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CLINICAL AND ELECTROPHYSIOLOGICAL STUDY OF THE PERIPHERAL NERVOUS SYSTEM IN THE ELDERLY PEOPLE IN DARBHANGA

Physiology

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ABSTRACT

The effect of age on the peripheral nervous system was investigated by clinical examination and neurophysiological studies in 59 subjects aged 60-103 years and 23 young subjects. A full laboratory screen for factors which, though clinically silent, may constitute risk factors (RFs) for peripheral neuropathy was also performed in the elderly subjects. Our findings show that the presence of RFs affects exceptionally the electrophysiological parameters in a statistically significant way.

The age-dependent changes in nerve conduction parameters were well predicted by non-linear models. The simultaneous electromyographical study demonstrates the re-innervation capacity of the motor system

KEYWORDS

Peripheral nervous system - Elderly – Electrophysiology

INTRODUCTION

Loss of vibration sense and absent ankle reflexes are common physical findings in the elderly. Age-related alterations of the peripheral nervous system (PNS) have been demonstrated in nerve conduction studies; a gradual decline in nerve conduction velocity and amplitude has been reported. A more rapid decline has been observed in the sensory nerves. Structural changes in peripheral nerves and muscles are also known to occur with age. It is difficult to determine the extent to which such impairment is due to age itself or to other age-related pathological factors. In the elderly, metabolic- and malnutrition-induced neurological impairment is more common; its low grade insidious development may account to an unrecognized extent for what is assumed to be age-induced PNS impairment. We report a cross-sectional clinical and electrophysiological study of the PNS in Caucasian subjects aged from 60 to 103 years, comprising a full laboratory screen for factors which, though clinically silent, may adversely affect peripheral nerve fibres. The electrophysiological data were compared with those of young subjects examined under the same conditions.

MATERIALS AND METHODS

Elderly subjects were selected according to the following criteria: age over 60 years; absence of symptoms suggestive of peripheral neuropathy (PN), assessed using a version (categories 1-19) of the Neuropathy Symptom Profile developed by Dyck et al.: subjects had to give negative answers to the first 2 categories assessing the motor function and to at least 14 of the 17 categories assessing the sensory function; this threshold of 3 allowed the presence of sensory complaints (e.g. cramps, aching), the occurrence of which is correlated with age but which are poorly correlated with nerve conduction changes; absence of any known potential cause of PN in the history of the subjects, assessed by a questionnaire including the list of PN causes established by the WHO and a complementary list of 60 marketed drugs with potentials neurotoxicity; absence of psychiatric disease, dementia, degenerative neurological disease or documented cerebrovascular accident.

All subjects gave their informed written consent. Sixty-three elderly subjects were recruited from Darbhanga region; all subjects were physically active, either living at home or in hospital for a short stay only, except for some very elderly subjects in permanent residential care for social reasons; in addition, we included 23 healthy young subjects (aged between 20 and 30 years) without any disease history, whose results on neurological examination were normal.

After selection, all subjects underwent a neurological examination and electrophysiotogical studies performed by the same neurologist. Concurrently, the elderly subjects underwent laboratory investigations, the results of which were not passed on to the neurologist.

Neurological examination

This included a sensory (touch, temperature, pain and proprioception) examination and tendon reflexes evaluation.

Electrophysiological studies

Electromyographic recordings were performed using a concentric needle electrode. Three muscles were tested in all subjects: tibialis anterior (TA), first dorsal interosseus (FDI) and extensor carpi radialis (ECR). The following parameters were determined using three programmes of the Nicolet Viking apparatus: maximum voluntary amplitude (MVA), interference pattern analysis (IPA) and automatic motor unit potential (AMUP). The maximal motor unit potential (MUP) amplitude was given by the MVA programme using the peak to peak amplitude of the greatest MUP of the 1 s recorded sequence. The mean amplitude was calculated by the IPA programme from the overall MUP recorded in one sequence.

After manual selection of the MUP to be studied, automatic analysis of the ECR was performed by the AMUP programme.

Median and common peroneal motor nerves were investigated conventionally using surface electrodes taped over the muscle belly of the abductor pollicis brevis (median nerve) and extensor digitorum brevis (common peroneal nerve). The distal latency (DL) was measured from stimulation of the median nerve at the wrist and the common peroneal nerve at the ankle to the onset of the negative phase of the compound motor action potential (CMAP). CMAP amplitudes were measured from baseline to the negative peak. The nerve conduction velocities (NCV) were measured using stimulation at the elbow (median nerve) and the capitulum fibulae (common peroneal nerve).

Orthodromic median sensory stimulation was performed using a ring electrode on the third digit; the recording electrode was placed on the wrist. The sural nerve was stimulated using a surface electrode situated behind the lateral malleolus with the recording electrode on the midcalf. Sensory NCV and sensory nerve action potential (SNAP) amplitude were determined.

The H-reflex was elicited by stimulating the tibial nerve in the popliteal fossa. The delayed H-response was recorded on the soleus muscle. The parameters determined were the latency and maximal amplitude of the H-wave.

For all tests, skin temperature was maintained constant between 32 and 34.5°C, and the limb extremities were warmed if required.

Laboratory investigations

In elderly subjects, potential causes of PN - metabolic (renal failure, diabetes, vitamin deficiency, alcoholism, hypothyroidism), toxic (iatrogenic, environmental), neoplastic, immunological, inflammatory (rheumatoid arthritis, active hepatitis, SjOgren's syndrome) and hereditary - were screened for by medical history and laboratory investigations. Among these laboratory investigations, the following were performed by the same laboratory in all subjects: serum protein immunoelectrophoresis, antinuclear factors, tumour markers (fetoprotein, CEA, CA125, CA19-9), vitamin B1, B6 and B12, serum and red cell folate levels. In some cases, the cutoff value used for the classification of normal-abnormal differed from the normal laboratory range. For creafinine clearance the cutoff was a value below 50 ml.mn - ~ (clearance estimated by Cockroft's formula). For serum folate the cut-off was a value below 6nmol.m1-1, irrespective of the red cell value; values between 6 and 10 nmol. ml -~ (normal laboratory range: 10-30 nmot. m1-1) were considered to be a risk factor only in the presence of a low red cell folate. Mild elevation of tumour markers in the absence of clinical signs was not considered a risk factor, given the low specificity of these markers.

Statistical analysis

The population was divided into five groups (Table 1) according to age and to the presence or absence of abnormal biological results, the latter having been considered risk factors (RFs) for peripheral nerve dysfunction: group 1, young subjects; group 2, subjects aged ~ 80 years, without RFs; group 3, subjects aged > 80 years, without RFs; group 4, subjects aged _< 80 years, with RFs; group 5, subjects aged > 80 years, with Rfs.

The age of 80 years was used, being the usual cut-off for the very old. The effect of age on the electrophysiological parameters were tested independently of RFs by comparing groups 1, 2 and 3 using one-way analysis of variance and the Newman-Keuls test if required.

The ratio of age-explained variance to total variance was calculated. The respective effects of age and RFs were tested by comparing groups 2, 3, 4 and 5, using two-way analysis of variance with replications. The ratio of age- and RF-explained variance to the total variance was also calculated. Linear and quadratic analyses were used to evaluate how age predicts the values of nerve conduction parameters.

RESULTS AND DISCUSSION

Subjects

Among the 63 elderly subjects included, 4 were secondarily excluded because of incomplete biological data.

Among the 59 remaining elderly subjects, 29 were considered to have RFs: 4 subjects because of clinical factors noticed by the neurologist; 2 subjects with peripheral vascular problems (abolition of pedial pulse); 1 subject who admitted retrospectively having experienced a period of alcohol abuse 20 years previously and 1 other subject who received amitriptyline for 2 weeks; 25 elderly subjects who had abnormal biological results and were considered to have Rfs.

Group 4 displayed the following RFs: low value of estimated creatinine clearance (n = 3), folate and/or vitamin B6 and/or B12 deficiency (n = 7, without haematological abnormality), abnormal globulin profile (n = 3), high glycated haemoglobin (n = 3), thyroiditis (n = 1), hepatitis (n = 2), peripheral vascular problem (n = 1), alcoholism (n = 1), amitriptyline treatment (n = 1). In group 5, RFs were: low value of estimated creatinine clearance (n = 4), folate and/or vitamin B 6 and/or B12 deficiency (n = 5, without haematological abnormality), abnormal globulin profile (n = 1), hepatitis (n = 1), peripheral vascular problem (n = 1).

Table 1 : Group Characteristics

Group Number	1	2	3	4	5
No. of subjects	23	16	14	17	12
Female-Male	(10-13)	(12-4)	(13-1)	(9-8)	(10-2)
Age Mean (SEM)	23.8(0.5)	68.3(1.5)	88.3(1.6)	72.5(1.7)	86.3 (1.4)
Age : Range	21-29	60-80	81-103	60-80	81-94
Height: mean (SEM)	172.8 (1.8)	163(2.3)	158.1 (2.6)	163.8 (2.2)	164.3 (2.0)

Table 2 : Mean values of nerve conduction parameters (SEM). NCV, Nerve conduction velocity (m.sq); CMAP, compound motor action potential amplitude (mV); DL, distal latency (ms); SNAP, sensory nerve action potential amplitude (gV); H-reflex, amplitude (gV), latency (ms)

Nerve	Parameters	Group 1	Group 2	Group 3	Group 4	Group 5
Median (Motor)	NCV	61.0(0.6)	55.6(1.0)	54.7(1.0)	53.0(1.5)	54.8(1.2)
	CMAP	7.6(0.6)	7.8(1.0)	6.5(0.7)	4.7(0.6)	5.7(0.5)
	DL	3.4(0.1)	3.6(0.1)	4.1(0.2)	3.9(0.1)	3.5(0.1)
Common Peroneal (Motor)	NCV	50.2(1.0)	46.8(1.6)	45.1(0.8)	42.8(1.2)	43.9(0.9)
	CMAP	4.6(0.5)	3.6(0.5)	2.2(0.3)	1.6(0.3)	1.0(0.2)
	DL	4.4(0.1)	4.0(0.2)	4.7(0.3)	4.6(0.2)	5.1(0.3)
Median (Sensory)	NCV	47.8(0.9)	44.2(1.7)	42.7(1.5)	42.0(2.1)	40.6(1.4)
	SNAP	34.3(4.2)	21.1(3.5)	16.3(1.8)	14.4(2.6)	11.2(2.0)
Sural (Sensory)	NCV	43.0(0.9)	40.7(1.8)	39.7(1.6)	37.6(1.4)	36.1(1.5)
	SNAP	22.6(2.7)	6.1(0.8)	4.4(1.0)	4.5(0.7)	5.2(1.3)
H-Reflex	Amplitude	0.7(0.17)	0.51 (0.14)	0.70 (0.21)	0.24 (0.04)	0.22 (0.06)
	Latency	29.7(0.5)	31.7 (0.5)	31.7 (0.9)	33.5 (0.8)	41.20 (3.80)

Clinical result

No abnormalities were observed in group 1; in the other groups, the main abnormalities observed were: impairment of vibration sense (tuning fork) and position sense (big toe) found in 37% of subjects in group 2, 57% of group 3, 41% of group 4 and 60% of group 5; ankle reflexes absent in 19% of subjects in group 2, 50% of group 3, 65% of group 4 and 70% of group 5; sensory symptoms in the legs (pins and needles and cramps) in 31% of subjects in group 2, 50% of group 3, 35% of group 4 and 50% of group 5.

Effect of age on the electrophysiological parameters

Conduction study. The mean values and the percentages of variation are shown in Tables 2 and 3 respectively. In patients under 80 years of age, the only motor parameter which demonstrated a statistically significant decrease was the median NCV; from the sensory point of view, there were significant decreases in the median and sural SNAP amplitudes. In patients over 80 years of age, all parameters demonstrated significant changes, apart from the motor DL of the common peroneal nerve and the Hreflex amplitude. Comparisons between groups 3 and 2 showed significant differences in three motor parameters: median and common peroneal CMAP amplitudes, and common peroneal NCV. Although not statistically significant, the decrease in the sural NCV mean value was greater between groups 3 and 2 than between groups 2 and 1.

The age-explained variance was at the best 47%.

Electromyographical study. Mean values are shown in Table 4. Differences were statistically significant in: muscle TA - in group 3 the number of turns.s -1 was significantly lower than in group 2 (-47%; P< 0.01) and than in group 1 (-56%; P< 0.01); muscle FDI – the number of turns.s -1 was significantly lower in group 2 than in group 1 (-19%; P<0.05), in group 3 than in group 2 (-22%; P < 0.05) and in group 3 than in group 1 (-37% ; P < 0.01); MUP analysis of ECR - the duration was significantly higher in group 2 than in group 1 (+118%; P<0.01) and in group 3 than in group I (+87%;P < 0.01).

Interaction of age and RFs on the electrophysiological parameters Nerve conduction study (Table 3). As regards the age/RFs interaction, a significant interaction (differences in mean values between groups 2 and 5 not equal to the addition of age and risk effects) was observed for the motor median DL and the H-reflex latency. Oddly, the lowest value of the motor median DL was observed in group 5.

Table 3. Conduction studies: percentages of variation (subjects without risk factors). *P < 0.05, **P < 0.01. NCV, Nerve conduction velocity (m.s-t); CMAP, compound motor action potential amplitude (mV); DL, distal latency (ms); SNAP, sensory nerve action potential amplitude (btV): H-reflex, amplitude (bLV), latency (ms)

Nerve	Parameters	Group 2 vs 1	Group 3 vs 1	Group 3 vs 2
Median (Motor)	NCV	-9%**	-13%**	-4.7%
	CMAP	+3%	-38%*	-40%*
	DL	+6%	+15%**	+8%
Median (Sensory)	NCV	-8%	-12%*	-5%
	SNAP	-38%*	-58%**	-32%
Sural (Sensory)	NCV	-5%	-13%*	-8%
	SNAP	-73%**	-80%**	-26%
H-Reflex	Amplitude	-27%	-66%	-53%
	Latency	+7%*	+12.8%**	+6%*

Table 4. Mean values of the elctromyographic parameters (SEM). TA, Tibialis anterior muscle; FDI, first dorsal interosseous muscle; ECR, extensor carpis radialis muscle; MUP, motor unit potential

Nerve	Parameters	Group 1	Group 2	Group 3	Group 4	Group 5
TA	Max. amplitude	4230 (550)	3837 (399)	3484.5 (428)	2603 (560)	2845 (635)
	Mean amplitude	271(42)	276(46)	185.5(29)	149(53)	138(34)
	Turns/s	667(42)	545(48)	413(60)	290(37)	330(56)
FDI	Max. amplitude	4280 (540)	4696 (485)	3959 (500)	3337 (395)	3292 (664)
	Mean amplitude	382(59)	320(42)	264(41)	226(43)	206.5(67)
	Turns/s	899(39)	724(57)	621(64)	568(47)	585.5(92)
ECR	Max. amplitude	4270 (510)	4463 (401)	4011 (352)	3441 (476)	3231 (462)
	Mean amplitude	259(32)	304(58)	255.5(27.4)	175(32)	184(44)
	Turns/s	916(80)	835(76)	798(76)	636(117)	613(68)
MUP Semi-automatic analysis	Duration	3.8(0.4)	8.3(0.8)	8.5(0.6)	7.1(0.8)	6.6(0.7)
	Amplitude	432.0 (47)	590.1 (62)	553.0 (48)	623.2 (60)	545.5(75)

The increase in H-reflex latency observed in group 5 was greater than expected from an additive age plus RF effect ($P < 0.05$).

Concerning the effect of age (groups 3 + 5 versus groups 2 + 4), the significant differences observed in the first analysis between groups 3 and 2 were confirmed: decreased CMAP amplitude in the median nerve, decreased CMAP amplitude and motor NCV in the common peroneal nerve. A significant decrease was also observed in two more parameters: median SNAP amplitude ($P < 0.05$) and H-reflex amplitude ($P < 0.05$).

With regard to the risk factor effect (groups 4 + 5 versus groups 2 + 3), a significant difference was observed for two motor conduction parameters in the common peroneal nerve: decrease in CMAP amplitude ($P < 0.05$) and increase in DL ($P < 0.05$).

The age- and RF-explained variance was at the best 34%.

Electrornyogram (Table 4). No significant age/risk interaction was observed. With regard to the effect of age, a significant decrease in turns per second, observed between groups 3 and 2, was confirmed in the muscle TA and in MUP analysis of ECR. Conversely, significant differences were seen in the following parameters: TA - slight decrease in mean amplitude ($P = 0.05$); ECR - decreased peak-to-peak and mean amplitudes ($P < 0.05$) and decreased turns/s ($P < 0.05$).

The only significant RF effect was observed for turns per second ($P < 0.05$) in MUP analysis of ECR.

CONCLUSION

In this study, age explains at best 47% of the variance; between 60 and 103 years, age and RFs account for 34% of variance at the most. Factors which play a role could be mainly genetic but also nutritional (which may contribute to a cohort effect) and toxic; toxic substances could affect sensory and motor systems differently and the long-term or delayed neurotoxicity of many substances in common use is unknown. It seems, however, that in the very old, inequalities related to the above factors may be blunted by cell loss and exhaustion of the compensatory mechanisms.

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