared to patients without reduced muscle strength.[20,32]

Skeletal muscle weakness may also be related with physical inactivity. Physical inactivity may result in decreased muscle wasting ('use it or lose it'). Inversely, muscle weakness due to general inflammation[35-37], sarcoid muscle involvement[38] or corticosteroid-induced myopathy[32,39] may lead to lower activity levels and further deconditioning.

Treatment

Most patients require no treatment, but several pharmacologic options exist for those patients with an indication for therapy.[1] Nevertheless, none of these drugs are curative. Non-steroidal anti-inflammatory drugs (NSAIDs) can be efficient for symptom relief in patients with arthralgia/arthritis.[40] Topical treatment can be very effective in cutaneous involvement. Decisions on whether to start systemic immunosuppressive treatment or not are based on clinical features, like organ dysfunction or, in selected cases, symptoms that affect quality of life, i.e. severe cutaneous involvement that does not respond to topical treatment. Although not so strict anymore the drug of first choice is still prednisone, limited evidence is available for the use of other immunosuppressive drugs like methotrexate, azathioprine, leflunomide or hydroxychloroquine and, more recently, TNF-α inhibitors.[41-43]

Non-pharmacological treatment fatigue and exercise limitations

Emerging evidence suggests that muscle impairment of respiratory and skeletal muscles is associated with functional limitations and fatigue in sarcoidosis.[20,32,44] Patients suffering from fatigue may reduce their physical activities, causing more perceived physical impairments. This mechanism is also called the negative vicious circle of physical deconditioning. Therefore, this deconditioning may explain fatigue

partially.[32] Rehabilitation or physical training has many benefits for patients chronic respiratory disease, including improving exercise capacity, maintaining levels of activity, psychological well-being and social participation.[45-47] Rehabilitation or physical training may also have comparable benefits in sarcoidosis patients. Only few studies have shown that physical training in sarcoidosis improves exercise capacity, muscle strength, functional status, quality of life and reduces sarcoidosis-associated fatigue.[44,48,49] Nevertheless, it is likely that improvement of physical functioning might have a positive effect on patients QOL.

Scopes and aims of the study

The aims of the studies presented in this thesis were to outline the consequences of the symptoms of sarcoidosis on the patients' lives. Furthermore, the possible relationship between fatigue, the most frequently described and most devastating symptom in sarcoidosis, and exercise capacity, muscle function and clinical parameters were assessed. Additionally, the benefits of physical training on exercise capacity, muscle function and fatigue were studied. Finally, recommendations regarding the use of physical training were established based on a literature search and expert opinion.

Chapter 2 provides an overview of the current literature regarding the wide ranging consequences of sarcoidosis. The most frequent described symptoms and their impact on patients daily life are outlined. Treatment options, both pharmacologic and non-pharmacologic treatment options are discussed.

Chapter 3 describes the validation process in a Dutch sarcoidosis population of the King's Sarcoidosis Questionnaire (KSQ). The KSQ is a brief questionnaire assessing health status using five modules (general health status, Lung, Medication, Skin and Eyes) in patients with sarcoidosis. Construct validity, internal consistency and repeatability were also determined.

Chapter 4 describes the relationship between fatigue, and both exercise capacity and clinical characteristics in the cohort of patients evaluated between November 2012 and September 2014 at the Department of Physical Therapy of Gelderse Vallei Hospital, Ede, NL. Used exercise tests were the Steep Ramp Test (SRT: maximal effort) and the 6 minute walk test (6MWT: submaximal exercise test).

Chapter 5 presents the results of a pilot-study in patients with idiopathic pulmonary fibrosis (IPF) and end-stage sarcoidosis with pulmonary fibrosis following a 12-week physical training program (including skeletal muscle and aerobic endurance training). The impact on exercise capacity, muscle strength and fatigue is determined.

Chapter 6 shows the impact of a 12-week physical training program (including skeletal muscle and aerobic endurance training) for one hour, twice a week, on fatigue, pulmonary function, exercise capacity and muscle strength in 90 sarcoidosis patients. In this cohort study ninety patients underwent baseline testing and returned for repeat testing at three months in the interim, 49 patients completed the training program, and 41 chose not to participate.

Chapter 7 provides an overview on the available literature regarding physical training and rehabilitation in sarcoidosis. In addition, sarcoidosis experts from all over the world were asked to give their detailed opinion on the indications, contra-indications, content and evaluation measures in physical training. Recommendations were established with the use of available data and expert consensus.

Chapter 8 gives a summary of the findings presented in this thesis and a general discussion. Additionally, the implications of the study outcomes for clinical practice are argued and suggestions for future research are briefly discussed

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