Disease Course and Prognostic Factors of Progressive Muscular Atrophy

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Objective: To investigate the natural history and prognostic factors in patients with nonhereditary, adult-onset progressive muscular atrophy.

Design: Inception cohort conducted for 18 months.

Settings: Three university hospitals in the Netherlands (referral centers for neuromuscular diseases).

Patients: Thirty-seven consecutive patients newly diagnosed (onset of weakness <4 years) with progressive muscular atrophy enrolled between 1998 and 2001.

Main Outcome Measures: Disease progression was measured at 0, 3, 6, 9, 12, 15, and 18 months by the Medical Research Council sum score, number of affected limb regions, and the Amyotrophic Lateral Sclerosis Functional Rating Scale score. Multivariate linear regression analysis was used to identify predictors of poor outcome. Clinical features and classification of phenotype during follow-up were evaluated. Survival analysis was planned after data collection, performed 5 years after the end of the study.

Results: Significant decline of muscle strength (mean, 6.01 Medical Research Council sum score points [95% confidence interval [CI], 3.84-8.18]; P value <.001) and significant increase in the number of affected regions (mean, 0.53 affected region [95% CI, 0.42-0.65]; P value <.001) and functional impairment (mean, 1.85 Amyotrophic Lateral Sclerosis Functional Rating Scale score points [95% CI, 1.38-2.33]; P value <.001) were 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.

Conclusions: This study shows that patients with progressive muscular atrophy have a relentlessly progressive disease course. Patients with a low VC at baseline and a sharp decline of VC during the first 6 months have an especially poor prognosis.

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PROGRESSIVE SPINAL MUSCULAR atrophy is an adult-onset, non-hereditary progressive disease of the lower motor neurons (LMNs). In 1850, Aran1 first reported this disease, which he called progressive muscular atrophy (PMA). In 1952, Müller2 introduced the term progressive spinal muscular atrophy, since then synonymously used with PMA. In this article, we use the term progressive muscular atrophy (PMA) to differentiate it from the familial form of spinal muscular atrophy (SMA).

The patients reported by Aran1 and Müller2 had muscle wasting and weakness with slow progression over years to decades.1 A proportion of these patients developed amyotrophic lateral sclerosis (ALS) in due course, manifesting with rapidly progressive muscle weakness and appearance of upper motor neuron (UMN) signs.4 In autopsy series, corticospinal tract involvement was demonstrated in 50% of patients with nonhereditary PMA.5 Therefore, PMA is regarded as a heterogeneous syndrome showing considerable overlap with ALS.

Studies of ALS show that age at onset beyond 55 years, bulbar onset, respiratory vital capacity (VC) lower than 60% of the predicted value, and rapid decline in pulmonary function are unfavorable predictors of prognosis and survival.7,10 Reports on the natural course of nonhereditary PMA are sparse. Interpretation of these studies is hampered because of the retrospective design of these studies, heterogeneous patient groups, and lack of standardized neurological assessment.2,11,12

Herein, we present the results of our study of 18 months of disease course and its prognostic factors in patients with PMA with a short disease duration. In addition, we have calculated the survival rate 5 years after the last patient’s end of follow-up.

METHODS

PATIENTS

Between 1998 and 2001, consecutive patients newly diagnosed with PMA in 3 university hospitals in the Netherlands were asked to partici-
pate in the study. All patients underwent a standardized neurological, laboratory, and electrophysiological examination.

Inclusion criteria were age at onset older than 18 years, disease duration of less than 4 years from the time of onset of weakness, and clinical and electrophysiological evidence of progressive LMN involvement (weakness, atrophy, and fasciculation) in 1 or more of 4 regions (bulbar, cervical, thoracic, and lumbosacral) according to the 1998 revised El Escorial criteria. The span of 4 years was short enough for relatively early inclusion but also long enough for inclusion of a sufficient number of patients. Exclusion criteria included motor conduction block(s) on extensive standardized nerve conduction studies according to previously defined criteria, definite clinical UMN signs (pseudobulbar symptoms, including forced laughter, yawning, and crying; clonus of masseter reflex; (sub)clonic myotatic reflexes; extensor plantar response; and spasticity), objective sensory signs (apart from mild vibration sense disturbances in elderly patients), history of diseases that may mimic motor neuron disease (ie, spinal radiculopathy, poliomyelitis, and diabetic amyotrophy), family history of inherited SMA, and deletion in the SMN1 gene or an expansion of CAG repeats (>40) in the androgen receptor gene.

Laboratory tests included erythrocyte sedimentation rate and levels of hemoglobin, hematocrit, thyrotropin, serum protein electrophoresis and serum immunoelectrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone), and serum IgM anti-GM1 antibodies. Neuroimaging studies ruled out structural lesions (tumors, intervertebral disk herniation, vascular lesions, and syringomyelia) of the spinal cord or craniocervical junction.

The electrophysiological investigation took place after warm- ing the limbs, as described elsewhere. Extensive standardized nerve conduction studies and concentric needle electromyography were conducted by the same investigator (H.F.) in all patients, according to a standardized protocol.

The study was approved by the local medical ethics committees and written informed consent was obtained from all participants.

### ASSESSMENTS

Follow-up was 18 months since we expected that patients with PMA, with a rate of progression comparable with that observed in ALS, would clearly deteriorate during that period. Patients had assessments every 3 months, including a standardized history and assessment of muscle strength, muscle atrophy, reflexes, VC, and functional impairment. Each patient was investigated by the same assessor (J.V. or R.M.VdB-V.). Prior to the study, examiners practiced performing and interpreting reflexes in a standardized manner to minimize interobserver bias.

Muscle strength was scored with the modified 9-grade scale of the Medical Research Council (MRC). Table 1 shows the measured muscle groups. The MRC sum score, which is the sum of the MRC scores of 42 measured muscle groups, was calculated at each visit (MRC 5 = 5.00; MRC 5− = 4.67; MRC 4+ = 4.33; MRC 4 = 4.00; MRC 4− = 3.67; MRC 3 = 3.00; MRC 2 = 2.00; MRC 1 = 1.00; MRC 0 = 0.00; maximum score, 210). We pooled the separate muscles in 8 limb regions (Table 1). We considered a limb region affected when 1 or more muscle groups per region had an MRC score of MRC 4+ or less. We recorded the number of affected limb regions at each visit.

Muscle atrophy was determined in muscle groups and limb regions. Biceps, triceps, and knee and ankle reflexes were scored according to the National Institute of Neurological Disorders and Stroke myotatic reflex scale.

Slow respiratory VC was measured and expressed as a percentage of the predicted value. Functional impairment was evaluated with the ALS Functional Rating Scale (ALSFRS), which is a 10-item scale that rates the function on activities of daily living (best score is 40, worst score is 0).

To document the progression of PMA, we used the MRC sum score, the number of affected limb regions, and the ALSFRS score at each visit as outcome measures. We documented the development of clinical UMN signs during follow-up. We looked for pseudobulbar symptoms (forced laughter, yawning, and crying), clonus of masseter reflex, (sub)clonic myotatic reflexes, extensor plantar response, hyperreflexia in a weak, wasted muscle, and positive Hoffmann sign. Retained reflex in a weak, wasted muscle is defined as hyperreflexia (score 3 on the National Institute of Neurological Disorders and Stroke myotatic reflex scale) in combination with frank atrophy and weakness rated as an MRC score of MRC 4 or less. We documented the development of bulbar signs during follow-up (ie, tongue atrophy with or without fasciculations and diminished tongue strength, dysarthria, or dysphagia).

### PROGNOSTIC FACTORS

Based on the results from previous studies in ALS, we chose the following 4 potential prognostic factors: age at onset, VC at baseline, difference in VC between baseline and 6 months, and site of onset (arm or leg), the latter because of the supposed earlier involvement of respiratory muscles in patients with arm weakness onset compared with patients with leg onset.

### CLASSIFICATION OF CLINICAL PHENOTYPES

Patients were classified at baseline and reclassified at the end of follow-up into the following clinical phenotypes: patients with generalized SMA in whom more than 50% of the limb regions were affected and patients with nongeneralized weakness (≤50% affected limb regions), consisting of individuals with distal symmetrical weakness in the legs and/or arms (dystal SMA) and individuals with mainly asymmetrical weakness in the arms or legs (segmental SMA).

### SURVIVAL

We hypothesized that most of our patients with PMA would have a fast disease progression like in ALS, and therefore, we decided to perform a survival analysis 5 years after the last patient’s end of follow-up. We contacted the patient’s general physician to obtain information on the date and cause of death.

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### Table 1. Categorization of Muscle Groups per Limb Region

<table>
<thead>
<tr>
<th>Region</th>
<th>Muscle Groups</th>
<th>Myotomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper cervical region</td>
<td>Shoulder abduction, elbow flexion, elbow extension</td>
<td>C5-C7</td>
</tr>
<tr>
<td>Lower cervical region</td>
<td>Wrist flexion, wrist extension, extension of fingers, flexion of fingers, spreading of fingers, abduction of thumb, adduction of thumb, and opposition of thumb</td>
<td>C8-Th1</td>
</tr>
<tr>
<td>Upper lumbosacral region</td>
<td>Hip flexion, hip adduction, knee extension, hip extension, hip abduction</td>
<td>L1-L3</td>
</tr>
<tr>
<td>Lower lumbosacral region</td>
<td>Knee flexion, plantar flexion of foot, flexion of toes, dorsiflexion of foot, extension of toes</td>
<td>L4-S1</td>
</tr>
</tbody>
</table>
Patient characteristics were analyzed using descriptive statistics. To examine the disease progression of PMA, as expressed by the MRC sum score, the number of affected regions, and the ALSFRS score, a linear mixed-effects model (repeated measurements) was used. The impact of the potential prognostic factors on each outcome measure of disease progression was additionally analyzed using multivariate linear regression. Statistics were expressed in standardized regression coefficients and total variance, explained ($R^2$). In case no complete patient data set could be obtained, we analyzed the data by the last observation carried forward approach. Patient survivals were presented by Kaplan-Meier curves (censoring date, June 19, 2006). In conformity with ALS studies, we chose the date of initial weakness as the start of the survival time observed.

**RESULTS**

After screening approximately 600 potential eligible patients, 37 patients met our inclusion criteria. Their characteristics and clinical phenotypes are presented in Table 2. No patients had a bulbar onset. In 9 patients, follow-up was not completed to the end of the study because of physical inability to visit our clinic. In 4 of them, follow-up to the end of the study was done by telephone. Therefore, a complete data set was obtained for 28 patients, and 32 patients had a complete ALSFRS score. For all patients, survival data were available.

**PROGRESSION OF DISEASE OVER TIME**

Figure 1 shows the progression of disease as expressed by the 3 outcome scores. On average, muscle strength decreased...
During follow-up, UMN signs appeared in 13 patients (95% confidence interval [CI], 3.84-8.18) (P value <.001), and the number of affected regions increased by mean 0.53 per 3 months (95% CI, 0.42-0.65) (P value <.001). Patient functioning decreased by mean 1.85 ALSFRS score points per 3 months (95% CI, 1.38-2.33) (P value <.001). After a follow-up of 18 months, 8 patients (22%) had died. All died of respiratory muscle weakness (with or without pneumonia).

PROGNOSTIC FACTORS

Univariate analysis showed that all the prognostic factors were significantly associated with each of the outcome measures (data not shown). Multivariate analysis (Table 3) showed that VC at baseline was a significant prognostic factor of PMA progression as measured by the ALSFRS score. Decrease of VC during the first 6 months of the study was a significant prognostic factor as measured by the ALSFRS score and the number of affected regions. Age at onset was a prognostic factor as measured by the MRC sum score, implying that PMA progression was faster in younger patients.

CLINICAL FEATURES AND EVALUATION OF CLINICAL PHENOTYPES

UMN Signs

During follow-up, UMN signs appeared in 13 patients (Table 4). Two of 13 patients had pseudobulbar signs (forced laughter, crying, or yawning), with no additional UMN signs on examination. Both had generalized SMA at inclusion. Four of 13 patients developed extensor plantar response. Three of them were initially classified as having generalized SMA and also demonstrated other UMN signs (clonic reflex, hyperreflexia in a weak and wasted muscle, Hoffmann sign) in 1 or more limbs. One patient, initially classified as having distal SMA, developed no other UMN signs. He progressed to generalized SMA during follow-up. Seven of 13 patients developed hyperreflexia in a weak and wasted muscle in 1 or more limbs during follow-up. Three of these 7 also developed a Hoffmann sign. Six of 7 had generalized SMA at inclusion. The patient with initial segmental SMA progressed to generalized SMA during follow-up.

Bulbar Signs

None of our patients had a bulbar onset. At inclusion, 10 of 37 patients were found to have bulbar signs. Another 6 patients developed bulbar signs during follow-up. Of the 16 patients who eventually developed bulbar signs, 13 had early respiratory symptoms, 8 developed UMN involvement, and 15 died less than 5 years after onset of weakness (Table 4). In contrast, of the 21 patients without bulbar symptoms, only 4 developed respiratory symptoms, 7 developed UMN involvement, and 5 died less than 5 years after onset of weakness.

Classification of Clinical Phenotypes

The classification of the phenotypes at baseline and at 18 months of all patients is presented in Table 4.

Table 3. Effects of Prognostic Variables on Outcome Measures of PMA Progression

<table>
<thead>
<tr>
<th>Outcome Measures of PSMA Progression β Coefficients*</th>
<th>ALSFRS Score</th>
<th>MRC Sum Score</th>
<th>No. of Affected Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC at baseline</td>
<td>0.320</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Decrease in VC 0-6 mo</td>
<td>0.511</td>
<td>...</td>
<td>−0.400</td>
</tr>
<tr>
<td>Age at onset</td>
<td>...</td>
<td>0.431</td>
<td>−0.400</td>
</tr>
<tr>
<td>Total R²†</td>
<td>42</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

*β Coefficients are standardized regression coefficients.
†R² is the percentage of the total variation of the dependent variable score that is explained by the independent variables together.

SURVIVAL

Five years after the end of the study, median 7 years after inclusion (range, 7-95 months), 11 patients were alive (Table 4). Figure 2 shows the Kaplan-Meier survival curve for the 37 patients with PMA. Calculated from the time of initial weakness, the 1-, 3-, 5-, and 9-year survival rates were 100%, 67%, 45%, and 30%, respectively, with a median survival duration of 56 months. All the patients with bulbar signs at inclusion died, with a median survival from the date of inclusion of 17.5 months (range, 4.6-35.4 months). Calculated from the time of initial weakness, median survival in all these patients was 38.1 months (range, 12.7-55.4 months).

Four of our patients received noninvasive respiratory aids as a life-prolonging measure: 1 patient used nocturnal bilevel positive airway pressure and 3 patients used intermittent positive-pressure ventilation. One patient used tracheostomy, intermittent positive-pressure ventilation until death.

Our prospective study on 37 patients with well-defined PMA who were followed up from early on in the disease course demonstrated that the prognosis in PMA is almost as poor as in ALS.24-27 Nearly all our patients demonstrated relentless disease progression, leading to death in 8 patients and to rapid spread of weakness in 24 other patients within 18 months. Five years after the end of the study, 26 patients (70%) had died. However, the mortality probabilities presented may be an underestimate because of the possible selection bias of patients with PMA who had died before potential inclusion into our study.

Five of our patients with either distal symmetrical or asymmetrical unilateral muscle weakness had a (nearly) static disease course, which supports the hypothesis that patients with various diseases may fulfill our inclusion criteria for PMA, especially early on in the disease course. The distribution of weakness in 3 of the 4 patients with a phenotype of symmetrical distal weakness in the extremities remained unchanged during follow-up. There-
before, we classified them as having (hereditary or sporadic) distal SMA. Two patients with PMA with a phenotype of segmental asymmetrical weakness restricted to the hand and forearm showed no progression during follow-up. This relatively good prognosis is in agreement with previous studies reporting on this phenotype. On the other hand, 6 of 8 patients with this segmental phenotype evolved into the phenotype of generalized PMA or ALS within 18 months. Two of them had predominant proximal arm weakness at inclusion. This is in contrast to previous studies reporting a benign prognosis of patients with proximal segmental SMA, also known as the flail arm syndrome. Although unique cases with a more benign prognosis exist, data in these studies were collected retrospectively, which may have led to selection bias. Although none of our patients had a bulbar onset, we noted that 15 of the 16 patients who eventually showed bulbar features developed either ALS or had an ALS-like disease course.

Our study showed a significant decline of muscle strength and a significant increase in the number of affected limb regions and functional impairment as measured by the ALSFRS score. Predictors for an unfavorable outcome were VC at baseline lower than 90% of the predicted value, decline in VC in the first 6 months, and a younger age at onset. This latter association is remarkable since numerous studies in ALS demonstrated the opposite; older patients tended to show faster disease progression. Subsequently, a repeat analysis after removal of 3 outliers who were all young and demonstrated rapid progression showed no significant effect of age at onset. Therefore, the finding that a younger age at onset was associated with a worse prognosis may simply reflect the relatively small sample size, which allowed for 3 young patients with rapid disease progression to skew the overall results.

As in ALS, the results of our study support the hypothesis that there is a strong relation between respira-

<table>
<thead>
<tr>
<th>Patient No./ Sex/Age, y</th>
<th>Disease Duration, mo</th>
<th>Phenotype at Onset*</th>
<th>Phenotype at 18 mo*</th>
<th>Early Respiratory Symptoms</th>
<th>Bulbar Symptoms</th>
<th>UMN Signs</th>
<th>Deceased?</th>
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<td>1/M/52</td>
<td>39</td>
<td>Segmental</td>
<td>Segmental</td>
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<td>No</td>
<td>No</td>
<td>No</td>
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<td>No</td>
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<td>Yes</td>
<td>Yes</td>
<td>Yes, 34 mo</td>
</tr>
</tbody>
</table>

Abbreviation: UMN, upper motor neuron.

*“Generalized” indicates more than 50% of the limb regions affected; “distal,” distal symmetrical weakness in legs and/or arms; and “segmental,” asymmetrical weakness in arms or legs.
tory function parameters and outcome in PMA. In our study, the most powerful predictor of rapid progression was decline in VC in the first 6 months. The effect of this predictor on the ALSFRS score may be explained by the item “breathing” of the ALSFRS score. However, decline in VC was also an independent predictor of outcome when measured by the number of affected regions. In addition, we found an independent unfavorable effect of low VC at baseline on outcome in our patients. The relatively small sample size of our study does not allow for more precise predictions of prognosis in individual cases. Thus, evaluation of respiratory function is needed soon after a patient is diagnosed with PMA. If initial VC is lower than predicted, this patient should be followed up with extra caution. If pulmonary function further declines during the following 6 months or the patient develops bulbar signs and/or generalization of weakness, a poor prognosis is very likely.

Vital capacity at baseline or change in VC did not show a significant effect on the MRC sum score. For the 9 patients with incomplete data sets, last observations were carried forward. Therefore, their MRC sum scores possibly underestimate disease severity at the end of follow-up, in contrast to the ALSFRS score, for which we obtained a complete data set in 4 of these 9 patients.

Although none of our patients had a bulbar onset, 10 patients (27%) demonstrated bulbar symptoms at inclusion. The notion in earlier reports that bulbar motor neuron involvement may not be feasible in a patient with ALS but without developing UMN signs (or detection of UMN involvement may not be feasible in a patient with predominantly LMN features). Moreover, the 3-year mortality rate of 33% in our patients with PMA closely resembles the reported rate of 50% in ALS. These findings suggest that PMA and ALS are variants of a clinical spectrum, which varies from purely LMN or UMN involvement to the classic condition ALS with a combination of UMN and LMN signs.

According to the 1994 El Escorial criteria, patients with PMA were included in the category “suspected ALS.” However, in the 1998 revised El Escorial criteria, this subgroup was omitted because a pure LMN syndrome was not regarded sufficiently certain for the diagnosis of ALS. As a consequence, patients with PMA are not included in ALS research studies. However, our data showed that most patients with PMA have a relentlessly progressive disease course as in ALS. This poor prognosis is determined by VC at baseline lower than 90% of predicted value or with declining VC during the first 6 months. Therefore, we recommend that patients with early PMA who meet at least 1 of these 2 criteria may also benefit from possible new treatment forms developed for ALS.

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