Chapter 1

Introduction
Progressive muscular atrophy

Progressive muscular atrophy (PMA) is an adult-onset progressive neurodegenerative disease. In PMA, the anterior horn cells of the spinal cord degenerate, with or without concomitant degeneration of bulbar motor nuclei. Clinically, this leads to weakness and atrophy of skeletal muscles, cramps and fasciculations. PMA is known under various names, including progressive spinal muscular atrophy (PSMA). We prefer the term PMA to differentiate it from the familial form of spinal muscular atrophy (SMA) caused by mutations in the SMN-gene.

There is accumulating evidence that PMA belongs to the spectrum of motor neuron diseases including amyotrophic lateral sclerosis (ALS). ALS is a devastating and fatal disease that results from degeneration of upper and lower motor neurons. A proportion of patients with PMA develops upper motor neuron (UMN) signs, or has a disease progression similar to ALS, reveal UMN pathology at autopsy, or has a mutation in the SOD1-gene. PMA is not a well described clinical entity as only anecdotal cases or retrospective studies of small groups of patients have been published. Moreover, adult patients with hereditary forms of lower motor neuron disease (LMND), SMA type IV and Kennedy disease, and multifocal motor neuropathy (MMN), an immune-mediated lower motor neuron syndrome, had not yet been recognized. In addition, familial ALS (FALS) may present with predominant lower motor neuron signs. Progression in PMA may vary to a great extent between patients: a slowly progressive course over many years to decades is not unusual. Therefore, questions about the disease course in PMA and prognosis are often difficult to answer.

Clinical features in PMA

Onset of weakness in PMA is usually unilateral in distal arm or leg muscles with associated fasciculation and hypo- or areflexia in the affected limb. Subsequent progression of weakness within a particular region or to other regions (bulbar, upper limbs, truncal, lower limbs) in the ensuing months or years result in difficulties with ambulation and activities of daily living. Muscles of the thoracic region can also become involved, causing respiratory insufficiency. Painful cramps may occur both in weak and normal muscles.

Ancillary investigations and differential diagnosis

There are no specific diagnostic tests for PMA. Clinical evaluation and electromyography (EMG) form the most important part of the diagnostic process. Motor nerve conduction studies, imaging studies, selected laboratory and DNA tests are used to rule out other diagnoses that can mimic PMA. Diagnosing PMA ‘early’ in the disease when the patient has only focal symptoms and signs may be difficult because LMND phenotypes that remain restricted to one limb or body region do exist and are called segmental SMA. They are known under various names and are described below under the heading of other subtypes of LMND.
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According to the 1994 El Escorial criteria – criteria that were designed as research diagnostic criteria for clinical trials in ALS – a diagnosis of PMA (or ‘suspected ALS’) can be made when LMN symptoms are present in at least two body regions. However, this subgroup was omitted in the 1998 revised El Escorial criteria.

Signs of active denervation (fibrillation potentials and positive sharp waves) at EMG provide evidence of LMN involvement in clinically affected and clinically unaffected regions, which is helpful in differentiating between segmental SMA and the more generalised form, PMA.

The most important differential diagnosis after clinical examination is MMN, a presumably immune-mediated and thus treatable condition in which life expectancy is normal. Most patients with MMN respond to treatment with intravenous immunoglobulin (IVIg). Extensive nerve conduction studies are essential to search for persistent motor nerve conduction block(s), which is the electrodiagnostic hallmark of MMN. Increased signal intensities on T2-weighted MRI of the brachial plexus and positive titres of IgM anti-GM1 antibodies may contribute to the diagnosis.

Neuroimaging studies should be performed to rule out structural lesions that may explain the observed signs and symptoms. Laboratory tests to exclude diseases that may mimic PMA/MND (e.g. myeloma, insulinoma with hypoglycaemia, hypo- or hyperthyroidism, and hyperparathyroidism) are listed in table 1.

Presence of similar symptoms in family members may point to hereditary forms of LMND. These include ‘adult-onset SMN-gene linked spinal muscular atrophy’ (SMA type IV) sometimes SMN-gene linked, ‘bulbospinal muscular atrophy’ (Kennedy disease), and ‘familial ALS (FALS) with predominant lower motor neuron signs’ Genetic analysis for the presence of a telomeric deletion in the SMN1-gene (SMA type IV) or an expansion of CAG-repeats in the androgen receptor gene (Kennedy disease) should be carried out if clinically suspected.

Other sporadic forms of lower motor neuron diseases (LMND) include postpolio syndrome and radiation induced LMND. Other subtypes of LMND

‘Hirayama disease’ or ‘juvenile muscular atrophy of distal upper extremity’ (in this thesis we call this subtype ‘segmental distal SMA’) presents with insidious onset of unilateral weakness and atrophy in muscles of the hand and forearm. In about one-third of patients less pronounced contralateral weakness of the hand and forearm is reported. Initial progression over months to years is often followed by a spontaneous arrest. In the original descriptions by Hirayama, predominantly young men were affected. Chronic compression and flattening of the lower cervical spinal cord during neck flexion has been hypothesized as the pathogenetic mechanism in a number of MRI-documented cases. A clinical presentation of weakness and atrophy in muscles of the shoulder and proximal arm can point to a more benign form of LMND, namely ‘scapulohumeral muscular atrophy’
(in this thesis we use the term ‘segmental proximal SMA’ for this subtype). After years, slow progression to the contralateral shoulder occurs in most patients and to the lower limb and neck muscles in some of them. Respiratory insufficiency has not been reported in these patients and this phenotype appears to have a relatively favourable prognosis. However, in the ‘flail-arm’ variant of ALS, also called ‘person in the barrel’ syndrome, disease progression is rapid with death from respiratory insufficiency in a few years.

In ‘monomelic amyotrophy of lower limb’ or ‘wasted leg syndrome’ muscle weakness and atrophy are restricted to one leg. In these patients, an initially slowly progressive disease course of 1-2 years is followed by a stationary period lasting decades. This form occurs predominantly in males and is seen commonly in India. Only few cases with unilateral lower limb involvement have been reported in the Western world.

Early weakness of distal leg muscles is usually the first manifestation of ‘distal spinal muscular atrophy’ (dSMA), also known as ‘distal hereditary motor neuropathy’ (distal HMN). Progression of weakness is slow and most commonly restricted to distal muscles of both legs in a symmetrical pattern. After many years, the hands and later the forearms are affected. Rarely proximal muscles may also become involved. A positive family history can give a clue to an autosomal dominant or autosomal recessive inheritance but sporadic forms have been described as well. The hereditary forms have been classified in seven types based on mode of inheritance, age at onset and clinical progression.

In SMA type IV life expectancy is probably normal. Onset of symptoms is usually in the fourth decade, and legs are often more affected than arms. An autosomal dominant, autosomal recessive and X-linked pattern of inheritance have been described. Deletions in SMN1 – the gene which is linked to childhood autosomal recessive SMA – have been found in only a minority of SMA type IV patients. Kennedy disease or X-linked bulbo-spinal muscular atrophy is characterized by slowly progressive limb girdle weakness and atrophy with facial weakness, gynaecomastia (50%), dysarthria and dysphagia, fasciculation, sensory neuronopathy and hand tremor.

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**Table 1.** Recommended laboratory studies to exclude diseases that may mimic PMA / MND in adults

<table>
<thead>
<tr>
<th>Blood:</th>
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<tr>
<td>erythrocyte sedimentation rate (ESR), hemoglobin, hematocrit, thyrotropin (TSH),</td>
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<tr>
<td>serum protein electrophoresis and immunoelectrophoresis with immunofixation,</td>
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<tr>
<td>glucose, phosphate, and calcium (and, if elevated, parathyroid hormone)</td>
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</tbody>
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**Cerebrospinal fluid** (*CSF)*:

(examination performed, when a specific disease is suspected)

- cell count, protein, *Borrelia burgdorferi* and syphilis serology

* Examination performed when a patient with a lower motor neuron syndrome is suspected of *Borrelia burgdorferi* or syphilis infection
Pathogenesis and aetiology
The pathogenesis of PMA is largely unknown. In contrast to childhood-onset SMA, PMA is not a monogenic disease that follows a Mendelian inheritance. The current concept is that PMA forms part of a dynamic spectrum of adult-onset motor neuron diseases, characterized by a preferential degeneration of upper and/or lower motor neurons. ALS/MND have a complex multifactorial aetiology in which genetic factors interact with environmental factors, which have as yet not been unravelled. Currently, several pathological processes (e.g. excitotoxicity and oxidant stress) may contribute to motor neuron death in MND. There is accumulating evidence that susceptibility genes and modifier genes also have a role in sporadic ALS/MND. Recently, the role of deletions in the centromeric copy of the SMN gene (SMN2) as modifiers of phenotype in different forms of MND has been investigated. SMN2 can modify childhood-onset SMA disease severity in a dose-dependent manner. A few studies found an association between a homozygous deletion of SMN2 and sporadic adult-onset LMND. This may act as a susceptibility factor, increasing the risk of developing adult-onset lower motor neuron degeneration. Several mutations in the superoxide dismutase (SOD1) gene have been recognized in patients with familial ALS (FALS) with a predominant lower motor neuron syndrome. The most frequent of these mutations is the Ala4Val mutation, which is also the most common SOD1 mutation in ALS worldwide.

Natural course and prognosis
PMA can occur at any age in the adult population. Previous studies reported earlier onset of PMA, which may be explained by the inclusion of patients with MMN, in whom the disease usually starts in the second or third decade. Disease progression varies from slow to very rapid. Patients with a more benign disease course progress slowly over many years to decades. In patients with a rapidly progressive form of PMA prognosis may be as poor as in ALS.

Epidemiology
The incidence of PMA is not established. The estimated incidence of PMA is – extrapolated from the US – approximately 0.2/100,000 annually, which is ten times lower as compared with ALS.

Therapy
PMA cannot be cured. A small, but significant effect of the glutamate-inhibitor riluzole on survival in ALS has been demonstrated in two randomized, double blind, placebo-controlled, clinical trials. Patients with PMA have ‘suspected ALS’ according to the 1994 El Escorial criteria that were designed as research diagnostic criteria for clinical trials in ALS. However, this subgroup was omitted in the 1998 revised El Escorial criteria.
As a result, patients with PMA are not included in ALS trials. Further treatment is symptomatic. Referral to multidisciplinary ALS/MND clinics should take place early in the disease. Health care professionals with expertise in ALS/MND provide specialistic care and management services which help the patient stay independent longer. In case of progressive respiratory insufficiency non-invasive ventilatory support can be considered. The use of noninvasive ventilatory support improves quality of life and survival in ALS patients (without severe bulbar dysfunction). With progressive dysphagia percutaneous endoscopically placed gastrostomy (PEG) can be considered, preferably before a patient’s vital capacity falls below 50% of predicted.

Aim and outline of this thesis

The aims for this thesis were to determine the natural course of patients with sporadic LMND, especially adult-onset PMA, and to identify prognostic variables for disease progression at an early stage. In addition, we aimed at improving the classification of patients with a more benign form of LMND and to determine the long term natural course.

Chapter 2 includes a review on the history of PMA, highlighting the relation of PMA to ALS and the finding that PMA also comprises other manifestations which fundamentally differ from that of other MNDs.

Chapter 3 describes 17 LMND patients who did not meet the inclusion criteria for our prospective study and our cross-sectional cohort study. We analyzed which features led to a revised diagnosis of these ‘mimic’ patients.

In comparison to maximal voluntary isometric contraction (MVIC), the gold standard for assessing muscle strength in trials for MND, hand-held dynamometry (HH-Dyn) might be an improvement because it has the advantage of being inexpensive and quickly applicable. We therefore evaluated the intraobserver and interobserver reliability and correlation between both methods in patients with PMA (chapter 4).

In chapter 5 we describe clinical features, natural history, and predictive factors of poor outcome in 37 patients with sporadic LMND, most of them PMA, with a disease duration of less than four years. In the same group, electrophysiologic parameters were studied (chapter 6).

In chapter 7 we describe the clinical and electrophysiological characteristics in a cross-sectional cohort of sporadic LMND patients with longstanding disease duration (at least 4 years since onset of symptoms). In chapter 8, the long-term follow-up of these patients is reported. A general discussion and future prospects are given in chapter 9. A summary in English and Dutch concludes this thesis.
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References


35. De Visser M, Ongerboer de Visser B, Verbeeten B. Electromyographic and computed tomographic findings...
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