

Chapter 8

The Small Fiber Neuropathy Screening List: Construction and cross-validation in sarcoidosis

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Abstract

Background and aim

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 easily 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.

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.

Conclusions

We developed a brief and easy to administer screening list to assess SFN in sarcoidosis. The results of the present study support the idea that SFN is a relatively uniform disorder. Future studies in patient populations suffering from SFN associated with other causes are needed to establish the broad usefulness of this SFN screening list and expand knowledge on the psychometric properties.

Introduction

Sarcoidosis is a disseminated granulomatous disease of unknown origin.¹ 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 dyspnoea on exertion, patients often suffer from systemic non-specific symptoms such as fatigue and pain.²⁻⁶

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.^{7,8} SFN is a generalised peripheral neuropathy selectively involving A δ 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.

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.⁹ 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.

Patients and methods

Participants

From 2001 to 2004, 139 (82 males and 57 females) 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).

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 8.1.

Finally, 15 healthy controls (mean age 33.3 ± 9.8; 8 males, 7 females) were evaluated.

Table 8.1 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 (years)	37.3 ± 9.8	47.3 ± 10.7*	38.1 ± 8.9	45.1 ± 9.6
Sex (males / females)	12 / 19	34 / 19	9 / 10	25 / 11
Diabetes (yes / no)	1 / 30	2 / 51	1 / 18	3 / 33
Time since diagnosis (years)	2.5 ± 3.9	5.8 ± 8.2*	2.4 ± 2.6	5.9 ± 6.6*
Chest X-ray stage (0/1/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

TTT: temperature threshold testing. 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.

Pilot questionnaire of the small fiber neuropathy screening list (SFNSL)

Based on clinical experience and existing neuropathy questionnaires,¹⁰⁻¹⁹ 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.²⁰

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.⁶ Normative data according to Yarnitsky were used.²¹ 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).⁸

Statistical procedure and construction steps of the 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 screetest criterion²² to establish the number of underlying factors measured by the questionnaire and Cronbach's alpha was employed to measure internal consistency.²³ We used a criterion of 0.70-0.80 to indicate adequate internal consistency.²³⁻²⁵ 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 then 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 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 (25.8% of patients) indicated only patients with normal TTT and a cut-off score of > 48 (18.9% of patients) indicated only patients with abnormal TTT. A score range from 11 to 48 indicated a group of patients in which 33% had normal TTT and 67% had abnormal TTT (Figure 8.1).

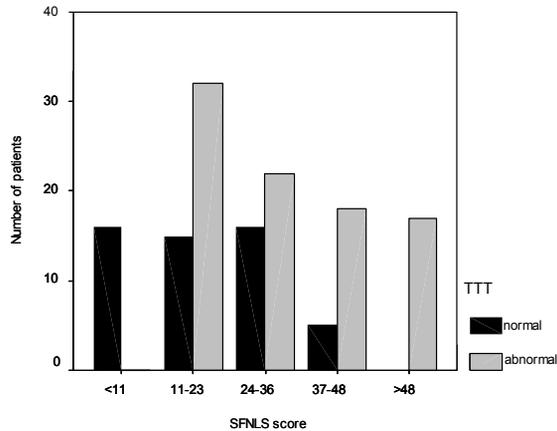


Figure 8.1 Temperature threshold testing (TTT) results in a group of sarcoidosis patients with a small fiber neuropathy screening list (SFNSL) score below 11, in a group of sarcoidosis patients with a SFNSL score from 11 to 23, from 24 to 36, from 37 to 48 and in a group of sarcoidosis patients with a SFNSL score above 48.

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 screetest. The screetest 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.²⁸ 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, 19.4% of the patients had an SFNSL above 48. They all had an abnormal TTT. The percentage of patients with a SFNSL score below 11 was 38.1%. They 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 0.32-0.67. 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 (figure 8.1).

Healthy controls

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

Discussion

We have developed a short and easy to administer questionnaire to screen for small fiber neuropathy (SFN) in sarcoidosis patients. The questionnaire was cross-validated in an other sarcoidosis patient group. Cut-off scores of below 11 for certainly no SFN and above 48 for certainly SFN were established based on temperature threshold testing (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 component to the symptoms of SFN.

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 preferred a high specificity of TTT in order to be relatively certain which patients do have SFN. Consequently, based on the present results patients with a SFNSL score above 48 can almost certainly be suspected of suffering from SFN. We strived to develop a screening list with the highest possible sensitivity because SFN is a disorder that probably develops over time with increasing symptom severity. Since a strict criterion for SFN was defined using TTT, it is possible that a considerable number of patients are suffering from SFN-related symptoms, but do not yet meet the TTT criteria. With these strict cut-off values it is possible to indicate which patients certainly have no SFN (SFNSL score below 11) and definitive do have SFN (SFNSL score above 48). In the intermediate group of patients 33% had normal TTT and 67% had abnormal TTT. These patients should be carefully monitored and tested for the presence of SFN. All 15 tested healthy controls had normal TTT results and SFNSL scores were all below 11. Thus, based on the results in healthy controls and the results in both groups sarcoidosis patients a SFNSL score below 11 seems to exclude the presence of SFN.

One of the limitations that this and other studies have to face is that unfortunately a proper gold standard to diagnose SFN is still lacking. SFN is clinically defined by paresthesias (abnormal sensations), pain, and sometimes numbness, in combination with normal strength and normal nerve conduction studies.⁹ A number of investigative tools are now available for confirming the diagnosis. TTT reaches sensitivity of 60-85%, and the test is validated and standardized.^{31,32} Epidermal nerve fiber density analysis has been used extensively by several groups, and sensitivities of 74.0-87.5% are reported.³² This latter method, however, is technically difficult and not widely available. The sparse availability of diagnostic tests for SFN urges for an easy to administer screening instrument. In the present study we used TTT to diagnose SFN, which, as already mentioned, does not reach 100 percent sensitivity. Therefore, 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 and cardiovascular autonomic function testing.

In the present study only sarcoidosis patients participated. Presumably, the SFNSL is also useful in idiopathic SFN or those due to other causes. However, this assumption has to be examined.

As SFN has only recently gained more attention, exact data on prognosis, clinical course and treatment efficacy are lacking. Furthermore, the condition may be easily missed as symptoms of autonomic dysfunction may not always be recalled spontaneously by the patient. Moreover, even if reported, symptoms such as diarrhoea,

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 diarrhoea 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. Moreover, the SFNSL can be easily used by physicians including pulmonologists who often are involved in the follow-up of sarcoidosis patients and are not so familiar with the clinical picture of SFN. Especially, the SFNSL might be helpful to distinguish those patients without SFN from those with probably or highly likely SFN. Therefore, the SFNSL is recommended as first screenings tool for various disciplines seeing patients with possible SFN.

Conclusion

In conclusion, the SFNSL is aimed to be a practical tool in screening for the presence of SFN. It is brief and offers the possibility of ready use in clinical practice, in epidemiological and pathophysiological research, and in clinical trials.

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