Paper III
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.5 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-
Healthy Subjects

bers per millimeter).10

IENFs was less than 1.96 SDs from normative values (3.4 fi-
sity of IENFs was considered abnormal when the number of
sity of IENFs per millimeter was reported as the mean of counts

patients (5%), of whom 1 had a renal transplant. One patient had
als, 16 (27%) azathioprine, 6 (10%) cyclosporine, and 3 (5%)
mycophenolate mofetil as monotherapy or as combinations.

SLE, 37 (62%) received corticosteroids, 34 (57%) antimalari-
ease duration was 12.3±9.0 years (range, 1.0-52.0 years).

dard 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 dis-
dial and neurologic examination, skin biopsies, NCSs, and stan-

Helsinki. Two patients withdrew their consent after inclusion.
Thus 60 patients, 51 women (85%) and 9 men (15%), were in-
cluded. All participants were subjected to a standardized gen-
eral and neurologic examination, skin biopsies, NCSs, and stan-

Spain, alcoholism, or other known causes of PN.

vanger University Hospital, Stavanger, Norway, were re-
viewed. Seventy-three patients, all white, fulfilled the revised
American College of Rheumatology criteria for the classifica-
tion of SLE.12 sixty-two patients gave informed consent to be
included in the study, which was approved by the regional re-
search ethics committee in accordance with the Declaration of

The densities of IENFs were below the reference lim-
its (3.4 fibers per millimeter) in only 2 of these pa-

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.

villus atrophy, and 1 patient had a history of oral lichen planus. One patient had
good intrinsic function of all 4 limbs. At the time of inclusion, 2 patients had a
cardiac pacemaker that was considered to be inactive.

The disease activity of SLE was measured according to the
the American College of Rheumatology revised criteria (remission, 6 or less
physician global assessment of disease activity in the previous 4 weeks).24 Par-
tients with SLE

One internist (L.G.G.) performed the general clinical ex-
aminations, and 1 neurologist (A.B.T.) performed the neuro-
logic 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 immuno-

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 electro-
physiologic criteria of abnormalities in 2 or more nerves;13
findings were sensory neuropathy in 6 (10%), sensori-
motor 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 neu-
ropathy. The IENF density was below the reference limit
in only 1 of these 4 patients.
small-diameter nerve fiber neuropathy (also known as generalized panneuronal neuropathy, involving all fiber types, represents the lower reference limit (3.4/mm) in healthy subjects. In the present study, 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.

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. However, diabetes mellitus in whom loss of IENFs suggests an ischemic etiology, or in combination with other factors, renders the small-diameter nerve fibers more vulnerable than larger fibers, or result in apoptotic signals that may be deleterious to small-diameter nerve fibers. 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.

At present, the optimal method for proving the diagnosis of small-diameter nerve fiber neuropathy is not established. No neuropathic symptoms, findings, or tests are consistently abnormal in PN, and various composite scores with combinations of clinical findings and test abnormalities have been proposed as criteria to establish a diagnosis. 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.

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. 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. 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.

The disease activity was low in our patients with SLE, as also reported in other studies on SLE from Scandinavia. 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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