Short report

Distal amyotrophy of predominantly the upper limbs with pyramidal features in a large kinship

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SUMMARY An autosomal dominant disease characterised by amyotrophy of predominantly distal upper limb muscles and mild pyramidal features is described. There are sensory changes in older patients, whilst in others the disease presents itself as a disorder of motor neurons. Owing to variations in the clinical picture, it may be difficult to distinguish this disease in individual patients from distal spinal muscular atrophy, or from pure pyramidal syndromes. There is an overlap in clinical signs between this disease and peroneal muscular atrophy with pyramidal features. Whether or not the latter two conditions are genetically distinct, is a matter of doubt.

In 1966, Silver¹ described two families in this Journal with an autosomal dominant disease characterised by amyotrophy of predominantly distal muscles of the upper limbs and pyramidal disturbances of predominantly the lower limbs. The onset of this disease was in the second decade and progress was very slight with no shortening of life. Classification of Silver's disease became a matter of divergent opinion. It was regarded by some as a variant of hereditary motor and sensory neuropathy type V², whilst others felt that it was a special form of spastic paraplegia with amyotrophy.^{3,4} We recently had the opportunity to examine 18 affected members of another large kinship with this disease. We undertook the investigation in order to delineate as accurately as possible the variability of the clinical picture.

Index patient

(Case V4, Figure and Table)

This patient experienced slight difficulty in walking from the age of 11 years. When he was 36 years old, neurological examination disclosed bilateral pes cavus, right thenar atrophy, bilateral peroneal muscle atrophy and weakness

of atrophic muscles. Tendon reflexes of the limbs were raised. We saw the patient for the first time when he was 60 years of age. His complaints then concerned decrease in hand power and increased difficulty in walking. He had no paraesthesiae and experienced only occasional cramping of the calf muscles. There was a marked degree of intrinsic hand muscle atrophy together with atrophy of the peroneal muscles. Tendon reflexes of the limbs were raised with the exception of the ankle reflexes which were absent. The tone of the lower limb muscles was raised and Babinski reflexes were present. The vibration sense was disturbed below the knees and there was hypaesthesia and hypalgesia from half way down the lower legs. Electromyography revealed denervation potentials and loss of motor units in distal limb muscles. Stimulation of the median nerve at the wrist did not elicit any potential. Motor and sensory conduction velocities and distal latencies of the ulnar nerve were normal. The sensory action potential at the elbow was regarded as abnormal, because of severe polyphasia. Myelinated nerve fibre density in a biopsy of the left sural nerve was decreased (740 per 0.2 mm², or 3900 per mm²; in normal adults >7000⁵). Nerve fibre diameters varied from 1–14 µm. A histogram of 1000 myelinated nerve fibres showed a normal first peak at 3 µm, whilst the second peak at 8 µm was not present, due to loss of large myelinated nerve fibres. Examination of 29 teased nerve fibres showed paranodal demyelination once and occasional remyelinated segments.

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Description of the family

Six generations are represented in the pedigree (fig). The disease was present in some members of each generation.

Fig Pedigree of six generations.

Table 1 Clinical data on affected subjects

No in pedigree	IV 1	V 3	V 4	V 6	V 43	V 18	V 11	VI 2	VI 3	VI 46	V 23	V 24	VI 7	VII 6	VI 39	VI 40	VI 64
Age (yrs)	91	69	63	55	52	48	46	45	45	44	35	32	25	22	21	19	17
Sex	f	f	m	f	f	m	m	f	f	m	m	f	f	m	f	m	m
<i>Upper limbs</i>																	
Distal atrophy and weakness	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	+
Raised tendon reflexes			+											+		+	
<i>Lower limbs</i>																	
Distal atrophy	+	+	+	+									+				
Distal weakness	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Raised knee jerk	+	+	+	+		+	+	+	+	+	+	+	+	+	+	+	+
Raised ankle jerk			+											+	+	+	
Babinski																+	
Hypertonia			+													+	
<i>Sensory impairment</i>																	
Clinical	+	+	+														

+ = positive

Examination of 43 members, revealed 10 females and eight males to be affected. On the basis of reliable information and by reviewing old family photographs, it was concluded that 14 other members were also affected. The onset of the neurological symptoms took place in the second decade, between the ages of 11 and 17. Excluding the children under 10 years of age, 37% of the descendants of affected members were also affected. In seven patients, the first symptoms and signs developed in the upper limbs and concerned weakness of the hand musculature. Initial complaints in other patients concerned walking difficulties. At the time of examination, all patients but one (table 1) had atrophy and weakness of the thenar and other distal upper limb muscles, and this was marked in 11 of these patients. In five cases, thenar atrophy was unilateral and located on the right side. Complaints (and electroneurographic abnormalities, *see below*) compatible with a carpal tunnel syndrome were present in V43. This patient was operated on and no evidence of median nerve compression was found. Three patients had raised tendon reflexes in the upper limbs. Obvious atrophy in the distal parts of the lower limbs was seen in five patients, whilst some degree of weakness was present in 17 patients. All affected subjects and two non-affected family members had pes cavus. The knee jerks were raised in 17 patients and the ankle jerks in

five patients. Two patients had Babinski reflexes and hypertonia of lower limb muscles. We were not convinced that absence of extensor plantar responses in other patients was due to weakness of the extensor hallucis muscle. Clinical evidence of sensory disturbance was found in the index patient and two other aged patients. The sensory changes in the latter were no less than in the index patient.

Abnormalities of sensory nerve conduction in the median nerve (four cases) and the ulnar nerve (three cases) were present in seven of the 12 patients examined (table 2) and concerned abnormal polyphasia of sensory action potentials in the elbow in five cases, decrease in sensory action potential amplitudes in the wrist in three cases, and an abnormal increase in distal sensory latency in two cases. Sensory conduction velocity between wrist and elbow was normal. Distal motor latency in the median nerve was prolonged in 11 patients. In two patients (V43 and V46) both sensory and motor distal latencies were prolonged. Motor conduction velocity between wrist and elbow was slightly decreased in two cases and normal in 10. Antibodies against thyroid tissue were present in three of the 18 affected subjects and in three of the 15 non-affected patients. Hypothyroidism was searched for in all these cases and was found to be present only in VI.7. Substitution therapy in this latter patient had no effect on the

Table 2 Data on nerve conduction (Median nerve unless indicated otherwise)

Age (yr)	V 4	V 43	V 18	V 46	V 23	V 24	VI 7	VII 6	VI 39	VI 40	VI 64	VI 14	Normal values
	63	52	48	44	35	32	25	22	21	19	17	14	
<i>Sensory conduction</i>													
Latency digit I-wrist		<u>4.3</u>	2.5	<u>3.6</u>	2.2	2.0	1.9	2.3	2.2	2.0	2.4	1.9	≤ 3.0 ms
Amplitude action potential (wrist)		<u>1.4</u>	30	<u>0.4</u>	50	25	45	7	35	50	25	40	> 52 yrs: ≥ 9 μV
Severe polyphasia (elbow)													> 22 yrs: ≥ 14 μV
Velocity (wrist-elbow)	*+ *64	*72	65	58	*+ *61	* *65	71	64	*+ *71	58		69	≥ 58 m/s
<i>Motor conduction</i>													
Distal latency	N.O.	<u>4.0</u>	<u>5.9</u>	<u>4.5</u>	N.O.	<u>4.4</u>	<u>4.3</u>	<u>5.2</u>	<u>3.7</u>	<u>4.6</u>	<u>6.8</u>	2.9	≤ 3.4 ms
Velocity (wrist-elbow)	*58	*64	<u>58</u>	<u>50</u>	*62	*63	<u>47</u>	<u>62</u>	*65	<u>54</u>		63	≥ 54 m/s

Conduction studies were performed with needle electrodes near the nerve. Skin temperature of the hand was kept at 36°C.

* = ulnar nerve

_____ = abnormal

N.O. = Not obtainable

+ = present

neurological abnormalities.

Discussion

Amyotrophy is known to develop in several chronic hereditary diseases of the pyramidal tract and these conditions have recently been reviewed.⁴⁻⁶ In one of these conditions, muscular weakness and atrophy develop early and are located predominantly in distal muscles of the lower limbs.⁶ Distal upper limb muscles in this condition are often also involved, and in occasional members of such families, hand muscle atrophy is even more severe than peroneal muscle atrophy. The disorder in the present kinship closely resembled the disease described by Silver.¹ Inheritance was autosomal dominant without preference for either sex. Atrophy of the hand muscles was often marked (11 out of 18 cases) and more severe and more frequent than atrophy of lower limb muscles. Thenar atrophy was in some patients unilateral and only present on the right side. Clinical evidence of sensory disturbances were only seen in aged patients. In some aspects, the syndrome in the present family differed slightly from that in Silver's families. Complaints of hand muscle weakness were less often the presenting symptoms and pyramidal disturbances were less severe and were never the only clinical findings. Histological and electrophysiological investigations showed nerve fibre degeneration to be neuronal or axonal in origin. These investigations were not performed by Silver.

Distal muscular atrophy of the upper limbs with pyramidal features presents in most patients as a disorder of motor neurons and classification as a mixed motor and sensory neuropathy is not, therefore, the most logical conclusion. Minor involvement of sensory neurons is well known in both hereditary⁷ and non-hereditary⁸ forms of motor neuron disease. In individual patients, the disease may be expressed as distal spinal muscular atrophy or as a pure pyramidal syndrome. The differentiation between hereditary distal lower and distal upper limb muscular atrophy with pyramidal features, is not always possible in individual patients and whether these two syndromes have to be distinguished as separate genetic entities is doubtful.

The discovery of thyroid antibodies in almost equal percentages of affected (16%) and non-

affected (20%) members of this kinship, came as a surprise. The incidence of these antibodies in the Dutch population is between 0% and 3%.^{9,10} The combination within one family of hereditary antibodies against thyroid tissue and the described neurological syndrome may be a coincidence.

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