We report an autosomal recessive neurodegenerative disorder in 25 white members from a large inbred Brazilian family, 22 of whom were evaluated clinically. This condition is characterized by (1) subnormal vision secondary to apparently nonprogressive congenital optic atrophy; (2) onset of progressive spastic paraplegia in infancy; (3) onset of progressive motor and sensory axonal neuropathy in late childhood/early adolescence; (4) dysarthria starting in the third decade of life; (5) exacerbated acoustic startle response; and (6) progressive joint contractures and spine deformities. Motor handicap was severe, and all patients were wheelchair bound after 15 years old. We performed a genome-wide screen including 25 affected individuals and 49 of their unaffected relatives. Linkage was detected at 11q13 region with a maximum logarithm of odds score of 14.43, obtained with marker D11S1883. The candidate region, which lies between D11S1908 and D11S1889, encompasses 4.8Mb and has more than 100 genes and expressed sequences. We propose the acronym SPOAN (spastic paraplegia, optic atrophy, and neuropathy) for this complex syndrome.

In this article, we describe a large inbred family with 25 affected individuals, of whom 22 were evaluated clinically, with a previously unrecognized neurological disorder. Major manifestations include congenital optic atrophy, early-onset progressive spastic paraplegia, distal axonal motor and sensory peripheral neuropathy, and acoustic startle. A genetic analysis for this condition was able to find a linkage with marker D11S1883 on 11q13.

Subjects and Methods
The index case (Patient VII-34; Fig 1) is a 26-year-old woman who was born after uncomplicated pregnancy and labor to healthy second-cousin parents. Early in life, she had jerky eye movements and poor vision. Her motor development was slightly delayed, but she was able to tiptoe walk alone at 15 months old. Nevertheless, the motor disability progressed, and she kept an independent gait up to aged 6 years; however, by 12 years old, she was wheelchair bound. At this age, a distal weakness that had a progressive course was also recognized.

Physical examination disclosed scoliosis, club foot deformity, and limited knee extension. Hands and feet were hyperhidrotic. Her neurological examination demonstrated spastic tetraparesis (MRC grade 0 in lower limbs, grade 3 in upper limbs) with absent plantar response, brisk patellar and upper limb reflexes, and absence of ankle reflexes. Hands amyotrophy and distal tactile, vibratory, and positional sensory insensitivity were also detected. Her speech was slightly dysarthric, with low-tone voice. Wrist cogwheel sign was present. She had spontaneous fixation nystagmus and low visual acuity, being able to count fingers at a distance up to 2m. Fundus oculi showed bilateral optic disk pallor. A startle response to unexpected sounds was constantly present. No ataxia, incontinence, dystonia, or cognitive impairment was detected.

Further family history analysis disclosed several additional affected relatives of Caucasian Ibero-European background who settled more than a century ago in an isolated area in Northeastern Brazil (Serrinha dos Pintos, Rio Grande do Norte State, population 4,295). Two authors (F.K., S.C.A.) were able to evaluate 18 affected individuals in this community and three more in nearby villages (see Fig 1). Four other patients were recognized later but were not evaluated clinically; nevertheless, three of them were included in the linkage analysis. In total, 19 consanguineous mates were parents of the 25 studied individuals. It was also known that, in the last 20 years, at least 4 more individuals (VI-18, VI-31, VI-50 and VIII-4) affected by a similar condition have died.
This syndrome was already recognized in this region by the end of 19th century and at least six more individuals were reportedly affected. Interestingly, the concept that this condition is genetically determined was not present in the community, and several other reasons were evoked to explain this phenomenon, most of them related to syphilis.

Twenty-two patients (15 female and 7 male patients), with ages ranging from 9 to 63 years, were evaluated clinically (Table 1). We collected, after obtaining informed consent for participation and publication of results, as well as institutional review board approval, blood samples from 25 affected subjects and 49 healthy family members.

Mapping Strategy
Genomic DNA was obtained following standard techniques. A genome-wide search was undertaken using 400 microsatellite markers that comprise an approximate 10cM human index map from ABI PRISM linkage-mapping set version 2.5 (Applied Biosystems, Foster City, CA). Those markers were amplified by polymerase chain reaction using standard protocols. The polymerase chain reaction products were sequenced in MegaBace 1000 DNA Sequencer (Amersham Biosciences, Little Chalfont, United Kingdom) and were analyzed with Genetic Profiler software (Amersham Biosciences). Required additional microsatellite markers primer sequences, as well as distances, were obtained from National Center for Biotechnology Information databases. These markers were amplified by polymerase chain reaction using $^{32}$P deoxycytidine triphosphate in a 10μl reaction volume. The amplification products were visualized by autoradiography after application to a standard sequencing gel.

Linkage Analysis
The disease was analyzed as an autosomal recessive trait with an allele frequency of 0.0001. Two-point logarithm of odds (LOD) scores were calculated under the assumption of equal allele frequencies and using the computer MLINK program from FASTLINK package version 5.1. (http://linkage.rockefeller.edu/soft/) Recombination frequencies were assumed to be equal in male and female subjects. Allele frequencies were assumed to be 1/N (N = number of different alleles observed on the pedigree). For linkage analysis, many loops of consanguinity were broken because the linkage software allows only eight loops. Therefore, the LOD score values were underestimated, because we used just 8 loops instead of the 19 present in this family.

Results
Clinical Features
Table 1 presents the main clinical features of the affected individuals. As already mentioned, cognitive decline, mental retardation, ataxia, or deafness were not detected in any patient. Symptoms intensity could vary among patients, but disease was fully penetrant.

CONGENITAL AND NONPROGRESSIVE OPTIC ATROPHY. Symptoms related to optic atrophy were recognized early in life and apparently were not progressive. Fixation nystagmus was observed in 18 patients (82%) and was caused by subnormal vision, which was seen in 21 of 22 patients (95.5%) who had pale optic disks. Patients were able to count fingers at a distance of 2m.
Only one affected woman (VI-49; 63 years old) did not report visual problems and had a normal fundus oculi.

PROGRESSIVE, INFANCY-ONSET SPASTIC MOTOR DEFICIENCY. Early motor signs presented as motor development delay and tiptoe walk; in three patients, independent gait was never achieved; all other affected subjects lost it by 10 years old. All types of independent locomotion expression, including walking with support or crawling, were lost before 20 years old. Interestingly, spontaneous but not provoked ankle clonus was present in eight patients. Babinski sign was seen in only two patients; all other patients had no response. Triple-flexion response also was detected in eight patients, all of whom had severe spastic paraplegia and no voluntary movements. Lower limb involvement was always more premature and intense than in upper limbs. In only a severely affected, 47-year-old woman (VI-46) was spasticity not detected, even though it was present in her disease history.

MOTOR AND SENSORY NEUROPATHY WITH ONSET IN LATE CHILDHOOD/ADOLESCENCE. Distal amyotrophy was seen in all patients older than 20 years; hyperhydrosis, tactile insensitivity, and lack of distal vibratory and positional senses were seen in 20 affected subjects. Pain and temperature sensory perception was not affected even later in life, and patients never reported spontaneous pain. We could not obtain reliable information on sensory abnormality in two patients (a 9-year-old child [VIII-8] and a severely dysarthric 47-year-old woman [VI-46]). Severe distal muscle wasting was seen in all patients older than 20 years. No fasciculation was observed. Because of a combination of pyramidal and peripheral signs, proximal reflexes were usually more easily obtained than distal ones. Bicipital, adductor, and knee reflexes were absent in 3 patients and were brisk in the remaining 19 patients; styloradial reflexes were absent in 14, present in 6, and brisk in 2 patients; ankle reflexes were abolished in 18 and present in 4 patients.

DYSARTHRIA AND EXTRAPYRAMIDAL SIGNS. Dysarthria, associated with low-tone voice, was present in all 19 patients older than 20 years of age. In a markedly affected, 47-year-old woman (VI-46), dysarthria and dysphonia were so intense her speech was barely understandable. Wrist cogwheel sign was present in four patients, and neck dystonia was present in one. One patient had myoclonic thumb movements.

STARTLE ACOUSTIC RESPONSE. Exacerbated startle acoustic response was detected in all patients, being recalled since early infancy, observed even late in adulthood, and easily elicited including in severely handicapped patients.
absence of lower limb spontaneous movement had involuntary muscle contractions precipitated by unexpected noise.

**SPINE AND JOINT DEFORMITIES.** Deformities and limited mobility were present in ankle, knee, wrist, and elbow joints in 21 of the 22 patients, with a variable degree of range limitation. Cervicothoracic kyphosis was seen in two patients and scoliosis in 12 and; it was so severe in five individuals that they were unable to sit independently. No clinical evidence of connective tissue disease was present.

**Diagnostic Tests**

Brain magnetic resonance imaging performed in three patients (VIII-8, VII-23, and VII-34) showed no conspicuous alterations. Spinal cord magnetic resonance imaging was suggestive of mild atrophy in Patient VIII-8. Electromyography, performed in Patients VIII-8 and VII-34 at 8 and 26 years old, respectively, was suggestive of axonal motor and sensory neuropathy, with normal motor nerve conduction velocity. An electroretinogram, performed in Patient VII-34, and cerebrospinal fluid study, done in Patient VII-38, were normal. In Patient VII-34, radiographs of the hands were normal, but spine radiographs disclosed scoliosis. Sural nerve biopsy was performed according to standard protocol3 in Patient VII-34 and was processed for light and electron microscopy (JEOL 100CX; JEOL, Peabody, MA). The densities of myelinated and unmyelinated fibers were determined. Morphometric analyses were performed by stereology-based measurements, and the results were expressed as median per square millimeter of fascicular area.4 Median densities of 2,570 myelinated fibers/mm2 and 10,630 unmyelinated fibers/mm2 were found (our referenceagematched median values for sural nerve were 10,479 myelinated fibers/mm2 and 32,560 unmyelinated fibers/mm2).5 The most striking pathological finding was several fibers with bizarre shape (Fig 2) that appear to have a disproportionately thin myelin sheath. Fibers with features of Wallerian degeneration were rare, and regenerative clusters were uncommon. There were few typical onion bulb formations around single axons, and some regenerative clusters were surrounded by a concentrically arranged Schwann cell process forming small onion bulbs (Fig 3). Some axons showed axoplasm vacuolization (Fig 4). We observed many Büngner’s bands and normal periodicity of myelin lamellae (data not shown). No specific abnormalities of axonal organelles, cytoplasmic inclusions in Schwann cell (SC), or focal myelin enlargements were found.

**Linkage**

A genome-wide screening was first performed using 12 members of this pedigree, 5 affected subjects and 7 unaffected relatives. Linkage was detected with marker D11S987 located at 11q13. Analysis of 25 affected subjects showed a maximum LOD score of +13.56 (θ = 0.01) with D11S987. Additional microsatellite markers closely linked to D11S987 between markers D11S4191 and D11S1314 were typed. The greatest two-point LOD score, Zmax 14.43 at θ = 0.0, was obtained with marker D11S1883 (Table 2). Haplotypereconstruction and analysis of the recombination events between markers and the disease locus in affected subjects (see Fig 1) placed the locus in a 4.79Mb region flanked by markers D11S1908 and D11S1889.

**Discussion**

The combination of inherited spastic paraplegia, axonal neuropathy, dysarthria, acoustic startle, and congenital optical atrophy as seen in the 22 patients described here has not been reported previously. This condition has clinical features that overlap with complicated forms of other neurodegenerative disorders, as hereditary motor and sensory neuropathies (HMSNs), currently better known as Charcot–Marie–Tooth (CMT) disease6; hereditary spastic paraplegias (HSPs)7,8; and hereditary optic atrophies.

Originally, HMSNs were divided into seven types9 that have in common distal weakness with atrophy and mild and variable degrees of sensory disturbance. Two more common types were recognized: I, which primarily affects myelin sheaths, and II, which shows axonal degeneration. Currently, HMSN type I is known as

![Fig 2. (A–C) Transverse electron micrographs of sural nerve (Patient VII-34), showing fibers with bizarre shapes, probably caused by myelin outfolding (arrows). ×4,000 original magnification.](image-url)
CMT1 when inherited as an autosomal dominant trait, CMT4 when transmitted as a recessive condition, and CMTX, when X-linked. HMSN type II currently is called CMT2, and HMSN III is known as CMT3, or Dejerine-Sottas disease, a severe demyelinating neuropathy with onset at infancy. Dick further recognizes HMSN types V, which is associated with pyramidal signs, and VI, which is associated with optic atrophy. The genetic basis of HMSN type V is largely unknown, but it is probably a heterogeneous condition, more commonly dominantly inherited, with axonal involvement being commonly described. In a large inbred family with CMT2 and mild pyramidal signs, Barhoumi and colleagues report linkage to 8q21.3, naming this disorder CMT2H.

Although description of combined optic atrophy and neuropathy (HMSN type VI) dates back from 1889, with several reports in recent years, its genetic basis remains largely unknown. Both autosomal dominant and recessive inheritance have been postulated, age at onset is usually before the third decade of life, and axonal involvement is the rule.

There exist, however, some reports of HMSN with features that do not fit Dick's original classification, either because of a combination of manifestations or the association of symptoms as mental retardation, thin corpus callosum, and glaucoma. MacDermot and Walker describe three adults from an inbred family affected by axonal neuropathy, mental retardation, pyramidal signs, and congenital optic atrophy. All patients remained ambulatory, and peripheral signs were more prominent than pyramidal signs.

Dillmann and colleagues report two siblings born to consanguineous parents, with a slowly progressive, infancy-onset spastic paraplegia followed by adolescence-onset axonal neuropathy and optic atrophy. No dysarthria or startle response, as seen in our series, was described.

HSPs are characterized by progressive and often severe lower limb spasticity. When this sign occurs alone, it is known as pure HSP. When accompanied by other deficits, including impaired position sense, bladder disturbances, extrapyramidal symptoms, neuropathy, mental retardation, dementia, or optic atrophy, it is known as complicated HSP. Inheritance of HSP can be autosomal dominant, autosomal recessive, or X-linked recessive. Pure forms of HSP are more common than complicated ones. Twenty-three loci of HSPs have been assigned so far, and nine genes have been identified.

Among the currently recognized complicated forms of HSP, seven can be inherited as a recessive trait: SPG7, SPG11, SPG14, SPG15, SPG20, SPG21, and SPG23, as shown in Table 3. Patients in our series do not have clinical features that fit the characteristics of any of these conditions.
The genetic basis of hereditary optic atrophy is less diverse than that of CMT or HSP, but a complicated form of autosomal recessive optic atrophy also has been recognized: OPA3, or 3-methylglutaconic aciduria type III, is an inborn error of metabolism characterized by congenital optic atrophy, pyramidal and extrapyramidal signs, and mental retardation.

Startle response to unexpected noises is a peculiar sign that has been reported in GM2 gangliosidosis (Tay–Sachs disease) and in hyperekplexia, a condition characterized by exaggerated response to both tactile and acoustic stimuli.

Sural nerve pathological findings suggested an axonal process with loss of myelinated and unmyelinated fibers. Axonal degeneration was characterized by axoplasm vacuolization, abundant Büngner’s bands that represent vestige of a degenerated nerves, and fibers with disproportionately thin myelin sheath, probably secondary to axonal atrophy. Although onion bulbs are characteristic of a demyelinating process, they are also found in axonal neuropathies. Schwann cells hypertrophy, seen in axonal neuropathy, might suggest its concomitant involvement or might represent cycles of axonal degeneration and repair. The abundance of fibers with bizarre shapes, also described in inherited neuropathies with myelin outfolding, probably result from profound abnormalities in axonal cytoskeleton or in its interaction with Schwann cells.

We suggest that the disorder described in this article represents a new neurodegenerative condition inherited as an autosomal recessive trait, and we propose the acronym SPOAN (for spastic paraplegia, optic atrophy, and neuropathy) for this complex syndrome. The burden of this condition in Serrinha dos Pintos is overwhelming, with estimates that 1 in every 250 of its inhabitants is affected by SPOAN syndrome, and that 1 of 9 individuals in this village are heterozygous carriers of the responsible mutated gene. Interestingly, according to the Brazilian 2000 census of 5,507 Brazilian municipalities, Serrinha dos Pintos is ranked 38th among the 50 communities with the most disabilities (see http://www.fgv.br/cps/deficiencia_br/Ranking/PPD for more detailed information). SPOAN syndrome might be partially responsible for this unfortunate position.

The candidate region for SPOAN syndrome lies in chromosome 11q13 flanked by markers D11S1908 and D11S1889 and is approximately 4.79Mb. No inherited neuropathy optic atrophy maps in this interval. Nevertheless, this region was previously assigned for a complicated dominant HSP, known as Silver syndrome, a condition characterized by lower limb spasticity associated with hands and feet weakness and amyotrophy. Patel and colleagues report linkage of Silver syndrome to chromosome 11q12-q14 in a region of ~13cM flanked by markers D11S1908 and D11S1889, with a 2cM overlap with the SPOAN syndrome candidate region. However, Silver syndrome has clinical features and mode of inheritance different from the disease described here. Some rare genes, such as lamin A/C, have been associated with both autosomal dominant and recessive inheritance. Therefore, we

Table 2. Two-Point LOD Scores for Linkage of Microsatellite Markers on Chromosome 11

<table>
<thead>
<tr>
<th>Marker</th>
<th>LOD Score at θ</th>
</tr>
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<tr>
<td></td>
<td>0.000</td>
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<tr>
<td>D11S908</td>
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</tr>
<tr>
<td>D11S1883</td>
<td>14.43</td>
</tr>
<tr>
<td>D11S1889</td>
<td>12.48</td>
</tr>
<tr>
<td>D11S987</td>
<td>~∞</td>
</tr>
<tr>
<td>D11S1314</td>
<td>~∞</td>
</tr>
</tbody>
</table>

LOD = logarithm of odds.

Table 3. Complicated Spastic Paraplegia with Autosomal Recessive Inheritance

<table>
<thead>
<tr>
<th>Type</th>
<th>Location</th>
<th>Gene Product</th>
<th>Accompanying Features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SPG7</td>
<td>16q24.3</td>
<td>Paraplegin</td>
<td>Optic, cortical cerebellar atrophy</td>
<td>23</td>
</tr>
<tr>
<td>SPG11</td>
<td>15q13–14</td>
<td>Unknown</td>
<td>MR, thin corpus callosum, PN</td>
<td>20</td>
</tr>
<tr>
<td>SPG14</td>
<td>3q27–28</td>
<td>Unknown</td>
<td>MR, PN</td>
<td>24</td>
</tr>
<tr>
<td>SPG15</td>
<td>14q</td>
<td>Unknown</td>
<td>MR, dementia, PN</td>
<td>25</td>
</tr>
<tr>
<td>SPG21</td>
<td>15q22.31</td>
<td>Masparadin</td>
<td>Dementia, extrapyramidal and cerebellar signs</td>
<td>26</td>
</tr>
<tr>
<td>SPG20</td>
<td>13q12.3</td>
<td>Spartan</td>
<td>Dysarthria, distal wasting</td>
<td>27</td>
</tr>
<tr>
<td>SPG23</td>
<td>1q24–32</td>
<td>Unknown</td>
<td>Pigmentary skin defects</td>
<td>29</td>
</tr>
</tbody>
</table>

MR = mental retardation; PN = peripheral neuropathy.
could not rule out the possibility that SPOAN and Silver syndromes are allelic. However, it is more likely that these two disorders are caused by different genes because there are at least 143 genes and expressed sequences located in the SPOAN candidate region and many more transcripts in the Silver syndrome critical region. Of the 143 transcripts in the SPOAN candidate region, 96 have a significant level of expression in the nervous system and should be seen as bona fide candidates for this syndrome.

Identification of the gene responsible for SPOAN syndrome might help the genetic counseling of individuals belonging to this at-risk population and also might help to increase our understanding about the pathophysiology of hereditary optic atrophies, spastic paraplegias, and axonal neuropathies.

This work was supported by grants from Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Grant 99/1151-0), Centro de Excelência de Pesquisa Inovação e Difusão (CEPID), Grant 98/14254-2, Programa Apoio a Núcleos de Excelência, PRONEX, and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

We are indebted to all patients, their families, and the Municipality of Serrinha dos Pintos for their full support. M. Queiroz Carvalho and S. Queiroz were particularly helpful. We are grateful to M. R. Passos-Bueno, R. C. Pavanello, and Dr P. Otto for their comments and also Dr I. Lopes-Cendes, Dr L. Raymond, and A. M. Camara for their support. Finally, we express our gratitude to C. Urbani, R. Rivelino, and K. Rocha for technical support and to T. Marcourakis and S. Matosinhos for their friendship and logistics support in the field trip.

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