SHORT REPORT

Characteristics of patients with sensory neuropathy diagnosed with abnormal small nerve fibres on skin biopsy

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Clinical, laboratory and electrodiagnostic (EDX) characteristics of 62 patients with sensory neuropathy with abnormal skin biopsies were reviewed. Reduced epidermal nerve fibre density (ENFD) was seen in 71% and morphological changes with normal ENFD were seen in 29% of the patients. Patients with small fibre sensory neuropathy may have associated large fibre loss undetected by routine EDX. Identified associations included abnormal glucose metabolism, Lyme vaccination, monoclonal gammopathy, vitamin B_{12} deficiency, coeliac disease, and diseases of the connective tissue, inflammatory bowel and thyroid. Sensory neuropathy remained undetermined in 50% of the patients.

Patients with small fibre sensory neuropathy present with (1) sensory disorders (numbness, tingling and pain); (2) normal or mildly abnormal neurological examinations (mild sensory deficits); and (3) normal or minimally abnormal electrodiagnostic (EDX) studies.

By assessing epidermal nerve fibre density (ENFD) and morphology, skin biopsies can be useful in diagnostic confirmation of small fibre sensory neuropathy.

We reviewed the clinical and laboratory characteristics of patients with sensory symptoms and skin biopsy specimens showing small nerve fibre involvement.

DESIGN AND METHODS

Patients with suspected small fibre sensory neuropathy underwent skin biopsies as part of their evaluation at our tertiary care facility. Patients with small fibre sensory neuropathy were defined as having sensory symptoms, no definite evidence of a distal symmetric large fibre polyneuropathy on EDX and small nerve fibre abnormalities on skin biopsy. We analysed data on patients with small fibre sensory neuropathy with abnormal skin biopsies. This study was approved by the Weill Cornell Medical College University Institutional Review Board.

The following clinical data were obtained: (1) manual muscle testing of toes, ankles, knee extensors and hip flexors; (2) ankle deep tendon reflexes—graded normal, reduced or absent; (3) pinprick sensation (PPS) at the toes by using a disposable safety pin—graded normal, reduced or absent; and (4) vibration sensation threshold at the toes by using a 128 Hz tuning fork—graded normal, reduced or absent.

EDX studies

Nerve conduction studies and needle electromyography were carried out with a Viking Select (Nicolet Biomedical, Madison, WI, USA) machine, with disposable surface and ground electrodes, and concentric electromyographic needles. Each patient underwent (1) tibial, peroneal, median and ulnar motor nerve conductions with F-wave tests; (2) median, ulnar and bilateral sural orthodromic sensory nerve conduction studies; and (3) bilateral tibial H-reflex studies. Other nerves were studied as deemed appropriate.

Skin biopsy data

From two standardised sites (distal leg and proximal thigh), 3-mm punch-biopsy specimens were obtained, stained and prepared. ENFD was measured and compared with normative data by using the method of McArthur *et al*.[1] Patients were categorised into two groups: (1) those with reduced ENFD (below the 5th centile of normality) (group 1) and (2) those with morphological changes of epidermal nerve fibres (such as axonal swellings, abnormal nerve fibre orientation, very fine calibre axons, excessive or complex nerve fibre branching) with normal ENFD (group 2).[2]

All patients underwent 2-h glucose tolerance tests, immunoprotein electrophoresis with immunofixation, and tests on quantitative immunoglobulins, cryoglobulins and vitamin B_{12} levels. Other tests were conducted as deemed appropriate, and most patients underwent ELISA and Western blot for Lyme disease, viral panel for hepatitis virus A, B and C, tests for levels of thyroid-stimulating hormone, angiotensin-converting enzyme, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, homocysteine and methylmalonic acid. Antibody testing included tests for tissue transglutaminase, gliadin (IgA and IgG), myelin-associated glycoprotein, gangliosides (GM1, GD1a, GD1b, GQ1b), hydroxyurea, sulphatide, Sm, ribonucleoprotein, anti-Ro (SS-A), anti-La (SS-B), antinuclear antibodies, double-stranded DNA, antineutrophil cytoplasmic antibodies (proteinase 3 and myeloperoxidase). Selected patients ($n = 4$) underwent HIV testing.

Statistical calculations were carried out with SPSS V.13.0. Non-parametric correlations between skin biopsy and clinical findings (PPS, vibration sensation and ankle deep tendon reflexes) were calculated using Spearman's r test.

RESULTS

Demographic data

A total of 158 patients with suspected small fibre sensory neuropathy underwent skin biopsies as part of their evaluation, of whom 96 (61%) had normal results and 62 (39%) had abnormal results (group 1, 71%; group 2, 29%; sex (male:female) 1:1.8; mean age 56 (SD 14) years). No evidence of familial history of neuropathy, alcohol or other toxic exposure was found.

Clinical data

All patients had normal manual muscle testing. Ankle deep tendon reflexes were absent in 35% (group 1, 32%, group 2, 3%), reduced in 5% (3%, 2%) and normal in 60% (36%, 24%). PPS was absent in 8% (5%, 3%), reduced in 66% (45%, 21%) and normal in 26% (21%, 5%). Vibration sensation was

Abbreviations: EDX, electrodiagnostic; ENFD, epidermal nerve fibre density; PPS, pinprick sensation

absent in 13% (11%, 2%), reduced in 79% (56%, 23%) and normal in 8% (3%, 5%).

A strong correlation (Spearman's $r = 1.0$; $p<0.01$) was found between the percentage of group 1 patients and the severity of vibration sensation and ankle deep tendon reflexes findings. No direct correlation was found between group 1 patients (as opposed to group 2) and the severity of PPS findings.

EDX data

All 62 patients had normal sural orthodromic sensory nerve conduction studies: 26 (42%) had normal EDX, 15 (58%) of whom were group 1 patients and 11 (42%) group 2. In all, 36 (58%) patients had minimally abnormal studies (median neuropathy at the wrist or chronic reinnervation of some leg muscles on needle electromyography, but with normal motor nerve and sural sensory nerve conduction), of whom 29 (81%) were in group 1 and 7 (19%) in group 2. No significant correlation was found between EDX results (whether the study was normal or minimally abnormal) and severity of vibration sensation, PPS, ankle deep tendon reflexes findings.

Final diagnosis

Small fibre sensory neuropathy was considered to be undetermined in 31 (50%) patients, including the 11 patients with abnormal antibodies associated with coeliac disease (tissue transglutaminase, gliadin IgA and gliadin IgG antibodies), but a negative duodenal biopsy result was observed. Of the remaining 31 patients, three patients had more than one blood test abnormality. Table 1 shows the abnormalities found on the blood tests: diabetes, impaired fasting glucose, or impaired glucose tolerance (19%), duodenal biopsy-confirmed coeliac disease (10%), post-Lyme vaccination (10%), IgG monoclonal gammopathy (8%), vitamin B_{12} deficiency (7%), connective tissue disease (5%), inflammatory bowel disease (3%) and thyroid disease (3%).

DISCUSSION

The presumed diagnosis of sensory neuropathy may remain uncertain in patients with sensory signs or symptoms but without EDX confirmation. Quantitative sensory testing may be used to confirm small fibre sensory neuropathy. The quantitative sensory test, however, is a psychophysical test that is not always an objective measure, and may reflect dysfunction outside the peripheral nervous system.[3–5] Skin biopsy abnormalities are a more objective confirmation of small fibre sensory neuropathy. ENFD on skin biopsy has been previously shown to be more sensitive than sural nerve biopsy in disclosing small fibre neuropathy.[6]

Table 1 Final diagnosis and skin biopsy results*

Diagnosis	Group 1	Group 2
Undetermined	21 (34%)	10 (16%)
Diabetes mellitus	2 (3%)	0
Impaired fasting glucose	4 (6%)	2 (3%)
Impaired glucose tolerance	3 (5%)	1 (2%)
Coeliac disease†	4 (6%)	2 (3%)
Lyme vaccination	6 (10%)	0
IgG monoclonal gammopathy	4 (6%)	1 (2%)
Vitamin B_{12} deficiency	4 (6%)	0
Connective tissue disease	2 (3%)	1 (2%)
Inflammatory bowel disease	1 (2%)	1 (2%)
Hypothyroidism	1 (2%)	1 (2%)

Group 1, patients with reduced epidermal nerve fibre density (ENFD) below the 5th centile of normality for age, with or without morphological changes (71%).
Group 2, morphological changes without a reduced ENFD (29%).
*Three patients had two laboratory abnormalities.
†Patients with coeliac disease had duodenal biopsy confirmation.

Small nerve fibres (A-delta and C fibres) are presumably not associated with the pathway of deep tendon reflexes, vibratory or proprioceptive sensations. Therefore, patients with exclusively small fibre sensory neuropathy would not be expected to have abnormal deep tendon reflexes, vibratory and position sensations. In our analysis of 62 patients with abnormal skin biopsies, there was a strong correlation between group 1 patients and vibration sensation abnormalities, and also between group 1 patients and ankle deep tendon reflex abnormalities. In our opinion, this suggests that group 1 patients, in addition to having a small fibre sensory neuropathy, may have an associated large nerve fibre loss that may be undetected by routine EDX. We postulate that the same process that affects ENFD may affect large nerve fibres below the sensitivity of routine EDX. As expected, PPS examination could not distinguish group 1 from group 2 patients. Others have also found evidence of large fibre loss by non-standard nerve conduction studies in patients with reduced ENFD.[7] Plantar and superficial peroneal sensory nerve conductions were not routinely carried out in our patients because of issues regarding reproducibility and interpretation of abnormal findings.

In our patients, the conditions reported to be associated with peripheral neuropathy included diabetes mellitus, impaired fasting glucose or impaired glucose tolerance, post-Lyme vaccination, duodenal biopsy-confirmed coeliac disease,[8] IgG monoclonal gammopathy, vitamin B_{12} deficiency, connective tissue disease, hypothyroidism and inflammatory bowel disease.[9] The percentage of patients with diabetes or abnormal glucose metabolism may be lower than expected because their endocrinologist or primary care physician may have identified many of these patients, and therefore did not refer them to a tertiary neuropathy centre. The relatively high proportion of coeliac disease and post-Lyme vaccination may reflect a referral bias to our tertiary care centre. In our study, 18% of patients had abnormal antibodies associated with coeliac disease, but without confirmatory duodenal biopsy results, and we grouped them with other patients with undetermined associations. Others would consider these patients to have gluten sensitivity, but this remains an uncertain diagnostic entity as gliadin antibodies are seen in up to 12% of normal subjects.[10]

Periquet *et al*[11] found that about 90% of patients with painful small fibre neuropathy are idiopathic, although it was not described whether all patients had 2-h glucose tolerance tests.

About 20% of (large and small fibre) patients seen at peripheral neuropathy clinics are idiopathic, despite intensive evaluations.[12 13] The aetiology of the small fibre sensory neuropathy remained unknown in 50% of our patients. Small nerve fibre assessment by skin biopsy may help support the diagnosis of small fibre sensory neuropathy by showing evidence of pathological abnormalities.

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