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

Citation for published version (APA):
Chapter 6

Interpretation of electrodiagnostic findings in sporadic progressive muscular atrophy

J Visser, M de Visser, RM van den Berg-Vos, LH van den Berg, JH Wokke, JM de Jong, and H Franssen

*Journal of Neurology; in press*
Summary

Objective
We present the electrophysiologic data at baseline of 37 patients that were included in our prospective study on sporadic adult-onset progressive muscular atrophy (PMA). 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 that presented clinically with only lower motor neuron signs.

Methods
Thirty-seven patients that met our inclusion criteria for a prospective study on sporadic adult-onset PMA, underwent extensive standardized electrophysiological examination at baseline, consisting of concentric needle EMG in three regions (cervical, thoracic and lumbosacral) and standardized nerve conduction studies.

Results
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. Motor nerve conduction abnormalities were found in a substantial number of nerves and included reduced CMAP amplitude, increased distal motor latency, decreased motor conduction velocity, and F-wave abnormalities. Signs of demyelination and sensory nerve conduction abnormalities were rare.

Conclusions
Our electrophysiological data in patients recently diagnosed with sporadic progressive muscular atrophy are consistent with widespread LMN loss. Progression in patients with a segmental or distal onset of PMA may be likely if denervation is found in clinically unaffected regions, including the thoracic region.
Introduction

There is accumulating evidence that sporadic progressive muscular atrophy (PMA) belongs to the spectrum of amyotrophic lateral sclerosis (ALS). First, a proportion of patients with sporadic PMA develops signs of upper motor neuron (UMN) degeneration in due course, either detected clinically or found on autopsy studies. Second, when prospectively studied, most sporadic PMA patients have an “ALS-like” disease course with relentless disease progression and early death. Third, some patients with a pure lower motor neuron syndrome were found to have a Cu/Zn superoxide dismutase-1 (SOD1) mutation, as is also the case in 25% of familial ALS patients. However, in a minority of patients weakness remains focal and prognosis is consequently much better. Therefore it is of utmost importance to differentiate patients with a relatively benign disease course from patients with a disease course similar to that of ALS within this group of patients that present clinically with only lower motor neuron (LMN) signs. The term lower motor neuron disease (LMND) refers to this heterogeneous group of diseases of the lower motor neurons.

Electrophysiological studies are essential in the diagnosis of ALS. Needle EMG is used to identify lower motor neuron (LMN) loss at the subclinical level required for the application of the 1998 revised El Escorial criteria for diagnosis, and to rule out other neuromuscular diseases mimicking ALS, e.g., inclusion body myositis. Nerve conduction studies are required to exclude treatable disorders of peripheral nerve, especially multifocal motor neuropathy. Although nerve conduction studies are generally normal in ALS, mild to modest abnormalities in these studies have been described.

To date, no robust electrophysiologic data are available on sporadic PMA with a course resembling ALS. We present the results of our well-defined group of patients that were included in our prospective study on sporadic adult-onset PMA to address the following questions: (1) are electrophysiological signs of LMN loss detectable in regions with clinical signs of LMN loss; (2) are electrophysiological features of LMN loss demonstrable in regions without clinical signs of LMN loss; (3) can the distribution of electrophysiological abnormalities be indicative of prognosis and (4) are there motor and sensory nerve conduction abnormalities in sporadic PMA patients and if so, how do they relate to the reported electrophysiologic abnormalities in ALS?

Patients and methods

Patients

Thirty-seven consecutive patients that met our inclusion criteria for a prospective study on sporadic adult-onset PMA and in whom other causes for lower motor neuron loss such as multifocal motor neuropathy (MMN) had been excluded, were followed-up for 18 months between 1998 and 2001. Both patients with generalized and more localized involvement of muscle weakness were included (for description of this classification see below under the
subheading “clinical evaluation”). These patients would have been classified as suspected ALS according to the 1994 El Escorial criteria but not as having ALS according to the 1998 revised El Escorial criteria.

Before inclusion, all patients underwent standardized neurological, laboratory, and electrophysiological examinations. They all had clinical evidence of progressive LMN involvement (weakness, atrophy, fasciculation) in one or more of the four regions (bulbar, cervical, thoracic, lumbosacral) according to the 1998 revised El Escorial criteria. Duration since onset of weakness was less than four years in all patients. Survival was assessed by information taken from the patients’ general practitioners, five years after completion of the 18 months follow-up study.

We excluded patients with motor conduction block on extensive standardized nerve conduction studies (NCS) according to previously defined criteria, clinical signs of upper motor neuron (UMN) involvement (pseudobulbar symptoms, including forced laughter, yawning and crying, clonus of masseter reflex, (sub)clonic myotatic reflexes, extensor plantar response, spasticity), objective clinical sensory signs, patients with a family history of inherited (bulbo)spinal muscular atrophy (SMA), a history of diseases that may mimic a LMN syndrome (i.e. spinal radiculopathy, poliomyelitis, diabetic amyotrophy), structural lesions (tumours, intervertebral disc herniation, vascular lesions, syringomyelia) on magnetic resonance imaging (MRI) or CT-tomography with myelography of the spinal cord or craniocervical junction, and deletion in the SMN1 gene or an expansion of CAG-repeats (>40) in the androgen receptor gene.

The following laboratory tests were performed to rule out other diseases: sedimentation rate, haemoglobin, hematocrit, thyroid stimulating hormone, serum protein electrophoresis and serum immunoelectrophoresis with immunofixation, phosphate, calcium (and, if elevated, parathyroid hormone). In addition, serum IgM anti-GM1 antibodies were measured.

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

Clinical evaluation

To compare the distribution of electrophysiologic abnormalities with weakness on clinical examination we defined two limb regions: cervical and lumbosacral; for each, left and right were pooled. We considered a region as clinically affected when one or more muscle groups of a region had a Medical Research Council (MRC)-score less than or equal to MRC 4+. This was not possible for the thoracic region (mm.erector spinae) as a test to assess muscle strength in this region in a reliable manner is lacking.

Our patients were classified at baseline and at the end of follow-up according to the pattern of weakness as described previously, resulting in the following clinical phenotypes (table 1): progressive muscular atrophy (generalized weakness with >50% of limb regions affected), distal spinal muscular atrophy (non-generalized weakness: distal, symmetrical...
Electrodiagnostic findings in PMA

weakness, greater in the legs than in the arms) and segmental spinal muscular atrophy (non-generalized weakness: segmental, asymmetrical weakness of the arms).

Electrophysiologic studies
The electrophysiological investigation took place after warming the limbs in water at 37 °C for at least 30 minutes. Concentric needle EMG was performed by an experienced electromyographer (HF). For the investigation of the paraspinal thoracic muscles the patient was positioned prone, with a soft cushion under the abdomen and was asked to let the head, shoulders and arms towards the floor. If this was not possible, the patient was positioned on one side with the spine bent. Investigated were the m. biceps brachii, m. flexor carpi radialis, m. interosseus dorsalis I on both sides (cervical region), the m. rectus femoris, m. tibialis anterior, and the lateral head of the m. gastrocnemius on both sides (lumbosacral region), and in the mm. erector spinae at Th6 and Th10 levels on one side (thoracic region). For each muscle, the transversal plane was sampled by insertions made in three directions; for each direction, activity was sampled in at least five sites.

Denervation was defined as the occurrence of spontaneous muscle fiber activity (fibrillations, positive sharp waves, or complex repetitive discharges) in at least one insertion site. Reinnervation was defined as the occurrence of an abnormally long mean motor unit potential (MUP) duration, or an abnormally large proportion of MUPs that were polyphasic (more than four baseline crossings), or an abnormally large proportion of giant MUPs (amplitude exceeding 7 mV). MUPs were assessed according to a semi-quantitative method developed in our laboratory using normative values of Buchthal and Rosenfalck which were adapted depending on the number of MUPs that could be sampled. Per muscle we attempted to sample 10 - 20 MUPs during slight voluntary contraction. Only MUPs with high frequency content were taken into account. The mean MUP duration and the proportion of polyphasic or giant MUPs were estimated on visual inspection. If not enough MUPs could be sampled during slight voluntary contraction, we attempted to evoke additional MUPs by voluntary contraction at higher force levels including maximal voluntary contraction if necessary; in this instance half of the MUPs had to be polyphasic or of giant amplitude and these MUPs had to occur in a single or poorly mixed pattern to fulfill the criterion for reinnervation.

From the NCS studies which were previously performed to exclude MMN, we reviewed the following motor conduction variables from the median, ulnar, peroneal, and tibial nerves: amplitude and duration of the negative part of the compound muscle action potential (CMAP) on distal stimulation, distal motor latency (DML), motor conduction velocity (MCV) in lower arm or lower leg segments, and shortest F-M latency. If the CMAP was <0.5 mV, F-waves were not investigated. Sensory conduction variables included the negative peak amplitude of the sensory action potential (SNAP) and sensory conduction velocity (SCV) of the median and sural nerves on distal stimulation.
Chapter 6

NCS values were considered abnormal if they were below the lower limit of normal (LLN) or above the upper limit of normal (ULN) of our laboratory (appendix 1). We also evaluated DML, MCV, and F-M latency according to recently published criteria for demyelination, which include separate criteria for nerves with a distal CMAP amplitude below 1 mV.31

<table>
<thead>
<tr>
<th>Appendix 1. Limits of normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nerve</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>median</td>
</tr>
<tr>
<td>m.abductor poll brevis</td>
</tr>
<tr>
<td>ulnar</td>
</tr>
<tr>
<td>m.abductor dig minimi</td>
</tr>
<tr>
<td>peroneal</td>
</tr>
<tr>
<td>m.extensor dig brevis</td>
</tr>
<tr>
<td>tibial</td>
</tr>
<tr>
<td>m.abductor hallucis</td>
</tr>
</tbody>
</table>

Results

Patients

Of the 37 patients that were included in our prospective study on adult-onset sporadic PMA, 35 underwent standardized needle EMG and 36 standardized nerve conduction studies (NCS). Only the data of the patients who completed the standardized electrophysiologic studies were analyzed.

Table 1 shows the clinical characteristics of the patients at baseline and at the last visit. At baseline, twenty-four patients (68%) can be described as having a PMA phenotype. The other twelve patients had localized involvement of muscle weakness at baseline. At the last visit, thirty-one patients (86%) showed clinical progression of whom 19 developed UMN signs and were subsequently classified as having ALS; eight of these thirty-one patients died within the follow-up time of 18 months. Five years after the 18 months follow-up study (median seven years after inclusion) 26 (70%) patients had died. Three of the four patients with a distal spinal muscular atrophy phenotype remained clinically unchanged during follow-up. In one patient with distal spinal muscular atrophy phenotype at onset who showed generalization of weakness and developed UMN signs during follow-up, diagnosis was changed into ALS. Six out of eight patients who had segmental spinal muscular atrophy phenotype evolved into PMA (5 patients) or ALS (1 patient) within 18 months.

Needle EMG

Features of needle EMG are given in table 2. Denervation was found in 94% and reinnervation in 92% of the patients. Denervation was found in 53 out of 60 (88%) of clinically affected limb regions. Denervation was found in 4 out of 10 (40%) of clinically unaffected
Table 1. Clinical characteristics and phenotypes of 36 patients at baseline and after follow-up

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Baseline</th>
<th>Last Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men / women</td>
<td>24/12</td>
<td></td>
</tr>
<tr>
<td>Disease duration, months (median, range)</td>
<td>19 (5-48)</td>
<td></td>
</tr>
<tr>
<td>Age at onset of weakness, years (median, range)</td>
<td>57 (25-72)</td>
<td></td>
</tr>
<tr>
<td>Localization of muscle weakness at onset</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>respiratory muscles</td>
<td>20/15</td>
<td></td>
</tr>
<tr>
<td>arms / legs</td>
<td>26/9</td>
<td></td>
</tr>
<tr>
<td>distal / proximal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical phenotype</td>
<td></td>
<td>last visit</td>
</tr>
<tr>
<td>generalized</td>
<td>24 (68%)</td>
<td>31 (86%)</td>
</tr>
<tr>
<td>segmental</td>
<td>8 (21%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>distal</td>
<td>5 (11%)</td>
<td>3 (8%)</td>
</tr>
</tbody>
</table>

1 >50% affected limb regions
2 ≤50% affected limb regions, mainly asymmetrical weakness
3 ≤50% affected limb regions, distal symmetrical weakness

The distribution of weakness was ‘symmetrical’ if the difference in weakness on the left versus the right side was <1 on the MRC score in >50% of the affected muscle groups.

Table 2. Needle EMG abnormalities in limb and thoracic regions

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Clinically affected</th>
<th>Clinically non affected</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cervical</td>
<td>Lumbosacral</td>
</tr>
<tr>
<td>Denervation with or without reinnervation</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>Reinnervation only</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>No denervation or reinnervation</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Clinically affected = MRC score 4+ or less in at least one muscle group of a region.

limb regions. Neither denervation nor reinnervation was present in 2 out of 60 (3%) of clinically affected limb regions. Fasciculations were found in 10 patients (one region 3, two regions 4, and three regions 3).

Of the 12 patients with a distal or segmental phenotype at baseline, four patients had denervation in clinically unaffected limb regions; they all developed generalized weakness so that the diagnosis was changed into PMA (3 patients) or ALS (1 patient). Generalization of weakness was also found in three out of eight patients without denervation in clinically unaffected limb regions. All patients with a segmental or distal phenotype at the end of follow-up had no denervation in clinically unaffected limb regions at baseline. In four of them (distal phenotype 2, segmental phenotype 2), reinnervation only was found in clinically unaffected limb regions.

All patients with a segmental or distal phenotype at baseline who developed generalized weakness during follow-up were found to have denervation in the thoracic region at baseline. None of the patients whose weakness remained segmental or distal during follow-up had denervation in the thoracic region, except for one patient. Thirteen out of 23 patients
with generalized weakness at baseline had denervation in the thoracic region. In two patients reinnervation only was found in the thoracic region. One of them had generalized weakness at baseline and the other still had a segmental phenotype at the end of the study.

**Nerve conduction studies (NCS)**
Features of NCS are given in table 3. CMAPs were recordable but reduced in amplitude in 17-39\% and absent in 3-13\% of the different muscles of all patients. Ninety-four percent of these abnormal values were found in clinically affected limb regions. Increased DML was found in 11-44\% of the different nerves. Decreased MCV was found in 10-21\% of different nerves, only in clinically affected limb regions. Decreased MCVs were associated with low CMAPs in 28 nerves (10\%) or with normal CMAPs in 11 nerves (4\%), respectively. Normal MCVs were associated with decreased CMAPs in 49 nerves (18\%). Increased F-M latency was found in 10-23\% of the different nerves.
In one nerve, increased DML was consistent with demyelination; in this nerve the CMAP was greater than 1 mV. This patient had generalized PMA at inclusion and had a relentless disease progression leading to death in the follow-up period. Distal CMAP duration, MCV and F-M latency were not consistent with demyelination in any of the nerves. In 59 (22\%) of nerves, F-wave were not elicitable; in 14 of these nerves the CMAP was above 1 mV.
SNAP amplitudes were decreased in the median nerve in five out of 32 patients (in combination with slowed SCV in three of them) and in the sural nerve in two out of 30 patients (absent in one patient). Two of them had decreased amplitude of the sural and median nerve; two of the patients with slowed median nerve SCV had complaints suggestive of carpal tunnel syndrome.

**Discussion**
In our patients that were included in a prospective study on adult-onset sporadic PMA, enrolled within four years after onset, needle EMG revealed abnormalities to a variable degree in all patients, both in clinically affected and unaffected limb regions. Importantly, we found that progression in patients with a segmental or distal onset of generalized progressive muscular atrophy may be likely if denervation is found in clinically unaffected regions, including the thoracic region. We found abnormalities of motor nerve conduction studies including slowing of DML, MCV, and F-M latency, absent F-waves and low CMAP amplitudes in up to one third of patients. Abnormalities of sensory nerve conduction were rarely found.
In a small portion of clinically affected limb regions no denervation or reinnervation was found with needle EMG. The lack of EMG abnormalities in clinically affected limb regions has also been reported in ALS. In our study, it may have been caused by the investigation of a selection of three instead of all muscles in an affected region. In addition, denervation or reinnervation may not be found in grossly atrophic muscles.
Table 3. Motor nerve conduction findings in 36 patients with PMA

<table>
<thead>
<tr>
<th>clinical condition</th>
<th>Median nerve</th>
<th>Ulnar nerve</th>
<th>Peroneal nerve</th>
<th>Tibial nerve</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>clinically affected</td>
<td>clinically non-affected</td>
<td>clinically affected</td>
<td>clinically non-affected</td>
</tr>
<tr>
<td>no. of investigated nerves</td>
<td>60</td>
<td>12</td>
<td>60</td>
<td>12</td>
</tr>
<tr>
<td>CMAP amplitude (mV), median</td>
<td>4.6</td>
<td>8.6</td>
<td>5.9</td>
<td>8.9</td>
</tr>
<tr>
<td>DML (ms), median</td>
<td>4.3</td>
<td>4.1</td>
<td>3.0</td>
<td>3.0</td>
</tr>
<tr>
<td>MCV (m/s), median</td>
<td>53</td>
<td>53</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>F-M (ms), median</td>
<td>24.4</td>
<td>26.2</td>
<td>26.8</td>
<td>26.1</td>
</tr>
<tr>
<td>no. of nerves with:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>absent CMAP</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>decreased CMAP*</td>
<td>22</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>DML ↑</td>
<td>29</td>
<td>3</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>MCV ↓</td>
<td>14</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>absent F</td>
<td>19</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>F-M ↑</td>
<td>9</td>
<td>4</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>

Clinically affected or non-affected refers to cervical or lumbosacral region (Clinically affected = MRC score 4+ or less in at least one muscle group of a region); CMAP = compound muscle action potential; DML = distal motor latency; MCV = motor conduction velocity; F = F-wave; F-M = F-M latency; ↑, ↓ = decreased or increased; * absent CMAPs not included.
The five patients with a segmental or distal distribution of weakness at onset, who did not develop generalized weakness during follow-up, had no electrophysiologic signs of denervation in clinically unaffected regions. However, this finding does not predict the final clinical phenotype since three patients who did progress also lacked denervation in clinically unaffected limbs. On the other hand, our findings may well indicate that EMG studies performed at a time that the phenotype is distal or segmental enable us to predict evolution into a generalized form when denervation is found in clinically unaffected limb regions. Whether this is useful in clinical practice has to be reconfirmed in a study with a larger number of patients. Detection of electrophysiologic evidence of LMN loss in clinically uninvolved regions increases diagnostic certainty in patients suspected of ALS. The diagnostic importance of finding thoracic paraspinal denervation in patients with suspected ALS has been described before. We observed thoracic paraspinal denervation in all patients with a segmental or distal phenotype who developed generalized weakness during follow-up. Only one patient with a segmental phenotype manifesting in the shoulder region who did not develop subsequent progression had denervation in the thoracic region. Therefore, in a patient with a segmental or distal phenotype, the finding of thoracic paraspinal denervation early in the disease means an extra region is involved which can be helpful in predicting progression to generalized weakness. It should be emphasized that it may be difficult to obtain full relaxation of thoracic muscles. Therefore, our results are only applicable if special precautions to obtain full relaxation of thoracic muscles are taken. Furthermore, our results should be substantiated in a larger group of patients. In our patients, the NCS values did not fulfill criteria for demyelination, except for one DML, and they are therefore compatible with a diagnosis of MND according to the revised El Escorial criteria and in keeping with those reported in ALS. Decreased CMAPs occurred both in combination with decreased and normal MCV. Decreased amplitude of CMAPs on distal stimulation of a nerve, without evidence of distal temporal dispersion, usually indicates loss of motor units and is consistent with motor neuron disease. Prolongation of DML was found in a proportion of our patients, but was compatible with demyelination in only one nerve. This patient had complaints compatible with a carpal tunnel syndrome, which probably is an explanation for this finding. Prolongation of DML has also been found in ALS patients. In ALS, delayed F-wave latencies up to 130% of the ULN may occur. In most of our patients, delayed F-wave latencies were in this range as well. In none of our patients F-M latency was consistent with demyelination. In our study, absent F-waves (in combination with distal CMAP≥1 mV) were found in 5% of nerves. Absence of F-waves may provide indirect evidence of peripheral nerve demyelination. However, this was also found in patients with motor neuron disease (MND) and therefore we consider this finding as non-specific. Significant abnormalities on sensory NCS in patients suspected of MND may suggest a concomitant disorder or a disorder other than MND. Nevertheless, slight abnormalities of
Electrodiagnostic findings in PMA

sensory NCS in ALS have been reported by several investigators. Moreover, axonal degeneration of the sural nerve has been demonstrated in post mortem studies in ALS patients, suggesting a sensory neuronopathy in addition to motor neuron loss. We found sensory conduction abnormalities in only five of our PMA patients of whom two probably had carpal tunnel syndrome. Two patients with decreased sural and median nerve SNAPs did neither have sensory complaints nor a clinical picture compatible with polyneuropathy. Thus, this finding may well suggest a limited sensory involvement in sporadic PMA, comparable with the findings in ALS. As far as we know, post mortem sensory abnormalities have not been reported in sporadic PMA.

In conclusion, our electrophysiological data in patients with sporadic lower motor neuron disease, most of them with a progressive muscular atrophy phenotype, are consistent with widespread LMN loss. Progression in patients with a segmental or distal onset of generalized progressive muscular atrophy may be likely if denervation is found in clinically unaffected regions, including the thoracic region.

References

Chapter 6

Accessed 1998.htm


31. Van Asseldonk JT, Van den Berg LH, Kalmijn S, Wokke JH, Franssen H. Criteria for demyelination based on the maximum slowing due to axonal degeneration, determined after warming in water at 37 degrees C:


