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Electroneurographic Evidence of Polyneuropathy in Chronic Liver Disease

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Summary. An electroneurographic study performed on the peripheral nerves of 25 patients with severe cirrhosis following viral hepatitis showed slight slowing ($P > 0.05$) of motor conduction velocity (CV) and significant diminution ($P < 0.001$) of sensory CV and mixed sensorimotor-evoked potentials, associated with a significant decrease in the amplitude of sensory evoked potentials. The slowing was about equal in the distal (digital) and in the proximal segments of the same nerve. A mixed axonal degeneration and segmental demyelination is presumed to explain these findings. The CV measurements proved helpful for an early diagnosis of hepatic polyneuropathy showing subjective symptoms in the subclinical stage.

Key words: Motor nerve conduction – Sensory nerve conduction – Electroneurography – Hepatic polyneuropathy – Chronic liver disease.

Zusammenfassung. Elektroneurographische Untersuchungen der peripheren Nerven bei 25 Patienten mit postviralen Leberzirrhosen ergaben folgendes: geringe Verminderung ($P > 0.05$) der motorischen Leitgeschwindigkeit (LG) und eine signifikant verlangsamte LG in sensiblen Fasern ($P < 0.001$), in beiden proximalen und distalen Fasern. Es wurde in den gemischten evozierten Potentialen eine Verlangsamung der LG festgestellt, zwischen den Werten der motorischen und sensiblen Fasern. Gleichzeitig wurde eine Minderung der Amplitude des NAP beobachtet. Diese Befunde sprechen für eine axonale Degeneration und eine Demyelinisierung in den meisten untersuchten peripheren Nerven. Elektroneurographische Untersuchungen erlaubten den funktionellen Zustand des peripheren Nervens abzuschätzen und bestimmte Veränderungen bereits im Initialstadium der Erkrankung aufzudecken, wenn der Patient noch keine klinischen Zeichen einer peripheren Neuropathie bietet.

Schlüsselwörter: Motorische Leitgeschwindigkeit – Leitgeschwindigkeit sensibler Nervenfasern – Elektroneurographie – Hepatische Polyneuropathie – Chronische Leberkrankheit.

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Introduction

Chronic liver disease, when not associated with alcoholism or diabetes mellitus, seldom displays a clinical picture complicated by polyneuropathy (Erbslöh and Abel, 1970; Wieck, 1955). Peripheral nerve dysfunction has been described by a number of authors (Dayan and Williams, 1967; Martinov et al., 1970; Senevirante and Peiris, 1970; Knill-Jones et al., 1972; Kardel and Nielsen, 1974; Asbury, 1975). Knill-Jones et al. (1972) found a slowing of motor conduction velocity (CV) in the lower and upper limbs, while Kardel and Nielsen (1974) demonstrated an even decrease of CV in the digit-wrist and digit-elbow segments of sensory fibers of the median nerve. In a previous work (Balta and Vasilescu, 1973) we have shown that recording of electromyographic changes (EMG) at rest and at maximal contraction permits an early detection of peripheral neuropathy in cirrhosis. On the assumption that an early diagnosis might be facilitated by a more complex CV study, in the present study we performed CV measurements in the motor fibers of the peroneal, ulnar, and median nerves (with concomitant recording of EMG activity at rest and at maximal contraction) and in the sensory fibers of the median and ulnar nerves, in both their distal (digital) and proximal segments.

Clinical Material and Methods

The study was performed on 25 patients with liver cirrhosis secondary to viral hepatitis, of whom 13 were also chronic consumers of moderate doses of alcohol. In 6 of the 25 patients, objective signs of disturbance of superficial and deep, especially vibratory sensitivity, were distally present, particularly in the fingers and toes. They also exhibited gait impairment, their motor deficit being more marked distally in both limbs. The Achilles reflex was absent in two of them and diminished in the other four. The remaining 19 patients displayed exclusively subjective signs of neuropathy, such as paresthesia, prickling, tingling, and burning pain, distally in the limbs, and particularly in the fingers and toes. They also complained of a subjective motor deficit, distally in the limbs, especially when walking. The diagnosis of severe cirrhosis was made on the basis of clinical, biochemical (electrophoretic, immunoelectrophoretic, and serum transaminase), and hepatoscintigraphic examinations and liver biopsies.

The investigation was performed using a type 14A21 two-channel DISA electromyograph. EMG activity at rest and at maximal contraction was recorded through type 13K13 DISA electrodes. Measurements of CV were carried out in the fastest conducting motor fibers of the peroneal, median, and ulnar nerves, and distal latency was recorded. Concomitantly, CV in the sensory fibers of the median and ulnar nerves was measured. Stimulation was applied to the digital sensory fibers using type 13K69 surface-ring electrodes with the cathode oriented proximally. The evoked potentials (EPs) were recorded by DISA-insulated, monopolar needle electrodes with 2—3 mm bare tips. A number of 128—1024 potentials were summed using a type 14G01 DISA Averager, automatic reading of latency (at the peak of the first positive deflection of the sensory action potential evoked) and EP duration being thus obtained. Further technical details are given in a previous work (Vasilescu, 1976).

Results

The values of CV and of terminal latency (TL) in the motor fibers of the peripheral nerves studied are listed in Table 1.

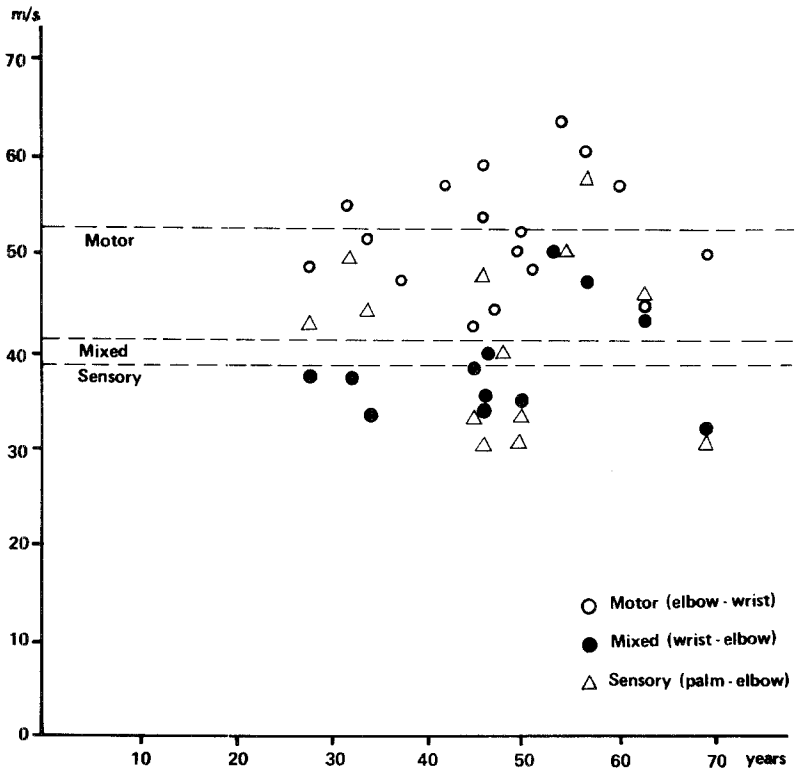

Fig. 1. Median nerve. Maximum motor, mixed and sensory CV in 12 patients without alcohol ingestion. *Interrupted lines:* mean CV in each group of fibers. ○ = Motor (elbow-wrist); ● = Mixed (wrist-elbow); △ = Sensory (palm-elbow)

One may note that, compared to the control values, CV in the peroneal, median, and ulnar nerves is slightly reduced, while TL is slightly increased. The slowing of CV in motor fibers lacks statistical significance (Table 1). The marked diminution of sensory CV (Table 1, Figs. 1 and 2) found in the whole segments studied in the median and ulnar nerves was statistically significant ($P < 0.001$). Also significant ($P < 0.001$) was the decrease in mixed sensorimotor potential in the wrist-elbow segments of the median and ulnar nerves (Figs. 1 and 2). Separate presentation (Fig. 1) of CV values in the 12 cases of cirrhosis nonassociated with alcoholism permits observation of a difference in the involvement of sensory fibers and mixed sensorimotor potentials in these cases and in the whole group studied (Fig. 2), which also includes the 13 cases of postviral cirrhosis associated with alcoholism.

We emphasize that the decrease in sensory CV, significant throughout the segments studied in the peripheral (median and ulnar) nerves (Figs. 1 and 2), was equal in the digital and proximal portions of a same fibre (Table 1).

The electroneurographic data point to a greater damage of distal than proximal segments of peripheral nerves in patients with postviral cirrhosis who

Table 1. Electroneurographic data in patients with chronic liver disease suspected of hepatic neuropathy (Temperature near the nerves: 35°C upper limbs; 33°C lower limbs)

Nerve fiber studied (segment)	Conduction velocity (m/s)		Terminal latency (ms)		Amplitude of evoked potential in motor (mV) and sensory (μV) fibers		Duration of evoked potential in sensory fibers (ms)	
	Patients	Control	Patients	Control	Patients	Control	Patients	Control
Peroneal								
Motor								
Knee-ankle	46.9 ± 1.1	49.8 ± 1.0	5.3 ± 0.5	4.9 ± 0.8	1.3 ± 0.3[a]	9.1 ± 0.8	—	—
Median								
Motor								
Elbow-wrist	52.0 ± 1.3	57.2 ± 0.9	4.2 ± 0.8	3.1 ± 0.4	5.6 ± 0.7[a]	10.5 ± 1.0	—	—
Sensory								
Palm-wrist Stimulation digit II	36.9 ± 1.2[a]	54.7 ± 1.5	—	—	19.4 ± 0.5[a]	35.4 ± 0.9	1.9 ± 0.3	1.6 ± 0.5
Palm-elbow Stimulation digit II	39.5 ± 1.4[a]	59.5 ± 2.1	—	—	6.0 ± 0.6[a]	15.0 ± 0.7	3.2 ± 0.4	2.4 ± 0.5
Wrist-elbow Subtraction	43.7 ± 0.9[a]	68.4 ± 2.8	—	—	—	—	—	—
Mixed								
Wrist-elbow	45.3 ± 1.3[a]	60.2 ± 1.4	—	—	28.7 ± 0.7	45.4 ± 0.5	2.5 ± 0.4	2.2 ± 0.6

Ulnar								
Motor								
Elbow-wrist	54.3 ± 0.3	57.3 ± 0.9	3.3 ± 0.6	2.7 ± 0.5	3.4 ± 0.5[a]	12.5 ± 0.6	—	—
Sensory								
Palm-wrist Stimulation digit IV	34.5 ± 1.5[a]	53.4 ± 1.7	—	—	13.2 ± 0.8[a]	25.0 ± 0.4	2.1 ± 0.5	1.5 ± 0.9
Palm-elbow Stimulation digit IV	39.9 ± 0.8[a]	58.9 ± 1.3	—	—	6.8 ± 0.3[a]	14.0 ± 0.8	2.2 ± 0.7	2.3 ± 0.6
Wrist-elbow Subtraction	44.7 ± 1.2[a]	69.1 ± 1.9	—	—	—	—	—	—
Mixed								
Wrist-elbow	44.5 ± 0.7[a]	61.5 ± 1.2	—	—	28.5 ± 0.3	48.1 ± 1.2	2.6 ± 0.7	2.1 ± 0.4

$n = 25$ patients (mean age: 50.1 years); 12 control subjects (mean age: 34 years)

[a] $P < 0.001$

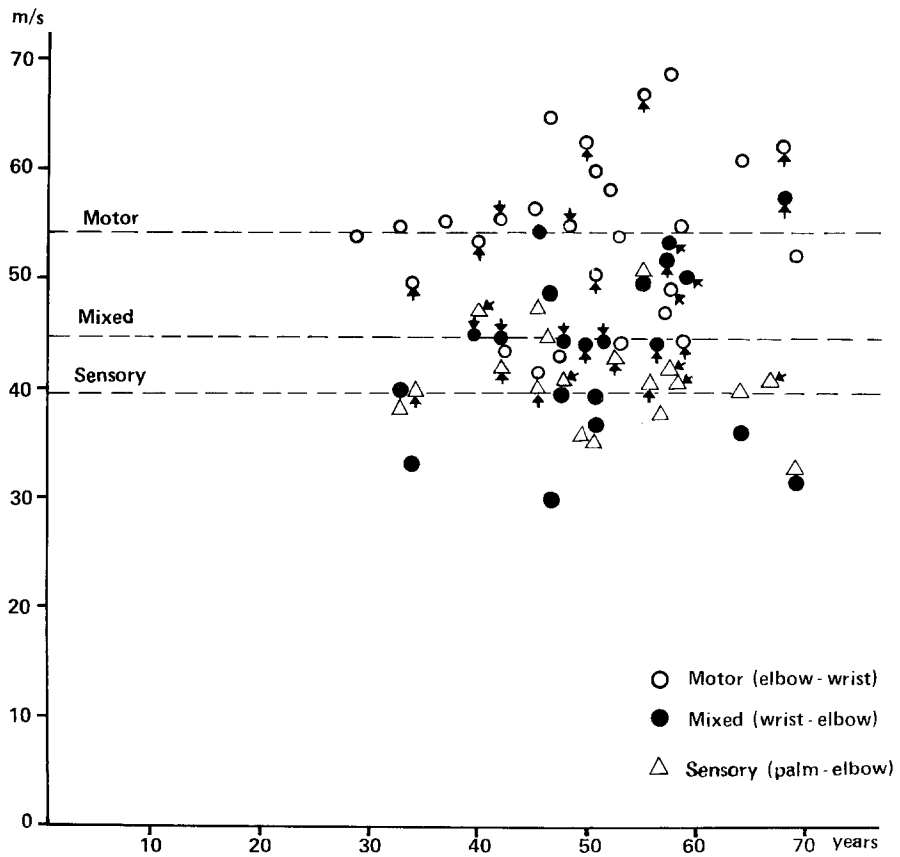

Fig. 2. Ulnar nerve. Maximum motor, mixed and sensory CV in the whole group of patients. *Interrupted lines:* mean CV in each group of fibers. ○ = Motor (elbow-wrist); ● = Mixed (wrist-elbow); △ = Sensory (palm-elbow). ↓ = Patients with alcohol ingestion

had been consuming moderate doses of alcohol, and to an almost even lesion throughout the segments studied in those who had not had this habit (Fig. 3).

CV slowing in our patients correlated with EMG alterations in the muscles innervated by the peripheral nerves studied. The anterior tibial muscle displayed fibrillation potentials at rest (7 cases), severe (5 cases) or slight (9 cases) loss of motor units at maximal contraction, increase in mean amplitude [4.5 (3—10) mV] and mean duration [13.5 (10—25) ms], and a more than 10% increase in the incidence of reinnervation polyphasic potentials (12 cases).

Discussion

The statistically significant diminution of sensory CV (in 75% of our patients) and the lack of statistical significance of the slowing in the motor CV of the peripheral nerves studied point to the presence, in the subclinical stage, of a

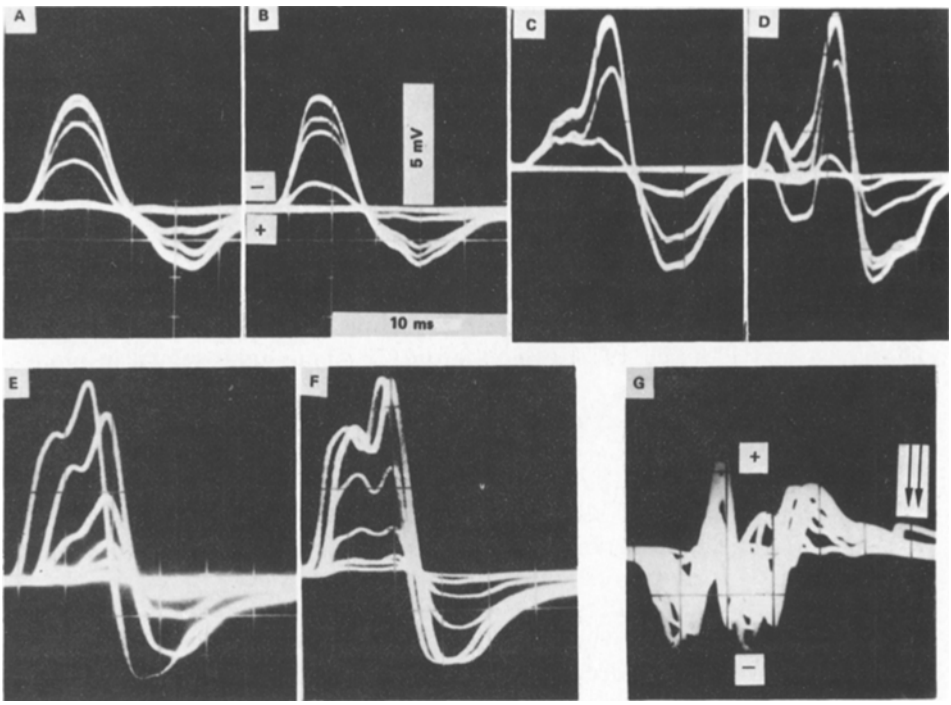

Fig. 3 A–G. Electroneurographic data in patients with postviral cirrhosis with and without chronic alcohol ingestion. **A.** Patient A. N., aged 47. Postviral cirrhosis + alcoholism. *Median* nerve. On proximal (elbow) stimulation, muscle evoked potentials (MEPs) in the musculus abductor pollicis brevis. The 7 incremental responses to the stimulus applied with progressively increased intensity from subthreshold (75 V) to threshold (90 V) and supramaximal (150 V) values. Latency: 8 ms. Calibration: 10 ms/5 mV/Division. **B.** Same patient as in A. *Median* nerve. On distal (wrist) stimulation, a marked hypoexcitability. The 6 evoked potentials whose amplitude increased with the increase of stimulation intensity from subthreshold (100 V) to threshold (200 V) and supramaximal (350 V) values. Latency: 3.5 ms. Motor (M) CV = 52.2 m/s. Calibration: 10 ms/5 mV/Division. **C.** Same patient as in A. *Ulnar* nerve. Proximal (elbow) stimulation. The amplitude of the 5 MEPs recorded from the musculus abductor digiti quinti increased with the increase of stimulation intensity from subthreshold (90 V) to threshold (135 V) and supramaximal (150 V) values. Latency: 7.5 ms. Calibration: 10 ms/2 mV/Division. **D.** Same patient as in A. *Ulnar* nerve. On stimulation at wrist, the amplitude of the 5 MEPs increased with the increase of stimulation intensity from subthreshold (75 V) to threshold (120 V) and supramaximal (150 V) values. Latency: 2.5 ms. Motor (M) CV (elbow-wrist) = 57 m/s. Calibration: 10 ms/1 mV/Division. **E.** Patient O. M., aged 52. Postviral cirrhosis without alcohol ingestion. *Ulnar* nerve. On stimulation at elbow the amplitude of MEPs increased with the increase of stimulation intensity from subthreshold (90 V) to threshold (150 V) and supramaximal (400 V) values. Each of the 8 stimulations elicited a response. Latency decreased from 8.7 ms (at threshold stimulation intensity) to 7 ms (at supramaximal intensity). Calibration: 10 ms/2 mV/Division. **F.** Same patient as in E. On stimulation at wrist the amplitude of the 9 MEPs increased with the increase of stimulation intensity from subthreshold (90 V) to threshold (150 V) and supramaximal (400 V) values. Latency decreased from 2.7 ms (at threshold intensity) to 2 ms (at supramaximal intensity). The electroneurographic data obtained on elbow stimulation approximated that noted on wrist stimulation. Motor CV = 50 m/s (at supramaximal stimulation) and 42 m/s (at threshold stimulation intensity). Calibration: 10 ms/2 mV/Division. **G.** Patient P. I., aged 26. Postviral cirrhosis and alcoholism. *Peroneal* nerve. On proximal (knee) stimulation the amplitude of the 12 MEPs increased with the increase in stimulation intensity from subthreshold (30 V) to threshold (60 V) and supramaximal (400 V) values. Unlike with distal stimulation, where only an increase in amplitude was obtained, a decrease of latency was also noted. On threshold (60 V) stimulation there occurred a polyphasic MUP with late component (LC) (*double arrow*). Most of the tracings had no LC potential. Latency: 12 ms. Motor CV (knee-ankle) = 50.9 m/s. Calibration: 10 ms/2 mV/Division

predominantly sensory peripheral neuropathy in our patients with severe chronic postviral hepatopathy.

Our finding of a significant sensory-CV diminution in the distal portions and whole segment (palm-elbow) within each (median or ulnar) nerve studied, pointing to an approximately equal damage in the distal and the proximal segments of each fiber, agrees with data reported by Knill-Jones et al. (1972), and Kardel and Nielsen (1974) in chronic hepatopathy. This is different from the CV data reported in segmental demyelination, e.g., in Charcot-Marie-Tooth disease (Vasilescu and Florescu, 1977), where mean CV diminutions (equal in motor, sensory, and sensorimotor potential in the antebrachial region) are greater in distal than in proximal segments of motor and sensory fibers. Instead, our findings approximate the CV data reported in axonal degeneration, e.g., in toxic neuropathy caused by carbon disulphide (Vasilescu, 1976), where mean diminution (very marked in sensory fibers, slight in the motor ones, and of intermediate value in sensorimotor potentials in the antebrachial region) is much greater in distal than in proximal segments of sensory fibers. In hepatic neuropathy there is a particular type of damage to peripheral nerve sensory fibers (accompanied by a very slight damage of motor fibers) in the proximal segments as well as in the distal ones. This suggests the coexistence of axonal degeneration and secondary segmental demyelination in patients with chronic liver disease. This mixed mechanism might be explained by the complex metabolic disturbances (involving proteins, carbohydrates, and vitamins, particularly B vitamins) characterizing chronic hepatopathy. In neuropathy resulting from chronic hepatopathy, a particularly important role may be played by deficiency of B vitamins owing to their insufficient absorption, disturbance in their hepatic storage, incomplete utilization of thiamine, and exaggerated consumption of vitamin B, particularly in patients taking regular doses of alcohol. Deficiency in B vitamins, especially thiamine, is known to cause peripheral nerve lesions such as axonal degeneration. However, Roy et al. (1972), in experimental research, have found that an alimentary diet normal in caloric and vitamin intake, but lacking in protein, results in ultrastructural alterations of the peripheral nerve, particularly concerning myelin, that are associated with a slowing of CV. Platts and Stewart (1969) demonstrated alterations in the anterior horn resulting from lack of protein and explained the possibly ensuing neuropathy as resulting from a lack of protein that causes alterations in the axoplasmic flow through which the cell in the anterior horn exerts a trophic action to preserve axon and muscle-fiber integrity. Asbury (1975), analyzing Dayan and Williams' (1967) assumption that hepatic neuropathy might be caused by segmental demyelination, and quoting Dyck et al. (1971), who had shown that nonrandom demyelination (i.e., concentrated on certain fibers) may occur as an early phase of axonal degeneration, concluded that the segmental demyelination identified by Dayan and Williams might be secondary to incipient axonal degeneration and not a primary demyelinating process.

Buchthal (1973), who found that a 20% slowing in maximum and minimum CV is associated with a slight decrease in amplitude (< 40%), assumed that such an association is to be expected when demyelination is slight and almost equally involves the fibers of different calibers contributing to sensory response. In our

patients, it appears that association of decreased CV values with decrease in sensory EP amplitude by 30% at the wrist and 40% at the elbow may be an additional argument supporting the hypothesis that, in our patients with hepatic polyneuropathy, complex damage that might be underlain by a process of axonal degeneration and secondary demyelination occurred in the peripheral nerve fibers (particularly the sensory ones).

Judging from the fact that in our patients with postviral cirrhosis who had habitually comsumed moderate doses of alcohol, CV and electroneurographic changes occurred first in the terminal portion of the long nerves (peroneal) and later in the distal portion of the shorter nerves (median and ulnar), one might presume that a 'dying-back' type lesion (Cavanagh, 1964) underlies the neuropathy in this category of patients.

In some of our cases a correlation could be established between the degree of severity of chronic liver disease (confirmed clinically and biochemically) and the degree of sensory slowing.

Presence in some of our patients having chronic liver disease and displaying significant sensory-CV slowing, of polyphasic reinnervation potential (associated with the denervation-type EMG changes) and polyphasic motor-unit potential (MUP) with a late component (LC) (in the electroneurographic recordings, Fig. 3 G) points to a regenerative process in the early stage of polyneuropathy. As shown by Desmedt and Borenstein (1976), the LC is the electrophysiologic sign of collateral innervation of available muscle fibers by a motor axon. The delay of LC potentials is presumably related to slow conduction in long, newly formed collateral axon sprouts. These authors first discovered LC phenomenon in patients with spinal atrophy or partial nerve lesions. It is in this latter category of patients that we encountered the LC phenomenon that we discuss in the present work. Presence of regeneration capacity, suggested in our patients by the EMG-polyphasic reinnervation potentials and polyphasic MUPs with LC, is of therapeutic importance. In conclusion, complex CV measurements and electroneurographic recordings permit diagnosis of polyneuropathy at an early stage, in which the patient displays only subjective signs and his regeneration capacity is still preserved.

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