Chapter 12

Summary, general discussion and directions for future studies

Summary

Sarcoidosis patients exhibit a broad variety of clinical features. Besides pulmonary symptoms which generally reflect disease activity, many patients present with symptoms such as pain, fatigue and autonomic dysfunction. So far, these symptoms have had little attention in the sarcoidosis literature, and have remained an enigma to physicians. We found that many of these apparently non-specific symptoms could be related to small fiber neuropathy (SFN) with autonomic involvement. This observation was the motive for this thesis.

First a literature search was performed. In ***chapter 2*** the existing literature regarding neurosarcoidosis was reviewed to provide an overview of the present knowledge and dilemmas clinicians are faced with in the diagnostic work-up and treatment of patients suffering from this complicated disease. In this chapter an approach for the diagnosis of neurosarcoidosis as well as treatment strategies are proposed. Furthermore, our novel observation SFN in sarcoidosis was added to the list of neurological complications attributable to this disease.

Chapter 3 reviews the literature regarding what is known about SFN. SFN is a neuropathy selectively involving small diameter myelinated and unmyelinated nerve fibers. Interest in this disorder has considerably increased during the past few years. Clinical presentation consists of peripheral pain and/or symptoms of autonomic dysfunction. Routine electrodiagnostic studies, which primarily test large myelinated fiber function, are generally normal in these patients. Therefore, the disorder SFN has been an enigma to practitioners because of the unexplained contrast between severe pain in the extremities and a paucity of neurological and electrophysiological findings. Diagnosis is achieved based on clinical features, normal nerve conduction studies, and abnormal specialized tests of small nerve fibers. Among others, these tests include assessment of epidermal nerve fiber density in skin biopsy, temperature sensation tests for sensory fibers and sudomotor and cardiovascular function testing (CAFT) for autonomic fibers. Unless an underlying disease is identified, treatment usually is symptomatic and directed towards alleviation of neuropathic pain.
SFN is often idiopathic, however, it occurs relatively frequently in several immune mediated diseases such as vasculitis,[1,2] Sjögren`s disease,[3] systemic lupus erythematosus (SLE),[4,5] Guillain-Barré syndrome[6,7] and to our own experience SFN occurs also in Wegener`s disease, and rheumatoid arthritis. Accordingly, it was hypothesized that in immune mediated diseases there might be a common pathway causing SFN. In sarcoidosis, SFN related symptoms not always occur parallel with disease activity assessed by general used diagnostic procedures and it does not seem to respond to

corticosteroids. In line with this, it is reasonable to assume that SFN in sarcoidosis is not directly caused by granuloma formation. Finally, we discussed candidate mechanisms involved in the pathogenesis of SFN including tumour necrosis factor (TNF)-α and oxidative stress.

Although pain is prevalent in sarcoidosis, this has never been studied systematically. The study described in ***chapter 4*** was aimed to evaluate the presence and impact of pain in sarcoidosis. Members of the Dutch Sarcoidosis Society without co-morbidity (n=821) participated in this study. The World Health Organisation Quality of Life assessment instrument (WHOQOL-100; see appendix) was completed, as well as a symptom inventory questionnaire addressing the presence of various categories of pain. Pain appeared to be a major problem in sarcoidosis, occurring in up to 72% of the studied sarcoidosis patients. Although negative feelings and fatigue were found to be related to pain, it could not fully explain pain.

Besides pain, many sarcoidosis patients suffer from fatigue[8,9] and sleep disturbances. Recently, it was demonstrated that obstructive sleep apnea (OSA) is rather common in sarcoidosis.[10] Moreover, sheet intolerance, painful legs and restless legs are frequently reported in sarcoidosis patients. Remarkably, restless legs syndrome (RLS) may be an early feature of SFN.[11,12] These symptoms might interfere with sleep quality. In order to determine the relationship between objective and subjective sleep disturbance in ***chapter 5*** full polysomnography, including leg EMG analysis, was performed in 46 chronic sarcoidosis patients indicating awakening unrefreshed in the morning. Both sleep disturbance (OSA and/or periodic leg movement (PLM)) and RLS were found in more than half of the studied sarcoidosis patients. Its relation with SFN and fatigue needs further exploration.

After we discovered a frequent occurring symptom pattern, consisting of peripheral pain accompanied by symptoms of autonomic dysfunction, suggestive of SFN, we established the presence of SFN using various types of testing.
In ***chapter 6*** various electrophysiological tests were used to assess the presence of SFN. Seventy-four sarcoidosis patients complaining of symptoms suggestive of SFN underwent temperature threshold testing (TTT) to assess thresholds for warm and cold sensation as well as for heat pain, sympathetic skin responses (SSR), nerve conduction studies and concentric needle electromyography. Furthermore, in 31 patients, CAFT was carried out. TTT revealed abnormalities in 51 of the 74 patients (69%), consistent with our clinical observation. This observation was in accordance with former studies that have also found sensitivity rates of TTT varying form 60 to 85%.[13-17] Nerve conduction studies in the legs showed slightly abnormal results in 6 of the 74 patients,

all of these had abnormal TTT results. The SSR was absent at the foot in 7 of the 74 patients. CAFT was abnormal in only a single case of the 31 tested patients, which is in accordance with data from others reporting low sensitivity of CAFT in SFN.[14,18]
In conclusion, we found in a subgroup of sarcoidosis patients TTT abnormalities suggestive of SFN. SSR and cardiovascular autonomic testing appeared to be of little diagnostic value.

In ***chapter 7*** the presence of SFN was further explored by obtaining skin biopsy specimens. Quantification of epidermal nerves in skin biopsies is an objective and valuable method to detect SFN. Reduced intraepidermal nerve fiber density (IENFD) can be the first and only detectable abnormality in patients with painful neuropathy. In 7 consecutive sarcoidosis patients and 6 age matched healthy controls IENFD in punch biopsies of the skin was determined. Reduced IENFD was found in all 7 patients compared to 6 healthy controls, consistent with the presence of SFN in these patients.

In clinical practice there is a need for an easily administered instrument to assess SFN which can be applied to all patients with suspicion of the disorder. In ***chapter 8*** we describe the development and validation of a questionnaire to screen for the presence of SFN. Such a questionnaire is aimed to be useful in clinical assessment, for research assessing prevalence and natural course and in therapeutic trials. We developed and validated a questionnaire in a group of 84 sarcoidosis patients that was short and easy to administer, the SFN-screening list (SFNSL)**.** Cut-off scores were determined based on TTT results. Thereafter, in another group of 55 sarcoidosis patients the SFNSL was cross-validated. The same cut-off scores were found appropriate. Internal consistency assessment revealed that the different questions of the SFNSL were strongly related to each other (Cronbach`s alpha 0.90). Furthermore, exploratory factor analysis showed that the SFNSL measures only one underlying factor. These results support the idea that SFN is a uniform disease and makes a psychogenetic component explaining for the symptoms of SFN highly unlikely.

Besides fatigue and peripheral pain many sarcoidosis patients report symptoms related to cardiac autonomic dysfunction such as orthostatic intolerance with dizziness, collapses in the shower, or pain in coat hanger area selectively in an upright position. However, as described in chapter 5 and by others, CAFT remain normal in most of them. Recognition of cardiac autonomic involvement is of clinical importance as cardiac autonomic dysfunction has been identified as a strong predictor of morbidity and mortality as this may cause sudden cardiac arrythmias. In ***chapter 9*** we describe the assessment of cardiac sympathetic innervation using ^{123}I-MIBG (metaiodobenzylguanidine) cardiac scintigraphy in sarcoidosis patients. Cardiac sympathetic

dysfunction was present and appeared to be related to SFN. The possible prognostic and therapeutic implications of cardiac sympathetic dysfunction need further study.

There is little doubt that genetic factors play an important role in the genesis of sarcoidosis and an association with the human leucocyte antigen (HLA) was found, in particular the DQB1 gene. In ***chapter 10*** we explored the association between HLA and SFN in sarcoidosis. Low resolution HLA typing was performed for 103 sarcoidosis patients by serological and molecular methods, high resolution DQB1 was obtained by sequence-based typing. SFN was established by TTT. Sixty-seven patients had abnormal TTT (SFN+), 36 patients had normal TTT (SFN-). Comparing HLA typings of SFN+ patients, SFN- patients and control individuals revealed a significant increase of the HLA class II allele DQB1*0602 in SFN+ patients compared to controls. Differences were found in progression of disease. Within the SFN+ group a higher percentage of patients suffered from persistent or current disease compared to the SFN- group. This implicates that both the presence of DQB1*0602 and the occurrence of SFN in sarcoidosis patients might be correlated with a more severe course of the disease.

Although patients report benefit from finally knowing the cause of their symptoms, SFN remains a major problem as therapy has been disappointing so far. Corticosteroids and methotrexate, the mainstay of therapy in sarcoidosis, did not appear to be beneficial in SFN (own observation). Therefore, so far, therapy is mainly symptomatic and directed towards alleviation of neuropathic pain. However, most of the drugs that are efficacious reduce pain intensity only in 30-50%, and such a reduction rarely meets patients` expectations. Furthermore, adequate therapy for autonomic dysfunction is lacking. In ***chapter 11*** we describe a patient with severe SFN with autonomic involvement, who was experimentally treated with infliximab, an anti-TNF-α therapy. His symptoms completely resolved, and his TTT as well as cardiovascular autonomic function test improved substantially after therapy.
This patient reveals two important issues. First, it shows that SFN seems not an irreversible disorder, even in severe cases. Second, TNF-α may be a crucial cytokine in the pathogenesis of SFN in sarcoidosis and presumably also in other immune mediated inflammatory diseases. The logic for the latter is that TNF has been found important in the development of neuropathic pain and has been related to disease activity in neuropathy in Guillain-Barré syndrome. Furthermore, SFN appears to occur frequent in several other immune mediated diseases. Thus, it is tempting to speculate that there might be a final common pathway in these immune mediated diseases resulting in SFN. Hypothetically, this similarity might be cytokine release related.

In conclusion, this thesis describes the spectrum of neurological involvement in sarcoidosis and moreover added and explored a new finding related to sarcoidosis: small fiber neuropathy. SFN appeared to explain some of the so far baffling symptoms in sarcoidosis. The recognition of SFN is important as patients report benefit form knowing the cause of their symptoms, and it may also have implications for health insurances in this group of relatively young patients. Different aspects of SFN in sarcoidosis are discussed, including pain, sleep disturbances, and autonomic cardiac dysfunction which eventually may have prognostic implications. The latter needs further study in longitudinal, prognostic studies. A SFN screening list was developed and validated. This list is easily applicable and not time consuming. In a clinical setting this list is recommended as a screening tool. Moreover, it can be used in future studies. HLA typing revealed that the presence of HLA-DQB1*0602 was related to the presence of TTT abnormalities and to a more severe course of sarcoidosis. Finally, we found in one of our patients that severe SFN completely resolved after anti-TNF-α therapy. This opens many directions for further study.

General discussion

The major conclusion of the current thesis is that SFN is a frequent and novel finding in sarcoidosis. Patients with SFN present a wide spectrum of symptoms such as neuropathic pain, symptoms of autonomic dysfunction such as diarrhoea, sweating, heat intolerance, sexual dysfunction, hot flushes, orthostatic intolerance and sicca syndrome. Moreover, restless legs may be a presenting feature of SFN.[11] Remarkably, SFN and especially symptoms of autonomic dysfunction frequently remain unrecognised. This may be due to the fact that neurologists do not focus on symptoms such as diarrhoea, sweating, flushes and sicca syndrome, and pulmonary and internal physicians are not familiar with the underlying neurological syndromes. Especially those cases without all features of the disorder, just some of them, often remain unrecognised. Moreover, techniques to diagnose SFN are not widely available.

Small fiber neuropathy assessment

TTT appeared to be a useful tool for measuring small fiber sensory impairment.[19] However, TTT is a psychophysical method and therefore requires the cooperation of the patient. This means that this test is liable to loss of attention, especially in older subjects, and to malingering.[19-21]. However, our patient population consists of relatively young patients. Furthermore, by using two types of testing as a control, the method of levels and the method of limits, false positive results may be reduced.[22,23] Moreover, TTT is a test of small nerve fiber function, and does not asses structural pathology.

The assessment of IENFD counting in skin biopsy provides an objective tool for SFN assessment and does assess structural pathology. The technique appears to be promising and deserves further exploration, especially because pathophysiology of SFN may herewith be explored at the site of the symptoms, the small nerve fibers in the skin. However, IENFD assessment is a relatively difficult technique only available in few centers. Normative values appear to vary considerably and before implementing in a clinical setting a subset of healthy controls need to be investigated to determine normative values in every laboratory. Moreover, it has to be explored whether SFN is caused by a reduction of the number of fibers (quantitative effect) or might be caused, at least in part, by impaired function (qualitative effect).

To enable the diagnosis of SFN there is a need for an easily administered instrument, which can be applied to screen for the presence of SFN. For this purpose we established the SFNSL. The SFNSL proved to measure only one underlying factor and supports our clinical observation that the wide spectrum of different symptoms of autonomic dysfunction and neuropathic pain are the result of one underlying condition, small nerve fiber dysfunction. These results strongly argue that SFN is a unified

condition and they argue against a psychogenetic component to the symptoms of SFN. The SFNSL is aimed to be a practical tool in clinical assessment. Furthermore, this list can be used for purposes of research, epidemiological and pathophysiological studies, and to guide the development of further therapy.

Cardiac denervation

We found that cardiac sympathetic denervation occurs in sarcoidosis (chapter 9), and according to our hypothesis, it seems to be related to SFN. ^{123}I-MIBG SPECT appeared a feasible, relatively non-invasive, approach investigating cardiac adrenergic innervation and localizes the territories of reduced sympathetic innervation. An imbalance of the autonomic tone is considered to increase the propensity to develop fatal arrhythmias. It is known from patients with neuropathy in diabetes mellitus, amyloidosis and Guillain-Barré syndrome that the involvement of small autonomic nerve fibers is a predictor of cardiovascular mortality.[7,24] Sudden death in sarcoidosis is a rare but dramatic complication and is thought to be due mostly to cardiac involvement. However, selecting patients at risk is one of the major obstacles facing clinicians.[25] Until now, sympathetic innervation has not been evaluated systematically. In line with our observations, it is recommended that the possibility of autonomic cardiac dysfunction should be considered in the management of sarcoidosis patients. Moreover, careful follow-up is mandatory to evaluate the prognosis. The results of such studies may not only provide new insight in the pathophysiology of arrythmogenesis in sarcoidosis but also have important therapeutic implications, because (pharmacological) interventions or implantation of an intracardial defibrillator (ICD) may reduce arrhythmias in sarcoidosis and presumably also in patients with SFN with involvement of cardiac denervation due to other causes.

Pathogenesis and treatment

The observation that SFN is rather common in sarcoidosis raised a lot of questions, including what the pathogenesis could be and which treatment might be beneficial?
It is remarkable that SFN seems to be frequent in several immune mediated diseases. This leads to the hypothesis that there might be a common pathway in immune mediated diseases resulting in SFN. The idea of an immune mediated mechanism as the cause of SFN has also been reported by others.[26,27] The pathogenetic role of oxidative stress, inflammatory cytokines such as TNF-α and neuropeptides such as substance P (SP) are interesting to explore as a common final pathway in several immune mediated inflammatory diseases.

Tumor necrosis factor-α

The benefit of TNF-α inhibitor treatment in sarcoidosis supports the fact that sarcoidosis is a TNF mediated disease.[28-33] The patient described in chapter 11 with severe SFN showed spectacular improvement after treatment with anti-TNF-α (Infliximab). This case supports the idea that TNF-α may be a crucial cytokine in the pathogenesis of SFN related to sarcoidosis and in SFN related to other immune mediated inflammatory diseases as well. Theoretical support for the effect of anti-TNF-α therapy on SFN may be found in the following. First, TNF-α plays an important role in immune-mediated neuropathies such as Guillain-Barré syndrome, in which small nerve fibers are also involved. [34,35] Elevated serum concentration of TNF-α shows a positive correlation with neuropathy severity in patients with Guillain-Barré syndrome.[34,35] Furthermore, the decrease in serum TNF-α and increase in serum soluble TNF receptors shows a positive correlation with neuropathy recovery following treatment in those patients. Second, pharmacological and physiological studies report that pro-inflammatory cytokines such as TNF-α are strongly involved in the generation and maintenance of neuropathic pain.[36-41]

Substance P

SP is a is a proinflammatory neuropeptide that is secreted by nerves and inflammatory cells such as macrophages, eosinophils, lymphocytes, and dendritic cells.[42] SP acts by binding to the neurokinin-1 receptor (NK-1R) and increases secretion of TNF-α in many cell types. SP is involved in transmission of pain and causes rapid contractions of the gastrointestinal smooth muscle, and modulates inflammatory and immune responses. It has pro-inflammatory effects in inflammatory diseases. In bronchoalveolar lavage fluid obtained from sarcoidosis patients increased SP levels and upregulated NK-1R expression are found.[43-46]

As shown in figure 1.2 of chapter 1 persistent antigenic stimulation together with tumour growth factor (TGF)-β may result in chronic inflammation and fibrosis in sarcoidosis. In the inflammatory process some T-cells produce soluble “immunoproteins” that bind specifically to non-processed antigen (TABM). TABM may function by antigen-specific “targeting” of cytokines, particularly TGF-β. TGF-β associated with TABM will induce the secretion of SP and will amplify the effect of SP on sensory neurons.[47] In figure 12.1 the mechanism is shown by which TABM-TGF-β bind the antigen and thereby activate TGF-β, which increases on one hand SP production by sensory neurons resulting in pain and muscle contraction and on the other hand the production of TNF-α by monocytes. Thus, one may conclude that the neuropeptide SP might - among others - have a role in SFN related to inflammatory diseases.

Oxidative stress

In the discussion of the pathogenesis of SFN the role of oxidative stress also needs further exploration. A growing body of evidence suggests that oxidative stress is implicated in the pathogenesis of diabetic neuropathy.[48-54] Furthermore, a decreased level of nicotinamide adenine dinucleotide phosphatase (NADPH) was found in the erythrocytes of sarcoidosis patients.[55] As NADPH is a necessary factor in the defence against oxidative stress, this suggests a decreased anti-oxidant defence capacity in sarcoidosis. Moreover, sarcoidosis is suggested to trigger an oxidative stress response, which is indicated by an increased activation of nuclear regulatory factor kappa-B (NFκB).[56-58] The possibility exists that in patients with inflammatory disorders in general a decrease of the redox-steate contributes to neuronal changes.

In figure 12.2 treatment strategies for sarcoidosis are presented. As discussed above the possible role of TNF-α and SP may guide new therapeutic approaches and initiate trials. At present it appears interesting to initiate a study of anti-TNF-α therapy in SFN related to sarcoidosis.

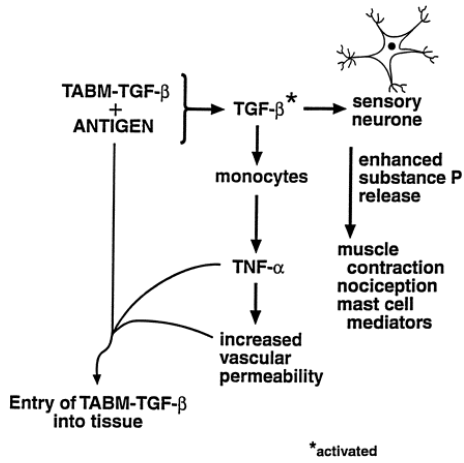

Figure 12.1 A model for the effect of TABM (soluble "immunoproteins" that bind specifically to non-processed antigen): antigen interaction on sensory neurons through TABM-associated tumour growth factor (TGF)-ß. TABM-TGF-ß produced by T cells binds specifically to antigen and TABM-associated TGF-ß is thereby activated. The activated TGF-ß increases the production of substance P by sensory neurons and induces the production of TNF-α by monocytes that increases the entry of TABM into tissue by increasing vascular permeability (Adapted from Cone et al.).[47]

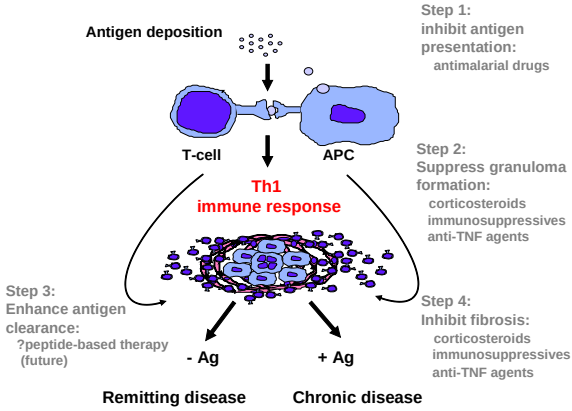

Figure 12.2 Schematic diagram of strategies for treatment of sarcoidosis based on stages of granulomatous inflammation in the disease. Step 1 involves inhibiting pathogenic antigen processing and presentation by antigen-presenting cells (APC) to CD4+ T cells with antimalarial drugs. Suppression of granuloma formation involves the use of Corticosteroids, immunosuppressive drugs and anti-TNF agents. Future peptide-based therapies can be envisioned to enhance or suppress relevant T-cell mediated immune responses that may accelerate disease remission. Finally, reducing fibrosis may be accomplished by suppressing granulomatous inflammation and accompanying tissue injury (adapted with permission from Moller).[64]

There is little doubt that genetic factors play an important role in the genesis of sarcoidosis.[59,60] Newly developed molecular genotyping techniques are now being applied to explore genetic aspects of the disease. It has been found that HLA-DR alleles have prognostic value for the course of sarcoidosis. There is a strong HLA class II association with the development of a persistent disease (HLA-DRB1*15 and HLA-DQB1*0602) or to resolution of the disease (DRB1*03 and DQB1*0201).[61-63] In chapter 10 we describe that HLA-DQB1*0602 and the occurrence of SFN in sarcoidosis patients are associated. Furthermore, it appeared that both might be correlated with a more severe course of the disease. Typing for HLA might prove to be helpful to recognize sarcoidosis patients with suspected severe course in conjunction with development of SFN.

Directions for future studies

Answers to scientific problems are born pregnant with new questions. Several questions that have arisen as a result of the present thesis seem interesting enough for further exploration. What is the most practical and reliable way to diagnose SFN? What are the prognostic implications of the presence of SFN? What is the natural course? Is fatigue related to SFN? What is the pathophysiology? Can we treat SFN and how?
For instance, future studies may further validate the SFNSL. Other tests to assess SFN may be used to validate the SFNSL, such as IENFD in skin biopsy, quantitative sympathetic axon reflex testing (QSART), and eventually newer techniques such as contact-heat evoked potential (CHEPS). This may lead to a higher sensitivity and specificity of the SFNSL. Subsequently, with the SFNSL the presence and prevalence of SFN in other immune mediated diseases may be evaluated.
Furthermore, future studies focussing on the role of cardiac denervation on prognosis and sudden death should be performed. Additionally, longitudinal studies to depict patients that are at risk of developing cardiac conduction disturbances are mandatory. In this regard, it is also of great clinical relevance to explore the preventive efficacy of implantation of an intracardial defibrillator (ICD).

It has been found that different HLA-DR and -DQ alleles have prognostic value regarding the course of sarcoidosis.[61-63] The results described in chapter 10 revealed that there is a difference between sarcoidosis patients with SFN and healthy controls regarding their HLA association. Thus, there might be a genetic predisposition to develop SFN in sarcoidosis. This needs to be explored in larger studies.
TNF-α polymorphism has also been found to have prognostic value for the course of the disease.[65] The TNF family consists of at least 15 cytokines that play an important role in inflammation and immune response and TNF polymorphism may influence the course of sarcoidosis. It is tempting to speculate that TNF polymorphism may influence the development of SFN in sarcoidosis. Thereofore, exploring the relationship of certain polymorphisms with the severity of sarcoidosis and the presence of SFN might guide the development of new therapeutic strategies.

As mentioned before fatigue is a major problem in sarcoidosis and deserves more attention. Up till now no disease activity marker has been found to depict fatigue. Moreover, fatigue may persist even after all parameters assessing disease activity have become within normal limits. However, it has been found that autonomic dysfunction is frequently accompanied by fatigue.[66] Therefore, the correlation of SFN and fatigue

appears interesting to explore, for which the SFNSL (see appendix) and fatigue assessment scale (FAS; appendix) may be helpful. As fatigue is present in many chronic diseases, among which also Guillain-Barré syndrome[67], in this regard the role of cytokines e.g. TNF-α and neuropeptides such as SP on fatigue also appear interesting to explore.
Finally, as RLS is some cases a first sign of SFN[11] and RLS and periodic leg movement disorder (PLMD) are related, the association between SFN and fatigue on one hand and RLS/PLM on the other hand is also interesting to explore.

Answers to these questions may lead to better understanding of the intriguing disorder SFN and sarcoidosis. This may guide more appropriate management of patients. Information can be focussed more to what patients might expect and to better treatment of those suffering from this devastating disorder.

References

1. Zafrir B, Zimmerman M, Fellig Y, Naparstek Y, Reichman N, Flatau E. Small fiber neuropathy due to isolated vasculitis of the peripheral nervous system. *Isr Med Assoc J* 2004;6:183-4.
2. Lacomis D, Giuliani MJ, Steen V, Powell HC. Small fiber neuropathy and vasculitis. *Arthritis Rheum* 1997;40:1173-7.
3. Kaplan JG, Rosenberg R, Reinitz E, Buchbinder S, Schaumburg HH. Invited review: peripheral neuropathy in Sjogren's syndrome. *Muscle Nerve* 1990;13:570-9.
4. Omdal R, Bekkelund SI, Mellgren SI, Husby G. C-fibre function in systemic lupus erythematosus. *Lupus* 1996;5:613-7.
5. Omdal R, Mellgren SI, Goransson L, Skjesol A, Lindal S, Koldingsnes W, Husby G. Small nerve fiber involvement in systemic lupus erythematosus: a controlled study. *Arthritis Rheum* 2002;46:1228-32.
6. Seneviratne U, Gunasekera S. Acute small fibre sensory neuropathy: another variant of Guillain-Barre Syndrome? *J neurol neurosurg psychiatry* 2002;72:540-542.
7. Tuck RR, McLeod JG. Autonomic dysfunction in Guillain-Barre syndrome. *J Neurol Neurosurg Psychiatry* 1981;44:983-90.
8. Wirnsberger RM, De Vries J, Wouters EFM, Drent M. Clinical presentation of sarcoidosis in The Netherlands an epidemiological study. *Neth J Med* 1998;53:53-60.
9. De Vries J, Rothkrantz-Kos S, van Dieijen-Visser MP, Drent M. The relationship between fatigue and clinical parameters in pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2004;21:127-36.
10. Turner GA, Lower EE, Corser BC, Gunther KL, Baughman RP. Sleep apnea in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1997;14:61-4.
11. Polydefkis M, Allen RP, Hauer P, Earley CJ, Griffin JW, McArthur JC. Subclinical sensory neuropathy in late-onset restless legs syndrome [In Process Citation]. *Neurology* 2000;55: 1115-21.
12. Schattschneider J, Bode A, Wasner G, Binder A, Deuschl G, Baron R. Idiopathic restless legs syndrome: abnormalities in central somatosensory processing. *J Neurol* 2004;251:977-82.
13. Jamal GA, Hansen S, Weir AI, Ballantyne JP. The neurophysiologic investigation of small fiber neuropathies. *Muscle Nerve* 1987;10:537-45.
14. Novak V, Freimer ML, Kissel JT, Sahenk Z, Periquet IM, Nash SM, Collins MP, Mendell JR. Autonomic impairment in painful neuropathy. *Neurology* 2001;56:861-8.
15. Holland NR, Crawford TO, Hauer P, Cornblath DR, Griffin JW, McArthur JC. Small-fiber sensory neuropathies: clinical course and neuropathology of idiopathic cases. *Ann Neurol* 1998;44:47-59.
16. Periquet MI, Novak V, Collins MP, Nagaraja HN, Erdem S, Nash SM, Freimer ML, Sahenk Z, Kissel JT, Mendell JR. Painful sensory neuropathy: prospective evaluation using skin biopsy [see comments]. *Neurology* 1999;53:1641-7.
17. Tobin K, Giuliani MJ, Lacomis D. Comparison of different modalities for detection of small fiber neuropathy. *Clin Neurophysiol* 1999;110:1909-12.
18. Stewart JD, Low PA, Fealey RD. Distal small fiber neuropathy: results of tests of sweating and autonomic cardiovascular reflexes. *Muscle Nerve* 1992;15:661-5.
19. Shy ME, Frohman EM, So YT, Arezzo JC, Cornblath DR, Giuliani MJ, Kincaid JC, Ochoa JL, Parry GJ, Weimer LH; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Quantitative sensory testing: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 2003;60:898-904.
20. Dyck PJ, Kennedy WR, Kesserwani H, Kesserwani H, Melanson M, Ochoa J, Shy M, Stevens JC, Suarez GA, O'Brien PC. Limitations of quantitative sensory testing when patients are biased toward a bad outcome [see comments]. *Neurology* 1998;50:1213.
21. Freeman R, Chase KP, Risk MR. Quantitative sensory testing cannot differentiate simulated sensory loss from sensory neuropathy. *Neurology* 2003;60:465-70.

22. Reulen JPH, Lansbergen MD, Verstraete E, Spaans F. Comparison of thermal threshold tests to assess small nerve fiber function: limits vs. levels. *Clin Neurophysiol* 2003;114:556-63.
23. Yarnitsky D, Sprecher E. Thermal testing: normative data and repeatability for various test algorithms. *J Neurol Sci* 1994;125:39-45.
24. Ewing DJ, Campbell IW, Clarke BF. Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications. *Ann Intern Med* 1980;92:308-11.
25. Case records of the Massachusetts General Hospital. Weekly clinicopathological exercises. Case 34-1996. A 50-year-old woman with cardiac disease, an electronic pacemaker, and cardiac arrest in ventricular fibrillation. *N Engl J Med* 1996;335:1378-86.
26. Suarez GA, Fealey RD, Camilleri M, Low PA. Idiopathic autonomic neuropathy: clinical, neurophysiologic, and follow- up studies on 27 patients. *Neurology* 1994;44:1675-82.
27. Gorson KC, Ropper AH. Idiopathic distal small fiber neuropathy. *Acta Neurol Scand* 1995; 92:376-82.
28. Morcos Z. Refractory neurosarcoidosis responding to infliximab. *Neurology* 2003;60:1220-1; author reply 1220-1.
29. Pettersen JA, Zochodne DW, Bell RB, Martin L, Hill MD. Refractory neurosarcoidosis responding to infliximab. *Neurology* 2002;59:1660-1.
30. Yee AM, Pochapin MB. Treatment of complicated sarcoidosis with infliximab anti-tumor necrosis factor-alpha therapy. *Ann Intern Med* 2001;135:27-31.
31. Zabel P, Entzian P, Dalhoff K, Schlaak M. Pentoxifylline in treatment of sarcoidosis. *Am J Respir Crit Care Med* 1997;155:1665-9.
32. Baughman RP, Lower EE, du Bois RM. Sarcoidosis. *Lancet* 2003;361:1111-8.
33. Meyerle JH, Shorr A. The use of infliximab in cutaneous sarcoidosis. *J Drugs Dermatol* 2003; 2:413-4.
34. Radhakrishnan VV, Sumi MG, Reuben S, Mathai A, Nair MD. Serum tumour necrosis factor-alpha and soluble tumour necrosis factor receptors levels in patients with Guillain-Barre syndrome. *Acta Neurol Scand* 2004;109:71-4.
35. Creange A, Belec L, Clair B, Raphael JC, Gherardi RK. Circulating tumor necrosis factor (TNF)-alpha and soluble TNF-alpha receptors in patients with Guillain-Barre syndrome. *J Neuroimmunol* 1996;68:95-9.
36. Sommer C, Marziniak M, Myers RR. The effect of thalidomide treatment on vascular pathology and hyperalgesia caused by chronic constriction injury of rat nerve. *Pain* 1998;74: 83-91.
37. Sommer C, Schafers M. Painful mononeuropathy in C57BL/Wld mice with delayed wallerian degeneration: differential effects of cytokine production and nerve regeneration on thermal and mechanical hypersensitivity. *Brain Res* 1998;784:154-62.
38. Schafers M, Geis C, Brors D, Yaksh TL, Sommer C. Anterograde transport of tumor necrosis factor-alpha in the intact and injured rat sciatic nerve. *J Neurosci* 2002;22:536-45.
39. Opree A, Kress M. Involvement of the proinflammatory cytokines tumor necrosis factor-alpha, IL-1 beta, and IL-6 but not IL-8 in the development of heat hyperalgesia: effects on heat-evoked calcitonin gene-related peptide release from rat skin. *J Neurosci* 2000;20:6289-93.
40. Empl M, Renaud S, Erne B, Fuhr P, Straube A, Schaeren-Wiemers N, Steck AJ. TNF-alpha expression in painful and nonpainful neuropathies. *Neurology* 2001;56:1371-7.
41. Cunha FQ, Poole S, Lorenzetti BB, Ferreira SH. The pivotal role of tumour necrosis factor alpha in the development of inflammatory hyperalgesia. *Br J Pharmacol* 1992;107:660-4.
42. O'Connor TM, O'Connell J, O'Brien DI, Goode T, Bredin CP, Shanahan F. The role of substance P in inflammatory disease. *J Cell Physiol* 2004;201:167-80.
43. Takeyama M, Nagai S, Mori K, Ikawa K, Satake N, Izumi T. Substance P-like immunoreactive substance in bronchoalveolar lavage fluids from patients with idiopathic pulmonary fibrosis and pulmonary sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1996;13:33-7.
44. Brunelleschi S, Nicali R, Lavagno L, Viano I, Pozzi E, Gagliardi L, Ghio P, Albera C. Tachykinin activation of human monocytes from patients with interstitial lung disease, healthy smokers or healthy volunteers. *Neuropeptides* 2000;34:45-50.

45. Brunelleschi S, Guidotto S, Viano I, Fantozzi R, Pozzi E, Ghio P, Albera C. Tachykinin activation of human alveolar macrophages in tobacco smoke and sarcoidosis: a phenotypical and functional study. *Neuropeptides* 1996;30:456-64.
46. O'Connor TM, O'Connell J, O'Brien DI, Bennett MW, Goode T, Burke L, Bredin CP, Shanahan F. Upregulation of neurokinin-1 receptor expression in the lungs of patients with sarcoidosis. *J Clin Immunol* 2003;23:425-35.
47. Cone RE, Georgiou GM, Little CH. Soluble T-lymphocyte antigen-specific immunoproteins: a progress report. *Exp Biol Med (Maywood)* 2002;227:438-44.
48. Manzella D, Barbieri M, Ragno E, Paolisso G. Chronic administration of pharmacologic doses of vitamin E improves the cardiac autonomic nervous system in patients with type 2 diabetes. *Am J Clin Nutr* 2001;73:1052-7.
49. Feldman EL. Oxidative stress and diabetic neuropathy: a new understanding of an old problem. *J Clin Invest* 2003;111:431-3.
50. Low PA, Nickander KK, Tritschler HJ. The roles of oxidative stress and antioxidant treatment in experimental diabetic neuropathy. *Diabetes* 1997;46 Suppl 2:S38-42.
51. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. *Diabetes* 1997;46 Suppl 2:S62-6.
52. Ziegler D, Hanefeld M, Ruhnau KJ, Hasche H, Lobisch M, Schutte K, Kerum G, Malessa R. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a 7-month multicenter randomized controlled trial (ALADIN III Study). ALADIN III Study Group. Alpha-Lipoic Acid in Diabetic Neuropathy. *Diabetes Care* 1999;22:1296-301.
53. Ziegler D, Hanefeld M, Ruhnau KJ, Meissner HP, Lobisch M, Schutte K, Gries FA. Treatment of symptomatic diabetic peripheral neuropathy with the anti-oxidant alpha-lipoic acid. A 3-week multicentre randomized controlled trial (ALADIN Study). *Diabetologia* 1995;38:1425-33.
54. Biewenga G, Haenen GRMM, Bast A. The role of lipoic acid in the treatment of diabetic polyneuropathy. *Drug Metab Rev* 1997;29:1025-54. ,
55. Rothkrantz-Kos S, Drent M, Vuil H, De Boer M, Bast A, Wouters EFM, Roos D, van Dieijen-Visser MP. Decreased redox state in red blood cells from patients with sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2002;19:114-20.
56. Culver DA, Barna BP, Raychaudhuri B, Bonfield TL, Abraham S, Malur A, Farver CF, Kavuru MS, Thomassen MJ. Peroxisome proliferator-activated receptor gamma activity is deficient in alveolar macrophages in pulmonary sarcoidosis. *Am J Respir Cell Mol Biol* 2004;30:1-5.
57. Drent M, van den Berg R, Haenen GRMM, van den Berg H, Wouters EFM, Bast A. NF-kappaB activation in sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 2001;18:50-6.
58. van den Berg R, Haenen GRMM, van den Berg H, Bast A. Transcription factor NF-kappaB as a potential biomarker for oxidative stress. *Br J Nutr* 2001;86 Suppl 1:S121-7.
59. Sharma OP. Tumor necrosis factor polymorphism in sarcoidosis. *Chest* 2001;119:678-9.
60. Yamaguchi E, Itoh A, Hizawa N, Kawakami Y. The gene polymorphism of tumor necrosis factor-beta, but not that of tumor necrosis factor-alpha, is associated with the prognosis of sarcoidosis. *Chest* 2001;119:753-61.
61. Grunewald J, Eklund A, Olerup O. Human leukocyte antigen class I alleles and the disease course in sarcoidosis patients. *Am J Respir Crit Care Med* 2004;169:696-702.
62. Berlin M, Fogdell-Hahn A, Olerup O, Eklund A, Grunewald J. HLA-DR predicts the prognosis in Scandinavian patients with pulmonary sarcoidosis. *Am J Respir Crit Care Med* 1997;156: 1601-5.
63. Sato H, Grutters JC, Pantelidis P, Mizzon AN, Ahmad T, Van Houte AJ, Lammers J-WJ, Van Den Bosch JMM, Welsh KI, du Bois RM. HLA-DQB1*0201: a marker for good prognosis in British and Dutch patients with sarcoidosis. *Am J Respir Cell Mol Biol* 2002;27:406-12.
64. Moller DR. Treatment of sarcoidosis - from a basic science point of view. *J Intern Med* 2003; 253:31-40.
65. Swider C, Schnittger L, Bogunia-Kubik K, Gerdes J, Flad H, Lange A, Seitzer U. TNF-alpha and HLA-DR genotyping as potential prognostic markers in pulmonary sarcoidosis. *Eur Cytokine Netw* 1999;10:143-6.
66. Goldstein DS, Robertson D, Esler M, Straus SE, Eisenhofer G. Dysautonomias: clinical disorders of the autonomic nervous system. *Ann Intern Med* 2002;137:753-63.

67. Merkies IS, Schmitz PI, Samijn JP, van der Meche FG, van Doorn PA. Fatigue in immune-mediated polyneuropathies. European Inflammatory Neuropathy Cause and Treatment (INCAT) Group. *Neurology* 1999;53:1648-54.