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

This thesis focuses on patients with sporadic lower motor neuron disease (LMND), especially progressive muscular atrophy (PMA), also known as progressive spinal muscular atrophy (PSMA). The aims of this study were to determine the natural course of patients with PMA and other sporadic LMND, and to identify factors predictive for a poor outcome.

A general introduction to PMA and other sporadic LMND, and the aims of the study are given in chapter 1.

In chapter 2 the history of progressive muscular atrophy is reviewed. Since its first description by Aran in 1850, there has been much debate about the diagnostic entity progressive muscular atrophy (PMA). Initially, PMA included all forms of progressive amyotrophy. With the identification of several myogenic and neurogenic diseases and the recognition of amyotrophic lateral sclerosis (ALS), PMA was deemed to disappear as a nosological entity at the end of the 19th century. In the last century, various other lower motor neuron syndromes (i.e., multifocal motor neuropathy (MMN), adult-onset form of hereditary spinal muscular atrophy, X-linked bulbospinal muscular atrophy) were distinguished which may previously have been designated as cases of PMA. In contrast, several observations provided evidence that PMA can be linked both clinically and pathologically to ALS. Because natural history and differential diagnosis of PMA may differ as compared with ALS, it seems rational to consider PMA as a syndromal subtype within a clinical spectrum of motor neuron diseases.

In chapter 3 we describe 17 of the 89 patients initially diagnosed with PMA or LMND, in whom further evaluation – as part of our prospective study (chapter 5) and our cross-sectional cohort study (chapter 7) – established another diagnosis. In 11 of the 17 patients with a revised diagnosis, a potential treatment was available: MMN (7), chronic inflammatory demyelinating polyneuropathy (2), inflammatory myopathy (1), and myasthenia gravis (1). The remaining six patients were diagnosed as having myopathy, syringomyelia, slowly progressive ALS, chronic idiopathic axonal polyneuropathy, lumbar disc herniation or idiopathic brachial plexus neuropathy. This study shows that several clinically less disastrous or even treatable diseases can mimic PMA or LMND. This finding stresses the need for careful follow-up and additional investigations, especially electrophysiological examination, in patients diagnosed with PMA or LMND.

We investigated the reliability and validity of quantitative muscle strength assessment with a hand-held dynamometer as compared with maximal voluntary isometric contraction (MVIC) in patients with PMA, which is reported in chapter 4. Quantitative assessment of muscle strength with MVIC has proven to be reliable, accurate, and sensitive in amyotrophic lateral sclerosis (ALS) and is being used as the ‘gold standard’ in treatment trials in motor neuron disease (MND). However, hand-held dynamometry (HH-Dyn) has the advantage of being less expensive and quickly applicable. In our study, involving 19 patients with PMA, intra- and interrater variation was found to be low in all six bilaterally measured muscle groups (intraclass correlation coefficients varying between 0.86 and 0.99). Correlation between
both methods was found to be good as well in all muscle groups (Pearson’s correlation coefficients ranging between 0.78 and 0.98). A trend to under-estimate muscle strength above 250 N by HH-Dyn as compared with MVIC was observed. We conclude that for longitudinal evaluation of muscle strength in patients with PMA (i.e., between 0 and 250 Newton) both HH-Dyn and MVIC can be used. However, our results indicate that HH-Dyn is less sensitive than MVIC in detecting subnormal muscle strength in strong muscle groups (i.e., >250 Newton) due to limited strength of the tester.

In chapter 5 a prospective study is reported, in which we investigated the natural history and prognostic factors in 37 patients with newly diagnosed PMA, i.e. onset of weakness less than four years. Follow-up was 18 months and a survival analysis was performed five years after the end of study. Disease progression was measured at 0, 3, 6, 9, 12, 15 and 18 months with MRC sum score, number of affected limb regions and ALS Functional Rating Scale (ALSFRS). Multivariate linear regression analysis was used to identify predictors of poor outcome. Significant decline of muscle strength (6.01 MRC sum score points, p<0.001) and significant increase in the number of affected regions (0.53 affected region, p<0.001) and in functional impairment (1.85 ALSFRS score points, p<0.001) was found. Vital capacity (VC) at baseline and decrease of VC during the first 6 months were significantly associated with outcome. Median survival duration after initial weakness was 56 months. We concluded that most patients with PMA have a relentlessly progressive disease course. Especially patients with a low VC at baseline and a sharp decline of VC during the first 6 months have poor prognosis.

In the same group, we investigated the electrophysiological data at baseline, which is reported in chapter 6. The aim was to correlate electrophysiological signs of lower motor neuron (LMN) loss with clinical signs of LMN loss, and to determine the prognostic value of the distribution of electrophysiological abnormalities in patients with sporadic PMA. All patients underwent extensive standardized electrophysiological examination at baseline, consisting of concentric needle electromyography (EMG) in three regions (cervical, thoracic and lumbosacral) and extensive nerve conduction studies (NCS). Denervation on needle EMG was found in 88% of clinically affected and in 40% of clinically unaffected limb regions. All patients with a segmental or distal phenotype at baseline who developed generalized weakness had denervation in the thoracic region. We found a substantial number of motor nerve conduction abnormalities (reduced CMAP amplitudes, decreased motor conduction velocity, increased distal motor latency, and F-wave abnormalities). Signs of demyelination and sensory nerve conduction abnormalities were rare. We conclude that our electrophysiological data in sporadic PMA patients are consistent with widespread LMN loss. Progression in patients with a segmental or distal onset of PMA is very likely if denervation is found in clinically unaffected regions, including the thoracic region.

In chapter 7 we studied the clinical and electrophysiological features of 49 patients with sporadic adult-onset LMND in a cross-sectional study. Disease duration was more than 4 years to exclude the majority of patients with amyotrophic lateral sclerosis. Based on the pattern
of weakness, we identified three groups: 13 patients with generalized weakness (group 1, slowly progressive spinal muscular atrophy), 8 patients with symmetrical, distal weakness (group 2, distal spinal muscular atrophy), and 28 patients with non-generalized asymmetrical weakness of the arms in most patients (group 3). Group 3 could be subdivided into patients with weakness in predominantly the distal muscle groups (segmental distal spinal muscular atrophy) or the proximal muscle groups (segmental proximal spinal muscular atrophy), both with disease progression to adjacent spinal cord segments. Distinctive features of group 1 were an older age at onset, more severe weakness and muscle atrophy, lower reflexes, greater functional impairment, more widespread abnormalities on concentric needle EMG, respiratory insufficiency and serum M-protein. In groups 2 and 3, concentric needle EMG findings also suggested a more widespread disease process. Retrospectively, the prognosis of sporadic adult-onset LMND appears to be favourable, because clinical abnormalities were still confined to one limb in most patients after median disease duration of 12 years. The described clinical phenotypes may help to distinguish between different LMND forms.

In chapter 8 the long-term follow-up of 35 patients of the group mentioned in chapter 7 is described. The aim was to determine whether specific LMND phenotypes might help to predict future disease progression and functional loss. All 35 patients were classified according to the criteria defined in chapter 7: slowly progressive spinal muscular atrophy (sPSMA; 10 patients), distal spinal muscular atrophy (3 patients), segmental distal spinal muscular atrophy (8 patients) and segmental proximal spinal muscular atrophy (14 patients).

Muscle strength, functional impairment and respiratory function were assessed at 0, 6, 12, 18 and around 72 months after inclusion. The diagnosis had to be changed to ALS in 3 patients (classified at inclusion as sPSMA in 2 patients and as segmental proximal spinal muscular atrophy in 1 patient) due to the development of upper motor neuron signs in 2 patients and familial ALS in 1 patient, but of the 32 other patients the phenotype classification remained the same during long-term follow-up. Progression of disease and loss of function was most pronounced in patients whose diagnosis was changed into ALS and in patients with sPSMA. Respiratory insufficiency developed in six of these 11 patients, 5 of whom died. No significant change in muscle strength, functional impairment or vital capacity was found in patients with distal-, segmental distal-, and segmental proximal spinal muscular atrophy, but a segmental spreading of weakness was found in both segmental distal and proximal spinal muscular atrophy. We conclude that classifying patients suffering from sporadic adult-onset LMND with disease duration of at least four years according to different phenotypes is useful with a view to predicting disease course and prognosis. Patients with the sPSMA phenotype had a significantly progressive disease course and shortened life expectancy, while patients with the distal and segmental spinal muscular atrophy phenotypes show only very mild progression with normal life expectancy.

In chapter 9 the findings from the previous chapters and its implications for clinical practice are discussed. Furthermore, suggestions for future research are given.