Adult-onset sporadic progressive muscular atrophy: natural history, diagnosis, and prognostic factors
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Chapter 3

Mimic syndromes in sporadic cases of progressive spinal muscular atrophy

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Chapter 3

Summary
Described are patients initially diagnosed as progressive spinal muscular atrophy (PSMA), in whom further evaluation established another diagnosis. The authors prospectively investigated incident and prevalent cases of PSMA. Seventeen of 89 patients, after initial registration, were later excluded because reassessment revealed a diagnosis other than PSMA. In 11 of the 17 patients with a revised diagnosis, a potential treatment was available: multifocal motor neuropathy (7), chronic inflammatory demyelinating polyneuropathy (2), inflammatory myopathy (1), and MG (1). Other misdiagnoses included myopathy, syringomyelia, ALS, idiopathic chronic axonal polyneuropathy, and idiopathic brachial plexus neuropathy. One patient with a possible herniated lumbar disk recovered spontaneously.
Introduction
Progressive spinal muscular atrophy (PSMA) is a nonhereditary progressive disease of the lower motor neurons (LMN). This disease entity has been described under various names. In 1850, Aran first described this disease, which he called “progressive muscular atrophy.”
Progressive muscular atrophy was later termed “progressive spinal muscular atrophy.” Because a proportion of these patients eventually develop clinical signs of upper motor neuron (UMN) degeneration or show UMN pathology at autopsy, PSMA and ALS are often considered part of a clinical spectrum. Therefore, in the United Kingdom and elsewhere, PSMA and ALS are often termed “motor neuron disease” (MND).
PSMA may run a rapidly progressive course comparable with that of ALS or may have a slowly progressive course over many years. Focal types have been described.
In 1994, the El Escorial criteria based on clinical and electrophysiologic features were proposed for ALS. These criteria define four categories: definite, probable, possible, and suspected. In the 1994 El Escorial criteria, PSMA met the criteria for suspected ALS. Within the 1998 revised El Escorial criteria, PSMA is no longer present. However, familial ALS (Ala4Val SOD mutation) may present as a LMN syndrome. Recent studies showed that less severe or even treatable diseases can mimic early MND. In particular, multifocal motor neuropathy (MMN) and chronic inflammatory demyelinating polyneuropathy (CIDP) should be differentiated from PSMA. We describe patients initially included in a follow-up study on sporadic cases of PSMA in whom the initial diagnosis of PSMA proved to be incorrect.

Patients and methods
In 1998 the Academic Medical Center and the University Medical Center Utrecht started a joint prospective study on the natural history and prognosis of PSMA. Consecutive patients with a prior diagnosis of PSMA were asked to participate in the study. All patients had been diagnosed by experienced neurologists. We selected patients by screening of the files of both outpatient neuromuscular departments for all patients diagnosed as having PSMA, focal SMA, segmental SMA, and LMN disease. Nine patients were recruited from other hospitals.
All patients underwent reappraisal before inclusion. They were seen at different stages of their illness. Inclusion criteria of the natural history PSMA study were (1) clinical signs of LMN involvement (weakness, atrophy, and fasciculation) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral) according to the 1994 El Escorial criteria and (2) electrophysiologic evidence of LMN involvement in clinically affected and nonaffected regions without evidence of conduction block (CB) (see below). Exclusion criteria were (3) objective sensory signs (apart from mild vibration sense disturbances in elderly patients), (4) a history of diseases that may mimic MND (i.e., spinal radiculopathy, poliomyelitis, diabetic amyotrophy), (5) family history of inherited SMA, and (6) definite symptoms and signs...
of UMN involvement (Babinski sign, pseudobulbar symptoms, and (sub)clonic reflexes). Patients in whom the diagnosis of PSMA had to be rejected on the basis of one or more of these criteria are the subject of this article.

**Obligatory ancillary investigations.** The following laboratory tests were performed: sedimentation rate, hemoglobin, hematocrit, thyroid-stimulating hormone, serum protein electrophoresis, and serum immunoelectrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone), and serum IgM anti-GM1 antibodies. If appropriate neuroimaging studies were lacking (either spinal cord myelography with CT or MRI), MRI of the craniocervical junction or pertinent spinal cord was performed. If patients met criteria for adult SMA or Kennedy disease, DNA analysis was performed. If an alternative diagnosis was suspected, specific ancillary investigations were performed, such as muscle biopsy, serum creatine kinase activity, electromyography (EMG) with repetitive stimulation, and anti-acetylcholine receptor (anti-AChR) antibodies.

**Electrophysiologic studies.** The electrophysiologic investigation took place after warming the limbs in water at 37 °C for at least 30 minutes. Motor nerve conduction on both sides was investigated up to Erb’s point in the median (recording: abductor pollicis brevis and flexor carpi radialis muscles), ulnar (recording: abductor digiti minimi muscle), radial (recording: extensor carpi ulnaris muscle), and musculocutaneous (recording: biceps brachii muscle) nerves and up to the popliteal fossa in the deep peroneal (recording: extensor digitorum brevis muscle) and tibial (recording: abductor hallucis muscle) nerves. Sensory conduction on distal stimulation was investigated in at least one median and sural nerve. In case of motor CB in the median or ulnar nerve, sensory conduction was measured over the affected segment. EMG was performed on both biceps brachii, flexor carpi radialis, interosseus dorsalis I, rectus femoris, tibialis anterior, and gastrocnemius (lateral head) muscles and on one side in the erector spinae at Th6 and Th10 levels. We measured the amplitude and area of the negative part of each compound muscle action potential (CMAP). We defined definite CB as an area reduction on proximal versus distal stimulation (P/D) of at least 50% and possible CB as amplitude reduction P/D of at least 30% in an arm nerve.

**Results**

From a total of 89 patients who were referred for the PSMA prospective study, in 17 (19%), PSMA turned out to be an incorrect diagnosis. There were 13 men (76%) and 4 women (24%). The median age at the current analysis was 58 years (range 33 to 89 years). Age at onset ranged between 23 and 87 years (median 50 years). Disease duration ranged between 1 and 25 years (mean 10 years).

After thorough electrophysiologic analysis, MMN was demonstrated in seven patients and CIDP in two. Other treatable diagnoses were autoimmune limb girdle MG (n = 1) and inflammatory myopathy (n = 1). Six of seventeen patients (30%) had untreatable diseases: idiopathic chronic axonal polyneuropathy, idiopathic brachial plexus neuropathy, syringo-
myelina, and myopathy. One patient with a possible herniated lumbar disk recovered spontaneously, and only one patient had slowly progressive ALS.

Case reports. A 50-year-old man presented in 1992 with weakness and minimal atrophy of arms and legs without ocular or bulbar symptoms. EMG in 1993 showed fibrillations, complex repetitive discharges, and polyphasic long-duration motor unit action potentials (MUAP) in proximal and distal arm and leg muscles. Motor and sensory conduction studies revealed no abnormalities. A diagnosis of PSMA was made. In 1999 he was reviewed for the natural history study. During this time, his weakness had become remarkably exertion dependent. EMG in 1999 showed complex repetitive discharges and occasionally positive sharp waves in the deltoideus, trapezius, iliopectas, and paraspinal muscles. Slight voluntary effort elicited small polyphasic MUAP, and maximum voluntary effort a severely reduced pattern or a low-amplitude full pattern. Repetitive stimulation with 3 Hz that was performed because of the exertion dependence revealed CMAP amplitude decrement of 12% in the abductor digiti minimi muscle and of 19% in the trapezius muscle. Although the absence of ocular and bulbar symptoms does not support a diagnosis of MG, anti-AChR antibodies were found, and the diagnosis of chronic limb girdle MG was made. Weakness improved on pyridostigmine.

A 42-year-old man presented in 1981 with purely LMN signs in the arms, confirmed by electrophysiology, and was diagnosed as segmental SMA. At reassessment for our study in 1999, he displayed generalized weakness in all extremities with additional dissociated sensory loss in the arms and a pyramidal syndrome of the lower limbs. MRI showed an extended syrinx from the cervical into the thoracic cord.

A 61-year-old man presented with a 1-year history of weakness of arms and legs. On re-examination, there were tetraparesis, proximal more than distal, and atrophy of particularly the shoulder girdle muscles. EMG at presentation in 1999 showed fibrillations and positive sharp waves and polyphasic MUAP of low or high amplitude in proximal and distal arm and leg muscles. These findings, in combination with weakness and wasting of all limbs, were thought consistent with a diagnosis of PSMA. EMG in 2000 showed fibrillations and positive sharp waves in the biceps brachii, flexor carpi radialis, iliopectas, rectus femoris, tibialis anterior, and gastrocnemius muscles. In most of these muscles, light voluntary effort elicited low-amplitude, short-duration, polyphasic MUAP with greatly increased recruitment and maximum voluntary effort a low-amplitude full pattern. Nerve conduction studies were normal except for severe conduction slowing consistent with demyelination across the fibular head segment of the right peroneal nerve. As this examination was consistent with myopathy and as serum creatine kinase was elevated (852 IU/L; upper limit of normal 190 IU/L), a muscle biopsy was performed. Muscle biopsy of the left biceps brachii revealed marked variation in the size of muscle fibers, numerous necrotic fibers (some undergoing phagocytosis), occasional regenerating fibers, a few small mononuclear cell infiltrates localized around small blood vessels in the perimysium, many clumps of nuclei, and the
occasional atrophic fiber, moth-eaten fiber, and ragged red fiber. Rimmed vacuoles were not present. Since the patient reported spontaneous improvement, no treatment has been given. Nevertheless, he still displays evident muscle weakness and atrophy.

A 33-year-old man presented with weakness and atrophy of the right abductor pollicis brevis and interosseus dorsalis I muscle. In 1993 nerve conduction studies revealed neither CB nor demyelinating features, and the diagnosis of juvenile muscular atrophy of the distal upper limb (Hirayama’s disease) was made. In 1998 extensive nerve conduction studies revealed CB of the right median nerve in the upper arm segment, and the diagnosis was modified to MMN. Owing to the slow progression of signs and symptoms and minimal weakness, the patient has not been treated with IV immunoglobulin.

Discussion

Our prospective study on patients with PSMA aimed at establishing prognostic determinants and the course of the disease. Following careful reexamination of patients with this diagnosis before inclusion into our study, 17 patients (19%) were ultimately rediagnosed with conditions other than PSMA. PSMA was still the correct diagnosis in the other 80% of patients, but these patients are subject of a separate report.

The frequency of misdiagnoses in MND was analyzed in the Scottish Motor Neuron Disease Register. In 8% (46/552), an alternative diagnosis was made. In a study on Irish ALS patients, a percentage of 7.3% (32/437) misdiagnoses was reported. However, these studies are not entirely comparable with our study because the methodologies are different. Both the Scottish and the Irish study concentrated mainly on patients with ALS, whereas we focused on patients with PSMA. The Scottish and Irish study report mainly on recently diagnosed patients, whereas in our study, the majority of patients had a longer disease duration. As a consequence, the patients with a LMN form of ALS (either PSMA with rapid progression or PSMA turning into ALS) have already been filtered from our group. Our study is thus dealing with patients with PSMA that has not evolved into ALS after a certain period, except for one patient with a slowly progressive form of ALS.

Our study yielded a high percentage of MMN (41%) as compared with 4% in the Scottish study and 22% in the Irish study. This can be explained by our selection of patients with pure LMN syndromes and by our extensive and standardized electrodiagnostic protocol. Previously performed electrophysiologic examination has contributed to the wrong diagnosis in a number of our patients. In two patients, a typical myopathic pattern on EMG consisting of spontaneous muscle fiber activity, low-amplitude, short-duration, polyphasic MUAP, and increased recruitment was not recognized as such. The diagnosis of MMN was missed either because the entity was not known at the time of the first investigation or possibly because an insufficient number of nerves was examined. An extensive examination is often necessary to detect CB. In a previous study, we have shown that in 12 of 21 patients
with definite MMN, CB was detected in only one nerve segment, despite our extensive protocol.14
Our study shows that patients with PSMA should be followed up meticulously in order to
detect development of features or a course not consistent with PSMA. Tailored investiga-
tions should then be performed to establish the correct diagnosis and, in particular, to
identify potentially treatable disorders.

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