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PERIPHERAL NEUROPATHY IN CHRONIC ALCOHOLISM: A RETROSPECTIVE CROSS-SECTIONAL STUDY IN 76 SUBJECTS

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Abstract — A consecutive sample of 76 chronic alcoholic patients was studied clinically, biochemically and electrophysiologically to assess clinical and/or subclinical signs of alcohol-related neuropathy as well as the most important and disputed risk factors for neuropathy such as age, parental history of alcoholism, nutritional status, alcoholic disease duration and total lifetime dose of ethanol (TLDE). The results show that alcohol-related neuropathy, especially when subclinical, seems to be frequent and mostly characterized by axonal degeneration of peripheral nerve fibres with earlier and more frequent involvement of sensory fibres and lower limbs. Moreover, positive family history of alcoholism, but above all alcoholic disease duration and TLDE, could be more important factors than malnutrition in determining neuropathy.

INTRODUCTION

Peripheral neuropathy is a pathology which can be associated with chronic alcoholism. Although neuropathy is frequent among chronic alcoholics, there are no uniform data about its prevalence. The literature reports a 9–50% prevalence (Bolton, 1987; Charness *et al*., 1989; Victor, 1994; Monforte *et al*., 1995; Pessione *et al*., 1995; Vuadens and Bogouslasky, 1998).

Moreover, alcohol-related neuropathy is associated with several risk factors, such as malnutrition, thiamine deficiency, direct toxicity of alcohol and recently family history of alcoholism (Victor, 1975; Bosch *et al*., 1979; Claus *et al*., 1985; Huas *et al*., 1993; Dyck *et al*., 1994; Monforte *et al*., 1995; Pessione *et al*., 1995), but which of these plays a primary role in inducing neuropathy is still unclear (Estruch *et al*., 1993; Palliyath and Schwartz, 1993; Windebank, 1993).

In the present work, we carried out a retrospective, cross-sectional study on a group of chronic alcoholics to evaluate parameters in alcohol-related neuropathy, such as (1) prevalence of clinical and electrophysiological alterations, (2) type of electrophysiological alterations, (3) presence of correlations between some clinical parameters such as parental history of alcoholism, age, nutritional status, alcoholic disease duration and total lifetime dose of ethanol (TLDE), and peripheral neuropathy.

PATIENTS AND METHODS

Patients

Seventy-six chronic alcoholics (55 men and 21 women), age range 24–69 years, were consecutively enrolled in this study over a period of 28 months. Each patient asked to be admitted to the hospital for alcohol abuse. All patients reported a consumption of ≥100 g of alcohol per day over the 2 years preceding admission. We excluded all patients with other diseases which could damage the peripheral nervous system. To evaluate the real dose of alcohol consumed, a detailed history was taken and then confirmed by family members. Special events in each subject's life were used to jog their memory, such as military service, marriage, a new job, etc. ('time look follow-back method') (Sobell *et al*., 1979).

Methods

Each patient received assessment for the following aspects. (1) Careful history, paying particular attention to family history of alcoholism, defined as positive when father and/or mother presented alcohol abuse. (2) Clinical and neurological examination: neurological assessment was carried out using a neuropathy symptom score and neurological disability score (Dyck, 1988). Clinical peripheral neuropathy was considered when the patient had two or more of the following clinical abnormalities: muscle weakness, paraesthesia, symmetrically depressed or absent tendon reflexes and sensory deficit. (3) Calculation of TLDE expressed in kg of ethanol/kg of body weight; this was estimated by first multiplying the daily consumption of ethanol by the number of days in the periods exposed to alcohol and then dividing the product by the body weight of the patient when first admitted. Alcoholic disease duration was identified as the number of years corresponding to the sum of alcohol intake periods. (4) Laboratory tests: these included glucose, creatinine, cholesterol, triglycerides, electrolytes, serum aspartate and alanine aminotransferases, γ-glutamyl transpeptidase, protein electrophoresis, lactate dehydrogenase, creatine kinase, aldolase, red blood cell, white blood cell and platelet counts, haematocrit, total protein, prealbumin, albumin, iron, transferrin, prothrombin time and ethanol levels in blood and urine. (5) Evaluation of nutritional status: comparison between the actual weight and the ideal weight; study of the lean body mass calculated from the circumference of upper non-dominant arm and the thickness of the tricipital skin fold (expression of total body fat); study of nutritional proteins, evaluating total protein, albumin, prealbumin, total lymphocytes, transferrin, and of serum folate with vitamin B_1 by chromatographic method (pathological values <16 ng/ml) and vitamin B_{12} studied with a fluorimetric enzyme-linked assay (pathological values ≤226 pg/ml, that is the 5th percentile of our general population). Caloric or protein malnutrition was considered whenever body weight

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was <90% of the ideal weight or a lean body mass was <90% of the normal value or at least three of the examined nutritional serum parameters were deranged (Durnin and Womersley, 1974; Blackburn *et al*., 1977; Burrit and Anderson, 1984). (6) Electroneurographic evaluation of the ulnar, median, peroneal and sural nerves: this involved a study of maximum motor conduction velocity of the median and peroneal nerves with their compound action potential amplitude; study of sensory orthodromic conduction velocity of the ulnar and sural nerves with their sensory-evoked potential (SEP) amplitude. The evaluated parameters were considered pathological when they differed from the average value ± 2.0 SD, obtained from a control group of 40 subjects aged between 30 and 60 years, who did not consume alcoholic drinks. Subclinical peripheral neuropathy was considered to be present if the patient had one or more of the above-reported electrophysiological parameters altered at least in two of the examined nerves, but no clinical symptoms or signs.

Data analysis

All 76 patients were subdivided into two groups: the first group was made up of patients with neuropathy, the second group were subjects without neuropathy. In these two groups, some clinical risk factors such as age, nutritional status, family history of alcoholism, alcoholic disease duration and TLDE were compared. Moreover, considering sural nerve SEP amplitude as a suitable parameter for the evaluation of sensory axonal dysfunction, a comparison and statistical evaluation (Student's *t*-test) of sural nerve SEP amplitude was performed between alcoholics '*in toto*' and the control group and then among neuropathic alcoholics '*in toto*' and neuropathic alcoholics respectively with advanced age, altered nutritional status, positive family history of alcoholism, long alcoholic disease duration and high TLDE. Advanced age, long alcoholic disease duration and high TLDE were considered when these parameters exceeded their respective average values obtained from our series of cases. Finally, risk factors for neuropathy (age, nutritional status, positive family history of alcoholism, alcoholic disease duration and TLDE) were correlated with sural nerve SEP amplitude in chronic alcoholics with neuropathy through the Pearson's correlation coefficient multivariate analysis.

Table 1. Clinical and instrumental data of chronic alcoholics studied

Cases	76
Sex	
Male	55
Female	21
Average age (years)	43.26 ± 9.29
Mean alcoholic disease duration (years)	14.51 ± 9.3
Mean daily ethanol intake (g)	284.0 ± 142.0
Mean total lifetime dose of ethanol (kg ethanol/kg body weight)	23.6 ± 22.7
Altered nutritional status	13 (17.1%)
Positive family history of alcoholism	35 (46.0%)
Alcoholic neuropathy	51 (67.1%)
clinical	23 (30.2%)
subclinical	28 (36.8%)

Values are numbers and/or means ± SD.

RESULTS

Table 1 reports the main clinical–instrumental findings from the study. The group of alcoholic patients was composed of 76 subjects, 55 men and 21 women (age range: 24–69 years; mean 43.2). The average alcoholic disease duration was 14.5 (minimum of 2; maximum of 40) years; the mean daily alcohol intake of patients was 284.0 (minimum of 100; maximum of 750) g; the average TLDE was 23.6 (minimum of 1.2; maximum of 147.5) kg of ethanol/kg of body weight; the nutritional status was altered in 13 (17.1%) cases; all with caloric malnutrition, 10 with protein malnutrition. With regard to vitamins, mean values (± SD) of both B_1 and B_{12} were normal (vitamin B_1 = 31.0 ± 11.8 ng/ml; vitamin B_{12} = 625 ± 423 pg/ml) and only three patients had thiamine values slightly lower than normal. Parental history of alcohol abuse was present in 35 patients (46%). Finally, alcoholic neuropathy was present in 51 subjects (67.1%), of whom 28 (36.8%) had only subclinical neuropathy. The patients with clinical neuropathy were all aware of the symptoms presented, even if the symptomatology was not disabling in most of them.

Table 2 reports the influence of risk factors for peripheral neuropathy (sex, age, nutritional status, family history of alcoholism, alcoholic disease duration and TLDE) in patients with and those without peripheral neuropathy. The clinical signs of neuropathy were essentially represented by hyposthenia, symmetrically depressed or absent deep tendon reflexes and sensory deficit mostly in the lower limbs. The mean age was higher in the neuropathic patients (45.3 ± 9.4 years) compared to patients without neuropathy (39.1 ± 7.7 years). As for

Table 2. Correlation among presence or absence of peripheral neuropathy and risk factors for neuropathy considered (sex, age, nutritional status, family history of alcoholism, alcoholic disease duration, mean total lifetime dose of ethanol)

Alcoholic subgroups	Sex		Age (years)	Nutritional status		Family history of alcoholism		Alcoholic disease duration (years)	Mean total lifetime dose of ethanol (kg ethanol/kg body weight)
	Male	Female							
	n = 55	*n* = 21		Normal	Altered	Negative	Positive		
With neuropathy (*n* = 51)	37	14	45.3 ± 9.4	40 (78.5%)	11 (21.5%)	25 (49.0%)	26 (51.0%)	16.2 ± 9.4*	27.9 ± 24.4*
Without neuropathy (*n* = 25)	18	7	39.1 ± 7.7	23 (92.0%)	2 (8.0%)	16 (64.0%)	9 (36.0%)	11.1 ± 8.2	14.8 ± 15.9

Values are numbers or means ± SD.
Difference from group without neuropathy: *$P < 0.05$.

gender, 37 of 55 men and 14 of 21 women had neuropathy, whereas 18 of 55 men and seven of 21 women had no signs of disease. Nutritional status in the neuropathic group was normal in 40 cases, but altered in 11 patients, whereas the group without neuropathy was characterized by normal nutritional status in 23 subjects and altered status in only two patients. Moreover, parental history of alcoholism was absent in 25 but present in 26 of the neuropathic patients, whereas the corresponding numbers were 16 and nine of the group without neuropathy. The mean alcoholic disease duration was significantly greater ($P < 0.05$) in the neuropathic alcoholics (16.2 ± 9.4 years) than in alcoholics without neuropathy (11.1 ± 8.2 years) and the mean TLDE was significantly greater ($P < 0.05$) in the neuropathic cases (27.9 ± 24.4 kg of ethanol/kg of body weight) compared to patients without neuropathy (14.8 ± 15.9 kg of ethanol/kg of body weight).

Figure 1 shows frequency, type and distribution of electroneurographic alterations (conduction velocity and evoked potential amplitude) in the 76 alcoholic patients. The electroneurographic alterations consisted fundamentally of slightly decreased sensory and/or motor conduction velocities, of a reduced SEP amplitude or its absence, and of a low composed muscle action potential amplitude. Furthermore, the most frequent changes concerned the sensory nerves and they predominated in the lower limb; the most altered parameter was SEP amplitude (lower limb = 51.3% and upper limb = 37.0% of the cases), followed in decreasing order by sensory conduction velocity (lower limb = 47.3% and upper limb = 37.0% of the subjects), motor-evoked potential amplitude (lower limb = 23.6% and upper limb = 7.4% of the patients) and motor conduction velocity (lower limb = 7.8% and upper limb = 3.7% of the cases).

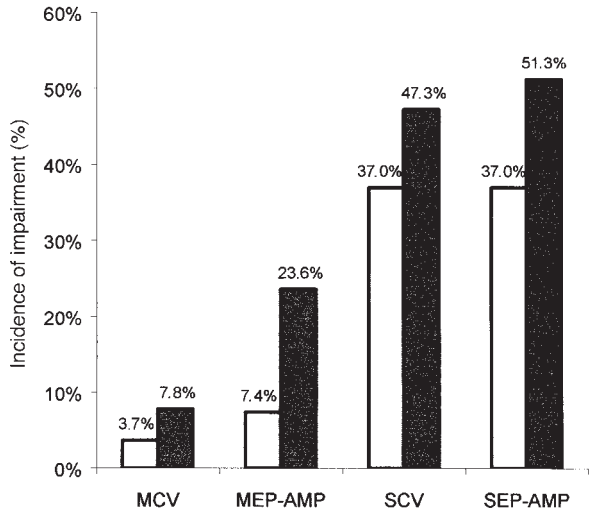

Fig. 1. Frequency of kind of electroneurographic alterations in 51 patients with peripheral neuropathy.

MCV, motor conduction velocity; MEP-AMP, motor-evoked potential amplitude; SCV, sensory conduction velocity; SEP-AMP, sensory-evoked potential amplitude. □, upper limb; ■, lower limb.

Table 3 reports the comparison and significance of the main electroneurographic data (evoked potential amplitude and nerve conduction velocity) between chronic alcoholics '*in toto*' and controls. The alcoholics showed evoked potential amplitude and conduction velocity of all examined nerves lower than the controls and this decrease was statistically significant for median (motor conduction velocity: $P < 0.01$), peroneal (motor-evoked potential amplitude: $P < 0.001$; motor conduction velocity: $P < 0.01$), ulnar (sensory-evoked potential amplitude and sensory conduction velocity: $P < 0.001$) and sural (sensory-evoked potential amplitude and sensory conduction velocity: $P < 0.001$) nerves.

Table 4 shows the comparison and statistical significance of the mean sural nerve SEP amplitude between neuropathic alcoholics '*in toto*' and neuropathic alcoholics respectively with advanced age, altered nutritional status, positive family history of alcoholism, long alcoholic disease duration and high TLDE. The mean (± SD) SEP amplitude, compared to neuropathic alcoholics '*in toto*' (2.5 ± 1.6 μV), more or less overlapped in neuropathic alcoholics with advanced age (2.6 ± 1.5 μV) and positive parental history of alcoholism (2.7 ± 1.7 μV), decreased, but not significantly, in neuropathic alcoholics with malnutrition (1.9 ± 1.7 μV) and with long alcoholic disease duration (2.3 ± 1.6 μV), but significantly reduced ($P < 0.05$) in neuropathic alcoholics with high TLDE (1.7 ± 1.3 μV).

In Table 5, we evaluated the relationship between sural nerve SEP amplitude and the risk factors for neuropathy considered (age, nutritional status, positive family history of alcoholism, alcoholic disease duration and TLDE) in chronic alcoholics with peripheral neuropathy. Pearson's correlation indicated a significant inverse correlation ($P < 0.01$) only between sural nerve SEP amplitude and both alcoholic disease duration and TLDE in these patients.

Table 3. Comparison and significance of the nerve conduction studies between controls and chronic alcoholics

	MMCV				SCV			
	Median (E–W)		Peroneal (CF–A)		Ulnar (DV–W)		Sural (LM–S)	
Group	Amp* (mV)	CV (m/s)	Amp* (mV)	CV (m/s)	Amp (μV)	CV (m/s)	Amp (μV)	CV (m/s)
Chronic alcoholics (n = 76)	13.2 ± 3.1	54.2 ± 4.5**	7.7 ± 4.0***	46.4 ± 6.1**	7.9 ± 6.8***	46.1 ± 6.5***	4.2 ± 3.3***	41.6 ± 14.5***
Controls (n = 40)	13.1 ± 3.1	56.7 ± 4.3	11.3 ± 3.2	49.7 ± 5.4	17.4 ± 5.2	54.4 ± 6.1	10.5 ± 3.2	50.6 ± 3.2

Values are means ± SD.

MMCV, maximum motor conduction velocity; SCV, sensory conduction velocity; E–W, elbow–wrist; CF–A, capitulum fibula–ankle; DV–W, digit V–wrist; LM–S, lateral malleolus–sura; NS, not significant; Amp*, distal stimulation amplitude.

Significantly different from controls: **$P < 0.01$; ***$P < 0.001$.

DISCUSSION

This retrospective study performed on 76 chronic alcoholics revealed frequent peripheral neuropathy, especially when clinical examination was followed by an electrophysiological investigation. In our series of cases, the prevalence of clinical neuropathy was 30.2%, but increased to 67.1% when patients with established clinical neuropathy were added to those with subclinical neuropathy.

Electroneurographic studies of alcoholic neuropathy show damaged sensory and motor nerve peripheral fibres caused by an axonal degeneration and consisting mainly of decreased sensory- and/or motor-evoked potential amplitudes with light involvement of conduction velocity (Kimura, 1989; Vuadens and Bogouslasky, 1998). Our electroneurographic findings indicate that the most frequent and earliest parameter to be affected is sensory-evoked potential amplitude, followed by sensory conduction velocity, motor-evoked potential amplitude and lastly motor conduction velocity. These results confirm the presence of mostly axonal neuropathy with more frequent and early involvement of sensory nervous fibres specially of the lower limbs.

As for aetiology and pathogenesis, the literature points out that alcoholic neuropathy is related to several factors: malnutrition, thiamine deficiency, direct toxicity of alcohol and, more recently, family history of alcoholism. According to some authors, alcoholic peripheral neuropathy is due mainly to malnutrition (Windebank, 1993), whereas according to other authors, neuropathy is related to the direct toxicity of alcohol on the peripheral nervous system (Estruch *et al*., 1993; Palliyath and Schwartz, 1993). In support of this latter hypothesis, an experimental investigation on animals showed that cytochrome *P* 4502E1, an ethanol-inducible isoenzyme of the *P*450-dependent pathway for ethanol oxidation in hepatocytes and neurons, may be involved in alcohol-related neurotoxicity (Wohrle *et al*., 1998). Moreover, a recent clinical cross-sectional study postulated that alcohol may have a dose-related toxic effect and could be considered an important risk factor for peripheral neuropathy (Monforte *et al*., 1995). With regard to family history of alcoholism and alcohol-related diseases, few studies have reported hereditary factors in chronic alcoholic patients in relation to hepatic (Hrubec and Omenn, 1981) or central nervous system diseases (Begleiter *et al*., 1983; Hill *et al*., 1986; Polich *et al*., 1994).

Our study indicates that, in chronic alcoholics with peripheral neuropathy, there are few cases with malnutrition (less than a quarter), a moderate prevalence of patients with positive family history of alcoholism (more than a half) and a statistically significant correlation between peripheral neuropathy and high TLDE. In agreement with Monforte *et al*. (1995), these findings suggest that alcohol could be an important risk factor for alcoholic neuropathy. On this basis, we cannot rule out positive family history of alcoholism as an important factor.

Furthermore, the hypothesis of a direct toxicity of alcohol on peripheral nervous fibres is strengthened by the fact that sural nerve SEP amplitude, a suitable parameter to evaluate sensory axonal dysfunction and the most frequently altered among the electroneurographic parameters in our series of cases, is significantly more decreased in neuropathic patients with high TLDE, than in subjects with altered nutritional status or positive family history of alcoholism.

Finally, a multivariate analysis performed to evaluate the independent effect of risk factors for neuropathy in relation to sural nerve SEP amplitude in neuropathic chronic alcoholics seems to support this hypothesis; based on Pearson's correlation coefficient study, SEP amplitude was significantly inversely correlated only to alcoholic disease duration and to TLDE, confirming a dose-dependent relationship between SEP amplitude decrease and increased alcohol consumption. As reported in our previous study (Ammendola *et al*., 2000)

Table 4. Comparison and significance of sural nerve sensory-evoked potential (SEP) mean amplitude among chronic alcoholics with peripheral neuropathy '*in toto*' and neuropathic alcoholics respectively with advanced age, altered nutritional status, positive family history of alcoholism, long alcoholic disease duration and high total lifetime dose of ethanol (TLDE) consumed

	Total	Advanced age	Altered nutritional status	Positive family history of alcoholism	Long alcoholic disease duration	High TLDE
Cases (*n*)	51	26	11	26	30	21
Mean sural nerve SEP amplitude (μV)	2.51 ± 1.6	2.6 ± 1.5	1.9 ± 1.7	2.7 ± 1.7	2.3 ± 1.6	1.7 ± 1.3*

Values (in μV) are means ± SD.
$P < 0.05$.

Table 5. Pearson's correlation of sural nerve sensory-evoked potential amplitude and risk factors for peripheral neuropathy in neuropathic chronic alcoholics ($n = 51$)

	Age	Nutritional status	Family history of alcoholism	Alcoholic disease duration	TLDE
Pearson's correlation	–0.126	–0.178	0.129	–0.540*	–0.516*
P (two-tailed)	0.378	0.213	0.368	0.000	0.000
Covariance	–1.946	–0.121	0.107	–8.333	–20.746

*$P < 0.01$.
TLDE, total lifetime dose of ethanol.

there seems to be a greater female sensitivity to the toxic effects of alcohol on peripheral nerve fibres.

In conclusion, our study indicates that in chronic alcoholism: (1) peripheral neuropathy seems to be very frequent especially when subclinical. Thus a routine use of electrophysiological investigations for chronic alcoholics could be helpful, especially for those patients receiving disulfiram treatment which can occasionally lead to neuropathy; (2) neurogenic damage is mostly characterized by axonal degeneration of sensory and motor nerve fibres with earlier and more frequent involvement of sensory nerves and lower limbs; (3) positive family history of alcoholism, but especially all alcoholic disease duration and TLDE, appear to be more important factors than malnutrition in determining neuropathy.

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