

ABSTRACT: The phenotype of 16 members of a family affected by a late-onset, dominant, progressive, motor and autonomic disorder is described. The *VAPB* (Pro56Ser) mutation was detected in Brazilian families with different phenotypes of motor neuron disorders. In this family, proximal and axial muscle weakness and atrophy, associated with abdominal protrusion, defined the motor phenotype. Death occurred in 10–15 years due to respiratory insufficiency. Tone and tendon reflexes were decreased and a distal tremor was common. Sensation was preserved. Autonomic abnormalities were also present, including choking, chronic intestinal constipation, sexual dysfunction, and sudomotor abnormalities, and on nerve morphology there was involvement of unmyelinated fibers. Electromyography disclosed ongoing denervation and reinnervation. Isolated dysfunction of motor and autonomic neurons is unusual among the spinal muscular atrophies. On this basis, this condition seems to represent a new category of disease.

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EXPANDING THE PHENOTYPES OF THE PRO56SER *VAPB* MUTATION: PROXIMAL SMA WITH DYSAUTONOMIA

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The spinal muscular atrophies (SMA) are inherited disorders characterized by muscle weakness and atrophy from progressive degeneration of lower motor neurons.³⁵ The most common form is the proximal, recessive, infantile-onset SMA, which in more than 95% of cases results from homozygous deletions in the survival motor neuron (*SMN1*) gene located on chromosome 5q.^{16,31} Late-onset SMAs are uncommon and heterogeneous.³⁰ Those with proximal weakness may be inherited as autosomal-recessive, autosomal-dominant, or X-linked conditions.

Occasionally, homozygous deletions in the *SMN1* gene are found in late-onset recessive families.³

Based on age of onset, the dominant and proximal SMAs of late onset manifest as childhood–juvenile and adult-onset forms, believed to be different disorders.^{9,24} The childhood–juvenile group encompasses a wide range of onset ages, even among members of the same family, up to the fifth decade of life. Progression is usually slow and the course is mild, although a severe disorder may be observed occasionally, with a marked reduction in life expectancy. In the adult-onset group, the disease usually begins between 30 and 40 years of age and as a rule follows a relatively benign course, with an ambulatory period of 5 years or more and a life expectancy of 20 years after clinical onset of the disease. Initially, marked muscular impairment is restricted to the proximal muscles; penetrance is nearly complete, and accounts for almost 30% of all adult SMAs.^{4,10,20,23,26,28,38,40}

We recently studied new cases in a five-generation family with adult-onset, autosomal-dominant

Abbreviations: ALS, amyotrophic lateral sclerosis; CMAP, compound muscle action potential; CT, computerized tomography; EMG, electromyography; MRC, Medical Research Council; MRI, magnetic resonance imaging; SMA, spinal muscular atrophy; SMN, survival motor neuron; *VAPB*, vesicle-trafficking gene

Key words: dysautonomia; motor neuron disorder; spinal muscular atrophy; *VAPB* gene

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disease exhibiting a progressive, proximal muscle weakness and atrophy previously described by others.¹⁰ We mapped the disease gene segregating in this kindred to chromosome 20q13.2-13.3,¹⁸ a region containing at least 33 known genes. While we were investigating several candidate genes in this region, Nishimura et al.²² found a point mutation in the synaptobrevin-associated membrane protein (*VAPB*) gene in several Brazilian families with different phenotypes of motor neuron disorders, including families with amyotrophic lateral sclerosis (ALS) type 8, families with atypical ALS, and three families identified as having late-onset spinal muscular atrophy of the type described by Finkel,¹⁰ although no detailed phenotypic description of these families was presented. The same group has shown a common founder for all the families they studied,²¹ including a branch of the family that we now describe.

We have characterized the natural history of the disease in a large family, described the distribution of weakness, and found involvement of the autonomic nervous system. These findings characterize a dominant, adult-onset, proximal SMA with autonomic involvement, a pattern of inherited neurological disorder that is extremely uncommon and results from mutations in the *VAPB* gene, expanding the phenotypic heterogeneity of the Prol56Ser mutation.

MATERIALS AND METHODS

Family and Clinical Data. The family pedigree was constructed based on information obtained independently from several relatives. Clinical evaluation of 50 members was carried out by two of us (V.D.M. and W.M.) on an outpatient basis. Five of the affected members volunteered for complete inpatient clinical, electrophysiological, laboratory, and radiological studies. Family members were considered affected if there was unequivocal evidence of a motor neuron disorder, including fasciculations, weakness, atrophy, hyper- or hypotonia, abnormal tendon reflexes, Babinski signs, and, when available, evidence of denervation and reinnervation on needle examination, with preserved motor and sensory nerve conduction velocities.

Age of onset was defined as the age at which the patient first noticed any symptoms of the disease, including weakness, atrophy, fasciculation, cramps, abdominal protrusion, and tremor. To those unaware of such manifestations but with abnormalities on neurological examination, age of onset was considered unknown. Strength was assessed, bilaterally when appropriate, according to the Medical Re-

search Council (MRC) scale.⁸ In the lower limbs, evaluation included flexion and extension of the first toe and feet and flexion and extension of hips and knees; in the upper limbs, flexion and extension of shoulders and arms were evaluated, as were the abductor pollicis brevis, first dorsal interosseous, and flexors and extensors of the wrist. In the cervical region, neck flexion and extension were evaluated. For each studied region we calculated the mean MRC score according to Van den Berg-Vos et al.³⁷ Reflexes were quantified as 0 if absent, 1 if hypoactive, 2 if normal, 3 if brisk, and 4 if abnormally hyperactive. We also tested pinprick appreciation, tactile sensation (with cotton), and vibration with a tuning fork (128 Hz). The functional index was evaluated according to the scale presented in Table 1.

Electrophysiological Evaluation. Nerve conduction studies and needle electromyography (EMG) were carried out using commercial equipment following standard techniques. The compound muscle action potentials (CMAP) of the median, ulnar, peroneal, and posterior tibial nerves were recorded from distal muscles with surface electrodes. Sensory nerve action potentials were recorded orthodromically (median and ulnar nerves) or antidromically (radial, sural, and superficial peroneal nerves) with subdermal needle electrodes. Needle examination was performed with concentric electrodes in at least five muscles, including a distal muscle and a proximal muscle in the upper and lower limbs and the rectus abdominis muscle.

Laboratory Investigations. All inpatients underwent blood studies for glucose level, glucose tolerance test, lipidogram, muscle enzymes (aldolase and creatine kinase), complete blood count, electrolytes, liver and renal function, serology for Chagas' disease, heavy metal levels, and lactic acid level at rest and after exercise. Hexosaminidase activity was evaluated in one patient.

Biopsies of the biceps brachii were obtained in patients IV-53 and IV-62 and examined with the following stains: hematoxylin and eosin, the modified Gomori trichrome method, oil red O, periodic acid-Schiff, NADH tetrazolium reductase, acid phosphatase, and ATPase with preincubation at pH 9.4, 4.65, and 4.3.⁷ Sural nerve biopsies were performed in patients IV-65 and V-17. Nerve samples were prepared for light and transmission electron microscopy as described previously.¹⁹ Transverse semithin sections (0.5 μ m), stained with 1% toluidine blue were observed with the aid of an Axiophot photomicroscope (Carl Zeiss, Jena, Germany) and the images

Table 1. Clinical features.

Case	Age* (years)	Duration (years)	Muscle strength (mean MRC score)						Cervical	Total	FI	Associated findings
			Legs		Arms							
			P	D	P	D						
V-16	44	4	4.3	4.9	4.4	5.0	4.5	4.6	2			
IV-74	46	13	4.5	5.0	4.5	5.0	5.0	4.6	1			
IV-65	47	3	3.0	3.5	3.0	4.0	5.0	3.4	5	choking, constipation, sexual dysfunction, tremor		
IV-62	50	3	4.1	5.0	4.4	5.0	4.5	4.6	2	choking, constipation, sexual dysfunction, tremor		
V-17	52	10	3.0	4.2	3.5	4.6	4.3	3.8	4	choking, constipation, sexual dysfunction, tremor		
V-5	52	16	3.4	3.6	3.4	4.0	4.3	3.6	5	choking		
IV-16	51	33	3.3	3.8	4.6	5.0	5.0	4.2	3	choking		
IV-61	55	10	1.8	3.1	0.8	3.4	3.5	2.4	6	choking, constipation, tremor		
IV-46	56	7	3.8	4.1	4.1	4.6	4.8	4.3	4	choking, tremor		
IV-7	56	2	3.9	5.0	4.3	5.0	5.0	4.6	4	choking, constipation, sexual dysfunction, tremor		
IV-75	56	23	—	—	—	—	—	—	3			
IV-26	57	11	3.3	3.8	3.4	4.5	4.3	3.8	5	choking, tremor		
IV-18	60	5	4.4	5.0	4.4	5.0	5.0	4.7	2			
IV-12	60	33	3.8	4.0	5.0	5.0	5.0	4.7	2	choking		
V-12	62	12	—	—	—	—	—	—	5	choking, tremor		
IV-53	65	14	2.3	2.9	3.1	3.4	4.5	3.1	5	choking, sexual dysfunction, tremor, diabetes melitus		

*Age at examination; D, distal; P, proximal. Functional index score (FI): 1. normal running (no incapacity); 2. normal walking but unable to run; 3. walking without help but not normally; 4. walking with canes or crutches; 5. wheelchair restricted; 6. bedridden. Subject IV-75 refused clinical examination, and V-12 had a stroke.

were sent via a digital camera to a personal computer where they were digitized. The myelinated fiber morphometry was performed as described elsewhere.¹⁴ Thin sections (500–600 nm), mounted on 300 mesh copper grids, stained with uranyl acetate and lead citrate were observed under a JEOL 1230 digital transmission electron microscope and at least 20 images at $\times 2,000$ original magnification were obtained at random for each nerve fascicle, without overlap of microscopic fields, and digitized. Morphometry of the unmyelinated fibers was performed with the aid of an image analysis system (KS 400, Kontron 2.0, Eching Bei München, Germany).

The autonomic evaluation included clinical evaluation, electrocardiogram, head-up tilt test, swallowing scintigraphy, barium esophagography, esophageal manometry, radioisotopic study of gastric emptying, intestinal transit, and a thermoregulatory sweat test in two patients (IV-62 and V-17), as systematized by Jardim.¹³

Spinal and brain magnetic resonance imaging (MRI) were also performed in two patients, and an abdominal computerized tomography (CT) in three.

The Pro56Ser mutation was searched by restriction analysis. Exon 2 of the *VAPB* gene was amplified with polymerase chain reaction (PCR) using the forward primer 5'-GCATTAACCTCAGCT CATCT-3' and the reverse primer 5'-GGGTGGAGAGAATTC-TATCA-3', following restriction with the endonuclease *Hae*III, which loses a restriction site in the mutant

allele. The restricted product was electrophoresed on 2.5% agarose gel, stained with ethidium bromide, and visualized with an ultraviolet lamp. The undigested PCR product has 423 bp, unaffected individuals present five bands of 263, 74, 38, 28, and 22 bp, whereas heterozygotes for the Pro56Ser mutation present an additional band of 291 bp. All 50 members of the family were screened.

RESULTS

Clinical Findings. The constructed pedigree (Fig. 1) shows disease in five consecutive generations, with male-to-male transmission, a similar number of females and males being affected, and all affected members descending from one affected relative. No evidence of anticipation was noted.

Seven females and nine males among the 50 members evaluated showed unequivocal signs of the disease. Most developed the first manifestations in their 30s or 40s, ranging from 20–53 years. The initial reported symptoms were cramps (10), fasciculations (10), tremor (7), proximal weakness in the lower limbs (4), abdominal protrusion (4), and fatigue (2). Cramps were painful, localized mainly in the lower limbs but also present in the abdomen and upper limbs, and appeared mostly with active movements, although they also occurred at rest and during sleep. Fasciculations were reported to occur mainly in the limbs. Abdominal protrusion was usu-

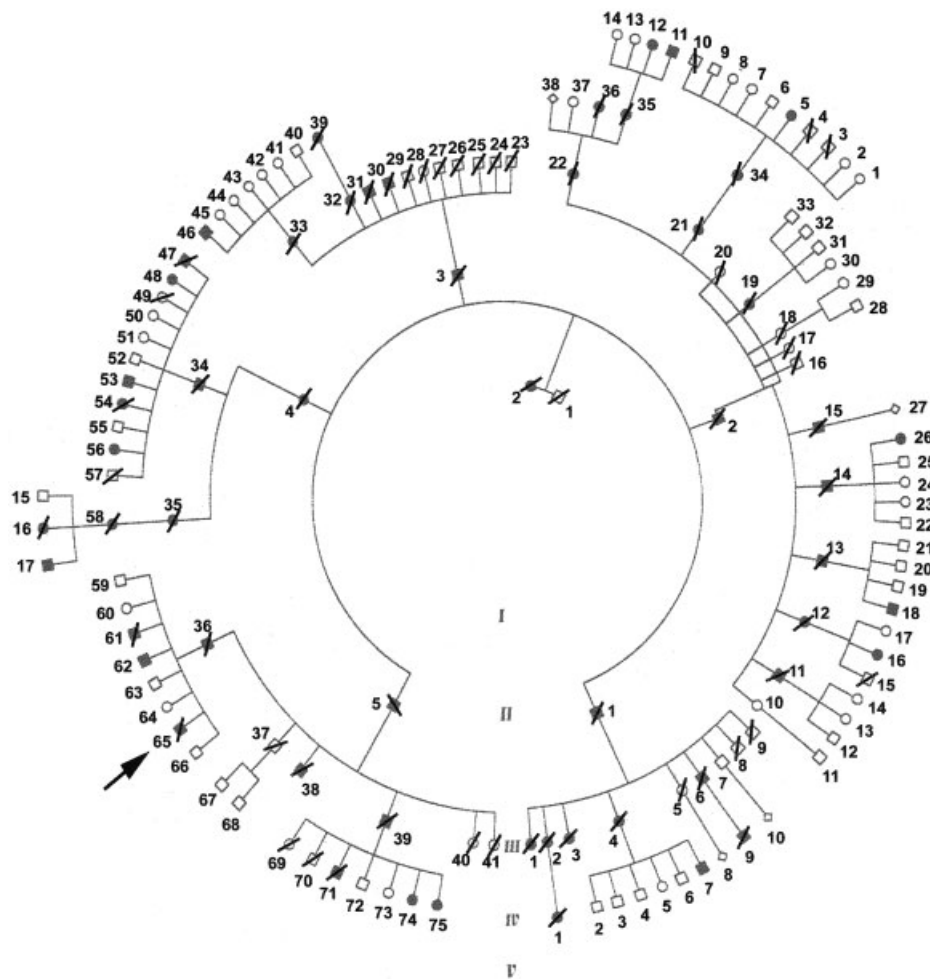


FIGURE 1. Family tree. Circles represent women and squares represent men. Black symbols represent affected members, either by history or by examination. Note that individual II-2 had descendants with three different women. No consanguineous mate was identified.

ally noted at the same time as limb weakness, occasionally being the first sign of the disease. Excluding four patients whose initial manifestation was weakness, the interval between the first manifestation and muscle weakness varied from 2 to 25 years.

In 15 patients weakness was first noted in the lower limbs between the ages of 36–55 years, was always progressive, and spread to other regions, mainly the proximal muscles of the upper limbs. In the remaining patient, a 43-year-old woman (IV-74), strength was so mildly decreased that she was unaware of it, although she complained of fasciculations for a prolonged period.

Twelve patients (Table 1) complained of sporadic choking that usually lasted for minutes. Five patients suffered severe constipation requiring stimulation of the rectum with the insertion of the hose of a hand-held shower spray and introduction of water to trigger evacuation; three of them (IV-65,

V-17, and IV-53) complained of episodic fecal incontinence. Four patients reported difficulty in initiating voiding (IV-65, IV-62, V-17, IV-7, and IV-53), requiring emptying maneuvers, and another (IV-61) eventually required bladder catheterization. Five patients (IV-65, IV-62, IV-7, V-17, and IV-53) reported a prolonged erection period with delayed orgasm and ejaculation. Libido was preserved over the course of the disease, but in the final stages three of the evaluated patients became impotent. At least two patients spontaneously reported decreased sweating. Apart from the choking episodes that were present early in the disease course, autonomic dysfunction was a late manifestation.

Neurological examination was performed in 14 patients, since one refused to be examined and a second was excluded because of a recent stroke. Mental status, sensation, and cerebellar function were always preserved. Generalized weakness was present,

most marked proximally, and affecting the lower more than the upper limbs. Weakness was grossly symmetric when sides were compared; however, impairment was selective, with a predominant impairment of arm abduction and external rotation in the upper limbs, and hip flexion and abduction in the lower limbs. The abdominal muscles were always weak, in contrast to those innervated by the cranial nerves, in which a late, and very mild impairment was restricted to the sternocleidomastoid muscle in 8 of the 14 patients.

There was a good correlation between the functional index and strength (Table 1), mainly with the mean MRC score of the proximal lower-limb muscles. Muscle atrophy paralleled weakness, and muscle tone was always decreased. Hypoactive or absent stretch reflexes were found in different combinations. There were no signs of upper motor neuron involvement: tendon reflexes were normal or decreased and there was a flexor response on plantar stimulation. Fasciculations were very common, being widespread in the limbs and trunk, but absent from the tongue and face. Cramps occurred spontaneously or after mild exercise.

An increased incidence of lordosis (9) associated with disproportionate abdominal protrusion (13 of 14 patients) resulted in a very characteristic phenotype. A postural hand tremor was the only abnormal movement observed.

Chronic arterial hypertension was highly prevalent among the patients and, from the family history, also in deceased affected members. Among the five patients observed daily at our institution, three (44, 52, and 65 years) showed high blood pressure levels, around 160–180 mmHg for systolic values and 100–120 mmHg for diastolic values. There was no evidence of cardiac arrhythmia or postural hypotension.

The natural history of the disease paralleled the progression of the weakness. After the onset of muscle weakness, patients could walk unaided for a period of 3–8 years; over the next 5 years they were able to walk only with canes or crutches, and over the subsequent 10 years they required a walker and later a wheelchair. A detailed evolution of the final stage of the disease was obtained from three patients (IV-61, IV-65, and V-5); two were bedridden for 8 and 2 years, and the third one died after 2 years in a wheelchair without becoming bedridden. The interval from onset of clinical weakness to death was 12, 17, and 10 years, respectively. In all three cases death was attributed to respiratory failure.

Neurophysiological Examination. Sensory nerve conduction studies were essentially normal, apart from mild abnormalities observed in the lower limbs of a diabetic patient, and a focal abnormality in the wrist

of a patient using a walker. Motor nerve conduction velocities were normal, with no evidence of temporal dispersion or conduction block. CMAP amplitudes were normal or decreased when recorded from weak and atrophic muscles.

On needle examination, insertion activity was usually increased; fasciculations, fibrillation potentials, positive waves, and repetitive discharges were present in almost all muscles examined, including the rectus abdominis and the paraspinal muscles. No myotonic discharges were observed. Motor unit action potentials showed increased duration and amplitude, a high frequency of discharge, and a reduction in number. These findings were also present in the abdominal wall muscles. Tongue examination was normal, and pharyngeal muscles showed very few potentials of mildly increased amplitude and duration, with no significant reduction in recruitment pattern.

The sympathetic skin response was normal in the two patients evaluated. The hand tremor, electrophysiologically evaluated in only one patient, showed a regular and rhythmic pattern at 5 Hz.

Laboratory Investigation. All five inpatients had increased cholesterol levels (202–289 mg/dl; normal <200 mg/dl), four had reduced HDL (20–31.9 mg/dl; normal >35 mg/dl), and three also exhibited hypertriglyceridemia (287–439 mg/dl; normal <200 mg/dl). One patient (IV-53) was diabetic. Serum creatine kinase was normal or mildly increased (192–895 U/L; normal: 24–204 U/L). Chagas' serology, serum lactate at rest and postexercise, hexosaminidase activity, liver and renal function tests, and Na, K, Mg, Pb, and Zn levels were all normal. Brain MRI performed in two patients (IV-65 and IV-53) was normal, as was the abdominal CT of three patients (IV-65, IV-62, and V-17).

Electrocardiograms, tilt tests, barium esophagography, and swallowing scintigraphy were normal. Radioisotopic examination of gastric emptying was initially normal in one patient and clearly abnormal in two others (IV-62, IV-65), with gastric emptying half-times of 80, 113, and 114 min, respectively (normal values, 30–75 min). In a period of 2 years, gastric emptying also became abnormal (96 min) in the first patient. A thermoregulatory sweat test showed decreased sweating in four patients, and was normal in controls.

Both sural nerves studied were abnormal (Fig. 2). By visual inspection of the semithin sections, the major findings were a reduction in the number of small myelinated fibers and the presence of axons with disproportionately small diameters in relation to

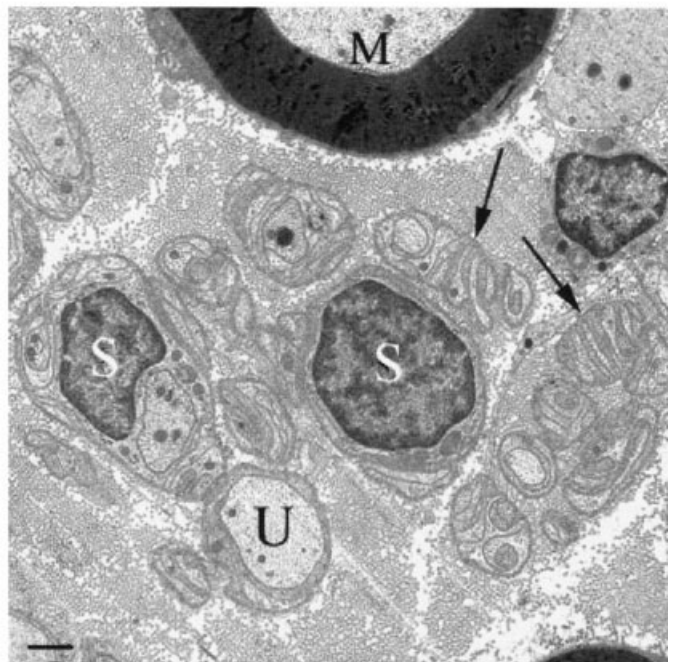
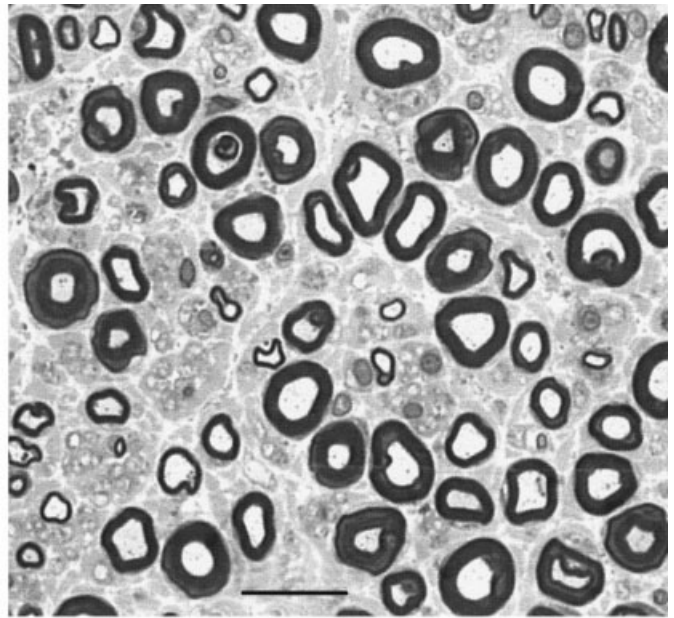
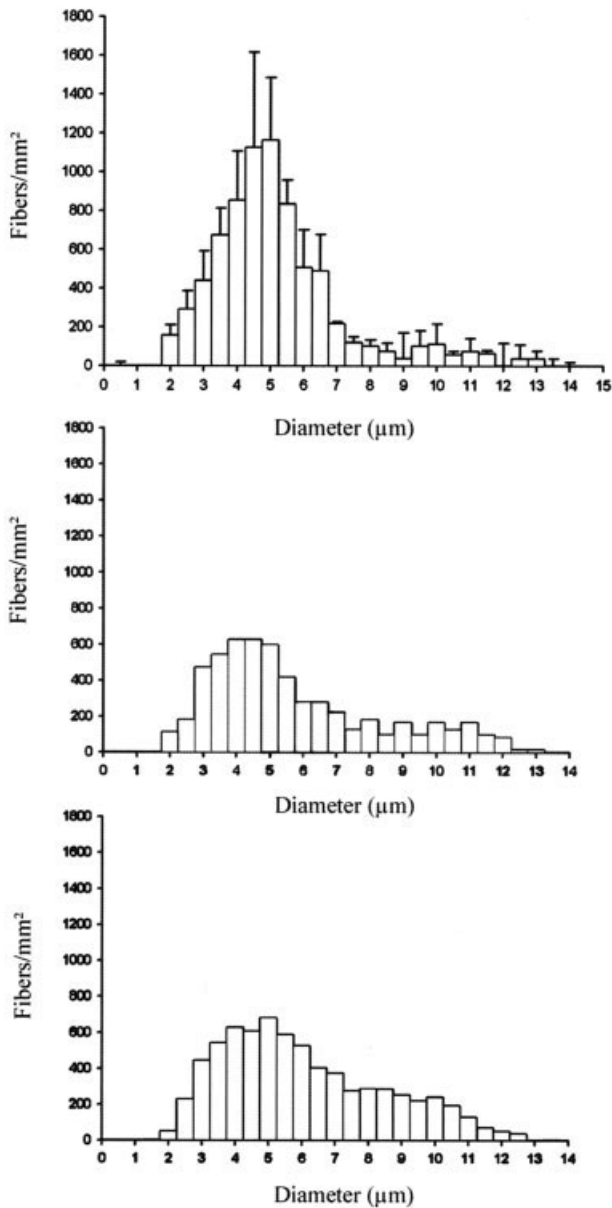


FIGURE 2. Nerve biopsies were performed on individuals IV-65 and V-17. Myelinated size distribution histograms are plotted on the left side. The upper histogram shows a normal sural nerve pattern. The middle and the bottom ones are from different patients. Note the reduction in the number of the small myelinated fibers. The upper image on the right side shows a semithin section corresponding to the left middle histogram. There is an evident loss of the small myelinated fibers (scale bar, 20 μm). Transmission electron micrographs of representative areas in which unmyelinated fibers were present are shown in the bottom right image. M, normal myelinated fibers; S, Schwann cell nuclei; U, a large unmyelinated fiber. Arrows show the unmyelinated fibers and Schwann cell processes arranged in tacks, a marked characteristic of both nerves (scale bar, 1 μm).

the thickness of their myelin sheath. A small amount of axonal sprouting was also seen. Morphometry showed an evident loss of the small myelinated fibers, with a myelinated fiber density of 5,681 and 7,112 fibers/mm², respectively (control, 7,573 \pm 342). Under transmission electron microscopy the

unmyelinated fibers were morphologically normal but their number was clearly reduced, with densities of 6,188 and 8,001 fibers/mm² (control, 31,486 \pm 5,363). Their histogram distribution was unimodal, with a peak at 0.9 μm in patient 1 and bimodal, with peaks at 0.5 and 1.0, for patient 2. Also, a large

number of Schwann cell processes not enveloping any axon and arranged in stacks were present on both nerves (Fig. 2). Apart from type grouping and mild irregularity in muscle-fiber diameter, no other abnormalities were found in the muscle biopsies performed on patients IV-53 and IV-62.

Mutation Screening. All the affected members tested presented the Pro56Ser mutation on exon 2 of the *VAPB* gene, which was absent in the remaining 34 nonaffected members.

DISCUSSION

In this inherited lower motor neuron disorder there is a predominantly proximal weakness, with autonomic involvement and an accompanying dyslipidemia. No associated sensory loss, upper motor neuron involvement, cerebellar dysfunction, or mental status impairment was found. The pattern of inheritance was clearly autosomal dominant and no evidence of anticipation was seen. Penetrance seemed to be complete, and no mutation was detected in the 34 normal members evaluated. The age of onset is late, however, as the earliest patient noticed the first abnormality at the beginning of the third decade, and onset of weakness was always after 36 years of age, both values being well above the limit of 15 years² arbitrarily established to distinguish early- and late-onset SMA disorders.

Some features seem to be very particular to this condition. Although bilaterally symmetric, patients exhibited an atypical proximal pattern of muscle weakness: in the upper limbs the infraspinatus and deltoid muscles were more affected than the other proximal muscles; in the lower limbs the flexors and abductors of the hip were more severely affected than the others, and in the trunk the abdominal wall muscles were also severely affected at an early stage. This pattern results in a very characteristic phenotype due to severe, proximal lower- and upper-limb weakness and atrophy, and prominent abdominal protrusion that, based on our neurophysiological data, can be attributed to weakness of the abdominal wall, secondary to denervation. Although not always present, this abdominal protrusion is a characteristic and feared sign of the disease among family members, since its presence is considered unequivocal evidence that the disease is already present. The whole muscular picture is indicative of selective involvement of the lower motor neurons innervating the proximal and axial muscles. It is interesting that there was definite asymmetry in the degree of involvement of muscles with the same segmental in-

ervation. Although uncommon, this kind of asymmetrical involvement has been described in ALS.¹⁵ This finding may be a link with the ALS phenotype of the *VAPB* gene.

Finkel¹⁰ analyzed different members of the same family studied here and characterized many features of the disease, including the neurogenic origin of the weakness, based on a muscle biopsy, but initially interpreted the inheritance as autosomal recessive. Finkel did not report the proximal and axial distribution of muscle impairment or the natural history of the disease, and did not mention the involvement of other systems. Richieri-Costa et al.²⁹ studied the same family and recognized the autosomal-dominant inheritance, confirmed the neurogenic origin by EMG and muscle biopsy, mentioned choking, and reported the presence of myotonia that was clinically and electrophysiologically absent in all the cases examined by us. Neither Finkel nor Richieri-Costa et al. mentioned autonomic symptoms, abdominal protrusion, or dyslipidemia, nor did they detail the natural history of the disease.

The other reported adult-onset, proximal SMAs all seem to be phenotypically different from this family. Zatz et al.⁴⁰ reported a malignant autosomal-dominant neurogenic muscular atrophy that affected seven members of a family, beginning at the ages of 28–62 years, resulting in death within a brief period of 3 months to 1 year. Based on clinical examination of a single patient and on family information, those authors characterized a very asymmetric muscle weakness and atrophy beginning in the upper limbs in four cases and in the lower limbs in the remaining three, with rapid progression to the other limbs and the respiratory muscles, leading to respiratory failure and death. No pyramidal tract signs were described. In 1978, Pearn²³ performed a clinical and genetic study of six kindreds (13 patients) with autosomal-dominant SMA, which he postulated to exist in two different forms, a childhood–juvenile form and an adult-onset form. The latter was characterized based on seven patients whose mean age at clinical onset was 37 years, with marked proximal muscle impairment, inability to run within 5 years from the appearance of symptoms, and an average life expectancy of 20 years. Rietschel et al.³⁰ reported three families exhibiting an adult-onset proximal autosomal-dominant SMA, and three other families with the childhood–juvenile condition. The adult-onset cases exhibited proximal muscle weakness with no atypical distribution, a mild rate of progression, and no involvement of other systems. Two families described by Van den Berg-Vos et al.³⁶ displayed an autosomal-dominant, adult-onset, lower

motor neuron disease with rapid progression to respiratory failure and death within 1–5 years.

A common complaint among our patients was spontaneous choking fits; when this occurred during meals it caused severe swallowing difficulties. These episodes lasted a few minutes, leading to a sensation of suffocation and triggering cough. This phenomenon was not frequent, but was always present among the patients, its characteristics remaining unchanged throughout the course of the disease. The origin of these manifestations may derive from episodic autonomic dysfunction, since esophageal manometry revealed completely normal functioning of the esophageal smooth muscles, and needle examination of the tongue and pharyngeal muscles revealed no significant denervation, even in patients with advanced disease. The presence of paroxysmal cough was attributed to a combination of denervation hypersensitivity of the upper airways and gastro-esophageal reflux in patients with hereditary sensory neuropathy.³⁴ A similar mechanism could be involved in the choking that occurred in our patients. The radioisotopic study of gastric emptying showed delayed clearance of the stomach in two of the three patients examined.

Patients usually developed chronic and severe constipation, although some patients alternated constipation with episodes of fecal incontinence. Upper gastrointestinal images, barium enema, and abdominal CT were normal, excluding mechanical obstruction. The symptoms may thus result from functional dysmotilities of the gastrointestinal tract, such as gastroparesis, colonic inertia, intestinal pseudo-obstruction, or dysfunction of the anorectal motor apparatus.²⁷ Such abnormalities may result from dysfunction of the enteric nervous plexus, suggesting involvement of the efferent pathways responsible for autonomic control of gut movements. Weakness of the abdominal wall muscles may be contributory, but does not explain the incontinence and evacuation after initial stimulation of the rectum by the rapid introduction of water into the rectal ampoule, a procedure that probably causes rectal distention and triggers the recto-anal inhibitory reflex.²⁷ Also indicative of autonomic involvement is the prolonged erection with delayed orgasm and ejaculation reported by many patients or family members. Finally, there is also an abnormal pattern of sweating in the thermoregulatory sweat test. Camilleri and Fealey⁵ reported on patients with apparently functional gastrointestinal disorders and generalized or patchy anhidrosis, and proposed that when an apparently functional gastrointestinal disorder is associated with dysautonomic features, its origin can be attributed to autonomic denervation. Although there are some

descriptions of intestinal pseudo-obstruction in adult¹² and infantile SMAs,^{6,25} no other reports describe such widespread evidence of autonomic involvement in these disorders. Confirming the origin of these clinical findings, there was a mild loss of thin myelinated fibers and a severe loss of unmyelinated fibers in both sural nerves studied.

A recent review has shown that dysautonomia is frequently present in ALS,¹ testifying to the involvement of autonomic neurons in predominantly motor neurons disorders. At least one family with familial visceral neuropathy (MIM 609629) has had neurophysiological evidence of motor neuron involvement, but this involvement is mild and distal,³² whereas in our family the lower motor neuron dysfunction was the main feature of the disease. Lisker et al.¹⁷ also described a family with a distal neurogenic weakness and dysautonomia, but nerve conduction velocities were all decreased, suggesting a demyelinating neuropathy.

All five family members evaluated at our hospital showed hyperlipidemia, with a moderate increase in cholesterol and triglyceride levels. Although we have not presented the data obtained elsewhere, most of the other affected members were also dyslipidemic. Quarfordt et al.²⁸ described four brothers who, during investigation of familial hyperbetalipoproteinemia, were observed to exhibit mild proximal muscle weakness, occasional cramps, and diffuse fasciculations. In contrast to the family studied here, facial muscles were impaired, but no significant disability was present. The neurogenic basis of the disease was defined by EMG and muscle biopsy. Other reports on SMA and abnormal lipid metabolism concern only cases of Kennedy's disease, in which both hyperbetalipoproteinemia^{11,33} and hypobetallipoproteinemia³⁹ have been found. It is still unknown whether the *VAPB* gene is involved in this abnormality or whether it occurred by chance, as we were unable to screen all the family members. However, abnormal lipid levels were present even in the youngest patients.

It is interesting that the same mutation in the *VAPB* gene can result in several different disorders, including typical and atypical ALS and a late-onset SMA described by Nishimura et al.²² as having the Finkel phenotype. It would be interesting to check whether the members of these families also have the same manifestations as we describe, or whether the Pro56Ser mutation is associated with a fourth related phenotype. A better understanding of the *VAPB* gene function will certainly elucidate these heterogeneities.

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