Small-Diameter Nerve Fiber Neuropathy in Systemic Lupus Erythematosus

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**Background:** Systemic lupus erythematosus (SLE) is an inflammatory, autoimmune, multiorgan disease often involving the central and peripheral nervous systems.

**Objective:** To determine whether there is a selective small-diameter nerve fiber neuropathy in patients with SLE.

**Design:** Cross-sectional study.

**Setting:** Stavanger University Hospital, Stavanger, Norway.

**Patients:** Sixty patients with SLE, aged 43.2 ± 13.5 years (mean ± SD).

**Interventions:** Skin biopsies, nerve conduction studies, and clinical neurologic examinations.

**Main Outcome Measures:** Density of intraepidermal small-diameter nerve fibers in skin biopsy specimens and large-diameter nerve fiber function as determined by nerve conduction studies and clinical examinations.

**Results:** The mean density of intraepidermal small-diameter nerve fibers in patients with SLE was 7.5 ± 3.8/mm. Eight patients (13%) had densities below reference values, consistent with small-diameter nerve fiber neuropathy, and results of nerve conduction studies were normal in 6 of them. Eleven patients (18%) had abnormal results of nerve conduction studies, reflecting large-diameter nerve fiber neuropathy, and 4 patients (7%) were classified by an experienced neurologist as having polyneuropathy after the clinical examination.

**Conclusions:** An abnormal reduction in intraepidermal small-diameter nerve fiber densities is evident in some patients despite normal function of their larger nerve fibers. This adds further support to the theory that a pure small-diameter nerve fiber neuropathy may occur in SLE.

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The densities of IENFs were below the reference limit in 47 patients (78%), and 13 patients (22%) had abnormal results. Eleven of these 13 patients (18% of total) had PN defined by electrophysiologic criterion for PN.13 Positive neuropathic symptoms were used as end-point measures because they are the symptoms of which patients complain and may outweigh the negative neuropathic symptoms.15 One internist (L.G.G.) performed the general clinical examinations, and 1 neurologist (A.B.T.) performed the neurologic examinations. The disease activity of SLE was measured according to the SLE Disease Activity Index.16

Antinuclear antibodies were detected by HEp-2000 assay (Immuno Concepts, Sacramento, Calif), and antibodies to double-stranded DNA were verified by an indirect immunofluorescence assay (Nova Lite dsDNA Crithidia luciliae 708200; NOVA Diagnostics, San Diego, Calif).

STATISTICS
Several fundamental variables, such as scores for SLE Disease Activity Index, were not normally distributed, and the Spearman rank correlation test was thus used to test associations between IENFs and these data. Remaining important variables were normally distributed and subjected to parametric statistics. When appropriate, results are reported as mean ± SD as well as median and range. Simple or multiple regression analyses with IENFs as the dependent variable were used to test associations between IENFs and normally distributed quantitative variables. Unpaired t tests (2-tailed) or analyses of variance were applied when testing for 2 or more groups of quantitative data. P < .05 corrected for ties was considered significant.

RESULTS
The median disease activity assessed by the SLE Disease Activity Index was 2.0 (mean, 2.4; range, 0.0-24.0).

The mean number of IENFs was 7.5 ± 3.8/mm compared with 12.4 ± 4.6/mm in a sample of healthy control subjects previously examined for determining normative values (P < .001) (Figure 1).10 Eight patients (13%) had small-diameter nerve fiber densities less than 3.4 fibers per millimeter, fulfilling the morphometric criterion for small-diameter nerve fiber neuropathy (Figure 2).

Large-diameter nerve fibers were examined by NCSSs. Results of NCSSs were normal in 41 patients (78%), and 13 patients (22%) had abnormal results. Eleven of these 13 patients (18% of total) had PN defined by electrophysiologic criterion for PN.13 Findings were sensory neuropathy in 6 (10%), sensorimotor neuropathy in 4 (7%), and motor neuropathy in 1. The densities of IENFs were below the reference limits (<3.4 fibers per millimeter) in only 2 of these patients, 1 with sensory and 1 with sensorimotor neuropathy. In addition, 1 patient had unilateral and 1 patient bilateral carpal tunnel syndrome. Another 4 patients had increased F-wave latencies as the only abnormal finding on NCSSs, which may indicate subclinical motor neuropathy. The IENF density was below the reference limit in only 1 of these 4 patients.
On neurologic examination, 6 patients (10%) had clinical evidence of stroke. Four patients (7%) were classified as having polyneuropathy on the basis of the clinical examination. Three of these patients had an abnormal nerve conduction velocity, 2 classified as sensorimotor neuropathy and 1 as sensory neuropathy, and the IENF densities were within the normal reference interval in all of them. Forty-six patients (77%) had a modified Neuropathy Symptom and Change Score greater than 0 for positive sensory symptoms.

Age, disease duration, SLE Disease Activity Index, the concentrations of anti–double-stranded DNA antibodies, the complement factors C3 and C4, and the erythrocyte sedimentation rate were not associated with IENF densities.

The present study supports the hypothesis that, in some patients with SLE, there is a pure small-diameter nerve fiber neuropathy. This observation is based on normal results of clinical and electrophysiologic evaluation of large-diameter nerve fiber function with simultaneous significant loss of IENFs compared with normative values.10 With the exception of 2 patients, no evidence of a generalized panneuronal neuropathy involving all fiber types could be documented in the patients with small-diameter nerve fiber neuropathy (Figure 3).

Many patients with SLE report neuropathic symptoms despite normal results of NCSs, normal IENF densities, and normal results of clinical neurologic examination.8 We found no association between reduced IENF densities and positive neuropathic symptoms. A plausible explanation for this is that positive neuropathic symptoms are present only when an active pathogenic process is taking place in the nerve fibers, and that negative neuropathic symptoms will be the main findings when the IENFs are severely affected or destroyed. Alternatively, or in addition to this, it is well known that patients with chronic diseases like SLE tend to develop emotional and personality traits similar to those of patients with chronic pain syndromes, complaining of pain and other sensory phenomena without an obvious somatic background.17

At present, the optimal method for proving the diagnosis of small-diameter nerve fiber neuropathy is not established.10 No neuropathic symptoms, findings, or tests are consistently abnormal in PN,14 and various composite scores with combinations of clinical findings and test abnormalities have been proposed as criteria to establish a diagnosis.14 In this setting, measurement of IENF densities in skin biopsy specimens is considered an objective and reproducible method for evaluation of small-diameter nerve fibers.9,10

Eleven patients (18%) had abnormal results of NCSs, indicating large-diameter nerve fiber neuropathy; findings were sensory neuropathy in 6, sensorimotor in 4, and motor in 1, confirming the polynervopathy pattern demonstrated in previous SLE studies.2-4 Only 2 of these patients with abnormal results of NCSs had reduced densities of IENFs and 3 had clinical abnormalities, leaving 6 patients with the constellation of reduced densities of small-diameter nerve fibers, normal results of NCSs, and normal findings on clinical examination. This observation may indicate different pathogeneses for large- and small-diameter nerve fiber involvement in patients with SLE. This is analogous to findings in patients with diabetes mellitus in whom loss of IENFs suggests an independent and early phenomenon possibly due to metabolic, nutritional, or toxic disturbances.19 In patients with SLE, specific immunoglobulin deposits on neural surfaces or a low-grade inflammation of small blood vessels with an activated endothelium (vasculopathy) may, alone or in combination with other factors, render the small-diameter nerve fibers more vulnerable than larger fibers, or result in apoptotic signals that may be deleterious to small-diameter nerve fibers.20-22

The disease activity was low in our patients with SLE, as also reported in other studies on SLE from Scandinavia.23-25 Despite this, the extent of small-diameter nerve fiber neuropathy was high, and one may therefore speculate whether this process is a rather predominant phenomenon among the clinical manifestations of SLE. Although there was no association with disease activity in our patients, comparative studies should be performed...
in patients of other ethnicities and also in patients with higher disease activity than ours.

Antimalarial and cytotoxic drugs are often prescribed in SLE, and neuromyotoxicity has been reported in some patients. However, in this study we found no association between the densities of IENF and any medical treatment.

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