Chapter 1

General introduction

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Sarcoidosis is a multisystem inflammatory disorder of unknown etiology. The disease is characterized by the formation of non-caseating granulomas in various organ systems, mainly the lungs and lymphatic system.[1,2]

Epidemiology

The incidence of sarcoidosis is approximately 1–40 per 100 000 persons. Sarcoidosis occurs in both women and men, with a slight predominance in women. It can affect people of all ages, but predominantly between 25–45 years.[3] Sarcoidosis occurs all over the world, but the incidence and prevalence of sarcoidosis in general as well as of different sarcoidosis manifestations differs in various countries due to genetic and environmental differences.[4] For example, cardiac sarcoidosis is more common in Japan,[5,6] while Lofgren syndrome (an acute variant with fever, arthralgia, erythema nodosum, and bilateral hilar lymphadenopathy) is more common in Scandinavian countries.[7-9]

The natural history and prognosis of sarcoidosis are highly variable.[1] Within 3 years of diagnosis, more than 50% of patients have achieved remission, and after a decade, approximately one-third of patients have persistent disease, leading to a significant burden on their lives.[10] Several patient characteristics, like African-American descent, advanced pulmonary disease, extrapulmonary involvement, uveitis, hypercalcemia, and lupus pernio are associated with a chronic course of sarcoidosis.[11] Moreover, genetic variants (HLA-DRB1*14 and *15) tend to increase the risk of a more progressive course of the disease and of non-resolving disease.[9]

Pathogenesis

The exact cause of sarcoidosis is still unknown, but is likely to depend on both genetic and environmental factors, probably antigen-driven. It involves an interaction between a putative triggering antigen, probably inhaled, and a genetically susceptible host (specific HLA-genotypes) resulting in an exaggerated T-cell-mediated immune response.[12] Different antigens/environmental factors have been identified, such as infection (mycobacterial, Propionibacterium acnes),[13-20] insecticides, pesticides, organic/wood/metal dust, and mold.[21,22]

Hallmark features of sarcoidosis are well-developed granulomas, consisting of macrophages (fusing to form multinucleated giant cells) and epithelioid cells surrounded by lymphocytes, especially CD4+ T-helper (Th) cells.[23] Macrophages play a fundamental role, for instance as antigen-presenting cells (APCs). The antigen is

ingested by the APC, inserted in the antigen-binding groove of a major histocompatibility complex (MHC) class II molecule, and transported to the surface for presentation to the T-cells (see figure 1.1).[24] The interaction between macrophages and T-cells is essential for T-cell activation.[10] Activation of antigen-specific CD4+ T-cells by MHC class II restricted APCs leads to a type 1 helper (Th1) differentiation of CD4+ T-cells. Th1-cells then release increased amounts of interferon-gamma (IFN-γ) and interleukin-2 (IL-2). IL2 acts as a local growth factor for T-lymphocytes. IFN-γ enhances the accessory and cytotoxic functions of T-cells and regulates the secretion of other lymphokines (IL-12, IL-18, and tumour necrosis factor-alpha [TNF-α]), which in turn will induce IFN-γ production and enhance T-cell toxicity.[10,22] Moreover, IFN-γ amplifies the activation of alveolar macrophages, leading to increased release of nuclear factor (NF)-kB-dependent proinflammatory cytokines, such as several interleukins and TNF-α.[25] TNF-α is an important granuloma-promoting factor in sarcoidosis. This immune response induces granuloma formation and maintenance.

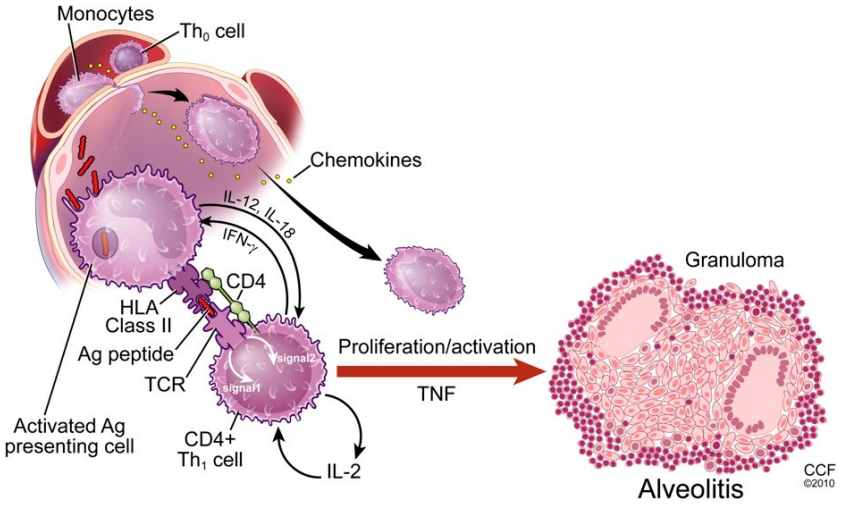

Figure 1.1 A schematic representation of granuloma formation in sarcoidosis.
Th=T-helper; Ag=antigen; HLA=human leukocyte antigen; IFN-γ=interferon-gamma; IL=interleukin; TCR=T-cell receptor; TNF=tumour necrosis factor (adapted from Baughman).[26]
Hypothetical model of the pathogenesis of sarcoidosis, an antigen-induced, antigen-specific, Th1-mediated granulomatous inflammation with production of Th1 cytokines (IFN-γ, IL-2). The efficiency of antigen processing, antigen presentation, and cytokine release is probably under genetic control; evidence strongly supports a role for macrophage HLA and butyrophilin-like 2 (BTNL2) alleles in sarcoidosis susceptibility and phenotype. Granuloma formation is set in motion by activated macrophages and T-cells along with other effector cells (e.g. fibroblasts) under the regulatory influence of local cytokine production. Removal of the antigen allows transforming growth factor beta (TGF-β) to downregulate the immune response. Alveolar macrophages activated in the context of a predominant Th2 response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis.[3]

Neurosarcoidosis

The clinical presentation of sarcoidosis is highly variable and its course unpredictable. Clinical manifestations vary, depending on the organs involved. All organs can be affected, but the most commonly affected organs are the lymphatic system and the lungs.[2] Involvement of the nervous system, neurosarcoidosis, is present in approximately 5–15% of patients with sarcoidosis.[2,27] However, autopsy studies have found granulomatous inflammation of the nervous system in up to 25% of patients.[28] It is a rare and serious sarcoidosis manifestation, which often requires treatment. Neurosarcoidosis has a heterogeneous clinical presentation, including cranial and peripheral neuropathy, meningitis, hydrocephalus, cerebral lesions, and spinal cord disease (see figures 1.2 and 1.3).[29]

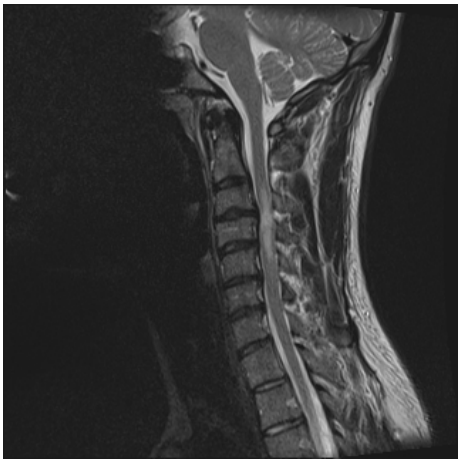

Figure 1.2 36-year-old male, presenting with numbness in both arms and cervical pain. The MRI showed a cervical myelitis (C3-C5). A chest X-ray showed bilateral mediastinal lymphadenopathy, and the diagnosis of sarcoidosis was confirmed with endobronchial ultrasound fine-needle aspiration (EBUS-FNA).

The range of clinical manifestations and the fact that neurosarcoidosis can be the first presenting symptom of sarcoidosis make it hard to diagnose this disorder. Previous literature has predominantly reported on retrospective studies. Since neurosarcoidosis is a rare, complex, and serious manifestation of sarcoidosis, more research into this disease entity is warranted (see also chapters 2 and 5).

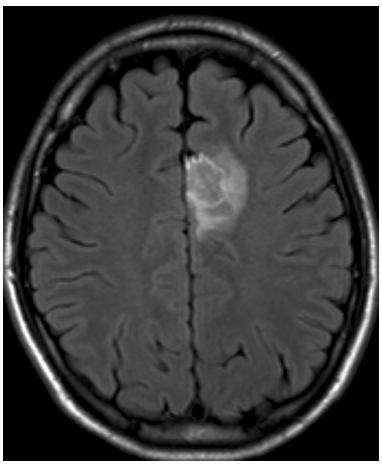

Figure 1.3 23-year-old male, presenting with epilepsy. The MRI showed an intracerebral lesion. A PET-CT demonstrated mediastinal lymph node and pulmonary involvement compatible with sarcoidosis. The diagnosis of sarcoidosis was confirmed with endobronchial ultrasound fine-needle aspiration (EBUS-FNA).

Non-specific symptoms

Apart from organ-related symptoms, sarcoidosis patients often suffer from a variety of nonspecific, non-organ-related, disabling symptoms that cannot be explained by granulomatous inflammation of an organ, such as fatigue, symptoms associated with small fiber neuropathy (SFN), and cognitive failure.

Fatigue is the most frequently reported and devastating non-specific symptom, with a reported prevalence ranging from 50 to 90%.[30,31] Although it is globally recognized as a disabling symptom, no organic substrate has been found for sarcoidosis-associated fatigue. Its etiology is poorly understood and is likely to be multifactorial.[32] In order to objectify fatigue in sarcoidosis patients, the fatigue assessment scale (FAS) has been developed. The FAS has been shown to be an easy-to-use, reliable, and valid scale for the assessment of fatigue, and it has good psychometric properties.[33,34]

Another substantial problem in sarcoidosis patients is SFN, with an estimated prevalence of 40-60%.[35] Symptoms associated with SFN are disabling and probably underrecognized, causing patients to feel misunderstood and imposing limitations on daily life activities. It is a generalized sensory nerve disorder with structural and functional abnormalities of small fibers. It is characterized histopathologically by degeneration of small fiber nerve endings, selectively involving thin myelinated Aδ- and unmyelinated C-fibers.[36] Small fibers are associated with thermal and nociceptive

sensations (somatic) and autonomic function, resulting in symptoms of neuropathic pain and autonomic dysfunction.[35,37] A screening tool for SFN-associated symptoms has been developed for patients with sarcoidosis, called the SFN screening list (SFNSL),[38] which was intended as a first attempt to achieve early identification of patients with symptoms related to SFN (see also chapter 6).

Everyday cognitive failure, including concentration problems, memory loss, and decreased perception, was found in 35% of patients in a general sarcoidosis population.[39] Cognitive failure can lead to difficulties in managing the disease and can adversely affect the treatment.[40] Everyday cognitive failure and depressive symptoms are the most important predictors of high levels of fatigue,[41] whereas other variables (time since diagnosis, sex, age, and social support) appeared not to predict fatigue.

All these non-specific symptoms account for many problems in the daily lives of sarcoidosis patients, leading to a high burden of disease and an important impact on their quality of life (QoL).[42,43]

Treatment

Neurosarcoidosis

The general purpose of systemic sarcoidosis treatment is to prevent end-organ damage. Decisions on whether to start systemic immunosuppressive treatment depend on the severity of the disease, e.g. the involvement and function of organs, or, in selected cases, on its impact on QoL. No curative treatment exists, only suppression of the disease. There are three lines of therapy for sarcoidosis. Corticosteroids are still the first-line treatment. For patients intolerant to corticosteroids, methotrexate (MTX) or azathioprine are well-established second-line options. Third-line treatment consists of anti-TNF antibodies, and is reserved for patients non-responsive to first- or second-line treatment.[44]

Although some patients require no systemic treatment, treatment is almost always warranted in neurosarcoidosis. The intensity of treatment depends on the severity of the neurosarcoidosis manifestations. For example, a facial nerve paralysis can mostly be treated with prednisone monotherapy or no treatment at all, while for spinal cord disease one will choose a second-line (MTX, azathioprine, mycophenolate mofetil (MMF)) or third-line (TNF-α inhibitors; infliximab and adalimumab or more recently biosimilars) agent earlier on in the treatment of this manifestation. Limited data is available on the best treatment for neurosarcoidosis, and is mainly based on expert opinion and small retrospective studies. No randomized controlled trials have been performed comparing treatments for neurosarcoidosis. MTX seems to significantly

increase the survival time without relapse, compared to MMF, and is therefore preferred.[45] In another study, most patients treated with a TNF-α inhibitor, infliximab, responded with partial or complete remission.[46] Further studies are needed to evaluate the prognosis and optimal treatment strategy (see also chapter 5).

Small fiber neuropathy

Currently, there is no curative treatment for SFN. Symptomatic treatment for neuropathic pain can be initiated, but unfortunately these drugs often provide only partial relief from pain, have no effect on autonomic dysfunction and are associated with (sometimes severe) side effects in a high proportion of patients. Some data suggest effectiveness of immunoglobulins and TNF-α inhibition.[47-50] Whether these very expensive treatments should be initiated as treatment for SFN is unclear and currently being investigated. Cibinetide® (ARA290) seems a promising new drug to relieve pain and increase corneal and skin nerve-fiber density in sarcoidosis-associated SFN.[51-53] Further clinical trials are needed before this drug can be authorized (see also chapter 6).

Fatigue

Despite effective treatment of their sarcoidosis with immunosuppressive agents, many patients continue to experience fatigue even after contributing factors (e.g. vitamin D deficiency, hypothyroidism, or obstructive sleep apnea) have been treated. Recent studies have demonstrated the effectiveness of various neurostimulants, including methylphenidate, for the treatment of sarcoidosis-associated fatigue, and these and other agents may be useful adjuncts to its treatment.[54] Moreover, it has been shown that muscle impairment is associated with fatigue and functional limitations.[31,55] Symptoms of fatigue induce exercise limitation and lead to physical inactivity, resulting in general deconditioning.[43] Several studies have reported that a physical training program can reduce fatigue and improve exercise capacity.[32,56-58]

Scopes and aims of the studies

The aims of the studies presented in this thesis were to outline the manifestations of neurosarcoidosis and the burden and/or impact of this disorder, such as cognitive impairment. In addition, they assessed the burden of sarcoidosis, focusing on fatigue and SFN-associated symptoms reported by the patients themselves. The third study determined the minimal important difference on the SFNSL instrument, which makes it possible to follow-up the SFN-related complaints experienced by patients. Finally,

predictors of the QoL of patients and their partners (mainly concerning non-specific, non-organ-related complaints) were studied.

Chapter 2 provides an overview of the current literature regarding neurosarcoidosis. Clinical characteristics and various ancillary investigations are outlined, and treatment options and prognosis are discussed.

Chapter 3 describes the neurosarcoidosis manifestations in a large cohort of neurosarcoidosis patients in the Netherlands (obtained from the Amsterdam University Medical Centre, the ILD Center of Excellence, St. Antonius Hospital Nieuwegein, and the neurosarcoidosis registry). In addition, race and gender differences were studied and treatment options are described.

Chapter 4 discusses the high cognitive failure rate in neurosarcoidosis patients compared to the general sarcoidosis population. Many patients in the sample we studied experienced cognitive failure in their everyday lives.

Chapter 5 provides an overview of current literature regarding the management of neurosarcoidosis, including SFN, mainly focusing on diagnosing and treating neurosarcoidosis and SFN in sarcoidosis.

Chapter 6 summarizes the current literature regarding SFN, describing its pathophysiology and symptoms. The problems faced in diagnosing SFN are discussed, including the different diagnostic tests available. Various treatment options are presented.

Chapter 7 describes the determination of the minimal important difference (MID) on the SFNSL instrument. The MID is the smallest change in a score that a patient perceives to be important. For evaluative purposes, interpretability was assessed by the change in scores.

Chapter 8 describes the burden of sarcoidosis symptoms from a patient's perspective. This study was conducted in Denmark, Germany, and the Netherlands. Organ-related as well as non-specific, non-organ-related symptoms were assessed, as were treatment options.

Chapter 9 describes the QoL in sarcoidosis patients and their partners, as well as predictors of the QoL of patients and partners.

Chapter 10 provides a summary and general discussion of the findings reported on in this thesis. Additionally, the implications of the study outcomes for clinical practice and suggestions for future research are briefly discussed.

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