HEREDITARY MOTOR SYSTEM DISEASES
(CHRONIC JUVENILE AMYOTROPHIC LATERAL SCLEROSIS)

CONDITIONS COMBINING A BILATERAL PYRAMIDAL SYNDROME
WITH LIMB AND BULBAR AMYOTROPHY

by MONGI BEN HAMIDA, FAYÇAL HENTATI
and CHRISTIANE BEN HAMIDA

(From the Institut National de Neurologic, Tunis)

SUMMARY

Forty-three patients with hereditary motor system diseases belonging to 17 families were studied. The clinical features consisted of a bilateral pyramidal syndrome, weakness with atrophy and fasciculation of the hands and/or the legs, with or without a bulbar or a pseudobulbar syndrome and without sensory disturbance. Electromyography in 31 cases (including all index cases) showed evidence of denervation. Motor and sensory nerve conduction velocity was normal; sensory nerve action potential amplitudes, examined in 11 cases, were also normal. Nerve and muscle biopsies taken in 29 cases (including all index cases) showed neurogenic atrophy in the peroneus brevis muscle and minor changes only in the superficial peroneal nerve. The mean age of onset was 12.06 (range 3–25 years), and progression was very slow. Inheritance appeared to be autosomal recessive. Depending on the clinical presentation, the patients were subdivided into three groups comprising (1) upper limb and sometimes bulbar amyotrophy with a bilateral pyramidal syndrome (17 patients: 11 familial and 6 isolated); (2) spastic paraplegia with peroneal muscular atrophy (14 patients: 11 familial and 3 isolated); and (3) a spastic pseudobulbar form (12 patients in a large kinship). These entities are discussed and compared with other cases reported in the literature.

INTRODUCTION

The association of a bilateral pyramidal syndrome with amyotrophy in the limbs and fasciculation in a young subject (infant or adolescent) raises an important nosological distinction between classical amyotrophic lateral sclerosis (ALS), or 'Charcot's disease', and more protracted and often inherited forms. The term juvenile ALS has sometimes been used to designate such syndromes, even in the absence of anatomical documentation (van Bogaert, 1925; Ford, 1960; Bonduelle, 1975, 1982; Emery and Holloway, 1982; Ben Hamida and Hentati, 1984). With the exception of rare instances of rapidly progressive juvenile ALS, comparable with Charcot's disease (Berry et al., 1969; Nishigaki et al., 1971; Nelson and Prensky, 1972), this is usually a chronic disease. It is sometimes isolated but quite often familial, and can take various forms. In its commoner form, it variously combines amyotrophy and fasciculation of the hands with spastic paraplegia and a bulbar or pseudobulbar syndrome. We have grouped with
this commoner form other familial or isolated cases with a juvenile or infantile onset in which a spastic paraplegia is associated with distal amyotrophy in the lower limbs, with or without a spastic pseudobulbar syndrome.

**PATIENT AND METHODS**

The patients were examined at or investigated in hospital at the National Institute of Neurology between 1974 and 1988. Cases of severe spinal amyotrophy of the Werdnig-Hoffman type (death within 2 yrs of birth), the infantile and juvenile forms of progressive proximal spinal muscular atrophy (SMA), and the scapuloperoneal atrophies, were excluded. We also excluded 5 cases conforming to the definition of the Vialetto-Van Laere syndrome (progressive bulbar paralysis with deafness (Vialetto, 1936; Van Laere, 1966)) which probably constitutes a separate genetic entity.

The criteria for diagnosis were (1) onset usually before the age of 25 yrs; (2) the simultaneous or dissociated appearance of muscle weakness with atrophy and fasciculation in the arms and sometimes in the legs, a pyramidal syndrome, and labioglossaryngeal paralysis and/or pseudobulbar syndrome; (3) a neurogenic electromyogram (EMG) with normal motor nerve conduction velocity (MNCV); (4) normal sensory nerve conduction; and (5) denervation changes on muscle biopsy and normal appearance on sensory nerve biopsy.

Of the 17 cases chosen, a survey in the field made it possible to reexamine all the living index cases, to determine their current condition, to examine all available family members, and to discover 26 secondary cases belonging to 8 families. The group studied thus comprised 43 patients belonging to 17 families. A family pedigree was established in all the familial cases. In consanguineous kindreds the coefficient of inbreeding (CI) was calculated by the method of Wright (1922). Segregation analysis was performed using the sibship method (Fisher, 1934) and the Weinberg proband method (Weinberg, 1928).

Superficial peroneal nerve and peroneus brevis muscle biopsies were performed in 29 cases, including all the index cases. The sections were studied using previously described techniques (Ben Hamida et al., 1983, 1987). The cerebrospinal fluid (CSF) protein content was measured in 34 cases. The results were analysed statistically using Student's t test, and the results expressed as means ± 2 SEM.

We identified three different clinical presentations: (1) upper limb (± bulbar) amyotrophy with bilateral pyramidal involvement; (2) spastic paraplegia with peroneal muscular atrophy; and (3) a spastic pseudobulbar syndrome with spastic paraplegia.

**CASE REPORTS**

*Group 1: upper limb (± bulbar) amyotrophy with bilateral pyramidal involvement*

This group was characterized by muscle atrophy and a pyramidal syndrome with or without bulbar involvement. The muscle atrophy began in the small hand muscles (fig. 1), sometimes extending progressively in the upper limbs to the shoulders. Fasciculation was visible in the atrophic muscles. The pyramidal syndrome produced a spastic gait. The bulbar syndrome appeared gradually in the form of labioglossaryngeal paralysis. There was no bladder dysfunction and no sensory disturbance. In this group there were 17 cases belonging to 10 families; 11 were familial and 6 were isolated. The clinical features of the index cases are detailed below and those of affected members are summarized.

*Family 1*

*Case 1*, propositus, 28-yr-old male. Onset was at 10 yrs with weakness. Examination showed a spastic gait, brisk tendon reflexes, extensor plantar responses, atrophy of the hand muscles with fasciculation, and no bulbar signs. CSF protein: 0.20 g/l. Muscle biopsy: denervation; nerve biopsy: normal. EMG: denervation in all four limbs. MNCV: 51 m·s⁻¹ (ulnar), 48 m·s⁻¹ (peroneal). Sensory nerve action potential (SAP) amplitude: 28 μV (median), 11 μV (sural); sensory nerve conduction velocity (SNCV): 50 m·s⁻¹ (sural), 50 m·s⁻¹ (median).
Case 2, the 36-yr-old bedridden sister of Case 1 whose history was identical to that of the propositus. CSF protein: 0.15 g/l.

Family 2

Case 3, propositus, the 18-yr-old daughter of consanguineous parents (CI = 1/16). Onset was at 16 yrs with progressive difficulty in handling articles and in walking. Examination showed a spastic gait, extensor plantar responses, moderate atrophy of the muscles of the left hand with fasciculation, and no bulbar signs. CSF protein: 0.27 g/l. Muscle biopsy: denervation; nerve biopsy: normal. EMG: denervation in all four limbs. MNCV: 40 m·s⁻¹ (median), 58 m·s⁻¹ (ulnar), 44 m·s⁻¹ (peroneal). SAP amplitude: 18 μV (ulnar), 18 μV (saphenous). SNCV: 60 m·s⁻¹ (median), 58 m·s⁻¹ (ulnar), 47 m·s⁻¹ (peroneal).

Case 4, the 27-yr-old sister of Case 3. Onset was at 10 yrs with an identical clinical picture but, in addition, difficulty in swallowing and dysarthria. CSF protein: 0.57 g/l. Muscle biopsy: denervation; nerve biopsy: normal. EMG: denervation in all four limbs. MNCV: 65 m·s⁻¹ (median), 45 m·s⁻¹ (peroneal). SAP amplitude: 39 μV (median), 23 μV (saphenous). SNCV: 58 m·s⁻¹ (median), 54 m·s⁻¹ (saphenous).

Family 3 (fig. 2)

Case 5, propositus, the 16-yr-old daughter of consanguineous parents (CI = 1/16). From the age of 7 yrs progressive weakness of the left hand then of both hands developed. A few years later difficulty in walking appeared. Examination showed a spastic gait and marked amyotrophy of the hands. There were no bulbar signs. CSF protein: 0.11 g/l. Nerve biopsy normal; muscle biopsy: denervation. EMG: denervation in all four limbs. MNCV: 38 m·s⁻¹ (ulnar), 35 m·s⁻¹ (peroneal). SAP amplitude: 45 μV (median), 26 μV (ulnar), 26 μV (saphenous). SNCV: 45.5 m·s⁻¹ (saphenous), 52 m·s⁻¹ (ulnar), 56 m·s⁻¹ (median).

Case 6, the 12-yr-old sister of Case 5. Onset was at 6 yrs. The course was more aggressive than in the propositus.

Family 4

Case 7, propositus, 30-yr-old female. At the age of 16 yrs progressive difficulty in walking appeared. On examination, her gait was spastic and waddling. There were pyramidal signs in all four limbs with spasticity, brisk tendon reflexes apart from absent ankle jerks, extensor plantar responses and amyotrophy of the hands with fasciculation. EMG: denervation. MNCV: 39 m·s⁻¹ (peroneal), 58 m·s⁻¹ (ulnar). CSF protein: 0.21 g/l. Nerve biopsy: normal; muscle biopsy: denervation.
Fig. 2. Pedigree of family 3. □ = male nonaffected; ■ = male affected; ○ = female nonaffected; ● = female affected.

Case 8, the 33-yr-old brother of Case 7. Onset was at 13–14 yrs with an identical clinical picture.
Case 9, the 25-yr-old brother of Case 7 with an identical history.
Case 10, the 23-yr-old sister of Case 7 with an identical history. CSF protein: 0.20 g/l. Nerve biopsy: normal.
Case 11, the 13-yr-old sister of Case 7 with an identical history.

Family 5
Case 12, propositus, the 17-yr-old daughter of consanguineous parents (CI = 1/16). At the age of 13 yrs, the weakness of the right arm, then of the left arm, and then of the lower limbs appeared. Examination showed wasting of the hands, a spastic paraplegia, brisk tendon reflexes, bilateral extensor plantar responses and pes cavus. Bulbar involvement (mild atrophy of tongue and dysarthria) developed recently. EMG: denervation. MNCV: 40 m·s⁻¹ (peroneal), 51 m·s⁻¹ (ulnar). CSF protein: 0.22 g/l. Nerve biopsy: normal; muscle biopsy: denervation. Hexosaminidase activity: A, 1268 U/l, B, 556 U/l (normal).

Family 6
Case 13, propositus, the 20-yr-old son of consanguineous parents (CI = 1/16). Onset was at 6 yrs. Examination showed muscle wasting in the hands with fasciculation, and brisk tendon reflexes in all four limbs. EMG: denervation. MNCV: 40 m·s⁻¹ (peroneal), 50 m·s⁻¹ (ulnar). CSF protein: 0.17 g/l. Muscle biopsy: denervation; nerve biopsy: normal.

Family 7
Case 14, propositus, the 19-yr-old daughter of consanguineous parents (CI = 1/16). Onset was at 12 yrs. Examination showed distal amyotrophy in the upper limbs with fasciculation, a spastic paraparesis, brisk tendon reflexes, extensor plantar responses, and a bulbar syndrome with palatal paralysis, marked atrophy of the tongue and difficulty in swallowing. EMG: denervation. MNCV: 41 m·s⁻¹ (peroneal), 45 m·s⁻¹ (ulnar). CSF protein: 0.15 g/l. Muscle biopsy: denervation.

Family 8
Case 15, propositus, a 38-yr-old male, the son of consanguineous parents (CI = 1/16). Weakness and atrophy of the hands appeared by the age of 24 yrs. Examination showed distal amyotrophy in the upper limbs with fasciculation, and pyramidal signs in all four limbs with brisk tendon reflexes and extensor plantar responses. A bulbar syndrome developed at the age of 30 yrs with atrophy and fasciculation of the tongue. EMG: denervation. MNCV: 54 m·s⁻¹ (ulnar), 41 m·s⁻¹ (peroneal). CSF protein: 0.10 g/l. Muscle biopsy: denervation; nerve biopsy: normal.
Family 9

Case 16, propositus, a 30-yr-old male. At the age of 25 yrs, there was weakness and wasting of the hand muscles with fasciculation, pyramidal signs in all four limbs with brisk tendon reflexes and extensor plantar responses. Bulbar weakness appeared at the age of 28 yrs. EMG: denervation. MNCV: 53 m·s⁻¹ (ulnar), 43 m·s⁻¹ (peroneal). CSF protein: 0.23 g/l. Muscle biopsy: denervation; nerve biopsy: normal.

Family 10

Case 17, propositus, a 31-yr-old male, the son of consanguineous parents (CI = 1/16). At the age of 25 yrs there was weakness of the right hand. Examination showed distal amyotrophy, fasciculation, and a pyramidal syndrome in all four limbs, with brisk tendon reflexes and bilateral extensor plantar responses. MNCV: 55 m·s⁻¹ (ulnar). CSF protein: 0.37 g/l. Muscle biopsy: denervation; nerve biopsy: normal.

Group 2: spastic paraplegia with peroneal atrophy

In this group there were 14 cases from 6 families (3 isolated cases and 11 familial cases with normal parents). This form was characterized by spastic paraplegia and lower limb atrophy (fig. 3) with frequent abolition of one or both ankle jerks. There was no bladder dysfunction and no sensory disturbance.

Fig. 3. A, marked atrophy of the legs (Case 18) and B, atrophy of lower part of thigh (Case 25).

Family 11 (fig. 4)

Case 18, propositus, a 27-yr-old male, the son of consanguineous parents (CI = 1/8). Onset was at 6–7 yrs, with progressive difficulty in walking. Examination showed a spastic gait, distal amyotrophy in the lower limbs, and brisk tendon reflexes. EMG: denervation. MNCV: 44 m·s⁻¹ (peroneal). CSF protein: 0.23 g/l. Nerve biopsy: normal.
Case 19, the 31-yr-old brother of Case 18 with an identical clinical history. EMG: denervation. MNCV: 43 m·s⁻¹ (peroneal). CSF protein: 0.16 g/l. Muscle biopsy: denervation; nerve biopsy: normal.

Case 20, the 16-yr-old sister of Case 18 with an identical history. EMG: denervation. MNCV: 52 m·s⁻¹ (peroneal). CSF protein: 0.21 g/l.

Case 21, the 19-yr-old brother of Case 18 with an identical history. EMG: denervation. CSF protein: 0.20 g/l. Muscle biopsy: denervation; nerve biopsy: normal. Hexosaminidase activity: A, 1380 U/l, B = 950 U/l (normal).

Family 12

Case 22, propositus, a 16-yr-old male, the son of consanguineous parents (CI = 1/16). Onset was at 8 yrs with progressive difficulty in walking. Examination showed a spastic gait, severe peroneal atrophy with paralysis of the extensor muscles of the feet, brisk tendon reflexes, absent ankle jerks, and extensor plantar responses. EMG: denervation. MNCV: 38 m·s⁻¹ (peroneal), 42 m·s⁻¹ (ulnar). CSF protein: 0.13 g/l. Muscle biopsy: denervation; nerve biopsy: normal.

Case 23, the 20-yr-old brother of Case 22 with an identical history. EMG: denervation. MNCV: 41 m·s⁻¹ (peroneal), 42 m·s⁻¹ (ulnar). CSF protein: 0.18 g/l.

Case 24, the 14-yr-old brother of Case 22, again with an identical history. EMG: denervation. MNCV: 38 m·s⁻¹ (ulnar), 31 m·s⁻¹ (peroneal). The CSF protein was 0.12 g/l. Muscle biopsy: mild denervation; nerve biopsy: normal.

Family 13

Case 25, propositus, a 38-yr-old male, born to consanguineous parents (CI = 1/16). Onset was at 15 yrs with progressive difficulty in walking. Examination showed a bilateral steppage gait, peroneal atrophy, pes equinovarus, paralysis of the peroneal and triceps sural muscles, brisk tendon reflexes, and absent ankle jerks. CSF protein: 0.29 g/l. Muscle biopsy: denervation; nerve biopsy: normal. EMG: denervation in all four limbs. MNCV: 38.5 m·s⁻¹ (peroneal), 52 m·s⁻¹ (median), 50 m·s⁻¹ (ulnar). SAP amplitude 24.5 μV (sural); SNCV: 40 m·s⁻¹ (sural).

Case 26, a brother of Case 25 with an identical but less severe clinical picture. EMG: denervation in all four limbs. MNCV: 41 m·s⁻¹ (peroneal), 48 m·s⁻¹ (median), 47 m·s⁻¹ (ulnar). SAP amplitude 11.5 μV (sural); 21 μV (median), 17 μV (ulnar). SNCV: 41 m·s⁻¹ (sural), 58 m·s⁻¹ (median), 46 m·s⁻¹ (ulnar). CSF protein: 0.35 g/l.
Case 27, 25-yr-old male, a brother of Case 25 with an identical history. CSF protein: 0.17 g/l. Nerve biopsy: normal. EMG: denervation in all four limbs. SNCV: 41 m·s⁻¹ (sural), 56 m·s⁻¹ (median), 59 m·s⁻¹ (ulnar); SAP amplitude: 13.5 μV (sural), 11.5 μV (ulnar). MNCV: 52 m·s⁻¹ (median).

Case 28, 20-yr-old girl, the sister of Case 25 with an identical history. EMG: denervation. MNCV: 58 m·s⁻¹ (median), 42 m·s⁻¹ (peroneal); SAP amplitude: 14 μV (saphenous), 30 μV (median). SNCV: 45 m·s⁻¹ (saphenous), 52 m·s⁻¹ (median). Hexosaminidase activity: A, 1000 U/l; B, 300 U/l (normal).

Family 14

Case 29, propositus, 27-yr-old female, born to consanguineous parents (CI = 1/32). Onset was at 25 yrs, with difficulty in walking. Examination showed a steppage gait, paralysis of the extensors of the feet, amyotrophy of the hands, pyramidal signs in all four limbs with brisk tendon reflexes. The ankle jerks were absent. The plantar responses were not extensor. EMG: denervation. MNCV: 42 m·s⁻¹ (ulnar). CSF protein: 0.22 g/l. Nerve biopsy: normal.

Family 15

Case 30, propositus, 29-yr-old male. Onset at 25 yrs with cramps and wasting of the left leg. Examination showed a steppage gait, muscle wasting in both legs, more severe on the left, fasciculation (thigh), brisk tendon reflexes, and an absent left ankle jerk. EMG: denervation. MNCV: 38 m·s⁻¹ (peroneal), 45 m·s⁻¹ (ulnar). Normal myelogram and lumbar CT scan. CSF protein: 0.22 g/l. Nerve biopsy: normal.

Family 16

Case 31, propositus, 28-yr-old male. Onset at 25 yrs with difficulty in walking. Examination showed a steppage gait, peroneal atrophy, fasciculation in the calves, brisk tendon reflexes and absent ankle jerks. EMG: denervation. MNCV: 38 m·s⁻¹ (peroneal), 58 m·s⁻¹ (median). CSF protein: 1.16 g/l. Normal nerve biopsy and myelogram.

Group 3: spastic pseudobulbar syndrome with spastic paraplegia

In this group all 12 cases belonged to one large family, apparently with autosomal recessive inheritance (fig. 5). This form presented an association of considerable spasticity of the facial muscles with uncontrolled laughter and weeping and a spastic dysarthria. Muscle atrophy and fasciculation were rare or absent and the gait was spastic. In some patients mild atrophy of the legs and/or of the hands was present (Fig. 6). There was no bladder dysfunction and there were no sensory disturbances.

Fig. 5. Pedigree of the large family with spastic pseudobulbar syndrome and spastic paraplegia. Symbols as in fig. 2.
Family 17

Case 32, propositus, a 60-yr-old male, the son of consanguineous parents. Progressive dysphonia began at the age of 10 yrs and a progressive spastic paraplegia at age 20. He became bedridden at age 50. Examination showed pseudobulbar paralysis of the tongue with no atrophy or fasciculation, a bilateral pyramidal syndrome in the limbs, and mild peroneal atrophy. EMG and muscle biopsy: denervation. MNCV: 45 m·s⁻¹ (ulnar). CSF protein: 0.38 g/l. Nerve biopsy: normal.

The clinical data for the affected members of this family are summarized in Table 1 (Cases 32–43).

RESULTS

The general clinical data are summarized in Table 2.

Group 1: upper limb (± bulbar) amyotrophy with a bilateral pyramidal involvement

The average age at onset was significantly older (17.6 yrs) for the isolated than for the familial cases (10.6 yrs) with no significant difference between the sexes. Bulbar involvement with atrophy and fasciculation of the tongue occurred in 1 familial case and 4 isolated cases. All cases studied are still living. The average time between onset and the date of the last clinical examination was 12 yrs (range 2–28 yrs). The mean
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<th>Pyramidal syndrome</th>
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<th>SAP amp. (μV)</th>
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* Mean age 6.5. pp = pseudobulbar palsy, sg = spastic gait; +++ = severe; + + = moderate; + = mild; b = bedridden, age when bedridden bracketed; ** = normal hexosaminidase A and B activity; MNCV = motor nerve conduction velocity; SAP amp. = sensory nerve action potential amplitude; SCV = sensory conduction velocity; uln = ulnar; med = median; per = peroneal.
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</table>

Values in parenthesis represent ranges. * Values = means ± 2 SEM. M = male; F = female; T = total.
CSF protein concentration was 0.21 ± 0.13 g/l. The genealogical data suggest autosomal recessive inheritance. This was supported by the normal clinical examination of the parents and the high frequency of consanguinity, which was present in 7 out of 10 siblings (the mean rate of consanguinity in Tunisia is 25–30%). It was confirmed by segregation analysis; the expected risk of 0.25 lay between the segregation ratios calculated by the sibship method (P = 0.27) and the Weinberg proband method (P = 0.15 ± 0.10, P < 0.5). Biopsies from the superficial peroneal nerve were obtained in 12 cases. The results, included in our previous study (Ben Hamida et al., 1987), revealed a non-significant reduction in the average density of small myelinated fibres (diameter < 8 μm) (patients: 8707 ± 1176, controls: 11316 ± 4077/mm²) while the reduction in the total density was significant (P < 0.05) (patients: 10686 ± 1306, controls: 13351 ± 3015/mm²). The reduction in the average density of the unmyelinated fibres of small diameter (diameter < 1 μm) (patients: 43937 ± 3033, controls: 64239 ± 31838/mm²), as well as in the total density (patients: 50326 ± 4868, controls: 66306 ± 30426/mm²), was not significant, whereas there was a highly significant increase (P < 0.01) in the large diameter unmyelinated fibres (diameter ≤ 1 μm) (patients: 6388 ± 3004, controls: 2067 ± 1717/mm²).

**Group 2: spastic paraplegia with peroneal atrophy**

There was no bulbar involvement in this group; atrophy of the upper limbs with fasciculation was noted in 1 case. The pyramidal syndrome was present in the lower limbs in all cases, but with extensor plantar responses in only 4. The ankle jerks were absent bilaterally in 4 cases and unilaterally in 1. The average age at onset was 14.2 yrs (range 6–25 yrs). The average age at the date of examination was 23.2 yrs (range 14–38 yrs). The genealogical data suggest autosomal recessive inheritance. This was supported by the normal findings on examination of the parents. Consanguinity was present in 4 families out of 6. Segregation analysis confirmed autosomal recessive inheritance; the expected risk lay between the segregation ratios calculated by the sibship method (P = 0.34) and by the Weinberg proband method (P = 0.23 ± 0.13, P < 0.5). The EMG revealed denervation in all cases, and motor nerve conduction velocity was within normal limits. The amplitudes of the sensory action potentials and sensory conduction velocity were normal in all cases studied. Superficial peroneal nerve biopsies were examined in 9 familial cases and in the 3 isolated cases, and showed no significant abnormalities. The average densities and distributions of the large myelinated fibres (diameter ≥ 8 μm) (patients: 1532 ± 481, controls: 2035 ± 1072/mm²), small myelinated fibres (patients: 10270 ± 1304, controls: 11316 ± 4077/mm²), small unmyelinated fibres (patients: 49889 ± 15189, controls: 64239 ± 31848/mm²) and large unmyelinated fibres (patients: 3819 ± 2546, controls: 2067 ± 1717/mm²) showed no significant differences in comparison with the controls. There was a moderate but a nonsignificant reduction in the average density of myelinated fibres (patients: 11803 ± 1169, controls: 13351 ± 3015/mm²) and unmyelinated fibres (patients: 53709 ± 15310, controls: 66306 ± 30426/mm²) comparable with that reported in the group 1 cases.
Group 3: spastic pseudobulbar syndrome with spastic paraplegia

A pseudobulbar syndrome and a spastic paraplegia constituted constant features in all patients in this group: atrophy of the legs was noted in 6 cases, and atrophy of the hands in only 2. There was no atrophy or fasciculation of the tongue.

The average age at onset was 6.5 yrs. The pseudobulbar syndrome, which was the initial symptom in 6 cases, was severe in 5, moderate in 5, and mild in the other 2. Spastic paraplegia, the initial symptom in 6 cases, had confined the patient to bed in 3 cases, was mild in 2, and moderate in 7. The EMG showed denervation in the 6 cases in which it was performed, and MNCV was within normal limits. SNCV and SAP amplitudes were normal in the 3 cases studied.

Examination of superficial peroneal nerve biopsies showed no significant abnormalities. The average densities and distributions of the large myelinated fibres (patients: 1779 ± 122, controls: 2035 ± 1072/mm²), small myelinated fibres (patients: 8159 ± 2132, controls: 11316 ± 4077/mm²), large unmyelinated fibres (patients: 8391 ± 6838, controls: 2067 ± 1717/mm²) and small unmyelinated fibres (patients: 43004 ± 21632, controls: 64239 ± 31848/mm²) showed no significant difference with the controls. The moderate reduction in the average densities of the myelinated fibres (patients: 9939 ± 2084, controls: 13351 ± 3015/mm²) and the unmyelinated fibres (patients: 51396 ± 17883, controls: 66306 ± 30426/mm²) was comparable with that reported in the group 1.

DISCUSSION

The absence of sensory disturbances and the purely motor nature of the distal limb deficits make it possible to group all our cases within the framework of the motor neuron diseases. Pyramidal involvement is attested to by the brisk and irradiating tendon reflexes, while anterior horn cell involvement is indicated by the distal amyotrophy, fasciculation, EMG evidence of denervation, normal MNCV, normal SAP amplitudes and normal or near normal findings on sensory nerve biopsy. This is quite distinct from the usual forms of progressive SMA, in which pyramidal involvement is lacking (Harding, 1984b; Ben Hamida et al., 1988).

Group 1: upper limb (± bulbar) amyotrophy with spastic paraplegia

All the cases included in this category, whether familial (11) or isolated (6), presented a uniform clinical picture of juvenile ALS. The inheritance in the familial cases was autosomal recessive. The evolution of the disorder was very slow and benign. A bulbar and/or pseudobulbar syndrome sometimes completed the clinical picture. Comparable observations have been reported and classified within the hereditary spastic paraplegias (Refsum and Skillcorn, 1954; Silver, 1966; Cross and McKusick, 1967). Rarely, they have been classified with juvenile ALS (van Bogaert, 1925; Emery and Holloway, 1982; Ben Hamida and Hentati, 1984). The concept of very slowly progressive juvenile or infantile onset ALS has not been generally adopted, perhaps because of the rarity
of these cases and clinical differences from the usual sporadic cases of adult-onset ALS.

As early as 1905, Holmes described observations of 2 sisters aged 15 and 13 yrs, born of healthy parents who were first cousins. The elder had nasal speech, amyotrophy of the hands and legs, pes cavus, brisk and irradiating tendon reflexes, and extensor plantar responses. In addition, nystagmus was present. The picture was the same in the younger sister, but without nystagmus. These 2 cases are very similar to our own observations on 2 sisters (Cases 5 and 6, family 3). In 1954, Refsum and Skillicorn reported a 12-member sibship, 3 of whom had, between the ages of 3 and 5 yrs, developed slowly progressive paraparesis, with diffuse amyotrophy and fasciculation, as well as bulbar disturbances and skeletal deformities. The authors related this picture to that of ALS, and alluded to an autosomal recessive transmission. Much more similar are the observations on 2 brothers made by Gragg et al. (1971), and the observations of Myllylä et al. (1979), in which a pseudobulbar syndrome completed a clinical picture that could be described as juvenile ALS.

The 20 cases reported by Cross and McKusick (1967) as the Troyer syndrome were characterized by spastic paraparesis associated with distal amyotrophy, beginning in early childhood and confining the patients to bed by their third or fourth decade. There was an accompanying pseudobulbar syndrome, and in some cases choreoathetostic movements and cerebellar signs. Such a picture is clearly quite different from that of pure juvenile ALS. The same is true of the large series of Bouchard et al. (1978) in which there were objective sensory disturbances and histological changes in sensory nerves.

Among descriptions of cases with autosomal dominant transmission are the families reported by Silver (1966) in which neurological disturbances began, in the 12 affected subjects, between the ages of 15 and 30 yrs, associating amyotrophy of the small muscles of the hand, a pyramidal syndrome of the lower limbs, and amyotrophy of the legs. In 3 cases, there was impairment of vibration sense. Transmission was autosomal dominant, as in the 18 observations belonging to a family reported later by van Gent et al. (1985) in which the older subjects showed some sensory disturbances.

Group 2: spastic paraplegia with peroneal muscular atrophy

In addition to the commoner type in which amyotrophy is mainly confined to the hands, there is an autosomal recessive form in which spastic paraplegia predominates, associated with peroneal atrophy and, to a lesser extent, with atrophy of the hands. Discussion of these cases has been based on hereditary spastic paraplegia (HSP) which, in the 'pure form' does not include distal atrophy. Nevertheless, Harding (1984a) discussed certain cases from the literature in which atrophy may appear. Mention has occasionally been made of peroneal atrophy (of the distal SMA type) arising during the course of spastic paraplegia (Maas, 1904; Garland and Astley, 1950). The observations we report here are completely different from the Charcot-Marie-Tooth (CMT) type of peroneal muscular atrophy associated with a pyramidal syndrome, designated hereditary motor and sensory
neuropathy type V by Dyck (Dyck and Lambert, 1968; Dyck, 1984), which has been well analysed in a recent review (Harding and Thomas, 1984). In this study, involving 25 individuals, the illness was clearly a sensorimotor neuropathy of the CMT type, associated with pyramidal signs (and with autosomal dominant transmission). Sensory disturbances were evident clinically and electrophysiologically. This differs from our own patients who showed no objective sensory disturbance and in whom the sensory nerve studies showed insignificant changes similar to those mentioned in cases of typical juvenile ALS (Ben Hamida et al., 1987), unlike what was reported by Dyck and Lambert (1968) and by Dyck (1975, 1984). Our study in fact concerns a pure motor type of peroneal muscular atrophy, consistent with lesions of the anterior horn cells of the thoracolumbar cord, with accompanying involvement of the pyramidal system. Given the familial nature of our cases and the electrophysiological and histopathological arguments, we consider that such a clinical picture can best be designated as a rare type of juvenile ALS. In the group 1 cases, the amyotrophy of the small muscles of the hand reflects an anterior horn cell involvement in the cervical cord, while in these group 2 cases, also purely motor, the amyotrophy, which is essentially peroneal, corresponds to involvement of the lumbosacral anterior horn cells, and is associated with a spastic paraplegia without bulbar signs. The severity of the lower motor neuron involvement in the lumbosacral cord could explain the abolition of the ankle jerks and the failure to obtain a plantar response at times.

Group 3: spastic pseudobulbar syndrome with spastic paraplegia

The appearance of an isolated, slowly progressive paraplegia or tetraplegia led Charcot (1865), Charcot and Joffroy (1869) and Erb (1875) to discuss the possibility that this might be a variant of ALS in which involvement of the anterior horn cells had remained undetectable. Thus primary lateral sclerosis could be considered to be a rare clinical form of ALS (Beal and Richardson, 1981; Russo, 1982). In his extensive review, Fisher (1977) distinguished four primary lateral sclerosis syndromes, which were recently discussed by Gastaut et al. (1988). Within this framework it is interesting to note the description of two syndromes called ‘chronic progressive spastic bulbar paralysis’ and ‘chronic progressive bilateral spinobulbar spasticity’, which affect only middle-aged or elderly patients. Gastaut et al. (1988) classified their 5 examples of chronic progressive spinobulbar spasticity as a rare form of primary lateral sclerosis. The 12 patients we report here show similarly, but at an infantile and a juvenile age, a chronic spastic pseudobulbar syndrome with spastic tetraplegia which is entirely comparable with what Fisher (1977) and Gastaut et al. (1988) termed chronic progressive spinobulbar spasticity. What sets them apart is the familial character of our cases, and the associated peroneal amyotrophy and, more rarely, atrophy of the hands, without sensory disturbances. The disease is very slowly progressive; transmission seems to be autosomal recessive. The appearance of muscle atrophy indicates involvement of the anterior horn cells, and constitutes a firm argument in favour of classifying this condition within the juvenile ALS group as a rare and particular expression of it.
CONCLUSIONS

The existence of slowly, progressive, benign infantile and juvenile motor system disease (chronic juvenile ALS) is indisputable. Whether the clinical picture is that of juvenile ALS comparable with classical Charcot’s disease, or whether it simulates hereditary spastic paraplegia with accompanying anterior horn cell involvement or primary lateral sclerosis but with peroneal atrophy, in either case the clinical signs indicate a combined disorder of the lower and upper motor neurons. This is supported by neurophysiological investigation and histopathological studies on sensory nerve biopsies. This has made it possible to eliminate a diagnosis of uncomplicated SMA and of CMT disease with an accompanying pyramidal syndrome.

Infantile and juvenile ALS is a rare condition. Its authenticity has been difficult to establish because of the lack of any comprehensive study of a large series, as in the present report. These disorders seem to be much more frequent in this geographical region. The high frequency of consanguinity in Tunisia could play an important role. The disease is most often familial and, in our experience, transmission is autosomal recessive. More detailed genetic studies on the three syndromes that we have described will make it possible to specify more precisely the relationships between them and with the other degenerative diseases that affect the motor system.

In recent years there have been descriptions of cases of juvenile onset with clinical features that resemble ALS but which usually show multisystem involvement and in which underlying hexosaminidase deficiency has been established (e.g., Mitsumoto et al., 1985). Although hexosaminidase activity was not studied systematically in the present series of cases, in those in which it was examined, normal values were obtained.

ACKNOWLEDGEMENTS

It is a pleasure to thank Professor P. K. Thomas for helpful discussion and for examination of some of our patients. We thank Dr N. Attia-Romdhane and Dr S. Oueslati for their cooperation, Miss S. Braham and Mr E. Khemiri for technical assistance.

REFERENCES


DYCK PJ, LAMBERT EH (1968) Lower motor and primary sensory neuron diseases with peroneal muscular atrophy. II. Neurologic, genetic, and electrophysiologic findings in various neuronal degenerations. *Archives of Neurology, Chicago*, 18, 619–625.


(Received October 28, 1988. Revised February 8, 1989. Accepted April 5, 1989)