Adult-onset sporadic progressive muscular atrophy: natural history, diagnosis, and prognostic factors
Visser, J.

Citation for published version (APA):
Chapter 9

Discussion
This thesis focuses on patients with sporadic lower motor neuron disease (LMND), especially progressive muscular atrophy (PMA). The main questions were: what is the natural disease course and which factors are predictive for a poor outcome? Before discussing these questions, the current classification and nomenclature of PMA in relation to the concepts of Motor Neuron Disease (MND) and Lower Motor Neuron Syndrome (LMNS) will be discussed.

Classification and nomenclature
The classification of MND and LMNS is schematically depicted in figure 1. MND includes the neurodegenerative diseases in which upper and/or lower motor neurons are affected, thus excluding diseases primarily affecting the motor axon or its surrounding myelin (motor neuropathies). From the clinical perspective it is useful to recognize the concept of LMNS, which includes sporadic lower motor neuron disease (LMND) and motor neuropathy, because both may present with similar clinical features. In LMND, the anterior horn cells in the spinal cord and/or the motor nuclei in the brainstem are affected. Clinically, there is no dysfunction of the upper motor neuron (UMN). We define PMA, one of the LMNDs, as (1) a sporadic disease, characterized by (2) progressive muscle weakness and atrophy due to degeneration of anterior horn cells and brainstem motor nuclei, (3) with onset in adulthood. The definition does not specify the rate of progression.

![Classification of Motor Neuron Diseases and Lower Motor Neuron Syndromes](figure1.png)

**Figure 1.** Classification of Motor Neuron Diseases and Lower Motor Neuron Syndromes
ALS = amyotrophic lateral sclerosis; PBP = progressive bulbar palsy; PLS = progressive lateral sclerosis; MMN = multifocal motor neuropathy; CIDP = chronic inflammatory demyelinating polyneuropathy; LMND = lower motor neuron disease; PMA = progressive muscular atrophy; PSMA = progressive spinal muscular atrophy; SMA = spinal muscular atrophy; LMN = lower motor neuron.
Chapter 9

We have used different synonyms for LMND and PMA throughout the thesis. Because the chapters were published in various medical journals, we had to comply with the journals’ preferred terminology. In the USA, United Kingdom, and continental Europe, there is no consensus in this respect. In our historical overview of PMA (chapter 2), we discuss that the current differences in nomenclature are based on the heterogeneity of PMA as a syndrome and the unsettled debate regarding the classification of PMA in relation to other motor neuron diseases, especially ALS.

Patients diagnosed with PMA may deteriorate as rapidly as ALS, with or without the development of UMN signs (chapter 5), but a slowly progressive course is also possible (chapter 8). Some authors lump the fast progressive variant of PMA with ALS and consider only the slow variant with pure LMN involvement as ‘true’ PMA. The term progressive spinal muscular atrophy (PSMA) is used synonymously with PMA, but some authorities advocate to use spinal muscular atrophy only for the survival motor neuron (SMN)-gene linked disorder (SMA) in order to avoid confusion.

Within the group of PMA it is possible to delineate phenotypes based on the distribution of weakness. We have described these phenotypes in a cohort of patients with longstanding sporadic LMND (‘generalized’, ‘segmental proximal SMA’, ‘segmental distal SMA’, ‘distal SMA’) in chapter 7. However, in due course the phenotype may change, especially during the first four years after onset of weakness (chapter 5). However, even after a considerable duration of the disease generalization of weakness may occur (chapter 8).

PMA – natural course and predictive factors

Outcome in PMA varies and can be very poor, with a rate of progression (almost) as rapidly as classical ALS (chapter 5), which is in contrast with the common belief that PMA has a better prognosis than ALS. This can be explained by (i) selection bias in previous retrospective studies, which may have overlooked the fast progressive variants of PMA; (ii) difficulties in defining the syndrome PMA, which according to some refers only to the slowly progressive variant (see above); (iii) inclusion of patients with MMN – an unknown entity before the late 1980s – in previous studies (chapter 3).

After diagnosis, low vital capacity (VC) at baseline (VC <90%) and rapid decline of VC in the first 6 months are both predictors of an unfavorable outcome in PMA (chapter 5). Therefore, it is important to measure VC once a patient is suspected of having PMA. However, our results do not allow for precise predictions of prognosis in individuals. This is caused by the relatively small sample size and the heterogeneity of our study group, and other as yet unknown prognostic factors causing an unexplained variability within risk groups. PMA rarely has a bulbar onset. However, the presence of bulbar signs was related to shorter survival in our study group: all 10 patients with bulbar signs at inclusion and 15 of the 16 patients that developed bulbar signs during follow-up, died. However, bulbar signs at inclusion were not an independent predictor of outcome. A likely explanation is the high specificity but
Discussion

relatively low sensitivity of this item: the presence of ‘early’ bulbar signs in a patient with PMA is highly predictive for a poor outcome, but prediction of favorable outcome can not be based on its absence. Arm-weakness onset was not significantly associated with outcome in our multivariate analysis.

Chapter 7 and chapter 8 show that a much more benign disease course in PMA patients is also possible. In our cross-sectional cohort study (chapter 7), we evaluated sporadic LMND patients with longstanding disease duration (median 12 years). We classified this cohort according to the pattern of muscle weakness into the following phenotypes: “slowly progressive spinal muscular atrophy” (sPSMA), “distal spinal muscular atrophy”, “segmental distal SMA”, and “segmental proximal SMA”. Categorization of phenotypes has the intention to (i) facilitate research as different motor neuron disease presentations may have different etiologies or at least different modifying factors, and (ii) to identify patients with specific disease characteristics and disease course which may help for prognostication. We demonstrated that sPSMA shows a progressive disease course, in which life expectancy may be limited by the development of respiratory insufficiency, even after relatively long disease duration (chapter 8). sPSMA thus shows overlap with PSMA and ALS. In contrast, disease progression in both segmental phenotypes was very slow with normal life expectancy, although segmental spreading of weakness may occur.

Other clinical implications from this thesis

PMA – distinction from MMN

Multifocal motor neuropathy (MMN) can mimic PMA (chapter 3). Clinically, the slowly progressive disease course and the absence of bulbar, UMN and respiratory involvement differentiate MMN from rapidly progressive PMA and ALS, but not from slowly progressive PMA and segmental SMA. The finding of motor nerve conduction block (CB) on nerve conduction studies, a positive titre of anti-GM1 antibodies or increased signal intensity on T2-weighted MR images of the brachial plexus may help to differentiate MMN from LMND.1-3 However, negative test values do not exclude MMN. Moreover, recent studies suggest the existence of an axonal form of MMN.4,5 Patients with the clinical phenotype of MMN showed a favorable response to intravenous immunoglobulin (IV Ig) treatment, irrespective if CB was found or not. It is as yet unclear whether (1) these patients ever or no longer had CB, (2) the current criteria for CB are too stringent, or (3) other techniques can improve detection of CB. Thus, the question is justified whether MMN and PMA can be distinguished at all times (chapter 1). Therefore, a trial with IV Ig treatment may be justified in patients with progressive distal asymmetric weakness in a multifocal peripheral nerve distribution with or without CB.
Chapter 9

PMA – mimic syndromes
A number of other – often less severe – diseases can mimic PMA in different stages of its disease course (chapter 3). Sixty-five percent of the patients in whom the initial diagnosis PMA had to be changed were found to have a potentially treatable disease; mostly multifocal motor neuropathy (MMN). This study (chapter 3) addresses two important issues: (1) the importance of extensive motor nerve conduction studies to differentiate PMA from other LMN syndromes, especially MMN, and (2) the need for following patients with PMA in case another diagnosis might surface, including diagnoses that could lead to effective therapy. The rate of mimic syndromes in our study was higher than those reported by previous studies on misdiagnoses in MND. A likely explanation is that these studies focused on misdiagnosis in patients diagnosed with ALS whereas the majority of our patients had a long disease duration, which already filtered patients that had evolved into ALS.

PMA – quantitative muscle measurement
Two methods for quantitative strength measurement, maximal voluntary isometric contraction (MVIC) and hand-held dynamometry (HHDyn), correlated well in all tested muscle groups in patients with PMA. Additionally, high intra- and interrater reliability was found (chapter 4). However, HHDyn is less sensitive than MVIC in detecting subnormal muscle strength in strong muscle groups, probably caused by ceiling effects. HHDyn can therefore not replace MVIC as the gold standard for assessing muscle strength in trials for MND. However, HHDyn can be used in a clinical setting as a method to evaluate muscle strength over time in moderately weak muscle groups of PMA patients. For reliable measurements with both methods, familiarity with the measurement technique and strict standardization of the testing procedure are prerequisites.

PMA – electrophysiologic studies
Up to 33% of the patients of our prospective study in PMA (chapter 6) showed abnormalities in motor nerve conduction (MNC) studies: mild to moderate slowing of motor conduction velocity (MCV); prolongation of distal motor latency (DML) and F-M latencies; and low compound muscle action potential (CMAP) amplitudes. Signs indicative of demyelination were a true exception. Many accept that MNC studies in MND are (near) normal. However, our findings suggest more variation in the findings of MNC studies in patients with PMA. This is in accordance with similar findings in studies on ALS. It emphasizes the importance of interpreting the electrophysiological results in the context of clinical presentation in patients with a LMN syndrome. Also, the separation between MMN and PMA may be less robust when the hallmark of MMN, i.e., motor nerve conduction block(s) outside compression sites, is not present or cannot be demonstrated.

The relative proportion of active and chronic denervation on EMG varied between muscles and between patients. Importantly, all patients with segmental SMA or distal SMA that
evolved to PMA demonstrated signs of active denervation in clinically unaffected regions, particularly the thoracic region. In contrast, absent signs of active denervation in subclinical regions did not provide prognostic information. A likely explanation is that the identification of denervation may be hampered by sampling errors. However, because the number of patients was small, larger studies are required to assess the prognostic value of signs of active denervation in clinically unaffected regions.

Future studies
Our finding that most patients who initially present with PMA have a disease course equally to ALS is in line with recent findings from post-mortem studies showing that most PMA cases with rapid progression – whether or not upper motor neuron signs evolve – have ubiquitinated inclusions in spinal motor neurons, typical of ALS. In the current diagnostic (El Escorial) system, devised for research, patients with PMA are excluded. An easily applicable and reliable test or marker for PMA and other MND could greatly improve diagnostic accuracy. In this respect, potential methods of detecting and quantifying subclinical upper motor neuron (UMN) involvement, such as MRDTI (magnetic resonance diffusion tensor imaging), $^1$H MRS (proton MR spectroscopic imaging), and transcranial magnetic stimulation (TMS), have been focus of recent research. To date however, their potential to detect early changes of the UMN is at present not sufficiently consistent to discriminate patients for diagnostic purposes. Other candidate biomarkers currently investigated are disease-specific proteins in the cerebrospinal fluid – using mass spectrometry and 2-D gel electrophoresis – and levels of Nogo-A protein in muscle biopsies.

There is growing awareness that the disease process of MND is not restricted to motor neurons. Pathological, neurophysiological, and neuroimaging studies provide evidence that abnormalities outside the motor system are widespread in both familial and sporadic MND. In addition, the association of MND with cognitive impairment, including frontotemporal dementia, and extrapiramidal signs and symptoms, suggest that some MNDs are a multi-system disorder instead of a pure motor neuron disease. It may well be possible that different aetiologies or modifying factors are responsible for these – partially overlapping – clinical phenotypes. Further research to identify these subtypes and consensus regarding its classification is a prerequisite for the success of genetic studies and the understanding of underlying disease mechanisms.

The identification of the causative (SOD1) gene mutation responsible for approximately 20% of familial ALS was an important step forward. Transgenic mice that over-express the mutant human SOD1 gene were found to develop progressive motor neuron degeneration. This mouse model offers the opportunity to explore the molecular biology of the motor neuron and greatly enhanced knowledge on pathogenetic mechanisms that may underlie both familial and sporadic MND.
The ultimate goal is the development of treatments that may slow down, stop, or preferably prevent the disease. Therefore, a major challenge is to identify more genes linked to MND, which may generate new insights into the various molecular pathways involved in motor neuron degeneration.

Little is known about the specific genes that contribute to the development of sporadic MNDs. Research in large patient groups, so-called population-based studies, is needed. Therefore, the ‘Prospective ALS study Netherlands’ (PAN) has been set up (on-line at http://www.als-centrum.nl), which will facilitate genome wide association studies. Because the aetiology of sporadic MNDs is probably complex and multifactorial, combining genetic factors, clinical characteristics, and other risk factors will be crucial for our understanding of molecular mechanisms that ultimately lead to motor neuron death.

References
13. Murphy J, Henry R, Lomen-Hoerth C. Establishing subtypes of the continuum of frontal lobe impairment in
Discussion


