Research letters

Small fibre neuropathy in sarcoidosis

E Hoitsma, M Marziniak, C G Faber, J P H Reulen, C Sommer, M De Baets, M Drent

Some patients with sarcoidosis have unexplained pain and dysaesthesia. We did quantitative sensory testing in 31 sarcoidosis patients with pain or autonomic dysfunction. 25 patients had reduced warmth sensitivity, cold sensitivity, or both. Intraepidermal nerve fibre density (IENFD) was measured in punch biopsy skin samples in seven consecutive patients. All seven patients had reduced IENFD compared with controls, which confirmed the presence of small fibre neuropathy in these patients. Some patients with sarcoidosis may have small fibre neuropathy with autonomic involvement.

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Sarcoidosis is a disseminated granulomatous disease whose cause is unknown. Estimates of prevalence range from 1–40 per 100 000 population, varying among ethnic and racial groups.[1] The clinical course of sarcoidosis is highly variable, and practically every organ can be involved. Spontaneous recovery may occur, but the disease is chronic and progressive, in about 25% of cases. About 5% of patients will die from sarcoidosis. Most cases (90%) have respiratoty symptoms, abnormal chest radiographs, or both when first diagnosed. In addition, many sarcoidosis patients report non-specific symptoms such as fatigue and pain. These non-specific symptoms are disabling for the patient and can become chronic. Although some groups have investigated possible causes of fatigue, the exact mechanism is still unknown.[2] By contrast, pain in sarcoidosis has received little attention.

Small fibre neuropathy is a generalised peripheral neuropathy that selectively involves the small thinly myelinated (Aδ) and unmyelinated (C) nerve fibres. Typically, symptoms consist of pain and dysaesthesias and a disturbed temperature sensitivity. Furthermore, autonomic fibres may be involved causing autonomic dysfunction.

However, few objective measures are available for the assessment of small nerve fibres. Routine neurological examination and standard electrophysiological tests evaluate only the large fibres. Therefore, small fibre neuropathy is often difficult to diagnose. A functional measure to evaluate the small fibres is quantitative sensory testing, in which thresholds for warmth and cold perception are determined.[3]

Quantification of epidermal nerves in skin biopsies is an objective and valuable method to detect small fibre neuropathy. Reduced intraepidermal nerve fibre density (IENFD) may be the first and only detectable abnormality in patients with painful neuropathy.[4]

From August, 2000, to February, 2001, 70 patients with chronic severe sarcoidosis (diagnosed with a bronchoalveolar lavage or biopsy according to international guidelines)[5] were referred to the Sarcoidosis Knowledge and Treatment Centre of the University Hospital Maastricht, Netherlands, for a second opinion. Of these patients, 31 (44%) had peripheral pain and paraesthesias, symptoms related to autonomic dysfunction, or both. They were all seen by the same neurologist (EH). The study group consisted of 16 men (53%) and 15 women (47%), the median age was 45 (range 20–64) years. Duration of sarcoidosis ranged from 0·5 to 25 years (median 4·0 years). None of the patients had diabetes. The following symptoms were present: peripheral pain (n=24, 77%), paraesthesias (20, 65%), sheet intolerance (14, 45%), hyperhidrosis (14, 45%), hypohidrosis (two, 6%), sicca syndrome (16, 52%), facial flushing (16, 52%), orthostatic intolerance (five, 16%), diarrhoea (11, 35%), constipation (one, 3%), micturition disturbances (12, 39%), and male sexual dysfunction (ten, 32%).

Nerve conduction studies and concentric needle examinations (measuring only large peripheral nerve fibre function), were within normal limits in all patients. Quantitative sensory testing was done with a Medoc TSA-2001 device (Medoc, Ramat Yishai, Israel). Thresholds for warmth and cold sensation were determined on the hand and dorsum of the foot using the levels and the limits method; normative data according to Yarnitsky[3] were used. Reduced temperature sensitivity was found in 25 of 31 patients (81%).

In order to further quantify small fibre neuropathy, a 4 mm punch biopsy sample of the skin was taken 10 cm above the lateral malleolus of the last seven consecutive patients (median age 36 years [30–51], six men [86%]) and of six healthy controls (median age 35 years [29–50], three men [50%]). Of these patients, three had severe abnormalities in quantitative sensory testing and four had only minor abnormalities. Two patients had been treated with corticosteroids in the past whereas the other five patients were never treated with corticosteroids or any other immunotherapy. After fixation and freezing, 50 µm sections were cut and stained with polyclonal antihuman PGP 9.5 (UltraClone Limited, Isle of Wight, UK). For each biopsy sample the average number of separate intraepidermal nerve fibres per mm length of epidermis was derived. A-priori counting rules

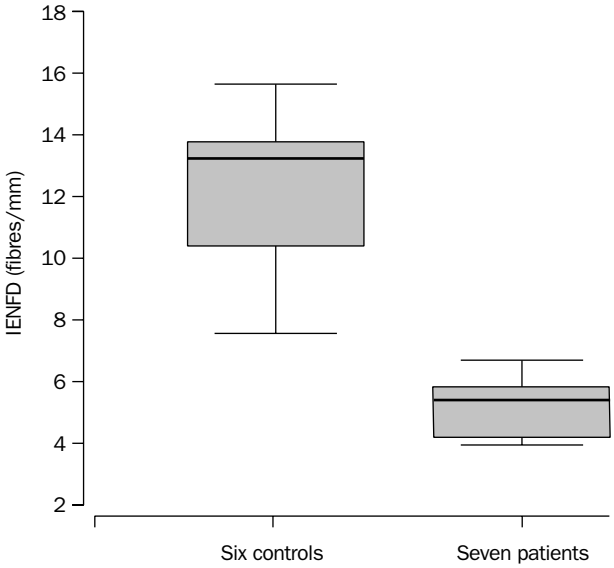

Figure 1: **Intraepidermal nerve fibre density (IENFD) in sarcoidosis patients and healthy controls**
Boxplots show medians, IQRs and ranges (p=0·003).

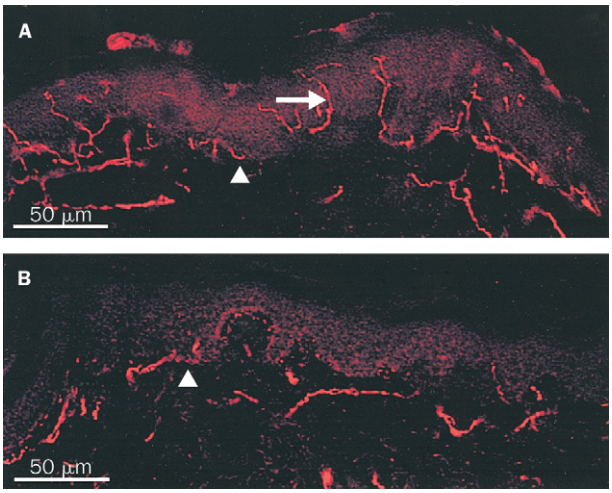

Figure 2: **Skin biopsy samples showing intraepidermal nerve fibre density (IENFD)**
Magnification 200×. Top panel shows punch skin biopsy sample from a healthy control with normal intraepidermal nerve fibre density. Lower panel shows punch skin biopsy sample from a sarcoidosis patient with a severe loss in intraepidermal nerve fibres. Arrow=intraepidermal nerve fibre. Arrowhead=basal membrane (the epidermis is shown above the basal membrane, under the basal membrane the dermis is shown with some nerve fibres).

were established to count only fibres that traverse the basal membrane. The analysis was done by two observers blinded to the allocation of the specimen (MM and CS). Statistical analysis used the non-parametric Mann-Whitney *U* test (two-tailed). Median IENFD values were 5·4 (3·9–6·7, IQR 2·1) and 13·2 (7·6 to 15·6, 4·6) in patients and controls, respectively. Figures 1 and 2 show the IENFD in patients and controls, revealing a significant reduction in IENFD in sarcoidosis patients (p=0·003).

Based on our clinical observations, quantitative sensory testing results, and skin biopsy data, small fibre neuropathy may occur in sarcoidosis, possibly related to pain and autonomic dysfunction. We wish to alert physicians who take care of sarcoidosis patients to this diagnosis, in particular pulmonologists, general practitioners, and neurologists. Since sarcoidosis patients are usually referred to non-neurologists, and only few objective measures are available for assessment of small nerve fibres, the diagnosis can be easily missed. The recognition of an organic basis of peripheral pain and autonomic symptoms in chronic sarcoidosis patients is important since patients report benefit from knowing the cause of their complaints. Symptomatic treatment of neuropathic pain with drugs such as amitriptyline, gabapentin, or carbamazepine should be considered. Moreover, autonomic dysfunction linked to small fibre neuropathy might cause life threatening events. Occasionally, sudden death of unknown cause occurs in sarcoidosis. Indeed, as seen in diabetes mellitus and in Guillain-Barré-syndrome, sudden death in sarcoidosis might be due to autonomic dysfunction. Future studies should address the pathophysiology and methods of treatment of this hitherto unrecognised feature of sarcoidosis.

Contributors
E Hoitsma assessed patients and diagnosed small fibre neuropathy on clinical grounds; M Marziniak assessed skin biopsy samples; C G Faber assessed patients; J P H Reulen assessed quantitative sensory testing; C Sommer assessed skin biopsies; M DeBaets coordinated the collaborative study with University Hospital, Wuerzburg; and M Drent selected patients. All authors helped to write the report.

Conflict of interest statement
None declared.

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1 Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med* 1997; **336:** 1224–34.
2 Sharma OP. Fatigue and sarcoidosis. *Eur Respir J* 1999; **13:** 713–14.
3 Yarnitsky D, Sprecher E. Thermal testing: normative data and repeatability for various test algorithms. *J Neurol Sci* 1994; **125:** 39–45.
4 Kennedy WR, Said G. Sensory nerves in skin: answers about painful feet? *Neurology* 1999; **53:** 1614–15.
5 Hunninghake GW, Costabel U, Ando M, et al. American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and other Granulomatous Disorders statement on sarcoidosis. *Sarcoidosis Vasc Diffuse Lung Dis* 1999; **16:** 149–73.

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Association of antipsychotic drug-induced weight gain with a 5-HT2C receptor gene polymorphism

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A side-effect of treatment with antipsychotic drugs for schizophrenia is increased body fat, which leads to further morbidity and poor adherence to treatment. The 5-hydroxytryptamine 2C receptor (5-HT2C) has been associated with this effect; we aimed to establish whether a genetic polymorphism of the promoter region of this receptor affects weight gain after drug treatment in first-episode patients with schizophrenia. We noted significantly less weight gain in patients with the –759T variant allele (p=0·0003) than in those without this allele, who were more likely to have substantial (>7%) weight gain (p=0·002). We have identified a genetic factor that is associated with antipsychotic drug-induced weight gain.

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A side-effect of treatment of schizophrenia with antipsychotic drugs is an increase in body fat. This drawback has become noticeable with the introduction of new atypical antipsychotics, two of which—clozapine and olanzapine—can induce substantial weight gain. Treatment with most other antipsychotics, both classic and atypical, results in some increase in weight.[1] This weight gain affects treatment adherence and morbidity.

The underlying mechanisms of weight gain are probably multifactorial, but are still unclear, although there are pharmacological clues. The 5-hydroxytryptamine 2C receptor (5-HT2C) has been implicated in particular, since knockout of this receptor in mice can result in obesity and increased feeding.[2] Clozapine and several other antipsychotics are 5-HT2C antagonists, which could contribute to their propensity to induce weight gain. Genetic studies of the 5-HT2C receptor in schizophrenia and its treatment have concentrated on the C23S polymorphism, although this mutation is not associated with abnormal bodyweight.[3] Results of a study of several other polymorphisms of genes related to 5-HT neurotransmission did not show any association with clozapine-induced weight gain.[4]