

ABSTRACT: The pathophysiology of hepatic neuropathy is poorly understood, but membrane depolarization due to a toxic inhibition of oxidative metabolism has been proposed. We investigated the relationship between nerve excitability properties, nerve dysfunction, and liver function in 11 pretransplant patients, the majority of whom were oligo- or asymptomatic for peripheral neuropathy. Abnormalities were detected on clinical examination (6), large-fiber nerve conduction (4), and thermal quantitative sensory testing (10). Small-fiber involvement was characterized by elevation of warm more than cold detection thresholds. Autonomic dysfunction was less frequent (4). Nerve excitability parameters in both upper and lower limbs provided evidence of membrane depolarization compared with controls, even in those patients without a history of alcohol abuse. No clear correlation was found between neurophysiological indices and scores of hepatic reserve or various blood parameters including ammonia level. Although chronic membrane depolarization may be involved, the degree of depolarization in large fibers was small, and its role in the pathophysiology of neuropathy uncertain.

Muscle Nerve 35: 730–738, 2007

CONDUCTION AND EXCITABILITY PROPERTIES OF PERIPHERAL NERVES IN END-STAGE LIVER DISEASE

KARL NG, MB, BS,¹ CINDY S.-Y. LIN, PhD,² NICHOLAS M.F. MURRAY, MB,¹
ANDREW K. BURROUGHS, MB, ChB,³ and HUGH BOSTOCK, PhD²

¹ Department of Clinical Neurophysiology, National Hospital for Neurology and Neurosurgery, London, United Kingdom

² Sobell Department of Motor Neurosciences, Institute of Neurology, University College London, London, United Kingdom

³ Liver Transplantation and Hepatobiliary Medicine Unit, Royal Free Hospital, London, United Kingdom

Accepted 25 January 2007

The symptoms and signs of a peripheral somatic and autonomic neuropathy in patients with chronic liver disease have been observed by several authors. At one time, the existence of a distinct hepatic neuropathy was questioned, since subjects had multiple comorbidities, such as chronic alcoholism or infectious hepatitis, that may have predisposed them to nerve damage.⁴² In more recent studies, the prevalence of somatic neuropathy has ranged from 39%–93% and small fiber neuropathy from 28%–60%,

even when prior alcoholism and diabetes were excluded.^{8,15,33} Autonomic studies indicate abnormalities in at least half of most case series.^{8,13,17,33,43} In addition, histopathological studies of nerve have revealed segmental demyelination, thinly myelinated nerve fibers, and axonal loss.^{6,9,11,29} Little appears to be known of the pathogenesis, but it is commonly assumed that unmetabolized endogenous neurotoxins are somehow responsible. Kardel and Nielsen²¹ interpreted the generalized nature of the nerve dysfunction as likely due to a reduction in the resting membrane potential, possibly caused by a toxic inhibition of cellular oxidative metabolism, as put forward by Sherlock.³⁹

The recent development of nerve excitability studies^{4,5} has produced a sensitive means of detecting such alterations in membrane potential. For example, application of a convenient test of multiple nerve excitability parameters²⁵ to patients with end-stage kidney disease has shown that their nerves are chronically depolarized, primarily due to hyperkale-

Abbreviations: AFT, autonomic function tests; CDT, cold detection threshold; CMAP, compound muscle action potential; EMG, electromyography; ESLD, end-stage liver disease; INR, international normalized ratio; MELD, model for end-stage liver disease; QST, quantitative sensory testing; SNAP, sensory nerve action potential; TE_d, depolarizing threshold electrotonus; TE_h, hyperpolarizing threshold electrotonus; TNS, total neuropathy score; WDT, warm detection threshold

Key words: autonomic neuropathy; hepatic neuropathy; nerve excitability; small-fiber neuropathy; threshold electrotonus

Correspondence to: K. Ng; e-mail: kng@med.usyd.edu.au

© 2007 Wiley Periodicals, Inc.

Published online 26 March 2007 in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/mus.20765

mia, and provided evidence that neuropathic symptoms are related to depolarization.^{27,30} We therefore examined the nature of the neuropathy in patients with end-stage liver disease (ESLD) by testing the function of small and autonomic as well as large fibers, and by using excitability studies to assess whether large motor and sensory fibers are depolarized, as proposed by Kardel and Nielsen.²¹

MATERIALS AND METHODS

Eleven ESLD patients (9 men, 2 women) with a mean age of 50 (range 29–69) years who were awaiting transplantation at the Royal Free Hospital, London, were studied. Nerve excitability and blood electrolyte values were compared with 27 normal volunteers with a mean age of 48.4 years (range 30–79), 17 with a mean age of 44.1 years (range 30–61), and 14 with a mean age of 45 years (range 23–61) for median motor, median sensory, and peroneal motor studies, respectively. All patients and normal volunteers gave informed consent in accordance with the Declaration of Helsinki and the study was approved by the institutional review board. Exclusion criteria were frank diabetes mellitus, renal impairment (elevated serum creatinine), an active encephalopathic state, and lack of independent mobility. Clinical and laboratory assessment for alternative causes of a neuropathy were performed and such patients were excluded, with the exception of those with a prior history of alcoholism or primary biliary cirrhosis. All patients had exhaustive pretransplant investigations, including erythrocyte sedimentation rate, treponemal/hepatitis/human immunodeficiency virus serology, serum protein electrophoresis, creatinine clearance, and serum levels of electrolytes, creatinine, antinuclear antibody, anti-neutrophil cytoplasmic antibody, extractable nuclear antigen, HbA1c, vitamin B₁₂, folate, vitamin E, and immunoglobulins.

Patient selection was independent of clinical indicators for a neuropathy. Subjects were graded according to severity of hepatic disease with two quantification systems in common use: Child–Pugh score/grade and the model for end-stage liver disease (MELD) score.^{32,37} The former utilizes serum levels of bilirubin, albumin, and prothrombin as well as clinical features of ascites and encephalopathy, rendering a score from 5 to 15. The latter is calculated according to the following formula:

$$\begin{aligned} \text{MELD score} = & 9.57 \times \log_e(\text{creatinine in mg/dl}) \\ & + 3.78 \times \log_e(\text{bilirubin in mg/dl}) + \\ & 11.2 \times \log_e(\text{INR}) + 6.43 \end{aligned}$$

where INR is the international normalized ratio. The MELD score range is 6 to 40 and may be more sensitive at predicting survival in patients with ESLD.²⁰

Standard nerve conduction studies²⁸ were performed assessing amplitude, latency, conduction velocity, and late responses in various nerves on the one side (sensory: sural, superficial peroneal, radial; motor: peroneal, tibial, median, ulnar). De Jesus' correction formula ($\text{CV corrected} = \text{CV recorded} \times (1.51)^{(\text{diff temp}/10)}$) for nerve conduction velocities was employed when limb temperature was below 32°C in the hand and 31°C in the foot. Results were deemed abnormal for that patient only if both lower-limb sensory potentials were outside limits for amplitude or conduction velocity. Needle electromyography (EMG) was performed of tibialis anterior and gastrocnemius muscles. All studies were performed on the right side.

Small-fiber function was assessed by means of the Marstock method of limits (Somedic systems v2.2; Hörby, Skåne, Sweden). Utilizing the Peltier principle, warm and cold detection thresholds were quantified in response to 1°C/s changes in a 2.5 × 5 cm thermode applied to the thenar eminence in the right upper limb and to the lateral dorsum of the foot in the right lower limb, starting at the patient's recorded limb temperature. The testing paradigm was constrained by cooling to a minimum of 10°C and warming to a maximum of 45°C.

Autonomic function was assessed by measuring heart rate variability to deep breathing, standing, and the Valsalva maneuver. In this fashion, expiratory–inspiratory RR interval (E-I interval), standing 30:15 ratio, and Valsalva ratio (VR) were obtained. Additionally, the sympathetic skin responses (SSR) to electrical stimulation in the hand and foot were measured, with the presence of a response defining normality. Nerve conduction and needle EMG were performed using commercial systems (Nicolet Viking v7.4; Madison, Wisconsin) including the assessment of heart rate variability with Nicolet MMP software. Conduction and quantitative sensory testing (QST) results were compared with existing laboratory-derived normal limits (mean ± 2.5 SD) and autonomic measurements were compared with published normative data.⁴⁵ Nerve conduction and autonomic testing conformed to published guidelines for their testing.¹²

Certain clinical and neurophysiological characteristics were amalgamated to provide a modified total neuropathy (TNS) score.¹⁰ The composite score in this study omitted vibration studies and

therefore carried a theoretical maximum score of 36.

Nerve excitability studies were performed using a previously described automated technique for assessing multiple excitability parameters.²⁵ For motor studies, compound muscle action potentials (CMAPs) were recorded from surface electrodes over abductor pollicis brevis and tibialis anterior. Stimuli were delivered via nonpolarizable circular gel disc electrodes (3M, Rochester, MN) with the cathode over the median nerve at the wrist or the common peroneal nerve at the fibular neck. The anode was placed at a point 14 cm proximal to and remote from the nerve on the same limb. For sensory studies, antidromic sensory nerve action potentials (SNAPs) were recorded from ring electrodes on the index finger using the same stimulation points as above for the median nerve. Skin temperature close to the stimulation site was monitored carefully throughout this recording and registered at least 32°C.

Stimulation, recording, and analysis of excitability data were carried out by QTRAC software (Institute of Neurology, Queen Square, London, UK), with the recording protocols TRONDCM for motor²⁵ and TRONDCS for sensory.²⁶ A stimulus–response curve was recorded using pulses of 1 ms duration, which were stepped up slowly to supramaximal intensity. A target response amplitude was then set to the steepest part of the curve, between 30% and 50% of the maximal response. Automatic threshold tracking was used to maintain this target response level as the stimulus conditions were changed. First, the strength–duration relationship was determined from 5 different pulse widths between 0.2 and 1 ms. A plot of stimulus charge vs. duration was then used to derive rheobase and strength–duration time constant according to Weiss' law.^{5,36,44} To record threshold electrotonus, 100 ms depolarizing and hyperpolarizing conditioning currents were delivered at $\pm 20\%$ and $\pm 40\%$ of the control threshold current and the test stimulus required to elicit the target response was determined at various latencies during and after the conditioning current.^{4,5,25} Current–threshold relationships were also recorded at the end of 200 ms conditioning currents of varying subthreshold intensity from 50% (depolarizing) to -100% (hyperpolarizing) of the control threshold current. Finally, test stimuli were delivered to track threshold changes at various latencies from 2–100 ms after a supramaximal conditioning stimulus to derive recovery cycle data.

All patients and control subjects had the following serum levels measured at the time of testing:

sodium, potassium, calcium, phosphate, bicarbonate, random glucose, urea, and creatinine. In addition, measurements of bilirubin, prothrombin, INR, albumin, alkaline phosphatase, alanine transferase, gamma glucoronyltransferase, and ammonia were made in the patients.

Etiological groups were examined for the prevalence of neurophysiological abnormalities. Age, severity scores, and biochemical indices were compared with various neurophysiological parameters. Where appropriate, chi square, Student's *t*-test, or Pearson's correlation analysis were applied and the results were considered significant for $P < 0.05$.

RESULTS

Clinical Features. The etiologies of cirrhosis for the 11 patients are listed in Table 1. All diagnoses were confirmed by liver biopsy and patients had normal fasting and random serum glucose profiles. The mean creatinine clearance was 84.9 ml/min (47.5–128 ml/min), with seven patients outside the normal range (100–130 ml/min).

No particular major etiological category had more severe liver impairment (Table 1). The age of subjects bore no clear relation to the severity of liver impairment. Eight patients had no symptoms of neuropathy. The remaining three had peripheral numbness or tingling parasthesias. None gave a history of weakness, although four had had cramps. Small- or large-fiber sensory signs were detected in six patients and there was no weakness detected in any patient. Patient 4 had reduced vibration to the knees and mild joint position sense impairment at the toes; patients 6 and 10 had a mild reduction in vibration sense at the first metatarsophalangeal joint; patients 2, 9, and 8 had reduced pinprick in a stocking distribution to the toes, ankles, and mid-leg, respectively.

Large- and Small-Fiber Function. Four subjects had definite abnormalities in large-fiber nerve conduction, with only one of these manifesting symptoms (Table 1). These four had abnormally small or slowed sensory action potentials in the lower limbs. Although three patients had small CMAP amplitudes in at least one of the motor nerves tested in the lower limbs, no patient had a needle EMG abnormality in the two muscles examined routinely. F-wave latencies were individually within normal limits but there was a general prolongation above published mean normative values for height. Values of median nerve motor conduction velocity and ulnar CMAP amplitude correlated with Child–Pugh (median CV Pear-

Table 1. Summary of clinical and standard neurophysiological assessments.

No.	Etiology	Age	MELD	CP score/ grade	Sensory symptoms	Sensory signs	NCS	AFTs	QST	TNS
1.	Polycystic disease	38	10	5/A	–	none	–	–	–	0
2.	Alcohol	60	11	6/A	–	SF	–	?	+	2
3.	PSC/HBV	35	11	6/A	+	none	–	–	+	1
4.	Secondary BC	69	12	6/A	–	LF	+	+	+	4
5.	Primary BC	58	12	8/B	+	none	+	–	+	2
6.	Alcohol	60	12	9/B	–	LF	+	–	+	4
7.	Alcohol/HCV	49	12	9/B	–	none	+	+	+	0
8.	Alcohol	46	13	8/B	+	SF	–	+	+	6
9.	PSC	29	14	8/B	–	SF	–	–	+	3
10.	HCV	61	15	9/B	–	LF	–	+	+	1
11.	Primary BC	50	21	11/C	–	none	–	–	+	0

Subjects listed in order of MELD score, secondarily Child - Pugh score. AFTs, autonomic function tests; CP, Child-Pugh; BC, biliary cirrhosis; HBV, chronic hepatitis B; HCV, chronic hepatitis C; LF, large-fiber signs; NCS, nerve conduction study; PSC, primary sclerosing cholangitis; QST, quantitative sensory thermal threshold testing; SF, small-fiber signs; TNS, total neuropathy score; +, symptoms present or abnormal result; –, symptoms absent or normal result. Heart rate variability measurement in patient 2 was not possible because of frequent ventricular ectopic beats.

son's $r = -0.72$; $P = 0.01$ and $r = -0.76$; $P = 0.01$, respectively) and MELD scores ($r = -0.63$; $P = 0.04$ and $r = -0.66$; $P = 0.04$, respectively) with lower values of velocity and amplitude in more severe disease. There was no relationship of the modified TNS to MELD scores. Autonomic function tests (Table 1) were outside normal limits for age in one of four tests in four subjects and in two of four tests in one subject, with no apparent relationship to severity scores.

QST revealed abnormalities in all but one patient. Abnormalities were more marked in the lower than upper limbs, showing a disproportionate elevation of the warm detection thresholds over that of cold, worst for those with alcohol and viral liver disease (Fig. 1). This pattern was compared against a consecutive series of 53 patients studied at the same institution. These were unselected except for the finding of small-fiber dysfunction using the same method. Such patients suffered from various conditions such as diabetes mellitus, paraproteinemic neuropathy, Guillain-Barré syndrome, and systemic amyloidosis. None had liver disease, and a definitive diagnosis for neuropathy was not possible in some. Mean ratios of warm to cold values were not significantly different in the study group compared to these patient controls [mean WDT: CDT ratio ESLD, 5.1 (range 1.5–9.3); patient controls, 4.8 (range 0.6–16)].

Nerve Excitability Abnormalities. For the median motor study, patients and controls were similar for age, temperature, and serum potassium, which have a significant influence on the study parameters. There was a shift to the right in the stimulus–

response curve with an increase in rheobase ($P = 0.02$), with comparable peak CMAP amplitudes (Fig. 2). Strength–duration time constants were identical. Threshold electrotonus (TE) demonstrated a fan-

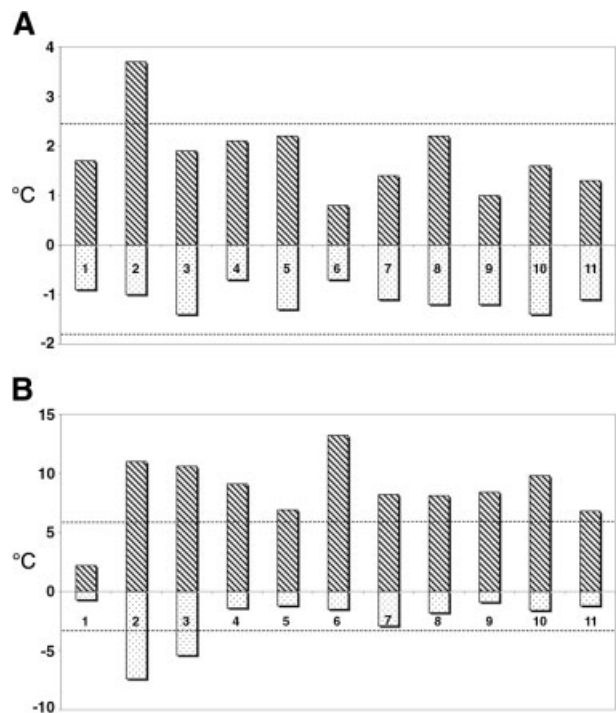


FIGURE 1. Just detectable warm and cold thresholds for upper (A) and lower (B) limb denoted by columns above and below the x axis, respectively. Dotted lines indicate the upper limits of normal detection as defined by mean \pm 2.5 SD of control values. Patients 2 and 3 had no upper detectable limit, constrained by the maximum 45°C testing paradigm. Group mean starting temperature was 33.1°C for the hand and 31.7°C for the foot.

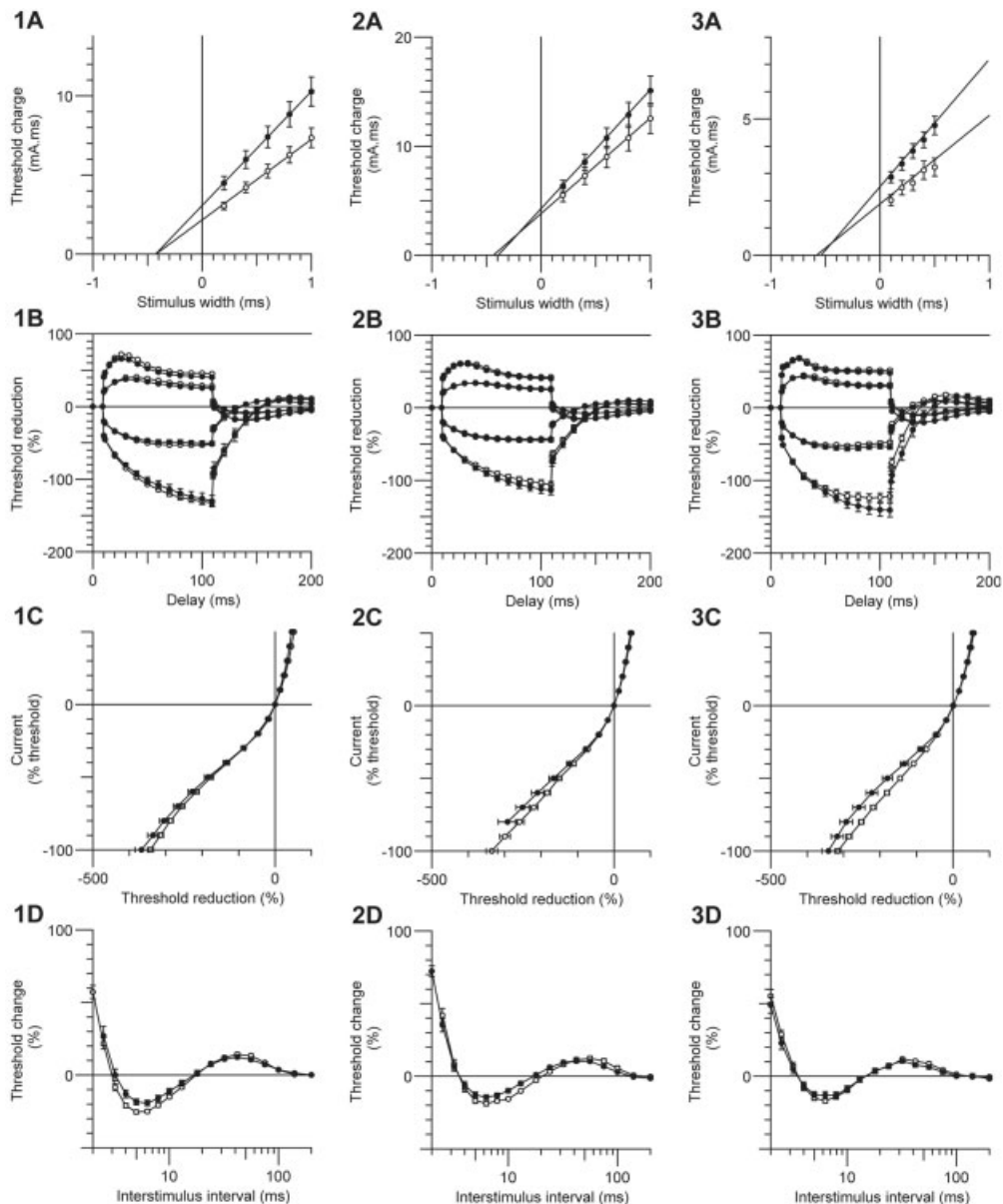


FIGURE 2. Comparison of excitability plots (mean \pm 1 SE) for median motor (1), peroneal motor (2), and median sensory (3) parameters, respectively: **(A)** threshold charge–stimulus duration relationship; **(B)** threshold electrotonus; **(C)** current–threshold relationship; **(D)** recovery cycle. Filled circles, liver disease; empty circles, controls.

ning-in or smaller threshold changes than normal to 100-ms depolarizing and hyperpolarizing currents. There were significantly reduced threshold changes to 40% of threshold depolarizing current at 10–20 ms [TEd (10–20ms)], peak and 90–100 ms ($P = 0.03$, 0.01 , and 0.01 , respectively), and a nonsignificant reduced threshold change to an equivalent hyperpolarizing current. The resting current–threshold (I/V) slope was steeper in patients than controls ($P = 0.008$). Recovery cycle parameters showed significantly reduced peak superexcitability ($P = 0.01$)

but nonsignificant reductions in subexcitability. The summary data for these and other excitability parameters are presented in Table 2. The abnormalities in TEd (90–100ms), superexcitability, and resting current–threshold slope occur in the parameters most sensitive to membrane potential and imply a state of resting membrane depolarization.²⁴

No difference existed between the patient subgroups subdivided by alcohol etiology for the three excitability parameters most dependent on membrane potential (Fig. 3). The nonalcohol subgroup

Table 2. Median nerve motor excitability data.

	Liver disease		Normal controls		Patients vs. controls
	Mean	±SE	Mean	±SE	P-value
Age (years)	50.55	±3.8	48.37	±2.49	0.63
Temperature (C)	33.56	±0.37	33.07	±0.20	0.22
Potassium (mmol/L)	4.05	±0.09	4.19	±0.05	0.15
Peak response (mV)	7.06	±1.1	7.74	±1.1	0.50
Stimulus response slope	5.10	±1.1	4.63	±1.1	0.28
Threshold (mA) for 50% CMAP	9.80	±1.1	6.87	±1.1	0.03
SDTC (ms)	0.42	±0.02	0.42	±0.02	0.90
Rheobase (mA)	6.83	±1.1	4.61	±1.1	0.02
TEd (10–20ms)	65.3	±2.0	70.1	±1.1	0.03
TEd(peak)	64.4	±1.9	69.5	±1.0	0.01
TEd(90–100ms)	40.8	±1.4	45.6	±1.0	0.01
TEd(undershoot)	−17.8	±1.2	−18.6	±0.8	0.58
TEh(10–20ms)	−73.2	±2.4	−76.3	±1.2	0.20
TEh (90–100ms)	−128	±7.8	−132	±4.2	0.70
TEh(slope 101–140ms)	2.02	±0.1	2.22	±0.1	0.16
TEh(overshoot)	12.2	±1.3	14.7	±1.0	0.15
Resting I/V slope	0.72	±0.06	0.58	±0.03	0.008
Minimum I/V slope	0.21	±9.9 × 10 ^{−3}	0.22	±8.1 × 10 ^{−3}	0.46
Hyperpolarizing I/V slope	0.30	±0.02	0.36	±0.02	0.07
RRP (ms)	3.19	±1.1	2.96	±1.0	0.16
Refractoriness at 2 ms	88.3	±22	82.2	±11	0.78
Superexcitability (%)	−18.8	±2.0	−24.8	±1.3	0.01
Subexcitability (%)	12.0	±1.0	13.8	±1.0	0.31

RRP, relative refractory period; SDTC, strength–duration time constant; TEd, depolarizing threshold electrotonus; TEh, hyperpolarizing threshold electrotonus. Comparisons made with Student's *t*-test. Significant values in bold.

was still significantly different from controls in TEd (90–100ms) and resting I/V slope ($P = 0.04$ and 0.006 , respectively). However, the subgroups were strikingly different with respect to relative refractory period, which was prolonged in the alcohol patients, as previously reported for sensory fibers.¹ This difference could not be accounted for by any difference in age or temperature.

Reduced superexcitability ($P = 0.03$) was also found in lower-limb motor excitability studies (Fig. 2). Median sensory studies demonstrated an increase in rheobase, a decrease in threshold to depolarizing electrotonus, and an increase in threshold to hyperpolarizing electrotonus.

None of the above significantly different excitability parameters were related to hepatic impairment scores, large- or small-fiber signs, autonomic dysfunction, or the modified total neuropathy score. Weak correlations were observed of TEd (90–100ms) to bicarbonate levels ($r = -0.61$; $P = 0.04$) and resting I/V slope to glucuronyltransferase levels ($r = 0.67$; $P = 0.03$).

DISCUSSION

This study confirmed previous evidence that liver failure, irrespective of its cause and accompanying

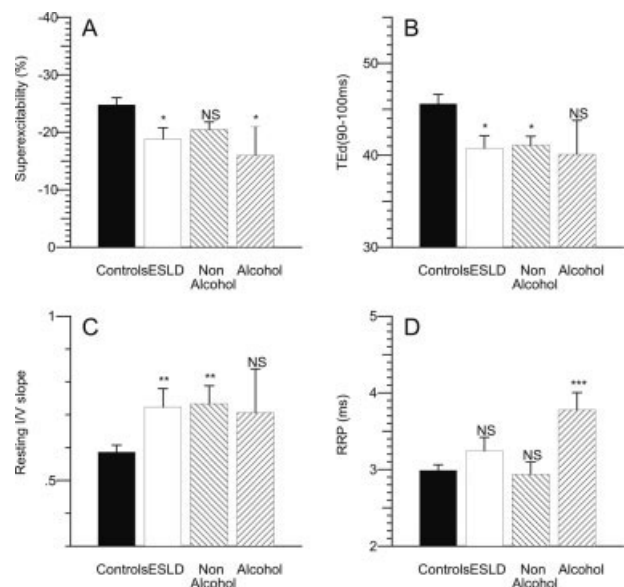


FIGURE 3. Comparison of subsets of liver disease by alcohol etiology and against controls in median motor excitability study. (A–D) Mean median motor excitability parameters +1 SE bars. Values expressed as percentages of threshold for TEd (depolarizing threshold electrotonus). ESLD, end-stage liver disease; RRP, relative refractory period. Significantly different mean value from controls: * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$. NS, not significant.

disorders, can damage somatic and autonomic nerves. After comparing the sensitivity of different measures of peripheral nerve dysfunction, this discussion focuses on the implications of our new nerve excitability data for the pathophysiology of hepatic neuropathy

Somatic Nerve Dysfunction. Large-fiber conduction studies were abnormal in a smaller proportion of our patients than in other studies, probably reflecting the relatively mild level of liver dysfunction in our subjects, with the majority in Child's class B. Most abnormalities were seen in the lower limbs, in keeping with a length-dependent process. These changes may be due to primary axonal degeneration.

We found that thermal detection determined by the method of limits was a more sensitive test of neuropathy than any electrophysiological method. Ten of our 11 patients (91%) had abnormal thermal perception, including in every case a raised warm detection threshold in the lower limb. In comparison, the yield was 82% utilizing both clinical and large-fiber conduction data.

Two other studies have quantified small-fiber dysfunction in hepatic disease. Chaudhry et al.⁸ only addressed cold detection, and the lower prevalence of abnormalities in thermal perception reported by Gentile et al.¹⁵ may have been due to their use of the forced choice method. Unmyelinated C-fiber function appears reduced, and A-delta fibers are probably also affected given the abnormalities of cold detection. These findings may be relevant to the observation that itch is a common complaint in liver disease, especially of cholestatic origin, and it may be mediated by a subset of C-fibers.⁴⁰ All our patients reported this complaint to some extent when questioned.

Autonomic Changes. The finding of small-fiber dysfunction in liver disease accords with the high prevalence of autonomic dysfunction.^{8,14,17,33,43} Most investigators report greater parasympathetic than sympathetic involvement, perhaps further supporting a length-dependent process. We did not find a clear relationship of autonomic disturbance to nociception. Autonomic neuropathy is frequently seen in alcoholic cirrhosis³ and the presence of autonomic dysfunction has been associated with increased mortality.^{14,17} In two of the four patients with an autonomic abnormality, past chronic alcoholism may have been contributory. The lower proportion of patients with autonomic disturbance may be due to our relatively smaller battery of tests. Autonomic and

somatic neuropathy often coexist,⁸ an association we did not find.

Potential Study Confounders. Alcohol is one of two potential confounding factors in hepatic neuropathy. All our patients with a history of alcoholism had been abstinent for at least a year, and most considerably longer. Gentile et al.¹⁵ were able to find altered thermal perception in their alcohol subgroup, whereas we did not, but it is unclear whether their patients had been abstinent. Others have argued that their observations were independent of alcohol, as their subgroup analyses showed no significant difference in neurophysiological results.^{21,29,38} One study of alcoholic polyneuropathy that also used QST found greater cold than warm detection abnormalities (62% vs. 24%), suggesting more A-delta than C-fiber involvement, a different pattern from our findings.¹⁹ We found greater refractoriness (Fig. 3D), an abnormality previously associated with alcoholism,¹ suggesting a prolongation of sodium channel inactivation, but the numbers were too small to draw any firm conclusions.

A second possible confounder is primary biliary cirrhosis, which has been associated with an autonomic and sensory demyelinating neuropathy.^{22,23} There were only two such patients in our group, which were not exceptional in any respect.

Nerve Excitability Abnormalities and Pathophysiological Inferences. The changes found in nerve excitability strongly suggest depolarization of the resting axonal membrane potential. Membrane depolarization is indicated most sensitively by reduced depolarizing threshold electrotonus (TEd 90–100ms), increased resting slope of the current–threshold relationship, and reduced superexcitability,²⁴ and these same abnormalities were the most significant in our study. It is by no means clear, however, that membrane depolarization is directly involved in the pathophysiology of the neuropathy. The degree of membrane depolarization implied by the excitability measurements is appreciably less than that in end-stage kidney disease and very small in absolute terms.²⁷ Rough estimates of membrane potential change can be made using the data from a nerve polarization study.²⁴ For example, superexcitability was reduced by 19.9% per mA depolarizing current, estimated as roughly equivalent to 4 mV, so that a reduction by 5.9% (from 24.75% to 18.82%, Table 2) in ESLD implies a depolarization of only 1.2 mV. Similarly, the reduction of 4.8% in TEd (90–100ms) implies a depolarization of about 1 mV. If the level of axonal depolarization in ESLD is only on the order

of 1 mV, and less than the variability between normal subjects, it is doubtful that this is responsible for the development of neuropathy. Interestingly, almost identical excitability changes were recently reported in motor axons in Fabry disease.⁴¹ Those findings were interpreted as indicative of mild depolarization, probably due to ischemia resulting from poor nerve perfusion. Although seven of the patients had a subnormal creatinine clearance, the mild axonal depolarization evidenced in our study cannot be ascribed to hyperkalemia as in kidney disease, and it seems likely that, as in Fabry disease, endoneurial ischemia was responsible. This interpretation is supported by histopathological studies.⁶

A possible mechanism for ischemia may be analogous to the situation in the kidney in hepatorenal syndrome. Here, an imbalance of potent vasoconstrictors such as endothelin, and vasodilators including nitric oxide, is thought to play a role in reduced microscopic vascular perfusion, and such factors may be similarly at play at the endoneurial level.^{16,34} Supporting evidence for an ischemic/anoxic environment of the axons in liver disease comes from the observation that they exhibit increased resistance to ischemia,^{21,38} a phenomenon that can be induced experimentally by chronic hypoxia.³¹ Although ischemia, sufficient only to depolarize axons by about 1 mV, may not appear a sufficient insult to cause a neuropathy, it should be remembered that the excitability testing sampled large axons only, and only those at a single site (wrist or fibular head), and for only a few minutes. More serious endoneurial ischemia and depolarization, sufficient to interfere with homeostatic mechanisms essential for axonal integrity, may occur in other fibers at other sites and times, especially if the process is linked to intravascular perfusion pressure.

A significant number of our patients reported cramps, probably as a result of intramuscular nerve axonal hyperexcitability.³⁵ Multiple factors have been proposed for its causal role in cirrhosis, but one experimental study showed that intravascular volume depletion was important.² This appears to be supported by our study, although the patients with cramps did not exhibit the most marked changes in nerve excitability.

The authors thank W. Z'Graggen, A. George, M. Koltzenburg, A. Baker, D. Dobson, and P. Allen for assistance with this study.

REFERENCES

- Alderson MK, Petajan JH. Relative refractory period: a measure to detect early neuropathy in alcoholics. *Muscle Nerve* 1987;10:323-328.
- Angeli P, Albino G, Carraro P, Dalla Pria M, Merkel C, Car-egaro L, et al. Cirrhosis and muscle cramps: evidence of a causal relationship. *Hepatology* 1996;23:264-273.
- Barter F, Tanner AR. Autonomic neuropathy in an alcoholic population. *Postgrad Med J* 1987;63:1033-1036.
- Bostock H, Cikurel K, Burke D. Threshold tracking techniques in the study of human peripheral nerve. *Muscle Nerve* 1998;21:137-158.
- Burke D, Kiernan MC, Bostock H. Excitability of human axons. *Clin Neurophysiol* 2001;112:1575-1585.
- Chari VR, Katiyar BC, Rastogi BL, Bhattacharya SK. Neuropathy in hepatic disorders. A clinical, electrophysiological and histopathological appraisal. *J Neurol Sci* 1977;31:93-111.
- Charron L, Peyronnard JM, Marchand L. Sensory neuropathy associated with primary biliary cirrhosis. Histologic and morphometric studies. *Arch Neurol* 1980;37:84-87.
- Chaudhry V, Corse AM, O'Brian R, Cornblath DR, Klein AS, Thuluvath PJ. Autonomic and peripheral (sensorimotor) neuropathy in chronic liver disease: a clinical and electrophysiologic study. *Hepatology* 1999;29:1698-1703.
- Chopra JS, Samanta AK, Murthy JM, Sawhney BB, Datta DV. Role of porta systemic shunt and hepatocellular damage in the genesis of hepatic neuropathy. *Clin Neurol Neurosurg* 1980;82:37-44.
- Cornblath DR, Chaudhry V, Carter K, Lee D, Seysedadr M, Miernicki M, et al. Total neuropathy score: validation and reliability study. *Neurology* 1999;53:1660-1664.
- Dayan AD, Williams R. Demyelinating peripheral neuropathy and liver disease. *Lancet* 1967;2:133-134.
- Deuschl G, Eisen A, editors. Recommendations for the practice of clinical neurophysiology. Guidelines of the International Federation of Clinical Neurophysiology. Amsterdam: Elsevier Science; 1999.
- Dillon JF, Plevris JN, Nolan J, Ewing DJ, Neilson JM, Bouchier IA, et al. Autonomic function in cirrhosis assessed by cardiovascular reflex tests and 24-hour heart rate variability. *Am J Gastroenterol* 1994;89:1544-1547.
- Fleckenstein JF, Frank S, Thuluvath PJ. Presence of autonomic neuropathy is a poor prognostic indicator in patients with advanced liver disease. *Hepatology* 1996;23:471-475.
- Gentile S, Marmo R, Orlando C, Peduto A, Montella F, Coltorti M. Alterations of vibratory and thermal peripheral sensitivity in liver cirrhosis. *Ital J Gastroenterol Hepatol* 1993;25:307-313.
- Gentilini P, La Villa G, Casini-Raggi V, Romanelli RG. Hepatorenal syndrome and its treatment today. *Eur J Gastroenterol Hepatol* 1999;11:1061-1065.
- Hendrickse MT, Thuluvath PJ, Triger DR. Natural history of autonomic neuropathy in chronic liver disease. *Lancet* 1992;339:1462-1464.
- Hendrickse MT, Triger DR. Autonomic and peripheral neuropathy in primary biliary cirrhosis. *J Hepatol* 1993;19:401-407.
- Hilz MJ, Zimmermann P, Claus D, Neundorfer B. Thermal threshold determination in alcoholic polyneuropathy: an improvement of diagnosis. *Acta Neurol Scand* 1995;91:389-393.
- Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33:464-470.
- Kardel T, Nielsen VK. Hepatic neuropathy. A clinical and electrophysiological study. *Acta Neurol Scand* 1974;50:513-526.
- Kempler P, Varadi A, Kadar E, Szalay F. Autonomic and peripheral neuropathy in primary biliary cirrhosis: evidence of small sensory fibre damage and prolongation of the QT interval. *J Hepatol* 1994;21:1150-1151.
- Keresztes K, Istenes I, Folhoffer A, Lakatos PL, Horvath A, Csak T, et al. Autonomic and sensory nerve dysfunction in primary biliary cirrhosis. *World J Gastroenterol* 2004;10:3039-3043.
- Kiernan MC, Bostock H. Effects of membrane polarization and ischaemia on the excitability properties of human motor axons. *Brain* 2000;123:2542-2551.

25. Kiernan MC, Burke D, Andersen KV, Bostock H. Multiple measures of axonal excitability: a new approach in clinical testing. *Muscle Nerve* 2000;23:399–409.
26. Kiernan MC, Lin CS, Andersen KV, Murray NM, Bostock H. Clinical evaluation of excitability measures in sensory nerve. *Muscle Nerve* 2001;24:883–892.
27. Kiernan MC, Walters RJ, Andersen KV, Taube D, Murray NM, Bostock H. Nerve excitability changes in chronic renal failure indicate membrane depolarization due to hyperkalaemia. *Brain* 2002;125:1366–1378.
28. Kimura J, editor. *Electrodiagnosis in diseases of nerve and muscle: principles and practice*, 2nd ed. Philadelphia: FA Davis, 1989. p 105–109.
29. Knill-Jones RP, Goodwill CJ, Dayan AD, Williams R. Peripheral neuropathy in chronic liver disease: clinical, electrodiagnostic, and nerve biopsy findings. *J Neurol Neurosurg Psychiatry* 1972;35:22–30.
30. Krishnan AV, Phoon RK, Pussell BA, Charlesworth JA, Bostock H, Kiernan MC. Altered motor nerve excitability in end-stage kidney disease. *Brain* 2005;128:2164–2174.
31. Low PA, Schmelzer JD, Ward KK, Yao JK. Experimental chronic hypoxic neuropathy: relevance to diabetic neuropathy. *Am J Physiol* 1986;250:E94–99.
32. Malinchoc M, Kamath PS, Gordon FD, Peine CJ, Rank J, ter Borg PC. A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology* 2000;31:864–871.
33. McDougall AJ, Davies L, McCaughan GW. Autonomic and peripheral neuropathy in endstage liver disease and following liver transplantation. *Muscle Nerve* 2003;28:595–600.
34. Menon KV, Kamath PS. Regional and systemic hemodynamic disturbances in cirrhosis. *Clin Liver Dis* 2001;5:617–627.
35. Miller TM, Layzer RB. Muscle cramps. *Muscle Nerve* 2005;32:431–442.
36. Mogyoros I, Kiernan MC, Burke D. Strength-duration properties of human peripheral nerve. *Brain* 1996;119:439–447.
37. Pugh RN, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60:646–649.
38. Seneviratne KN, Peiris OA. Peripheral nerve function in chronic liver disease. *J Neurol Neurosurg Psychiatry* 1970;33:609–614.
39. Sherlock S. *Diseases of the liver and biliary system*. Oxford: Blackwell; 1968. p 116.
40. Stander S, Steinhoff M, Schmelz M, Weisshaar E, Metzger D, Luger T. Neurophysiology of pruritus: cutaneous elicitation of itch. *Arch Dermatol* 2003;139:1463–1470.
41. Tan SV, Lee PJ, Walters RJ, Mehta A, Bostock H. Evidence for motor axon depolarization in Fabry disease. *Muscle Nerve* 2005;32:548–551.
42. Thomas PK. Metabolic neuropathies. In: Aguayo AJ, Karpatis G, editors. *Excerpta Medica*; 1979. p 255.
43. Trevisani F, Sica G, Mainqua P, Santese G, De Notariis S, Caraceni P, et al. Autonomic dysfunction and hyperdynamic circulation in cirrhosis with ascites. *Hepatology* 1999;30:1387–1392.
44. Weiss G. Sur la possibilite de rendre comparables entre eux les appareils servant l'excitation electrique. *Arch Ital Biol* 1901:413–416.
45. Ziegler D, Laux G, Dannehl K, Spuler M, Muhlen H, Mayer P, et al. Assessment of cardiovascular autonomic function: age-related normal ranges and reproducibility of spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses. *Diabet Med* 1992;9:166–175.