Paper III

ORIGINAL CONTRIBUTION

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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SYSTEMIC LUPUS ERYTHEMATOSUS (SLE) is a chronic inflammatory multiorgan disease characterized by a variety of clinical and immunologic abnormalities. The clinical spectrum of the disease is wide, from an almost asymptomatic clinical presentation to a severe life-threatening disease affecting several internal organs.

The prevalence of peripheral neuropathy (PN) in SLE varies from 5% to 27%, according to diagnostic criteria used and patient population studied, and is characterized by a length-dependent mild sensory or sensorimotor neuropathy.[1-4] Usually, the neuropathic process is modestly progressive over time, but it may fluctuate and is not necessarily irreversible.[5] Some patients with SLE have neuropathic symptoms despite normal results of nerve conduction studies (NCSs) and no clinical signs of PN.[6] Quantitative sensory testing demonstrates an impairment of the sense of warmth in patients with SLE compared with healthy subjects and patients with rheumatoid arthritis.[7] Such observations therefore indicate that there may be a pathogenic process selectively affecting small-diameter nerve fibers in some patients with SLE.

Immunostaining of the neuropeptide protein gene product 9.5, a panaxonal marker, visualizes the intraepidermal small-diameter nerve fibers (IENFs) in human skin.[8] Normative reference ranges for densities of these fibers in healthy persons have been reported,[9,10] and we have previously demonstrated a decrease of the IENF densities in a small cohort of patients with SLE.[11]

In the present study, we investigated whether small-diameter nerve fiber neuropathy is a selective condition exclusively affecting small-diameter nerve fibers or whether it is part of a more generalized neuropathic process affecting nerve fibers of all diameters.

METHODS

PATIENTS

The medical records of all inpatients and outpatients with a diagnosis of SLE from January 1, 1980, through December 31, 2003, at Sta-

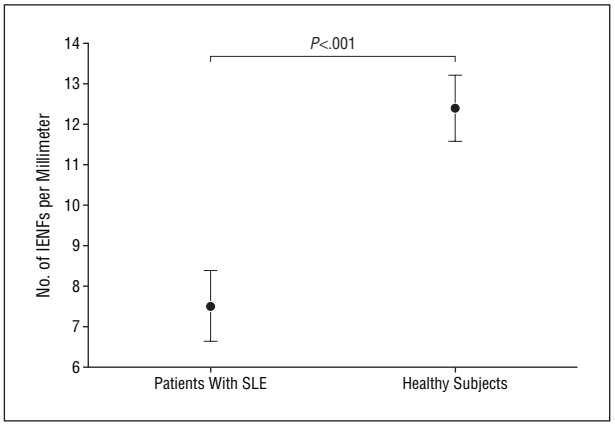

Figure 1. Densities of intraepidermal small-diameter nerve fibers (IENFs) in skin biopsy specimens from the distal part of the leg in 60 patients with systemic lupus erythematosus (SLE) and 106 healthy subjects.[10] Data are given as mean and 95% confidence interval.

vanger University Hospital, Stavanger, Norway, were reviewed. Seventy-three patients, all white, fulfilled the revised American College of Rheumatology criteria for the classification of SLE.[12] Sixty-two patients gave informed consent to be included in the study, which was approved by the regional research ethics committee in accordance with the Declaration of Helsinki. Two patients withdrew their consent after inclusion. Thus 60 patients, 51 women (85%) and 9 men (15%), were included. All participants were subjected to a standardized general and neurologic examination, skin biopsies, NCSs, and standard blood and urinary tests. Ages ranged from 20.0 to 75.0 years, with a mean±SD age of 43.2±13.5 years, and mean disease duration was 12.3±9.0 years (range, 1.0-52.0 years).

Of the 60 patients, 8 (13%) were taking no medication for SLE, 37 (62%) received corticosteroids, 34 (57%) antimalarials, 16 (27%) azathioprine, 6 (10%) cyclosporine, and 3 (5%) mycophenolate mofetil as monotherapy or as combinations. Forty-five patients (75%) received concomitant medications.

Possible complications of SLE were glomerulonephritis in 3 patients (5%), of whom 1 had a renal transplant. One patient had chronic renal failure, with a serum creatinine level between 1.7 and 2.3 mg/dL (150 and 200 µmol/L) (reference interval, 0.7-1.4 mg/dL [60-125 µmol/L]). No patients had diabetes mellitus, uremia, alcoholism, or other known causes of PN.

STUDIES

The skin biopsies were performed with a 3-mm disposable circular punch needle (Biopsy Punch; Stiefel Laboratories Ltd, Sligo, Ireland) with a sterile technique using local anesthesia (2% lidocaine and epinephrine). Two biopsy specimens were obtained from each person on the same leg in the same procedure approximately 10 cm above the lateral malleolus. The specimens were taken from the right leg unless the skin on that leg was inflamed or had scars. The biopsy specimens were immediately fixed and prepared as previously described.[11] The density of IENFs per millimeter was reported as the mean of counts in 6 sections, 3 from each of the 2 biopsy specimens. The density of IENFs was considered abnormal when the number of IENFs was less than 1.96 SDs from normative values (3.4 fibers per millimeter).[10]

For NCSs, surface stimulating and recording electrodes were used during standard temperature conditions. The amplitude, velocity, distal latency, and F-response of motor fibers of the median, ulnar, peroneal, and tibial nerves were recorded bilaterally, as well as the amplitude and the velocity of sensory fibers of the median, ulnar, and sural nerves. Normal values (mean ±1.96 SDs) were the neurophysiologic laboratory's own data for sensory NCSs and the manufacturer's (Dantec Keypoint apparatus; Dantec Medical A/S, Skovlunde, Denmark) recommendations based on data from the Department of Clinical Neurophysiology, University Hospital, Uppsala, Sweden, for motor NCSs. Abnormal results of NCSs in 2 or more nerves was the neurophysiologic criterion for PN.[13]

For quantitative evaluation of sensory symptoms, a modified version of the Neuropathy Symptom and Change Score was applied.[14] 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 NCSs. Results of NCSs were normal in 47 patients (78%), and 13 patients (22%) had abnormal results. Eleven of these 13 patients (18% of total) had PN defined by electrophysiologic criteria of abnormalities in 2 or more nerves[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 NCSs, which may indicate subclinical motor neuropathy. The IENF density was below the reference limit in only 1 of these 4 patients.

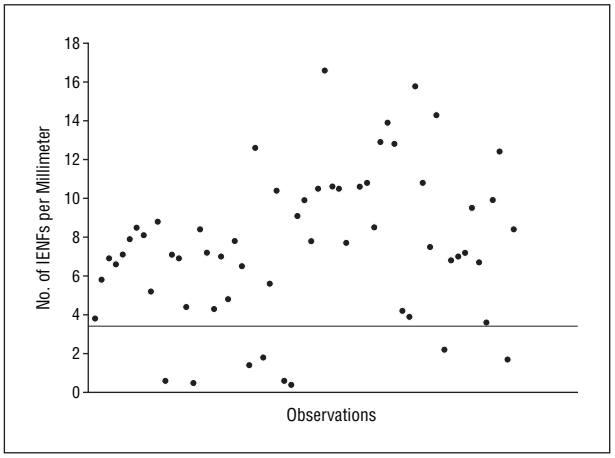

Figure 2. Scatter diagram demonstrating densities of intraepidermal small-diameter nerve fibers (IENFs) in skin biopsy specimens from the distal part of the leg in 60 patients with systemic lupus erythematosus. The line represents lower reference limit (3.4/mm) in healthy subjects.

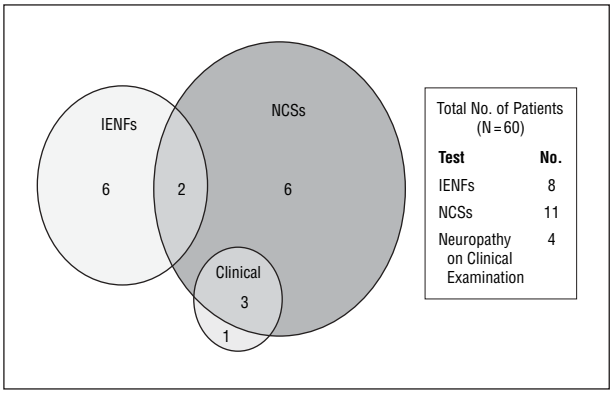

Figure 3. Venn diagram showing the number of patients with abnormal results on each type of test: reduced densities of small-diameter intraepidermal nerve fibers (IENFs), neuropathy on clinical examination, and abnormal results of nerve conduction studies (NCSs).

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.

COMMENT

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.[6] 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.[18] 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 polyneuropathy pattern demonstrated in previous SLE studies.[2-4,6] 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.[26] However, in this study we found no association between the densities of IENF and *any* medical treatment.

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