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The small fiber neuropathy screening list: Construction and cross-validation in sarcoidosis

Elske Hoitsma [a,b], Jolanda De Vries [b,c,d], Marjolein Drent [b,e,*]

[a] Department of Neurology, Diaconessenhuis, Leiden, The Netherlands
[b] ild care team, Maastricht University Medical Centre (MUMC), Maastricht, The Netherlands
[c] CoRPS, Department of Medical Psychology and Neuropsychology, Tilburg University, Tilburg, The Netherlands
[d] Department of Medical Psychology, St Elisabeth Hospital, Tilburg, The Netherlands
[e] Department of Respiratory Medicine, MUMC, Maastricht, The Netherlands

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Summary
Background: Small fiber neuropathy (SFN) appears to be relatively common in sarcoidosis patients. However, there is no golden standard to establish SFN and diagnostic tests for SFN are not widely available. There is a need for an easy to administer SFN screening instrument for clinical assessment, research or therapeutic trials. The aim of the present study was to develop a screening list to identify sarcoidosis patients with SFN in general clinical practice.
Methods: We studied 139 sarcoidosis patients. The first consecutive 84 patients (Group 1) underwent temperature threshold testing (TTT) and completed an extensive SFN-symptoms-questionnaire. Based on data from Group 1 and using distribution measures and discriminant analyses, a screening list for SFN in sarcoidosis consisting of 21 questions was constructed: the Small Fiber Neuropathy Screening List (SFNSL). Subsequently, this SFNSL was crossvalidated in the next 55 consecutive patients (Group 2).
Results: The same cut-off scores as found for Group 1 were appropriate in Group 2. The SFNSL was found to have high levels of internal consistency (Cronbach's alpha 0.90) and exploratory factor analysis showed that it measures only one underlying factor. Convergent validity seems good.
Conclusion: To assess the presence of SFN in clinical practice the SFNSL, a brief and easy to administer questionaire, was developed in a sarcoidosis population. The results of the present study support the idea that SFN is a serious problem in chronic sarcoidosis. Future studies are needed to establish the broad usefulness of this SFN screening list and expand knowledge on the psychometric properties.

* Corresponding author. Dept. of Respiratory Medicine, ild care team, Maastricht University Medical Centre, P.O. Box 5600, 6202 AZ Maastricht, The Netherlands. Tel.: +31 43 3877043; fax: +31 433875051.
E-mail address: m.drent@mumc.nl (M. Drent).

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Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin.[1,2] Depending on the organs involved and the severity of granulomatous inflammation, patients suffer from a broad range of persistent physical symptoms. Besides respiratory symptoms such as coughing and dyspnea on exertion, patients often suffer from systemic non-specific symptoms such as fatigue, pain and cognitive failure.[3–7]

Pain is considered to be a reflex response to underlying somatic pathology. In a previous study we found that many sarcoidosis patients with peripheral pain appeared to suffer from small fiber neuropathy (SFN) with involvement of autonomic nerve fibers.[8–10] SFN is a generalised peripheral neuropathy selectively involving Aδ and C fibers. When the somatic small afferent fibers are affected, symptoms typically consist of neuropathic pain. Furthermore, autonomic fibers may be involved, causing autonomic dysfunction.[11]

Routinely applied nerve conduction tests as well as tendon reflexes evaluate only large nerve fiber function and consequently remain normal in isolated SFN. Besides, symptoms of autonomic dysfunction are not always sufficiently severe to be mentioned spontaneously by the patient. Furthermore, sarcoidosis patients are generally seen by physicians, such as internists and pulmonologists, who may not be familiar with SFN. Therefore, the diagnosis of SFN can easily be missed. Tests for assessment of small nerve fibers include temperature threshold testing (TTT), quantitative sudomotor axon reflex testing (QSART), intraepidermal nerve fiber density assessment in skin biopsy and laser evoked potentials.[11,12] These tests are not widely available, however.

There is a need for adequate means of assessing the presence of SFN, both for clinical management and also for guidance of the development of further therapies. Assessment of SFN may also be useful in epidemiological and pathophysiological studies. The aim of the present study was to develop a short and easy to administer questionnaire that screens for the presence of SFN in sarcoidosis patients. The TTT was used to diagnose SFN.

Materials and methods

Participants

From 2001 to 2004, 139 (82 males and 57 females) consecutive sarcoidosis patients who visited the outpatient clinic of the University Hospital Maastricht, a referral centre for sarcoidosis, participated in the present study. Patients were diagnosed with sarcoidosis based on consistent clinical features and bronchoalveolar lavage (BAL) fluid analysis or biopsy results, according to the WASOG guidelines.[1] Informed consent was obtained from all participating patients. Relevant co-morbidity only included diabetes mellitus ($n = 7$). Glucose tolerance tests were not performed nor were other causes for SFN tested.

The first consecutive 84 patients seen before August 2003 (49 males and 35 females; mean age 44.2 ± 11.1) were evaluated with an extensive pilot questionnaire (Group 1). Based on these data and using distribution measures and discriminant analyses, a shorter screening list was constructed (see below). Patients seen after August 2003 (Group 2) were used for cross-validation of this screening list. This group consisted of 55 patients (34 males and 21 females; mean age 45.5 ± 10.7). Patient characteristics are summarized in Table 1.

Finally, 15 healthy controls (mean age 33.3 ± 9.8; 8 males, 7 females) were evaluated. Healthy controls were excluded if they had a history of chronic pain, hernia, diabetes, systemic disease, renal disease or alcohol abuse.

Pilot questionnaire of the Small Fiber Neuropathy Screening List (SFNSL)

Based on clinical experience and existing neuropathy questionnaires,[13–21] a pilot questionnaire consisting of 93 questions, covering some 30 different complaints, was constructed. It had three parts: questions in part I (35 questions) concerned presence or absence of complaints; questions in part II (29 questions) were aimed at the frequency of complaints; and part III (29 questions) concerned the severity of the complaints. The response scale for part II ranged from 0 *Never* to 4 *Always* and for part III the scale went from 0 *Never* to 4 *Severe*. The patients in Group 1 who reported pain also completed the Neuropathic Pain Scale.[22]

Temperature threshold testing (TTT)

TTT was used to assess function of small calibre sensory fibers by measuring temperature sensation thresholds. TTT was done with a Medoc TSA-2001 device (Medoc, Ramat Yishai, Israel). Thresholds for warm and cold sensation were determined on the hand and dorsum of the foot on both sides using the method of levels (MLE) and the method of limits (MLI) as described previously.[10] Normative data according to Yarnitsky were used.[23] Temperature sensation was considered abnormal if at least on one side both MLE and MLI testing resulted in *Z* values exceeding 2.5 (above the 99th percentile).[9]

Statistical procedure and construction steps of te SFNSL

Frequencies were used for the characteristics of the patient groups. A number of steps were performed using Group 1 to develop the SFNSL by reducing the number of questions of the pilot questionnaire. First, missing values were examined to identify questions with a percentage of missing values above 10%. Second, remarks from patients concerning the questionnaire were recorded. Furthermore, three series of discriminant analyses were performed starting with (i) the questions from Part II and (ii) the questions from Part III of the pilot questionnaire, and (iii) the remaining questions from Part II and III together. The criteria for the discriminant analyses were the size of the discriminant function, the percentage predicted in the correct category, and reducing the number of questions as much as possible. This resulted in the SFNSL. Subsequently, exploratory factor analysis (principle axis factoring) was performed using the scree test criterion[24] to establish the number of underlying factors measured by the questionnaire and Cronbach's alpha was

Table 1 Summary of the most relevant characteristics of the studied sarcoidosis population.

	Group 1 ($n = 84$)		Group 2 ($n = 55$)	
	TTT normal	TTT abnormal	TTT normal	TTT abnormal
Number of patients	31	53	19	36
Age (year)	37.3 ± 9.8	47.3 ± 10.7*	38.1 ± 8.9	45.1 ± 9.6
Sex (male/female)	12/19	34/19	9/10	25/11
Diabetes (yes/no)	1/30	2/51	1/18	3/33
Time since diagnosis (year)	2.5 ± 3.9	5.8 ± 8.2*	2.4 ± 2.6	5.9 ± 6.6*
Chest X-ray stage (0/I/II/III/IV)	6/4/6/12/3	8/9/18/13/5	3/2/4/4/6	6/8/12/8/2
Prednison (yes/no)	14/17	20/33	8/11	18/19
SFNSL score < 11	21	0	14	0
SFNSL score 11—48	10	37*	5	24*
SFNSL score > 48	0	16	0	12

TTT: temperature threshold testing. SFNSL: Small Fiber Neuropathy Screening List. Data are expressed as absolute numbers and, if appropriate, mean ± standard deviation. No statistical differences were found between group 1 and 2.*$p < 0.05$ between the subgroups with a normal TTT or an abnormal TTT.

employed to measure internal consistency.[25] We used a criterion of 0.70—0.80 to indicate adequate internal consistency.[25] In addition, Pearson correlations and *t*-tests were performed between the SFNSL and the neuropathic pain scale (NPS), depending on the questions of the latter questionnaire, to provide some preliminary information on construct or convergent validity. It is usually accepted that correlations above 0.40 indicate acceptable convergent validity.[26] The SFNSL was than completed by Group 2. The percentage of missing values was checked. Again, exploratory factor analysis (principle axis factoring) was performed and internal consistency was examined. The cut-off scores found in Group 1 were examined on applicability in Group 2. Statistical analyses were performed using the SPSS11.0 for Windows (SPSS, Chicago, IL, USA).

Results

Development of Small Fiber Neuropathy Screening List (SFNSL) in group 1

The examination of the answers to the questions of the first consecutive 84 patients (Group 1) revealed that seven questions had more than 10% missing values. One question concerned the partner and whether he/she informed the patient about frequent leg movement at night and the other questions concerned sexual intercourse related questions. Therefore, we decided to remove these questions from further analyses.

The remaining remarks from the patients concerned part I of the questionnaire. Patients indicated to find it difficult to answer these questions because of the yes/no response category. They were not comfortable with it because of lack of sophistication (not detailed enough). They frequently commented that they wanted to answer 'sometimes' and felt that yes was too strong and no was also not good. For this reason, all questions in part I were left out of the subsequent analyses. Thus, for the statistical analyses 51 questions (25 part II and 26 part III) were used.

Subsequently, three series of discriminant analyses were performed to find out which questions can correctly distinguish patients with normal and abnormal TTT results. These specific questions were selected. In the first series of analyses the questions from Part II, were used. The number of questions was reduced to 10. In the second series of analyses, the same was done for the questions from Part III of the pilot questionnaire. This resulted in 15 questions. In the final series, the remaining questions from parts II and III together (25 questions) were used to group patients according to their SFN status based on their TTT scores. This analysis showed that 83.9% of cases could be correctly classified as having SFN using the discriminant coefficients (Chi-square = 38.93, $p = 0.037$). Finally, we reduced the number of questions to 21 keeping the percentage correctly classified as having SFN at 83.9% (Chi-square = 40.94, $p = 0.006$). This resulted in the Small Fiber Neuropathy Screening List (SFNSL) questionnaire (see Appendix). Subsequently, a total score was made for the SFNSL by summing the scores of the 21 questions. It appeared that a cut-off score of <11 ($n = 21$; 25% of patients) indicated only patients with normal TTT and a cut-off score of >48 ($n = 16$; 19% of patients) indicated only patients with abnormal TTT. In 47 patients a score range from 11 to 48 was found (56%) of which the majority had an abnormal TTT.

Reliability and validity in group 1

Exploratory factor analysis was employed to examine content validity. Herewith the number of underlying factors measured by the questionnaire can be determined using the scree test. The scree test criterion clearly showed that the SFNSL consisted of only one underlying factor.

Furthermore, construct validity of the SFNSL was assessed. Construct validity is the extent to which the SFNSL actually assesses what it is intended to assess. This is examined by assessing the relationship of this questionnaire with other questionnaires. For this purpose the relationship with the neuropathic pain scale (NPS) was examined. Compared with patients without pain (mean SFNSL score = 18.4, SD = 12.1), patients who indicated to have pain (mean SFNSL score = 29.8, SD = 15.4) scored significantly higher on the SFNSL ($t = -2.58$, $p = 0.012$). Furthermore, in patients with pain, the correlation between pain at this moment

(question of the NPS) and the total SFNSL score was 0.49 ($p < 0.001$).

Internal consistency (Cronbach's alpha) was assessed to find out to what extent the different questions of the SFNSL were related with each other. The Cronbach's alpha was 0.89. Correlations between individual items (questions 1 through 21) and the total score of the questionnaire (minus that item) were always significant and positive. The item-total correlations ranged from 0.25 to 0.70.

Cross-validation of the SFNSL in Group 2

The SFNSL was then completed by the following consecutive 55 patients (Group 2). There were no missing values. The cut-off scores provided by Group 1 were also useful in Group 2. Now, 22% ($n = 12$) of the patients had an SFNSL above 48. They all had an abnormal TTT. The percentage of patients with an SFNSL score below 11 was 25% ($n = 14$). These latter cases all had a normal TTT.

Again exploratory factor analysis showed that the SFNSL measured one construct, since the scree test clearly showed one factor. The Cronbach's alpha was 0.90 and the item-total correlations ranged from 0.29 to 0.72.

Total group

Cronbach's alpha for the total scale was 0.90 and item-total correlations ranged from 0.32 to 0.67. Based on TTT results, sensitivity and specificity of the SFNSL was 100% and 31%, respectively, when a cut-off score of 11 is used and 19% and 100%, respectively, when a cut-off score of 48 is used.

Overall, 77 patients (55.4%) had an SFNSL score between 11 and 48, of which 79.2% ($n = 61$) had an abnormal TTT. When subdividing this category into three subcategories the TTT scores appeared to be as follows. In the patients with an SFNSL score between 11 and 24 an abnormal TTT was found in 81.8% ($n = 27$) of the 33 cases, in 71.4% ($n = 20$) of the patients with a score between 24 and 37 ($n = 28$) and in 87.5% ($n = 14$) of the patients with an SFNSL score between 37 and 48 ($n = 16$), respectively.

Healthy controls

All the 15 tested healthy controls had a normal TTT. Moreover, the SFNSL scores of all of them were below 11.

Discussion

A short and easy to administer questionnaire to screen for SFN in sarcoidosis patients was developed. The questionnaire was crossvalidated in a second group. Cut-off scores of below 11 for certainly no SFN and above 48 for certainly SFN were established based on TTT results. The reliability and validity analyses revealed results that exceeded minimum quality standards for an instrument of this kind. Internal consistency revealed that this scale was highly unified, a conclusion supported by content validity assessment that revealed that the SFNSL measured only one underlying factor. These results strongly argue that SFN is a unified condition and they argue against a psychogenetic origin of the symptoms of SFN. Therefore, we recommend the SFNSL as a screenings instrument to assess the possible presence of SFN in the management of patients suffering from sarcoidosis.

The SFNSL was found to be related to the TTT and therefore actually identifies those patients who have an abnormal TTT. Strict TTT criteria were used to diagnose SFN. Both MLE and MLI test results had to exceed the 99% value of a normal population to score TTT results as abnormal. These sharp cut-off scores were used as we wanted a high specificity of TTT in order to be relatively certain which patients do have SFN. Consequently, based on the present results patients with an SFNSL score above 48 can highly likely be diagnosed as suffering from SFN. At the same time a cut-off score for the questionnaire that indicated patients who certainly did not have SFN was mandatory. An SFNSL score below 11 indicated normal TTT results in all the examined patients. Moreover, in the 15 tested healthy controls the SFNSL scores all appeared to be less than 11 and TTT results were all normal. Consequently, an SFNSL score below 11 seems to exclude the presence of SFN.

A large range of patients had an SFNSL score between 11 and 48, indicating possible SFN. In this group of patients 21.4% had normal TTT and 78.6% had an abnormal TTT. We assume that those patients with abnormal TTT results most probably have SFN, based on the strict TTT criteria used. Former studies have found a sensitivity of TTT ranging from 60 to 85%.[9,14,27–30] Thus, patients with a symptom score between 11 and 48 with normal TTT may still have SFN, especially those with SFNSL scores above 37 and more closely to 48. In those cases other tests such as skin biopsy and QSART should be used to further analyse the presence of SFN. Consequently, if the SFNSL is used for screening, aiming at high sensitivity, a cut-off value of 11 appears appropriate.

A limitation of the present study is the fact that a golden standard for the diagnosis of SFN is lacking. We used TTT to diagnose SFN. Reported correlations between SFN screening methods differ.[29,31,32] Consequently, the diagnostic value and cut-off scores of the SFNSL should be examined further in future studies, using also other clinical tests that can be used to diagnose SFN, such as intra-epidermal nerve fiber density assessment in skin biopsy, QSART, laser evoked potentials, corneal confocal microscopy and cardiovascular autonomic function testing. Another limitation is that only sarcoidosis patients participated. Most probably, the SFNSL is also useful in idiopathic SFN or those due to other causes. However, this assumption has to be examined. Moreover, although the range of the time since diagnosis was 0–35 years, it is clear from the results that an abnormal TTT and clinical signs of SFN were more prominent in cases with a longer disease history. Possibly, longer duration of inflammation results in a larger chance of small nerve damage. However, also in patients with a short history of sarcoidosis SFN appeared to be present. The prevalence at different disease durations should be established in future prospective studies to gain more insight in the effect of it. Patients included in this study were patients referred to the sarcoidosis management team of our hospital. We are a tertiary referral centre in the Netherlands for refractory sarcoidosis patients. That means that a lot of the patients

are referred for a second-opinion. Once we have seen the patient we advice a colleague in another hospital in the Netherlands with regard to the diagnosis and management of the patient. This implicates that we not often have follow-up data of these patients. However, 10 patients with a normal TTT at inclusion in the study with an SFNSL score between 11 and 48, were followed. Seven of them (70%) appeared to have an abnormal TTT two years later. In our experience the neuropathy is waxing and waning in the majority of cases. Currently, no appropriate therapy is available. Data using anti-TNF-alpha drugs seem promising.[7,33] Moreover, some patients suffering from SFN may show increasing signs and symptoms over time.[34] However, exact data on progression of SFN in sarcoid patients are not jet available.

As SFN has only recently gained more attention, exact data on prognosis, clinical course, treatment and treatment efficacy are lacking.[33–37] Furthermore, the condition may be easily missed as symptoms of autonomic dysfunction may not always be recalled spontaneously by the patient.[12,35] Moreover, even if reported, symptoms such as diarrhea, micturation disturbances and sweating may not always be recognised as such. In this respect, recognition of SFN is important because it may prevent extensive investigations such as colonoscopy in the case of diarrhea or urodynamic investigation in case of micturation disturbances. And finally, tests for assessment of SFN are not widely available while routinely applied nerve conduction studies and EMG remain normal in SFN patients.

In conclusion, the SFNSL is strongly recommended as first screening tool for various disciplines involved in the management of sarcoidosis patients with possible SFN, such as pulmonologists, neurologists, rheumatologists, etc. The SFNSL is a practical, brief and easy to assess tool in screening for the presence of SFN. It is brief and offers the possibility of ready use in the management and follow-up of sarcoidosis patients with suspected SFN in clinical practice, in epidemiological and pathophysiological research, and in clinical trials.

Appendix: Small fiber neuropathy screening list

Below are a number of questions about possible complaints. Please circle the answer to each question that is applicable to you. Please give an answer to each question, *even if you do not have any complaints at the moment*.

The aim of this questionnaire is to find out how you experience your complaints. There are no correct or incorrect answers. It is important that you are honest.

Part 1:
These questions are aimed at finding out *how often* you experience the following complaints.

1. I have painful arms	never/sometimes/variably/often/always
2. I suffer from palpitations	never/sometimes/variably/often/always
3. I have problems with my bowel movements	never/sometimes/variably/often/always
4. I have difficulties with urinating (either in emptying my bladder or being able to hold my water)	never/sometimes/variably/often/always
5. My food does not seem to go down well	never/sometimes/variably/often/always
6. I suffer from muscle cramps	never/sometimes/variably/often/always
7. My feet and/or hands are colder than I am used to	never/sometimes/variably/often/always
8. I have chest pain	never/sometimes/variably/often/always

Part 2:
These questions are aimed at finding out *how serious* your complaints are.

9. I have the feeling that my food gets stuck in my throat	not at all/slightly/variably/moderately/seriously
10. At night I throw the bedclothes off my legs	not at all/slightly/variably/moderately/seriously
11. I have difficulties with urinating (either emptying my bladder or being able to hold my water)	not at all/slightly/variably/moderately/seriously
12. I have dry eyes	not at all/slightly/variably/moderately/seriously
13. I have blurred vision	not at all/slightly/variably/moderately/seriously
14. I feel dizzy when I get up	not at all/slightly/variably/moderately/seriously
15. I have sudden hot flushes	not at all/slightly/variably/moderately/seriously
16. My feet and/or hands are colder than I am used to	not at all/slightly/variably/moderately/seriously
17. I have painful arms	not at all/slightly/variably/moderately/seriously
18. The skin of my legs is over-sensitive	not at all/slightly/variably/moderately/seriously
19. I have a tingling sensation in my hands (pins and needles)	not at all/slightly/variably/moderately/seriously
20. I have a tingling sensation in my legs (pins and needles)	not at all/slightly/variably/moderately/seriously
21. I have chest pain	not at all/slightly/variably/moderately/seriously

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Conflict of Interest

None of the authors have any conflict of interest to report.

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