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Clinical Neurophysiology 114 (2003) 2326–2333

www.elsevier.com/locate/clinph

Abnormal warm and cold sensation thresholds suggestive of small-fibre neuropathy in sarcoidosis

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Accepted 17 July 2003

Abstract

Objective: A substantial number of sarcoidosis patients report apparently non-specific symptoms such as pain, for which no organic substrate has yet been found. Recently we observed symptoms suggestive of small-fibre neuropathy in a group of sarcoidosis patients. The aim of the present study was to verify this observation using various electrophysiological tests.

Methods: In 74 sarcoidosis patients complaining of symptoms suggestive of small-fibre neuropathy, thresholds for warm (WS) and cold sensation (CS) as well as for heat pain were determined at the thenar eminence and the foot dorsum. Furthermore, sympathetic skin responses (SSR), nerve conduction studies and concentric needle electromyography were performed. In 31 patients, cardiovascular autonomic testing was carried out.

Results: Thermal threshold testing (TTT) revealed abnormalities in 51 of the 74 patients. Abnormalities showed an asymmetrical distribution. WS was affected more often than CS and feet more often than hands. Nerve conduction studies in the legs showed slightly abnormal results in 6 patients; all of these had abnormal TTT results. The SSR was absent at the foot in 7 patients. Cardiovascular autonomic testing was abnormal in only a single patient.

Conclusions: In a subgroup of sarcoidosis patients we found TTT abnormalities suggestive of small-fibre neuropathy. SSR and cardiovascular autonomic testing appeared to be of little diagnostic value. Small-fibre neuropathy may be the cause of a number of hitherto unexplained symptoms in sarcoidosis.

Keywords: Sarcoidosis; Thermal threshold testing; Small-fibre neuropathy

1. Introduction

Sarcoidosis is a multi-organ disorder of unknown origin, characterized by granuloma formation, which is probably antigen driven. The disease occurs throughout the world, although prevalence varies among ethnic and racial groups. Prevalence ranges from 10 to 40 per 100 000 population, mostly young adults of either gender (Newman et al., 1997). The clinical manifestation of sarcoidosis is highly variable, depending on the intensity of the inflammation and the organ systems affected. Sarcoidosis occurs most frequently in the lungs or lymph nodes, although it can appear in other organs. Spontaneous recovery may occur, but the disease can also become chronic or have a progressive course. Apart from pulmonary symptoms such as dyspnea and coughing, patients often complain of symptoms such as fatigue, pain and sweating (James, 1993; Wirnsberger et al., 1998; Sharma, 1999; Hoitsma et al., 2003). So far, no organic substrate has been found for these symptoms. Treatment of sarcoidosis consists largely of immunosuppressive drugs such as steroids, methotrexate, cyclosporin and, more recently, infliximab (Baughman and Lower, 2001). When features of disease activity, for example radiological abnormalities and lung function impairment, resolve during treatment, fatigue and pain may persist. Therefore, objective test results such as chest X-ray and laboratory parameters do

Abbreviations: CS, cold sensation; ΔZ, absolute Z value side difference; EMG, electromyography; MLE, method of levels; MLI, method of limits; SSR, sympathetic skin response; TTT, thermal threshold testing; WS, warm sensation.

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1388-2457/$30.00
doi:10.1016/S1388-2457(03)00259-1

not always correlate with the well-being of the patient (Wirnsberger et al., 1998). Consequently, the question arises whether these symptoms are psychogenic or manifestations of the underlying organic disease.

Recently, we observed a pattern of symptoms suggestive of small-fibre neuropathy with autonomic involvement in a subset of sarcoidosis patients (Hoitsma et al., 2002).

Small-fibre neuropathy is a generalized peripheral neuropathy selectively involving Ad and C fibres. When the somatic small afferent fibres are affected, symptoms typically consist of pain, dysaesthesias and disturbed temperature sensitivity. Furthermore, autonomic fibres may be involved, causing autonomic dysfunction. Standard nerve conduction tests evaluate only large nerve fibre function. Quantitative techniques for the assessment of small nerve fibres are not routinely applied. Therefore, the diagnosis of small-fibre neuropathy can easily be missed.

Quantitative sensory testing has become an important tool in assessing small and large sensory fibre functions. Small-calibre sensory fibres are assessed by temperature threshold testing (TTT) and large-calibre fibres by vibratory threshold testing. TTT quantifies thresholds for warm and cold perception (Fruhstorfer et al., 1976; Jamal et al., 1987; Yarnitsky and Sprecher, 1994; Reulen et al., 2003). It is a non-invasive method, easy to perform, and mostly not painful. Furthermore, the testing does not require highly trained personnel.

Autonomic neuropathy can be assessed by cardiovascular autonomic reflex testing on the basis of heart rate variability and blood pressure investigations (Ewing and Clarke, 1982). Small-fibre sudomotor function can be assessed, among other functions, by the sympathetic skin response (SSR). Although the diagnostic value of SSR is limited, it is widely available and inexpensive. Quantitative sudomotor axon reflex testing (QSART) is a more sensitive technique for sudomotor assessment, but it requires special equipment which is available in only a few centres.

The aim of the present study was to investigate small fibre sensory function by determining TTT, EMG, SSR and cardiovascular autonomic tests in a subset of sarcoidosis patients.

2. Patients and methods

2.1. Patients

From August 2000 to July 2002, 125 patients with sarcoidosis, confirmed according to international guidelines (Hunninghake et al., 1999) were referred to the Maastricht Sarcoidosis Management Center, which serves as a tertiary referral centre for sarcoidosis patients in the Netherlands. A group of 74 patients (41 men, 33 women) were included in the present study. To be included, patients had to recall symptoms suggestive of small-fibre neuropathy (a combination of two or more of the following symptoms: peripheral pain, paraesthesias, intolerance of bedclothes, hyperhidrosis, hypohidrosis, sicca syndrome, facial flushing, diarrhoea, constipation, micturition disturbances, and male sexual dysfunction). Patients with diabetes, alcohol abuse, or renal insufficiency were excluded. Patient characteristics are summarized in Table 1. The 51 patients not enrolled in the study consisted of 31 males and 20 females, age 43.2 ± 11.1 and time since diagnosis in this group was 5.1 ± 6.4 years. All included patients underwent TTT, EMG and SSR. In the first 31 patients cardiovascular autonomic testing was performed.

2.2. Thermal threshold testing (TTT)

2.2.1. Equipment

All tests were performed using a TSA 2001 (Medoc, Ramat Yishai, Israel), which operates on the Peltier principle. A rectangular stimulator thermode with a surface of 3.2 × 3.2 cm was used for cutaneous stimulation. Thermode baseline temperature was 32 °C. In order to prevent thermal injury and to protect the Peltier element the high temperature limit was 50 °C and the lower limit 0 °C.

2.2.2. Test algorithms

The method of levels (MLE) and method of limits (MLI) were used. (Claus et al., 1990; Kemler et al., 2000; Reulen et al., 2003).

Table 1
Summary of the characteristics of the 74 sarcoidosis patients with symptoms suggestive of small-fibre neuropathy

	TTT normal ($n = 23$)	TTT abnormal ($n = 51$)
Male/female, (n)	9/14	32/19*
Age (years)[a]	42.9 ± 11.7 (25–65)	45.3 ± 11.7 (19–80)*
Time since diagnosis (years)[a]	3.8 ± 4.0 (0.5–12)	5.7 ± 6.8 (0.5–17) *
CXR 0/I/II/III/IV (n)	5/1/7/7/3	11/7/10/18/5*
ACE (U/l)	20.9 ± 11.1	24.1 ± 14.6#
Smoking, no/yes (n)	19/4	45/6*
Prednisone, no/yes (n)	11/12	24/27*
Other immunosuppressive therapy (prednisone + MTX), no/yes (n)	18/5	37/14*

TTT, thermal threshold testing; n, number of cases; CXR, chest radiographs graded according to DeRemee (0 to III), adding stage IV, the end stage of lung fibrosis (Hunninghake et al., 1999); ACE, angiotensin-converting enzyme, normal range: 9–25 U/l; MTX = methotrexate. *P = not significant.

[a] Data are expressed as mean ± SD with range in parentheses;

2.2.2.1. MLE. Subjects were asked to press YES on a switch held in the free hand if a thermal sensation was perceived and NO if this was not the case. For warmth there was an initial temperature step of 2 °C with the temperature returning to baseline immediately upon stimulus termination. After the first YES response the stimulus decreased by one-half of the initial step until a NO was given. Subsequently the step was halved for each successive stimulus and the direction changed according to the response: increase for NO, decrease for YES. The procedure was continued until the step size reached 0.1 °C. For cold an initial temperature step of 1 °C was given, this being the only difference compared with the procedure to assess the warm perception threshold. To optimize alertness, an auditory cue was given at stimulus onset. At random no change of temperature occurred (dummy stimulus) after an acoustic alert.

2.2.2.2. MLI. The test was performed with a rate of temperature change of 1 °C/s. Subjects were asked to press a switch held in the free hand immediately upon thermal sensation. Five readings at each recording site were obtained for each thermal sensation, and the results were averaged to obtain a single threshold score. An auditory cue at stimulus onset was given to optimize alertness. Patients were told in advance whether a cold or warm temperature stimulus was to be given and were instructed not to react until an obvious thermal sensation was perceived.

2.2.2.3. Heat pain. The procedure was the same as for MLI warm sensation. Subjects were asked to react immediately upon pain sensation. The order of tests was in all cases as follows: MLI for warm sensation (WS), MLI for cold sensation (CS), MLE for WS, MLE for CS, MLE for heat pain. The tests were performed in a draught-free, sound-proof room at a room temperature of 20 °C. The patient relaxed on a recliner without visual access to the display screen.

2.2.3. Test sites

Thresholds were assessed at the foot dorsum and thenar eminence on both sides. The thermode was attached to the skin by means of elastic Velcro tape. Care was taken to minimize the variation of the thermode application pressure. Duration of the examination ranged from 40 to 60 min.

2.3. Sympathetic skin response (SSR)

At irregular intervals of between 4 and 10 s the median nerve was stimulated at the wrist with pulses of 0.2 ms and amplitudes between 20 and 50 mA. Skin responses were recorded from the contralateral hand and foot. Room temperature was between 22 and 25°C and skin temperature was at least 32 °C. For recording Ag-AgCl electrodes were used. The active electrodes were on the palm of the hand and the sole of the foot, respectively, and the reference electrodes on the dorsal side of the hand and the foot. Filter settings were 2 Hz and 2 kHz. The patient was lying supine on the examination table. From each hand and foot 3 or 4 responses were recorded. Only absence of response was considered abnormal.

2.4. Cardiovascular autonomic function testing

Cardiovascular autonomic function was assessed using 5 tests recommended by the San Antonio Consensus Meeting (American Diabetes Association, 1988). Heart rate variability (HRV) and blood pressure were measured while the patient rested in a supine position for about 10 min, while the patient remained standing for about 5 min, during deep respiration (respiratory sinus arrhythmia) with a frequency of 0.1 Hz, during a Valsalva manoeuvre (forced expiration against 40 mm Hg during 15 s) and while rapidly changing posture from supine to upright. HRV was measured using a computerized system for automatic ECG QRS-complex detection and interval analysis. The following time and frequency parameters were determined for the different tests and compared with age-corrected reference values (Lanting, 1990). Lying supine and standing: coefficient of variation CV (CV = standard deviation × 100%/mean), the quotient of maximal and minimal heart rate, the spectral peak frequency in the mid-frequency range 0.5–0.15 Hz, and the difference in mean heart rate between standing and lying; Valsalva test: Valsalva ratio; respiration test: successive maximal expiration-inspiration difference; lying-to-standing: initial change in heart rate, 30/15-ratio and with 1 min interval manually measured sphygmomanometric systolic and diastolic blood pressure. Cardiovascular autonomic function was classified abnormal if at least 2 of the 5 tests were abnormal.

2.5. Nerve conduction studies and EMG

In all patients motor nerve conduction of the peroneal nerve, sensory conduction of the sural nerve, as well as the soleus H reflex were measured on both sides. In 6 of them, with TTT abnormalities limited to the hands, sensory conduction of the median and ulnar nerves was measured over the wrist-ringfinger segment. All nerve conduction studies were performed with surface electrodes using standard techniques. For the H reflex, values were taken from Visser et al. (1983). For peripheral motor and sensory nerve conduction studies, normal values of the own clinical neurophysiology department were used.

Needle-EMG was performed on both tibialis and gastrocnemius muscles in all patients.

2.6. Calculations and statistical analysis

Age and sex related reference values for WS and CS thresholds were taken from Yarnitsky and Sprecher (1994). These authors used the same apparatus, thermode size, and

stimulation protocol as we did in the present study. Classification of abnormality was based on Z value statistics. The Z value indicates how far and in what direction the measured value deviates from the mean of the reference distribution, expressed in units of the reference distribution's standard deviation. A measurement was considered abnormal when its Z value exceeded 2.5. For a sensation at an extremity to be classified as abnormal, results of both MLI and MLE testing had to be abnormal.

The relation between MLE and corresponding MLI Z values was established by simple linear regression analysis. Differences in median values of absolute right minus left Z values were compared using Mann-Whitney U test.

3. Results

3.1. Temperature threshold testing

TTT results at any measured site were considered abnormal only if both MLE and MLI were abnormal. This was the case in 51 of the 74 patients with symptoms suggestive of small-fibre neuropathy (69%). Of these 51 patients 28, 7 and 16 showed only WS, only CS, and both WS and CS abnormalities, respectively (Table 2). TTT findings were more often abnormal in the feet than the hands (54 vs. 38%). However, a combination of abnormal temperature sensation in the hands and normal temperature sensation in the feet occurred in 11 patients (15%). Foot WS was more often abnormal in men than in women (23 males vs. 5 females; male/female ratio = 3.3). Other abnormalities were equally distributed among males and females. Allodynia was found in 5 cases (7%) and always found in combination with other TTT abnormalities.

The distribution of abnormalities is shown in Table 3. TTT abnormalities were bilateral in 19 patients and unilateral in 22 patients. In 10 patients a combination of unilateral and bilateral abnormalities was found. Both for unilateral and bilateral TTT abnormalities the absolute value of the side difference in Z value (ΔZ) was calculated for WS and CS in both the hand and the foot. Absolute values were calculated in order to classify right-left and left-right differences in a comparable way. Median values and their interquartile ranges were computed per extremity and modality for unilateral abnormalities, bilateral abnormalities and normal thermal thresholds (Table 4). The median value of the side difference was significantly larger in unilateral abnormalities than the corresponding value in normal TTT results. This holds for thenar and foot WS and foot CS. Except for thenar WS, ΔZ was also significantly greater in bilateral abnormalities than in normal TTT results. Only for WS in the foot was ΔZ significantly lower for bilateral than for unilateral abnormal TTT values.

Two different measuring methods, MLE and MLI, were applied. The correspondence between the results of both methods at a single recording site was illustrated and quantified by plotting for every patient the MLI Z value as a function of the MLE Z value. This scatter plot of MLI vs. MLE Z values for WS in the right foot is illustrated in Fig. 1. Obviously there is a significant linear correlation ($r = 0.89$, $P < 0.001$) between MLI and MLE Z values. Similar linear correlation values were found for the other sites and modalities (mean $r = 0.81$, range 0.58–0.89). Regarding abnormality, both methods may be complementary to each other or may give supplementary information. Four areas in the MLI vs. MLE scatter plot can be distinguished (see Table 5), namely: area I (MLI $Z \leq 2.5$ and MLE $Z \leq 2.5$), area II (MLI $Z \leq 2.5$ and MLE $Z > 2.5$), area III (MLI $Z > 2.5$ and MLE $Z \leq 2.5$) and area IV (MLI $Z > 2.5$ and MLE $Z > 2.5$). In Table 5 the percentages as distributed over the different areas are summarized. Overall correspondence between the results of both tests was found to be 83.5% (range 78–89%). No consistent pattern was found in cases of disagreement. For WS in the hands (9.3 vs. 9.2%) there was no difference, whereas for WS in the foot (18 vs. 4%) and CS in the hand (7.3 vs.3.7%) MLE resulted in more abnormalities than MLI. Finally, for foot CS, MLI showed more abnormalities than MLE (10.8 vs. 2.5%).

3.2. Sympathetic skin response (SSR)

In 7 of the 74 patients suspected of small-fibre neuropathy, the SSR could not be recorded in the foot. TTT results were normal in 3 of these patients; WS in the hand was abnormal in 1 patient; CS in the foot was abnormal in 1 patient; and in 2 patients both WS and CS in the foot were abnormal.

3.3. EMG and nerve conduction studies

EMG of lower leg muscles did not reveal any abnormality. Nerve conduction studies showed an absent soleus H reflex in 3 patients (4%). Slightly decreased nerve conduction velocities were found in 3 other patients. These

Table 2
Thermal threshold testing (TTT) results for warm sensation and cold sensation in 74 sarcoidosis patients with clinical symptoms suggestive of small-fibre neuropathy

	Normal cold sensation, *n* (%)	Abnormal cold sensation, *n* (%)	Total, *n* (%)
Normal warm sensation	23 (31.1)	7 (9.5)	30 (40.6)
Abnormal warm sensation	28 (37.8)	16 (21.6)	44 (59.4)
Total	51 (68.9)	23 (31.1)	74 (100.0)

Table 3
Distribution of thermal threshold testing (TTT) results over the extremities in 74 sarcoidosis patients with symptoms suggestive of small-fibre neuropathy

	No abnormalities, *n* (%)	One hand, *n* (%)	Both hands, *n* (%)	One foot, *n* (%)	Both feet, *n* (%)
No abnormalities	23 (31.1)	–	–	–	–
One hand	–	7 (9.4)	–	2 (2.7)	5 (6.8)
Both hands	–	–	4 (5.4)	5 (6.8)	5 (6.8)
One foot	–	2 (2.7)	5 (6.8)	13 (17.6)	–
Both feet	–	5 (6.8)	5 (6.8)	–	10 (13.5)
	23 (31.1)	14 (18.9)	14 (18.9)	20 (27.0)	20 (27.0)

Table 4
Comparison of median values of absolute right minus left *Z* value differences in normal thermal threshold testing (TTT) results (A), bilateral TTT abnormalities (B) and asymmetrical TTT abnormalities (C), in 74 sarcoidosis patients with symptoms suggestive of small-fibre neuropathy

	Median[a] (IQR)			
	Thenar warm	Thenar cold	Foot warm	Foot cold
A: TTT normal	0.88 (0.7)	0.51 (0.6)	0.80 (0.7)	1.05 (1.2)
B: TTT bilaterally abnormal	4.61 (4.5)	5.20 (3.2)	0.60 (0.6)	3.20 (2.6)
C: TTT unilaterally abnormal	4.12 (1.4)	np	2.49 (0.7)	3.54 (0.8)
P value[b]				
A vs. B	**< 0.0001**	**0.001**	0.22	**0.002**
B vs. C	0.85		**< 0.0001**	0.21
A vs. C	**< 0.0001**		**< 0.0001**	**< 0.0001**

IQR, interquartile range; np, not present.
[a] Median of absolute differences in *Z* value between right and left side.
[b] Mann-Whitney *U* test.

6 patients all had abnormal TTT results. In 6 of the 11 patients with isolated TTT abnormalities in the hands, median nerve conduction in the wrist was normal.

3.4. Cardiovascular autonomic reflex tests

Of the first consecutive 31 patients, only a single patient showed abnormality of heart rate variability indicative of cardiovascular autonomic dysfunction. Therefore, and because autonomic tests are relatively time consuming we decided not to perform autonomic tests in the following 43 patients.

4. Discussion

To the best of our knowledge we are the first to report TTT abnormalities suggestive of small-fibre neuropathy in

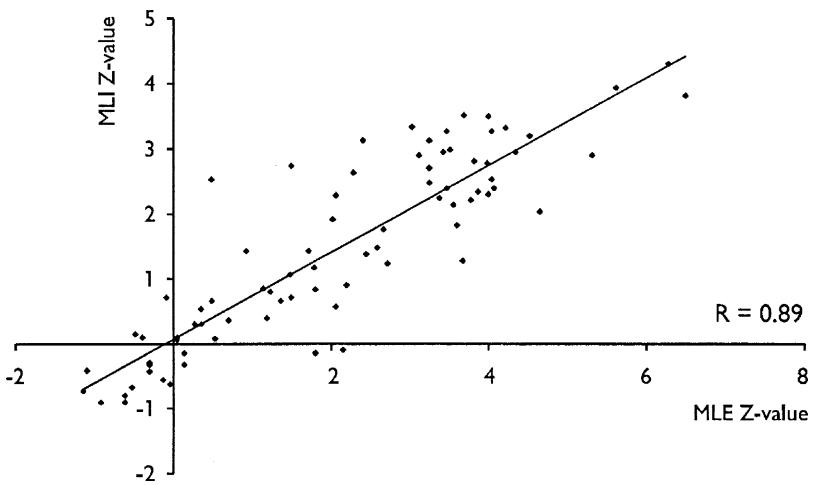

Fig. 1. Method of limits (MLI) *Z* value as a function of method of levels (MLE) *Z* value in a group of 74 sarcoidosis patients with clinical symptoms suggestive of small fiber neuropathy. Data are for warm sensation in the right foot. Linear correlation coefficient $R = 0.89$ ($P < 0.001$).

Table 5
Comparison of results by method of limits (MLI) and method of levels (MLE) in 74 patients with symptoms suggestive of small-fibre neuropathy. Numbers I through IV denote the 4 areas of the MLE-MLI scatter plot

	I and IV	II	III
Warm thenar	81.5	9.2	9.3
Warm foot	78.0	18.0	4.0
Cold thenar	89.0	7.3	3.7
Cold foot	85.5	2.5	10.8
Mean (range)	83.5 (78.0–89.0)	9.5 (2.5–18.0)	7.0 (3.7–10.8)

Results per test site were divided into 3 groups: MLE and MLI both normal (I) or both abnormal (IV); MLE abnormal whereas MLI is normal (II); MLI abnormal whereas MLE is normal (III). Abnormal: $Z > 2.5$. Percentages per group are shown for each modality and test site.

sarcoidosis, possibly explaining symptoms which so far have often been considered to be 'non-specific.' Fifty-one out of 74 patients with symptoms suggestive of small-fibre neuropathy had abnormal TTT results.

WS was more often affected than CS (59 vs. 31%). CS abnormalities in combination with normal WS were present in 7 of the 74 cases. Thus, unmyelinated C fibres seemed to be more involved than Ad fibres. However, as reported before in idiopathic small-fibre neuropathy (Jamal et al., 1987), sometimes Ad fibres seem to be selectively involved. Disturbed temperature sensation occurred more frequently in the feet than in the hands. This finding might be due to a greater vulnerability of the longest fibres. Length dependent axonal degeneration has indeed been reported in small-fibre neuropathy (McCarthy et al., 1995; McArthur et al., 1998; Lauria et al., 1999). However, in 11 cases (15%) temperature sensation was normal in the feet but abnormal in the hands. A possible explanation could have been compression of the median nerve in the wrist, which Niemer et al. (2001) found to be common in sarcoidosis. Furthermore, Goadsby and Burke (1994) found that abnormal thermal thresholds occurred in up to 25% of patients with CTS, remarkably both in the median and ulnar nerve supply areas. However, in the present study, median nerve conduction across the wrist was measured in 6 of the 11 above mentioned cases and was found to be normal in all. Apparently, in a minority of sarcoidosis patients with small-fibre neuropathy, hands are more or possibly even exclusively involved.

No sex differences were found in earlier studies on small-fibre neuropathy (McArthur et al., 1998). However, in the present study, males showed more WS abnormalities in the feet than did females.

Heat pain abnormalities were rare in our population and always occurred in combination with other abnormalities. Thus, for the diagnosis of small-fibre neuropathy, assessment of heat pain, a time consuming and unpleasant method, seems to provide no additional information.

In 22 cases we found unilateral TTT abnormalities (Table 3). Reference values for side differences are not yet available. However, when unilateral abnormalities were found, side differences were significantly greater than in those cases with normal TTT results. This was also true for bilateral TTT abnormalities, except for WS in the foot (Table 4). Thus, these measurements are highly suggestive of an asymmetrical distribution of the neuropathy. In sarcoid large-fibre neuropathy, pathological studies have shown asymmetrical involvement of nerve fascicles (Said et al., 2002). Idiopathic small-fibre neuropathy is mostly distal and symmetrically distributed, but a 'multifocal' non-length-dependent variant has been described (Lacomis et al., 1999; Holland, 2001; Lacomis, 2002). Furthermore, asymmetric presentation of small fibre dysfunction has been described in Sjögren's syndrome (Denislic and Meh, 1997). Similarly, a specific subset of nerve fibres can be affected in the peripheral autonomic nervous system, while another subset can be preserved (Ryder and Hardisty, 1990; Hanson et al., 1992).

The SSR was always obtained from the hand and was absent in the foot in only 7 of the 74 patients with symptoms of small-fibre neuropathy. Amplitude and shape of the SSR show habituation and great variability. Furthermore, sympathetic postganglionic fibres in peripheral neuropathy conduct with normal velocities or they do not conduct at all. Therefore, only an absent response should be considered abnormal (Gutrecht, 1994). Former studies report that the sensitivity of SSR is probably low. Evans et al. (1988) found that only 10% of 54 patients with suspected small-fibre neuropathy had an abnormal skin response. The specificity of SSR for small-fibre neuropathy is also considered to be low (Lacomis, 2002). Although widely available and inexpensive, SSR does not seem to be a valuable diagnostic tool in small-fibre neuropathy.

In a study on idiopathic small-fibre neuropathy, cardiovascular autonomic tests were found to be abnormal in 28% of the patients (Stewart et al., 1992). Despite the occurrence of clinical signs of autonomic dysfunction in some of our 31 investigated patients, cardiovascular autonomic testing was found to be abnormal in only a single case. This suggests a different pattern of involvement of the autonomic nervous system in sarcoidosis patients.

A disadvantage of TTT is that it is a psychophysical method. Consequently, the patient must be alert, concentrated, and not biased to a certain test outcome (Dyck et al., 1998, Reulen et al., 2003). The population studied consisted of relatively young adults (mean age 44 years, range 19–70). All subjects were cooperative and performed the testing without any problems. To improve outcome reliability, we used a 99% instead of 95% confidence interval and two instead of a single testing method. Moreover, the correlation between MLE and MLI was highly significant. Finally, as diagnoses should ideally not be based on a single test result, skin biopsy was performed in a subgroup of 7 consecutive patients with symptoms suggestive of small-fibre neuropathy: hyperhidrosis $n = 5$, diarrhea $n = 4$, Sicca syndrome $n = 3$, impotence $n = 2$, peripheral pain $n = 7$, paraesthesias $n = 5$, intolerance of bedcloth $n = 5$, micturition

disturbances $n = 4$. TTT in these patients showed abnormalities in both hands and feet in 3 patients. WS was abnormal at both feet in two patients, CS was abnormal at one foot in one patient and warm sensation was abnormal at both hands in one patient. The presence of small-fibre neuropathy was confirmed by skin biopsies in all 7 patients (Hoitsma et al., 2002). The quantification of epidermal nerves in skin biopsy appears to be an objective and valuable method for detecting small-fibre neuropathy (McCarthy et al., 1995; Lauria et al., 1999). Indeed, skin biopsy seems to be more sensitive than TTT (McArthur et al., 1998). However, the technique is available in only a few centres (Lacomis, 2002),

Large-fibre neuropathy is considered to be rare in sarcoidosis (Miller et al., 1989; Gainsborough et al., 1991). The pattern of large-fibre neuropathy reported in sarcoidosis includes multiple mononeuropathies, polyradiculopathy, Guillain-Barré syndrome, and symmetric distal polyneuropathy, which may be sensorimotor, pure sensory, or pure motor (Strickland and Moser, 1967; Oh, 1980; Nemni et al., 1981; Vital et al., 1982; Challenor et al., 1984; Galassi et al., 1984; Elkin and Willcox, 1985; Oksanen, 1986; Baron et al., 1989; Miller et al., 1989; Matthews, 1984; Scott et al., 1993; Koffman et al., 1999; Said et al., 2002). Apparently, there is a wide clinical and pathological spectrum of sarcoid neuropathy. The pathophysiology of small-fibre neuropathy may be immune mediated. We found unilateral abnormal TTT results in a subset of the investigated patients. Furthermore, in patients with bilateral TTT abnormalities, right-left differences were also significantly greater than they were in patients with normal TTT results. Large-fibre neuropathies with an asymmetrical distribution are predominantly immunologically determined, such as multiple mononeuropathies in vasculitis (Said, 1998) and multifocal motor neuropathy (Van den Berg-Vos et al., 2000). Recently, small-fibre neuropathy has been described in other immune mediated diseases, including systemic lupus erythematodes and Sjögren's syndrome (Denislic and Meh, 1997, Omdal et al., 2002). Some authors believe that a distal small-fibre neuropathy may even be the most common form of neuropathy in Sjögren's syndrome (Lacomis, 2002). Whether this may also be the case for sarcoidosis needs further study. Presumably, in some immune mediated diseases, there is a common pathway causing neuron damage, for which small fibres are more or even selectively vulnerable. In immune mediated diseases, prednisone is the most commonly used treatment. However, prednisone might also play a role in the pathogenesis as it may cause hyperglycaemia. Hyperglycaemia can cause small-fibre neuropathy. However, in the number of cases treated with prednisone we found no differences between patients with and without abnormal TTT results in sarcoidosis (Table 1).

In conclusion, the present study suggests that patients with sarcoidosis may develop small-fibre neuropathy. Thermal threshold testing showed abnormalities in a majority of patients in whom this diagnosis was suspected on clinical grounds. Moreover, these tests revealed indications of an asymmetrical involvement of both Ad and C fibres.

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