Chapter 7

Small fiber neuropathy in sarcoidosis

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Abstract

Background and aim

Some patients with sarcoidosis have unexplained pain and dysaesthesia.

Methods

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 fiber density (IENFD) was measured in punch biopsy skin samples in seven consecutive patients.

Results

All seven patients had reduced IENFD compared with controls, which confirmed the presence of small fiber neuropathy in these patients.

Conclusions

Some patients with sarcoidosis may have small fiber neuropathy with autonomic involvement.

Introduction

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 respiratory symptoms, abnormal chest radiographs, or both when first diagnosed. In addition, many sarcoidosis patients report nonspecific symptoms such as fatigue and pain. These nonspecific 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 fiber neuropathy is a generalized peripheral neuropathy that selectively involves the small thinly myelinated (A™) and unmyelinated (C) nerve fibers. Typically, symptoms consist of pain and dysaesthesias and a disturbed temperature sensitivity. Furthermore, autonomic fibers may be involved causing autonomic dysfunction.

However, few objective measures are available for the assessment of small nerve fibers. Routine neurological examination and standard electro-physiological tests evaluate only the large fibers. Therefore, small fiber neuropathy is often difficult to diagnose. A functional measure to evaluate the small fibers 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 fiber neuropathy. Reduced intraepidermal nerve fiber density (IENFD) may be the first and only detectable abnormality in patients with painful neuropathy.[4]

Patients and methods

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 Center 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.

Results

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 fiber 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 fiber 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 protein gene product (PGP) 9.5 (UltraClone Limited, Isle of Wight, UK). For each biopsy sample the average number of separate intraepidermal nerve fibers per mm length of epidermis was derived. A-priori counting rules were established to count only fibers 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 7.1 and 7.2 show the IENFD in patients and controls, revealing a significant reduction in IENFD in sarcoidosis patients (p=0.003).

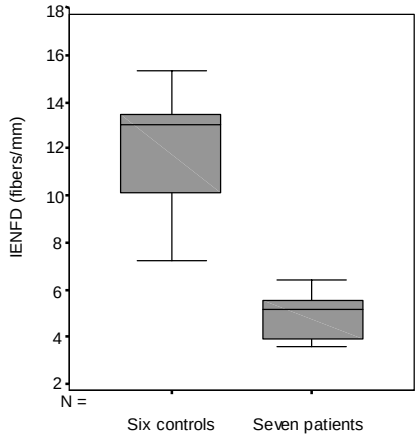

Figure 7.1 Intraepidemal nerve fiber density (IENFD) in sarcoidosis patients and healthy controls. Boxplots show medians, IQRs and ranges (p=0.003)

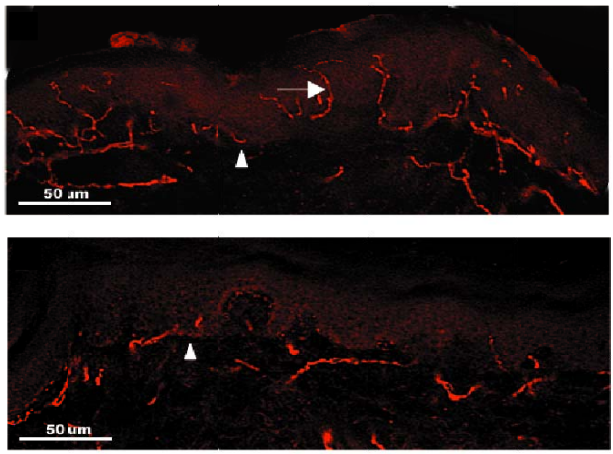

Figure 7.2 Skin biopsy samples showing intraepidermal nerve fiber density (IENFD). Magnification 200x. Top panel shows punch skin biopsy sample from a healthy control with normal intraepidermal nerve fiber density. Lower panel shows punch skin biopsy sample from a sarcoidosis patient with a severe loss in intraepidermal nerve fibers. Arrow=intraepidermal nerve fiber. Arrowhead=basal membrane (the epidermis is shown above the basal membrane, under the basal membrane the dermis is shown with some nerve fibers).

Discussion

Based on our clinical observations, quantitative sensory testing results, and skin biopsy data, small fiber 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 fibers, 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 fiber 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.

Conclusion

Future studies should address the pathophysiology and methods of treatment of this hitherto unrecognised feature of sarcoidosis.

References

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