Chapter 10

Summary and general discussion

Summary

Sarcoidosis is a multisystem inflammatory disorder characterized by the formation of non-caseating granulomas in various organ systems.[1,2] The lymphatic system and the lungs are most commonly affected, but any organ can be involved. Involvement of the nervous system, or neurosarcoidosis, is detected in 5% of cases during life,[3-6] although autopsy studies have shown neurologic involvement in 25-50%.[7,8] Although the pathogenesis of sarcoidosis has not been fully elucidated, environmental (i.e. infectious, metal, silica, silicones, ink) and genetic factors may contribute substantially to its pathogenesis, involving an exaggerated granulomatous reaction to a trigger.

Sarcoidosis occurs in men and women throughout the world, affecting all races and any people aged between 25 and 45 years who have a predisposition.[2] The influence of race and gender on the epidemiology of sarcoidosis is generally recognized. The incidence of sarcoidosis in patients of African descent is high compared to that in Caucasians.[9] Moreover, they often present with more severe organ involvement, a worse prognosis and higher mortality rates than Caucasians.[9-11] It has also been acknowledged that the prevalence of various organ manifestations differs between different ethnic subgroups, e.g. cutaneous and ocular sarcoidosis is more common in patients of African descent than in Caucasians, while hypercalcemia is more common in Caucasians.[4] In terms of gender differences, pulmonary and cardiac sarcoidosis is more common in men, whereas peripheral lymph node involvement, cutaneous, ocular and liver sarcoidosis are seen more often in women.[4,12]

The clinical manifestation, natural history and prognosis of sarcoidosis are highly variable, and its course is often unpredictable.[1] Depending on the organs involved and the severity of the granulomatous inflammation, patients present with a broad range of symptoms. In addition to organ-related symptoms, patients often suffer from disabling non-specific, non-organ-related symptoms,[13-15] such as fatigue, depressive symptoms, pain, anxiety and cognitive failure. All these symptoms have an impact on the quality of life (QoL).[13,16-22]

This thesis is divided into two parts:

The aims of the studies in the first part of this thesis were to investigate the prevalence of the different neurosarcoidosis manifestations and the influence of race and gender on this. Furthermore, we aimed to determine the prevalence of cognitive failure in these patients.

The aims of the studies in the second part were to describe the burden of non-specific symptoms (small fiber neuropathy (SFN), fatigue, cognitive failure, depressive

symptoms, and anxiety) in sarcoidosis patients and the impact on the QoL of these patients and their partners.

Overview of the main findings

Chapter 1, the general introduction, provides a summary of the epidemiology and pathogenesis of sarcoidosis, the clinical presentation of neurosarcoidosis, and non-specific symptoms. In addition, it presents a summary of treatment options of neurosarcoidosis and describes the non-specific symptoms of fatigue and SFN.

Chapter 2 presents an overview of the literature regarding neurosarcoidosis. The clinical presentation is heterogeneous. Most patients present with cranial nerve palsy, headache and sensory abnormalities. Patients are classified according to the probability of the diagnosis using the modified Zajicek criteria.[23] A crucial feature in these criteria is histopathological confirmation of non-caseating granulomas in affected tissue outside the nervous system. Radiological abnormalities on neuroimaging are non-specific. No biomarkers have been described that effectively identify patients with sarcoidosis. Despite the use of new therapies, a third of the patients remain unchanged, deteriorate or die. Diagnosing and treating patients with neurosarcoidosis remains a challenge. Long-term prospective studies evaluating patients suspected of neurosarcoidosis are needed to assess the sensitivity and specificity of ancillary investigations and the diagnostic criteria. Furthermore, studies are needed to evaluate the prognosis and the optimal treatment strategy.

Chapter 3 investigates neurosarcoidosis manifestations and the influence of race and gender, as well as the treatment strategies. In a multicenter observational cohort study, we included 194 neurosarcoidosis patients from two tertiary referral centers; the ILD Center of Excellence of the St. Antonius Hospital, Nieuwegein and the Amsterdam University Medical Centre (UMC), both in the Netherlands, as well as patients included in the Dutch Neurosarcoidosis Registry. The most common neurosarcoidosis manifestations were chronic meningitis (41%), cranial nerve dysfunction (39%), myelopathy (28%), and cerebral parenchymal disease (26%). There were no differences in age, gender and race between the various manifestations, except for peripheral polyneuropathy, which was more prevalent in men than in women (21% versus 10%). Most neurosarcoidosis patients were treated with prednisone (89%), methotrexate (46%), or infliximab (21%). A total of 102 patients (53%) received second- or third-line treatment. Over half of the patients required multiple immunosuppressive treatments.

Chapter 4 presents an evaluation of the cognitive failure rate in neurosarcoidosis patients compared to a general sarcoidosis sample. Cognitive failure is characterized by memory and concentration problems. Everyday cognitive failure was assessed using the Cognitive Failure Questionnaire (CFQ). A cross-sectional web-based survey was conducted in a national sample of 131 neurosarcoidosis patients. We found that the mean CFQ score was significantly higher in the neurosarcoidosis sample (45.6±20.7) compared to the general sarcoidosis sample (36.2±15.9; p<0.0001). High CFQ scores (≥43) were found in 55.7% (neurosarcoidosis) and 33.9% (general sarcoidosis) (p<0.0001). The fatigue assessment scale (FAS) score (OR 21.4) and the score on the small fiber neuropathy screenings list (SFNSL) (OR 4.3) were the strongest positive predictors of a high CFQ score. Cognitive failure is a significant problem in neurosarcoidosis.

Chapter 5 provides an overview of the current literature regarding the management of neurosarcoidosis, including SFN. The clinical manifestation and course of neurosarcoidosis are particularly variable. Although neurosarcoidosis occurs in up to ten percent of sarcoidosis patients, it can lead to significant morbidity and some mortality. Recent guidelines have helped to clarify criteria for diagnosing neurosarcoidosis. No firm guidelines exist for whether, when, and how treatment should be started. Treatment depends on the presentation and distribution, extensiveness, and severity of neurosarcoidosis. As regards evidence-based treatment, only a few randomized controlled trials have been done. Hence, several aspects of sarcoidosis and neurosarcoidosis management are not fully addressed by the current literature. A multidisciplinary approach to the management of sarcoidosis is strongly recommended.

Chapter 6 provides an overview of the current literature regarding SFN, which causes high morbidity with disabling symptoms and impact on QoL. Patients may benefit from being diagnosed with SFN, even if no underlying cause is identified and no specific treatment is yet available. Clinical diagnostic criteria have been proposed, but no gold standard exists, and each test has its limitations. The diagnosis requires a combination of typical symptoms, abnormal neurologic findings, and absence of large fiber involvement. Clinicians should be aware of overlapping symptoms of SFN and fibromyalgia. Treatment is often difficult, even when the underlying cause is identified and appropriately treated. Usually, only symptomatic relief of complaints is available. Awareness of SFN and related symptoms is of great clinical relevance. Guidelines for appropriate diagnostic workup using a stepwise approach involving a combination of tests are warranted.

Chapter 7 reports on the minimal important difference (MID) of the SFNSL. The MID is the smallest change in a score that a patient perceives to be important. Previous studies found that 40-60% of the sarcoidosis patients suffer from SFN, substantially affecting QoL. The usefulness of any questionnaire in clinical management and research trials depends on its interpretability, requiring the smallest detectable change (SDC) and minimal important difference (MID) to be known. Patients with neurosarcoidosis and/or sarcoidosis-associated SFN symptoms (n=138) included in the online Dutch Neurosarcoidosis Registry participated in a prospective, longitudinal study. The SFNSL was completed both at baseline and at 6-months' follow-up by 89 patients. The MID for the SFNSL is 3.5 points for a clinically relevant change over a 6-month period. The MID can be used in the follow-up and management of SFN-associated symptoms in patients with sarcoidosis, though with some caution, as the SDC was found to be higher.

Chapter 8 evaluates the burden of sarcoidosis symptoms from a patient perspective in three European countries. The clinical manifestations of sarcoidosis vary widely, depending on the intensity of the inflammation and the organ systems affected. A cross-sectional web-based anonymous survey about complaints (organ-related as well as non-specific, non-organ-related) was conducted among sarcoidosis patients in Denmark, Germany, and the Netherlands. The questionnaire was completed by 1072 sarcoidosis patients (152 Danish, 532 German, and 388 Dutch). Almost all patients reported having sarcoidosis-associated symptoms (organ-related as well as non-specific, non-organ-related). Fatigue was reported by almost all respondents (90%), followed by symptoms associated with SFN (86%), and pulmonary symptoms (72.4%). More than 50% of the respondents were being treated with prednisone, a finding which was comparable for all three countries. In contrast, second- and third-line treatment differed substantially between Denmark, Germany, and the Netherlands. Sarcoidosis patients in Denmark, Germany, and the Netherlands present with similar self-reported symptoms, organ-related as well as non-specific, non-organ-related.

Chapter 9 reports on a study of QoL in sarcoidosis patients and their partners. Consequences of sarcoidosis are wide-ranging and the symptom burden has a great impact on patients' QoL. However, the QoL of couples living with sarcoidosis has not yet been studied. Sarcoidosis outpatients, recruited at Maastricht University Medical Center (n=443), and their partners (n=208) completed several questionnaires, including the World Health Organization Quality of Life – BREF (WHOQOL–BREF), FAS, SFNSL, and CFQ. The QoL of the partners as well as of the sarcoidosis patients was reduced compared with healthy controls, though that of partners was less reduced than that of the patients, especially regarding the physical health domain. All non-specific

symptoms studied, as well as perceived social support, predicted one or more QoL domains in the sarcoidosis patients, but these factors did not predict the QoL of their partners. In the management of sarcoidosis is it important to focus not only on the patients, but also on their partners.

Discussion

Sarcoidosis is a complex, multisystem disorder of unknown cause(s) that imposes a burden on patients' lives.[24,25] The clinical presentation of sarcoidosis is highly variable and the course of the disease is unpredictable. In addition to specific organ-related symptoms causing functional impairments and symptoms associated with comorbidities, sarcoidosis patients are disabled by less specific symptoms, including fatigue.[9,25,26] All symptoms may have a significant influence on patients' daily activities and their social and professional lives. Many different clinical phenotypes of sarcoidosis exist; no two sarcoidosis patients are the same. Therefore, it is hard to develop a general diagnostic or treatment protocol for sarcoidosis patients. Currently, 20 years after the publication of the first guidelines[1] a new attempt has been started to update the diagnostic work-up and therapeutic options for sarcoidosis.

Neurosarcoidosis

Like sarcoidosis itself, the presentation of neurosarcoidosis is variable. Furthermore, diagnosing neurosarcoidosis remains a clinical challenge, due to its diversity and the absence of specific biomarkers. In most cases of suspected neurosarcoidosis, nervous system histology is not feasible and other biopsy sites outside the nervous system should be searched for. Moreover, it is important to rule out other causes, perform a complete work-up for suspected sarcoidosis, and use the diagnostic criteria established by Stern et al. to enable possible, probable, or definite neurosarcoidosis to be diagnosed (see Table 10.1).[27]

Table 10.1 Proposed diagnostic criteria for neurosarcoidosis.[27]

Possible	Probable	Definite
1. the clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations, MRI, CSF and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system, and after rigorous exclusion of other causes.	1. the clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations, MRI, CSF and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system, after rigorous exclusion of other causes.	1. the clinical presentation and diagnostic evaluation suggest neurosarcoidosis, as defined by the clinical manifestations, MRI, CSF and/or EMG/NCS findings typical of granulomatous inflammation of the nervous system, after rigorous exclusion of other causes.
2. there is no pathologic confirmation of granulomatous disease.	2. there is pathologic confirmation of systemic granulomatous disease consistent with sarcoidosis.	2. the nervous system pathology is consistent with neurosarcoidosis. type a. Extra-neural sarcoidosis is evident. type b. No extra-neural sarcoidosis is evident ("isolated CNS sarcoidosis").

Most manifestations of neurosarcoidosis are very debilitating and regularly lead to residual damage and high relapse rates, despite immunosuppressive treatment. That is why it is essential to raise awareness among practitioners, so that neurosarcoidosis is recognized and treated without delay to hopefully limit or prevent residual damage.

Treatment is almost always warranted in neurosarcoidosis. However, the treatment regime is not the same in all neurosarcoidosis patients. The intensity of treatment should depend on the severity of the manifestation and the burden to the patient. For example, a facial nerve dysfunction can often be treated with prednisone monotherapy or no treatment at all, whereas spinal cord disease should be treated without delay with second- (methotrexate, azathioprine) or third-line treatment (tumour necrosis factor-alpha [TNF-α] antagonists) (see chapters 2 and 5). In line with others, we found that in our neurosarcoidosis sample, more than half of the patients needed second- or third-line treatment (see chapter 3).[28-33] Chapters 2, and 5 discuss guidelines for ways to treat the various manifestations of neurosarcoidosis. To date, personalized medicine is mandatory in all sarcoidosis and neurosarcoidosis patients, guided by multidisciplinary discussions. However, to offer the clinician some help, Figure 10.1 presents a proposed treatment algorithm.

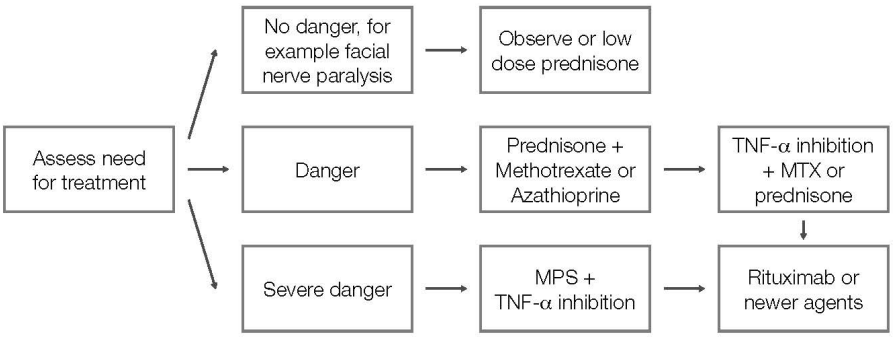

Figure 10.1 Proposed treatment algorithm in neurosarcoidosis.
MPS=methylprednisone; MTX=methotrexate; TNF-α=tumour necrosis factor-alpha

The difficulty in performing research into this extremely rare disease is that the samples studied are mostly small, especially when investigating each of the neurosarcoidosis manifestations separately. Due to the rarity of this disease, a randomized controlled trial (RCT) is almost never a realistic option. Many recommendations developed for neurosarcoidosis are therefore based on observational studies and experts' opinions. The research field is, however, currently shifting from RCTs to more real-world evidence.[34,35] RCTs have a strong internal validity, but overall a weaker external validity and are therefore mostly not generalizable to clinical practice for individual patients. Moreover, sarcoidosis patients are mostly not eligible for RCTs, due to comorbidities. Observational studies and precision-based (biomarker) studies can be a good or maybe even better alternative, especially for the patients. Larger, multicenter observational and biomarker studies are therefore the best option for research in this field (see the section entitled Future Studies).

Non-specific, non-organ related symptoms

Sarcoidosis is a burdensome disease, due to organ-related as well as non-organ-related, non-specific symptoms, such as those associated with small fiber neuropathy (SFN), fatigue or cognitive failure. These latter symptoms are highly prevalent, as shown in chapters 4 and 8 of this thesis, leading to a high burden. Since these symptoms are not visible and hard to objectify/diagnose, many patients feel misunderstood and not taken seriously. Hence, it is essential to identify all disabling symptoms, as this will ultimately enable healthcare providers, supported by researchers, to tailor interventions to individual patients and improve their quality of life (QoL). Given the wide variety of

symptoms, not limited to one discipline, and uncertainties regarding pathophysiology and possible causes, a multidisciplinary approach focusing on somatic as well as psychosocial aspects is recommended for this erratic disorder.

Diagnostic approach

Questionnaires, such as the Fatigue Assessment Scale (FAS) and the Small Fiber Neuropathy Screening List (SFNSL), have been developed to assess these complaints in sarcoidosis patients and quantify them. They are therefore useful to assess these non-specific symptoms, but they are not meant for diagnosing, and care providers should be aware of this. For example, the SFNSL should be used as a screening tool for SFN, and in case of a high score the patient should be referred to a neurologist for further evaluation and exclusion of other causes. Diagnosing SFN remains challenging, since a gold standard is lacking. Various diagnostic criteria have been proposed, but no set of well-defined criteria is as yet available. All diagnostic modalities (quantitative sensory testing, nociceptive evoked potentials, skin wrinkling, skin biopsy, corneal confocal microscopy) have their limitations, although skin biopsy is considered by some to be the 'silver standard'.[36-39] However, a normal skin biopsy does not completely exclude SFN, probably due to its patchy distribution in sarcoidosis patients. Moreover, skin biopsy does not always correlate with complaints.[40,41] Corneal confocal microscopy has high potential, since it can detect early nerve damage and a correlation has been established between the severity of neuropathy and progressive corneal nerve degeneration.[42-45] However, further research is necessary to establish a control group.
A pilot study into cognitive failure was performed by our group, examining standard neuropsychological tests that were used to assess the cognitive domains of memory sensorimotor speed, information processing speed and cognitive flexibility. It found that cognitive failure did not imply cognitive impairment. Thus, subjective cognitive failure was not associated with cognitive impairment.[14]

Treatment options

Previous studies have found that most of the non-specific symptoms are interrelated[13,14,46] (see also chapter 4), so specifically treating one symptom can help reduce other non-specific symptoms as well. For example, as might be expected, it has been shown that treating fatigue also resulted in an improvement of cognition.[47]

Symptoms of sarcoidosis-associated SFN are often disabling and difficult to treat. Usually, only symptomatic relief of complaints is achieved with neuropathic pain killers. Other options could be immunoglobulins (IVIG), TNF-α antagonists or Cibinetide®. The

largest case series for IVIG (n=76) suggests that up to 75% of patients will derive symptomatic benefit, but these results are limited by the absence of a defined standard for assessing treatment response, as well as by patient selection bias, differences in concomitant treatment regimens, and lack of a placebo group.[48] The putative mechanism for the effectiveness of IVIG is unclear but may relate to immunomodulatory effects. TNF-α is known to reduce mechanical nociceptive thresholds [49,50] and has been found in higher concentrations in distal skin biopsies of patients with length-dependent SFN.[51] The monoclonal TNF-α antagonist infliximab has been assessed in a retrospective cohort (n=26). Approximately 70% of patients experienced a reduction of SFN-associated symptoms, although the magnitude of the effect is difficult to ascertain from the available data.[48] Response rates for TNF-α antagonists may relate to the degree of TNF-α suppression, since the GG promoter variant, associated with less intensive TNF transcription, was also associated with better outcomes in treated patients.[52] Cibinetide®, previously known as ARA-290, is an innate repair receptor agonist that has anti-inflammatory and neuroprotective properties.[53-55] Multiple randomized, placebo-controlled, double-blind studies have previously shown effects of Cibinetide® in reducing SFN-associated symptoms and increasing nerve fiber density (skin and cornea).[56-58] It is disappointing that a drug that offers such benefits to patients is not yet on the market, and the question remains whether it will ever be.

A recently published placebo-controlled study (n=47) showed an effect of lacosamide on pain intensity in patients with SFN due to voltage-gated channel mutations (mutations in SCN9A, encoding Nav1.7).[59] Lacosamide is an anticonvulsant that acts on Nav1.3, Nav1.7, and Nav1.8. Perhaps this could also be an option for the treatment of neuropathic pain in sarcoidosis-associated SFN, although the pathophysiological mechanism is probably different. A recent study examined the effect of virtual reality (VR) technology on the recovery of the autonomic nervous system in volunteers affected by stress.[60] This might be an option in treating autonomic dysfunction in sarcoidosis-associated SFN. It is, however, still hard to recommend any treatment, because the evidence is not compelling and no guideline for the treatment of sarcoidosis-associated SFN yet exists.

Practical implications and directions for future studies

As stated above, sarcoidosis is a heterogeneous disease with a variety of clinical symptoms, organ-related as well as non-specific, non-organ-related. A complete evaluation of sarcoidosis could make use of a panel with four disease domains or dimensions: extent of disease, severity, activity, and impact.[13] Severity of sarcoidosis in

each organ is defined as the degree of organ damage sustained from sarcoidosis. The interpretation of the severity of sarcoidosis can be complicated by its heterogeneity. In the case of neurosarcoidosis, the most important aspect is awareness of the presenting symptoms and manifestations of neurosarcoidosis. This knowledge could enable earlier recognition of these manifestations and earlier introduction of treatment. Treatment is warranted for almost all patients with neurosarcoidosis.

The burden of non-specific, non-organ-related symptoms in sarcoidosis patients, but also in their caregivers/partners, is high. In addition to organ-related complaints and functional disorders, fatigue, pain, energy loss, and concentration and memory problems affect whether or not someone is capable of performing work and to what extent. A large percentage of sarcoidosis patients feel that their complaints were not taken seriously when their claims for work capacity were evaluated.[61] A review by Barth et al.[62] demonstrated considerable variation in judgements on work disability among medical examiners, which probably has to do with the limited knowledge that clinicians generally possess about sarcoidosis as a disease with extra-pulmonary involvement.

Since these problems are frequent and may have a major influence on patients' daily activities, their social and professional lives and their QoL, it is important to recognize and quantify these problems in the evaluation of sarcoidosis patients.[15] There should be a greater degree of understanding for this, and patients should feel that they are being taken seriously and are a partner in the management of their disease.

The above non-specific symptoms, including pain, are even more prevalent in neurosarcoidosis patients (see chapter 4). Pain, a complex phenomenon influenced by a range of genetic, biological, psychological and social factors, is a major component of SFN, and is the result of physiological interactions between central and peripheral nervous system signaling. The many different aspects of pain mean that neurologists, pulmonologists and other clinicians need to have enough expertise to diagnose the type of pain correctly and treat it appropriately. For both clinicians and patients, it is a complex disease, which should be treated by sarcoidosis specialists with experience in all sarcoidosis symptoms. Moreover, absence of evidence does not mean evidence of absence.

We recommend standardized assessment of non-specific symptoms (fatigue, SFN-associated symptoms, cognitive failure, depressive symptoms and anxiety), with validated instruments, in the work-up of sarcoidosis patients. This assessment is important in the management of these patients in the outpatient clinic but also for the evaluation of their capacity for work. Management of sarcoidosis requires a

multidisciplinary personalized approach that focuses on somatic as well as psychosocial aspects of the disease. When assessing individuals during an occupational disability assessment, the nature and severity of the condition, and especially the consequences for the specific patient, must be taken into account in the advice.

The rarity of sarcoidosis makes the care for these patients extra challenging, even more so in ultra-rare manifestations such as neurosarcoidosis. Future studies are warranted to enhance our understanding of the diversity of neurosarcoidosis, the determinants of its morbidity, severity, and mortality, as well as optimal treatment regimens, in order to determine the best treatment and to improve the quality of life of patients suffering from this rare form of sarcoidosis.

Diagnostic work-up

As mentioned above, neurosarcoidosis is a serious manifestation of sarcoidosis with generally a worse prognosis. Future research should focus on optimizing the diagnostic work-up of neurosarcoidosis and on establishing whether biomarkers such as TNF-α polymorphisms or other proteins (for example S100B, a calcium-binding protein) may be valuable diagnostic tools. Future studies regarding non-specific symptoms are also needed. Non-specific symptoms are difficult to objectify. Previously, the FAS and SFNSL were developed and validated to objectify fatigue and SFN-associated symptoms, respectively, in sarcoidosis. Several questionnaires also exist for cognitive failure, depressive symptoms and anxiety, which need to be validated in sarcoidosis in future studies.
A previous study by Hendriks et al. found a relation between fatigue and cognitive failure.[14] Since all of the non-specific symptoms seem to be interrelated, it is reasonable to look for a common pathway and treat this accordingly, in order to treat all non-specific symptoms.

Regarding SFN, research should focus on identifying and understanding the pathological basis of SFN, which will facilitate further studies on diagnostic methods and novel treatment approaches. Prospective research is warranted to improve the diagnostic work-up (for example by establishing a control group for the corneal confocal microscopy and formulating/validating diagnostic criteria), treatment, and outcome. Furthermore, research is needed specifically with regard to autonomic dysfunction in patients with SFN-associated symptoms.

Treatment

Currently, no treatment exists for sarcoidosis. Each sarcoidosis patient is unique, and what works for one person may not work for someone else. Therefore, future research should focus on the most effective treatment for sarcoidosis and neurosarcoidosis, considering various phenotypes and genotypes. Moreover, we should focus on treatment modalities beyond prednisone (quick effect, fewer side-effects) as the first-line treatment for sarcoidosis, since prednisone can cause many adverse side-effects and imposes a great burden on patients. Multiple more recent agents are currently being studied in Phase I and II trials.
As regards fatigue, short-term benefits of physical therapy/training have been found in previous studies. Long-term benefits of these interventions should be investigated in larger randomized controlled studies.

Guidelines

As mentioned above, non-specific, non-organ-related symptoms in sarcoidosis are disabling and difficult to objectify and treat. It is important to pay attention to these symptoms in sarcoidosis patients as well, in addition to the organ-related symptoms, and to also address this in national and international guidelines. To this end, more knowledge should be acquired by various organizations, including the Dutch association of physicians for pulmonary diseases and tuberculosis (NVALT) and the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG), but also organizations such as the Dutch institute for employee insurance (UWV). Sarcoidosis is an erratic disease that presents differently in each patient. When assessing individuals, such as during an occupational disability assessment, the nature and severity of the condition, and especially the consequences for that specific patient, must be taken into account in the advisory report on work capacity.

The development of a disease-specific core set for sarcoidosis under the framework of the International Classification of Functioning, Disability and Health (ICF),[63] with input from patients as well as physicians, rehabilitation specialists, specialist nurses, and so on, could be a first step in examining and structuring the multi-faced functional impact of sarcoidosis on employment. Further studies comparing the evaluation of disability as graded by the medical staff and the patients themselves would be very interesting. Are patients themselves capable of grading their own disability, and are the health care workers able to grade disability without objective parameters? Are care providers biased in making their final decision due to a lack of objective parameters? This is a very challenging problem, and should be evaluated in future studies. We believe that the

advantage would be that patients are involved in the management process, and their own judgments can be incorporated in the decision making. Patients want nothing more than to participate in social life again, but are highly frustrated that they simply are temporarily unable to make the most of their lives.

Last but not least, we believe it is very important to incorporate the patients themselves in developing new research questions and performing research, since, after all, they are the ones for whom we are doing all the research.

Key issues

- Neurosarcoidosis is a serious and highly heterogeneous manifestation of sarcoidosis.
- More than half of patients with neurosarcoidosis need second- (methotrexate, azathioprine, mycophenolate mofetil) or third-line (TNF-α inhibition) treatment to control the disease, the exception being patients with a facial nerve dysfunction.
- Sarcoidosis patients suffer not only from organ-related symptoms, but also from a wide spectrum of rather nonspecific disabling symptoms, which are common (>75%), such as cognitive problems, fatigue, depressive symptoms, anxiety, and SFN-associated symptoms
- The SFNSL is a useful questionnaire to assess SFN-related symptoms, but is not intended to diagnose SFN.
- Cognitive problems are even more prevalent in neurosarcoidosis patients than in the general sarcoidosis patient population (55% versus 33%).
- Management of sarcoidosis requires a multidisciplinary personalized approach that focuses on somatic as well as psychosocial aspects of the disease.
- Patient care should not be limited to patients but also include their caregivers/partners, since the latter also experience a reduced QoL.
- Different clinical phenotypes of sarcoidosis exist; no two sarcoidosis patients are the same. Therefore, it is hard to develop a general diagnostic or treatment protocol for sarcoidosis patients.
- Future research should focus on optimizing the diagnostic work-up in terms of imaging and biomarkers, on furthering our understanding of all aspects of this disease, and on developing new therapeutic strategies.

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