Electroneurophysiological studies in familial amyloid polyneuropathy—Portuguese type

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SUMMARY Electroneurophysiological studies were performed in 15 patients with familial amyloid neuropathy (ages 29 to 67 years) and in 16 symptom-free members of affected families (ages 9 to 64 years). These studies included needle EMG, motor conduction velocities of deep peroneal and median nerves, sensory conduction velocities, sensory potentials, and nerve potentials of the sural and median nerves. Results support the view that familial amyloid neuropathy is a peripheral neuropathy with predominantly axonal damage, which affects first the distal segments of the sensory fibres and then the motor fibres. It is suggested that, in some respects, this condition is akin to the dying-back neuropathies. Results also show that it is possible to detect the disease before it becomes obvious clinically, and this has important implications for genetic counselling.

Familial amyloid polyneuropathy is an autosomal dominant disease which affects various organs, mainly the peripheral nervous system. Clinically it is a chronic, slowly progressive polyneuropathy, symmetrical, distal, starting in the lower extremities, predominantly sensory, with trophic symptoms, generally associated with digestive complaints, sexual impotence, and ending inexorably in cachexia and death.

It was described for the first time in 1951 by Andrade who also established its relationship with the presence of amyloid in the peripheral nerves, as well as in the skin, muscles, and digestive system.

Nevertheless, the pathogenesis of the neuropathy has not yet been well established. Coimbra and Andrade (1971) expressed the opinion that the polyneuropathy is not directly related to the presence of amyloid. It is possible that the error of protein metabolism which is responsible for the deposition of amyloid is also the origin of the neuropathy. Biochemical and electroneurophysiological investigations of the pathogenesis of this disease are in progress to try to define the type of polyneuropathy and to establish its relationship with the amyloid substance.

It must be emphasised that this is a genetically determined, dominant disease which seems to be spreading in Portugal, and outside through emigration, at a rate which should be predictable and which it is important to try to reduce. Most of the patients with familial amyloid polyneuropathy have children before they develop impotence and frequently before they have the first symptoms.

Electromyography and motor conduction velocity studies have been performed in patients with familial amyloid polyneuropathy by Tomé and Coelho (1965) and Canijo and Andrade (1969) in Portugal, and Andersson and Blom (1972) in Sweden, and nerve fibre conduction velocities in teased preparations by Dyck and Lambert (1969).

We have carried out neurophysiological studies in patients and clinically normal members of affected families with two aims—to elucidate the physiopathology of the polyneuropathy, and to find a way of predicting which of the children and siblings of patients will be affected with a view to providing genetic counselling.

Subjects and methods

We looked at 15 patients (nine women and six men) aged between 29 and 67 years, moderately affected by the disease (ambulant, independent in regard to the activities of daily living, some carrying out professional duties). Biopsies of rectal

mucosa, skin, muscle, or nerve demonstrated the presence of amyloid in 10 patients. The other five did not agree to biopsy but results of the neurological examination and family history were typical of the disease.

We also studied 16 members of 10 affected families (siblings and children of patients) aged between 9 and 34 years. No neurological complaints nor symptoms were detected in these individuals with the exception of one who had sciatic pain.

We repeated the electroneurophysiological studies one year later in two members of affected families.

Electroneurophysiological studies were performed using a three-channel DISA machine type 14 A 30 with digital averager and input transformer which allowed a more accurate detection of sensory potentials.

The following studies were carried out: needle EMG of the tibialis anterior, extensor digitorum brevis, and abductor pollicis brevis; motor conduction velocities, distal conduction time, proximal and distal thresholds, shape and voltage of the motor response; sensory potentials and nerve potentials (distal and proximal segments) of the median and sural nerves, sensory conduction velocities, conduction times, and sensory thresholds.

Surface electrodes were used for nerve stimulation and bipolar needle electrodes for muscle response detection. Buchthal and Rosenfalck's (1966) technique was used for the sensory potentials with sensory potential averaging when necessary. To test our results for sensory potentials, previous studies were carried out in normal subjects (Sales Luís *et al.*, 1977), and the results compared with those described by Buchthal and Rosenfalck (1966). There were no significant differences.

Results

PATIENTS

Electromyography (Table 1)

Results of electromyography were abnormal in all the cases in anterior tibialis and extensor digitorum brevis (signs of chronic neurogenic involvement) more marked distally, with denervation potentials in only seven out of the 15 patients. In the thenar eminence the EMG was abnormal in only 46.6% of the patients.

Motor conduction velocities (Table 2)

In the deep peroneal nerve one case had completely normal values. In three cases (20%) no motor response was obtained in the extensor digi-

Table 1 *Results of electromyography in 15 patients with familial amyloid polyneuropathy*

Muscles	Maximum voluntary contraction	Fibrillation	High voltage long duration potentials	Polyphasic potentials
Anterior tibialis	Intermediate pattern 13 (86.6%) Discrete pattern 2 (13.4%)	5 (33.3%)	15 (100%)	13 (86.6%)
Extensor digitorum brevis	Discrete pattern 5 (33.3%) One small motor unit 5 (33.3%) Absence of potentials 5 (33.3%)	7 (46.6%)	5 (33.3%)	10 (66.6%)
Thenar eminence	Intermediate pattern 7 (46.6%)	—	7 (46.6%)	7 (46.6%)

Table 2 *Results of motor conduction velocity studies in the deep peroneal and median nerves in 15 patients with familial amyloid polyneuropathy*

Nerves	Motor conduction velocity	Distal conduction time	Motor response
Deep peroneal	> 40 m/s 8 (53.4%) > 27 m/s < 40 m/s 4 (26.6%)	≥ 5 ms < 7 ms 4 (26.6%)	Normal 1 (6.6%) ≥ 100 μV < 3 mV 11 (73.4%) Absent 3 (20%)
Median	≥ 50 m/s 8 (53.4%) > 40 m/s < 50 m/s 7 (46.6%)	≥ 5 ms < 7 ms 5 (33.3%)	Normal 4 (26.6%) ≤ 10 mV 9 (60%) Polyphasic 8 (53.4%)

torum brevis. In 11 patients (73.4%) low voltage polyphasic muscle response was obtained, with normal maximum conduction velocities in seven and moderately slowed maximum conduction velocities in four.

In the median nerve motor conduction velocities and motor responses were normal in four cases (26.6%). In 11 patients (73.4%) low voltage or polyphasic motor responses or both were obtained with normal or slightly decreased maximum conduction velocities.

Sensory studies (Table 3)

In the sural nerve sensory potentials were absent in all cases. Proximal sensory potentials were

Table 3 Results of sensory studies in the sural and median nerves in 15 patients with familial amyloid polyneuropathy

Nerves	Sensory potentials	Nerve potentials	Sensory conduction velocities	Nerve conduction velocities
Sural	Absent 15 (100%)	Absent 11 (73.4%) ≤5 μV 3 (20%) > 5 μV 1 (6.6%)		40 m/s 43.3 m/s 2 (13.4%) Normal 2 (13.4%)
Median	Absent 2 (13.4%) Normal 1 (6.6%) ≥7.5 μV spread 12 (80%)	11 patients < 20 μV 9 (81.8%) > 20 μV 2 (18.2%)	≥40 m/s ≤50 m/s < 65 m/s > 50 m/s 12 (80%) 1 (6.6%)	11 patients ≥53.3 m/s < 65 m/s ≥65 m/s 9 (81.8%) 2 (18.2%)

absent in 11 cases (77.4%), had low voltage in three, and were normal in only one case. Nerve conduction velocities in the latter four cases were normal or slightly slowed.

In the median nerve sensory potentials in the distal segment finger 2—wrist) was absent in two cases (13.3%), normal in one (6.6%), and low voltage, spread (1.7–7.5 μV) in 12 (80%), with maximum conduction velocities normal or slightly decreased.

In the proximal segment (wrist—arm) studies were performed in 11 patients: nine showed low voltage nerve potentials with slightly decreased conduction velocities and two had normal values.

MEMBERS OF AFFECTED FAMILIES

Results of EMG studies were normal in all cases. Motor conduction studies showed low voltage (<5 mV) polyphasic muscle response to stimulation of the deep peroneal nerve in six cases (37.5%).

As shown in Table 4 in the distal segment of the sural nerve there were absent or low voltage spread potentials in eight cases (50%) with sensory conduction velocities between 30 and 40 m/s. In the proximal segment of the sural nerve there were low voltage potentials in two cases (12.5%) with slightly decreased conduction velocity. In the distal segment of the median nerve there were low voltage spread potentials with normal conduction velocities in seven cases (46.6%) (Table 4).

REPEAT STUDIES (Table 5)

Electroneurophysiological studies were repeated one year later on two apparently normal members of affected families, and in both cases signs of the

Table 4 Results of sensory studies in the sural and median nerves in 16 members of affected families

Nerves	Sensory potential	Nerve potential	Sensory conduction velocity	Nerve conduction velocity
Sural	Normal 8 (50%) Spread 5 (31.2%) Absent 3 (18.8%)	Normal 14 (87.5%) 5 μV 2 (12.5%)	Normal 8 (50%) 30–40 m/s 5 (33.3%) Absent 3 (18.8%)	Normal 14 (87.5%) 30–40 m/s 2 (12.5%)
Median	Normal 9 (56.2%) Spread (≤10 μV) 6 (37.5%) Triphasic (<10 μV) 1 (6.3%)	Normal 16 (100%)	Normal 16 (100%)	Normal 16 (100%)

Table 5 Results of comparative studies in two members of affected families

Cases	Deep peroneal nerve muscle response	Sural nerve foot–ankle (μV)	Sural nerve ankle–leg (μV)	Median nerve sensory potential (μV)
MABS (39 yr)				
First study	Normal	5	Normal	17.5
Second study	Low voltage polyphasic	Absent	Normal	5
AFD (23 yr)				
First study	Normal	Spread	22.5	10 Spread
Second study	Low voltage polyphasic	Spread	5	10 Spread

disease were found—lower amplitude of the sural and median nerves sensory potentials; lower amplitude and spreading of muscle response to deep peroneal nerve stimulation.

Discussion

The mechanisms put forward to explain familial amyloid polyneuropathy—namely, compression of the nerve fibres by the presence of amyloid substance, ischaemia caused by vascular involvement of the “vasa nervorum,” or a local immunological reaction—leave open a number of questions. They do not explain, for example, the symmetrical and distal rather than multifocal distribution of the fibre lesions, the selection of predominantly sensory and sympathetic fibres, the relative independence of the nerve lesions and the sites of amyloid deposition.

Andrade's (1951) hypothesis that the neuropathy may be the consequence of a metabolic error still needs to be proved.

From the electroneurophysiological point of view our data indicate that in the patient group the most constantly found alterations were: absence of sensory potentials in the distal segment of sural nerve; decrease of amplitude and polyphasy of the muscle response to stimulation of the deep peroneal nerve; low amplitude, spread potentials in the distal segment of the median nerve; absence of or very low voltage of the potentials in the proximal segment of the sural nerve; low voltage potentials in the proximal segment of the median nerve; and normal or slightly decreased motor and sensory maximum conduction velocities.

In 50% of the clinically normal members of affected families, low voltage, spread potentials were detected only in the distal segment of the sural nerve or in the median nerve distal segment. Repeat studies in two members of affected families after a year showed evidence of the disease.

Thus, our data suggest that familial amyloid polyneuropathy is predominantly axonal, starting in the very distal portions of the sensory fibres of the lower limbs, then involving the distal parts of the motor fibres, and slowly ascending to more proximal segments of the nerve fibres.

These findings suggest that familial amyloid polyneuropathy should be considered, as other kinds of familial neuropathy, an axonal or neuronal form of dysfunction, probably of metabolic origin, leading to "atrophy" and "death" of the endings of the nerve fibres, and that the disease could be included among the neuropathies of the dying-back type.

The evidence that the small size sensory and sympathetic fibres are involved first, although the motor and deep sensation fibres are also affected later is, on the other hand, against this interpretation. The concept of dying-back neuropathy is not yet satisfactorily explained in terms of its cellular mechanism, although a recent model has been achieved with experimental acrylamide neuropathy.

Indeed, in these studies, the axoplasmic transport was not shown to be disturbed as would be expected.

Thus, it is still possible to speculate about familial amyloid polyneuropathy as a dying-back type of neuropathy arising from a metabolic error which affects primarily the sensory and sympathetic neurones even if they are not those with the largest and longest axons.

The results of the sensory studies in apparently normal members of affected families—namely, those who showed a subclinical evolution of the disease process on repeat testing—are significant enough to justify the attempt to detect patients in the preclinical stage and to give them genetic counselling.

References

- Andersson, R., and Blom, S. (1972). Neurophysiological studies in hereditary amyloidosis with polyneuropathy. *Acta Medica Scandinavica*, **191**, 233–239.
- Andrade, C. (1951). Note préliminaire sur une forme particulière de neuropathie périphérique. *Revue Neurologique*, **85**, 302–306.
- Buchthal, F., and Rosenfalck, A. (1966). Evoked action potentials and conduction velocity in human sensory nerves. *Brain Research*, **3**, 1–11.
- Canijo, M., and Andrade, C. (1969). Familial amyloidotic polyneuropathy. Electromyographic study. *Journal de Génétique Humaine*, **17**, 281–288.
- Coimbra, A., and Andrade, C. (1971). Familial amyloid polyneuropathy: an electron microscope study of the peripheral nerve in five cases. *Brain*, **94**, 199–212.
- Dyck, P. J., and Lambert, E. H. (1969). Dissociated sensation in amyloidosis. *Archives of Neurology (Chicago)*, **20**, 490–507.
- Sales Luís, M. L. P., Mendes, M. A. V., and Vieira, R. X. (1977). Velocidade de condução sensitiva, potenciais sensitivos e potenciais de nervo em neurofisiologia clínica. *O Médico*, **83**, 484–500.
- Tomé, F., and Coelho, B. (1965). Electromyography and muscular biopsy (motor endplate) findings in primary amyloid neuropathy. *Proceedings of the 8th International Congress of Neurology (Vienna)*, **9**, 5–10.