

File ID 94472
Filename Chapter 1 Introduction

SOURCE (OR PART OF THE FOLLOWING SOURCE):

Type Dissertation
Title Adult-onset sporadic progressive muscular atrophy : natural history, diagnosis, and prognostic factors
Author J. Visser
Faculty Faculty of Medicine
Year 2008
Pages 141
ISBN 9789090226439

FULL BIBLIOGRAPHIC DETAILS:

<http://dare.uva.nl/record/263079>

Copyright

It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use.

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.¹ Clinically, this leads to weakness and atrophy of skeletal muscles, cramps and fasciculations.² PMA is known under various names, including progressive spinal muscular atrophy (PSMA).³ 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.⁴ 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.⁵⁻¹⁰

PMA is not a well described clinical entity as only anecdotal cases or retrospective studies of small groups of patients have been published.^{2,3,11,12} 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.⁸⁻¹⁰ Progression in PMA may vary to a great extent between patients: a slowly progressive course over many years to decades is not unusual.² 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)¹³ 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.^{2,14}

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.

Chapter 1

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.¹⁵ However, this subgroup was omitted in the 1998 revised El Escorial criteria.¹³

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.¹⁶ Most patients with MMN respond to treatment with intravenous immunoglobulin (IVIg).^{17,18} Extensive nerve conduction studies are essential to search for persistent motor nerve conduction block(s), which is the electrodiagnostic hallmark of MMN.¹⁹ Increased signal intensities on T2-weighted MRI of the brachial plexus and positive titres of IgM anti-GM1 antibodies may contribute to the diagnosis.^{20, 21}

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’.^{8,22,23} 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.^{24,25} These possibilities should be specifically asked for.

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.²⁶⁻²⁸ 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.²⁹

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).³⁰ 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.³¹

In 'monomelic amyotrophy of lower limb' or 'wasted leg syndrome' muscle weakness and atrophy are restricted to one leg.³²⁻³⁴ 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.³⁵

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).^{36,37} 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.³⁸⁻⁴⁰ 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 bulbospinal muscular atrophy is characterized by slowly progressive limb girdle weakness and atrophy with facial weakness, gynaecomasty (50%), dysarthria and dysphagia, fasciculation, sensory neuropathy and hand tremor.⁴¹

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

Blood:

erythrocyte sedimentation rate (ESR), hemoglobin, hematocrit, thyrotropin (TSH), serum protein electrophoresis and immunoelectrophoresis with immunofixation, glucose, phosphate, and calcium (and, if elevated, parathyroid hormone)

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.⁴² 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.^{43,44} SMN2 can modify childhood-onset SMA disease severity in a dose-dependent manner.⁴⁵ 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.^{43,44}

Several mutations in the superoxide dismutase (SOD1) gene have been recognized in patients with familial ALS (FALS) with a predominant lower motor neuron syndrome.⁸⁻¹⁰ The most frequent of these mutations is the Ala4Val mutation, which is also the most common SOD1 mutation in FALS 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.^{2,3,14} 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.²

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.⁴⁶ 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.¹⁵ However, this subgroup was omitted in the 1998 revised El Escorial criteria.¹³

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.⁴⁷ 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).⁴⁸ With progressive dysphagia percutaneous endoscopically placed gastrostomy (PEG) can be considered, preferably before a patient's vital capacity falls below 50% of predicted.⁴⁹

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.

Chapter 1

References

1. Louwse ES, Sillevs Smitt PAE, de Jong JMBV. Differential diagnosis of sporadic amyotrophic lateral sclerosis, progressive spinal muscular atrophy and progressive bulbar palsy in adults. In: Vinken PJ, Bruyn GW, Klawans HL, de Jong JMBV, editors. Handbook of clinical neurology. Diseases of the motor system. Amsterdam: Elsevier Science Publishers 1991:383-423.
2. Norris FH. Adult progressive muscular atrophy and hereditary spinal muscular atrophies. In: Vinken PJ, Bruyn GW, Klawans HL, de Jong JMBV, editors. Handbook of clinical neurology. Diseases of the motor system. Amsterdam: Elsevier Science Publishers 1991:13-26.
3. Müller R. Progressive motor neuron disease in adults. A clinical study with special reference to the course of the disease. *Acta Psychiatr Neurol Scand* 1952;27:137-156.
4. Tyler HR, Shefner JM. Amyotrophic lateral sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, de Jong JMBV, editors. Handbook of clinical neurology. Diseases of the motor system. Elsevier Science Publishers 1991:169-215.
5. Brownell B, Oppenheimer DR, Hughes JT. The central nervous system in motor neurone disease. *J Neurol Neurosurg Psychiatry* 1970;33:338-357.
6. Ince PG, Evans J, Knopp M, Forster G, Hamdalla HHM, Wharton SB. Corticospinal tract degeneration in the progressive muscular atrophy variant of ALS. *Neurology* 2003;60:1252-1258.
7. Traynor BJ, Codd MB, Corr B, Forde C, Frost E, Hardiman O. Clinical features of amyotrophic lateral sclerosis according to the El Escorial and Airlie House diagnostic criteria. *Arch Neurol* 2000;57:1171-1176.
8. Cudkovic ME, McKenna Yasek D, Chen C, Hedley Whyte ET, Brown RH Jr. Limited corticospinal tract involvement in amyotrophic lateral sclerosis subjects with the A4V mutation in the copper/zinc superoxide dismutase gene. *Ann Neurol* 1998;43:703-710.
9. Valentino P, Conforti FL, Pirritano D, et al. Brachial amyotrophic diplegia associated with a novel SOD1 mutation (L106P). *Neurology* 2005;64:1477-1478.
10. Regal L, Vanopdenbosch L, Tilkin P, et al. The G93C mutation in superoxide dismutase 1: clinicopathologic phenotype and prognosis. *Arch Neurol* 2006;63:262-267.
11. Chiò A, Brignolio F, Leone M, et al. A survival analysis of 155 cases of progressive muscular atrophy. *Acta Neurol Scand* 1985;72:407-413.
12. Harding AE, Bradbury PG, Murray NMF. Chronic asymmetrical spinal muscular atrophy. *J Neurol Sci* 1983;59:69-83.
13. Revised criteria for the diagnosis of amyotrophic lateral sclerosis. Available at: <http://wfnals.org/Articles/elescorial1998.htm>
14. Norris FH Jr. Adult spinal motor neuron disease. Progressive muscular atrophy (Aran's disease) in relation to amyotrophic lateral sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, de Jong JMBV, editors. Handbook of clinical neurology. System disorders and atrophies. Part II. Amsterdam: North-Holland publishing company 1975: 1-56.
15. Brooks BR, and the subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases. El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. *J Neurol Sci* 1994;124 (Suppl):96-107.

16. Pestronk A, Cornblath DR, Ilyas AA, et al. A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. *Ann Neurol* 1988;24:73-78.
17. Van den Berg LH, Kerkhoff H, Oey PL, et al. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobins: a double-blind, placebo-controlled study. *J Neurol Neurosurg Psychiatry* 1995;59:248-252.
18. Léger JM, Chassande B, Musset L, Meininger V, Bouche P, Baumann N. Intravenous immunoglobulin therapy in multifocal motor neuropathy: a double-blind, placebo-controlled study. *Brain* 2001;124:145-153.
19. Biessels GJ, Franssen H, Van den Berg LH, et al. Multifocal motor neuropathy. *J Neurol* 1997;244:143-152.
20. Van Es HW, van den Berg LH, Franssen H, et al. Magnetic resonance imaging of the brachial plexus in patients with multifocal motor neuropathy. *Neurology* 1997;48:1218-1224.
21. Van Schaik I, Bossuyt PM, Brand A, Vermeulen M. Diagnostic value of GM1 antibodies in motor neuron disorders and neuropathies: a meta-analysis. *Neurology* 1995;45:1570-1577.
22. Ferlini A, Patrosso MC, Guidetti D, et al. Androgen receptor gene (CAG)_n repeat analysis in the differential diagnosis between Kennedy disease and other motoneuron disorders. *Am J Med Genet* 1995;55:105-111.
23. Nicole S, Diaz CC, Frugier T, Melki J. Spinal muscular atrophy: recent advances and future prospects. *Muscle Nerve* 2002;26:4-13.
24. Dalakas MC, Elder G, Hallett M, et al. A long-term follow-up study of patients with post-poliomyelitis neuromuscular symptoms. *N Engl J Med* 1986;314:959-963.
25. Bowen J, Gregory R, Squier M, Donaghy M. The post-irradiation lower motor neuron syndrome neuronopathy or radiculopathy? *Brain* 1996;119:1429-1439.
26. Hirayama K, Tsubaki T, Toyokura Y, Okinaka S. Juvenile muscular atrophy of unilateral upper extremity. *Neurology* 1963;13:373-380.
27. Hirayama K. Juvenile non-progressive muscular atrophy localized in the hand and forearm-observations in 38 cases. *Rinsho Shinkeigaku* 1972;12:313-324.
28. Hirayama K. Non-progressive juvenile spinal muscular atrophy of the distal upper limb (Hirayama's disease). In: Vinken PJ, Bruyn GW, Klawans HL, de Jong JMBV, editors. *Handbook of clinical neurology. Diseases of the motor system*. Amsterdam: Elsevier Science Publishers 1991:107-118.
29. Hirayama K, Tokumaru Y. Cervical dural sac and spinal cord in juvenile muscular atrophy of distal upper extremity. *Neurology* 2000;54:1922-1926.
30. Kaeser HE, Feinstein R, Tackmann W. Unilateral scapulohumeral muscular atrophy. *Eur Neurol* 1983;22:70-77.
31. Gamez J, Cervera C, Codina A. Flail arm syndrome of Vulpian-Bernhardt's form of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1999;67:258.
32. Felice KJ, Whitaker CH, Grunnet ML. Benign calf amyotrophy: clinicopathologic study of 8 patients. *Arch Neurol* 2003;60:1415-1420.
33. Dimachkie M, Justiz W, Vriesendorp FJ. Benign monomelic amyotrophy of the lower extremity: report of two cases and literature review. *J Clin Neuromusc Dis* 2000;1:181-185.
34. Prabhakar S, Chopra JS, Banerjee AK, Rana PV. Wasted leg syndrome: a clinical, electrophysiological and histopathological study. *Clin Neurol Neurosurg* 1981;83:19-28.
35. De Visser M, Ongerboer de Visser B, Verbeeten B. Electromyographic and computed tomographic findings

Chapter 1

- in five patients with monomelic spinal muscular atrophy. *Eur Neurol* 1988;28:135-138.
36. Harding AE, Thomas PK. Hereditary distal spinal muscular atrophy. A report on 34 cases and a review of the literature. *J Neurol Sci* 1980;45:337-348.
 37. 2nd Workshop of the European CMT Consortium: 53rd ENMC International Workshop on Classification and Diagnostic Guidelines for Charcot-Marie-Tooth Type 2 (CMT2-HMSN II) and Distal Hereditary Motor Neuropathy (distal HMN-Spinal CMT) 26-28 September 1997, Naarden, The Netherlands. *Neuromuscul Disord* 1998;8:426-431.
 38. Brahe C, Servidei S, Zappata S, Ricci E, Tonali P, Neri G. Genetic homogeneity between childhood-onset and adult-onset autosomal recessive spinal muscular atrophy. *Lancet* 1995;346:741-742.
 39. Kausch K, Muller CR, Grimm T, et al. No evidence for linkage of autosomal dominant proximal spinal muscular atrophies to chromosome 5q markers. *Hum Genet* 1991;86:317-318.
 40. Pearn J. Classification of spinal muscular atrophies. *Lancet* 1980;1:919-922.
 41. Kennedy WR, Alter M, Sung JH. Progressive proximal spinal and bulbar muscular atrophy of late onset. A sex-linked recessive trait. *Neurology* 1968;18:671-680.
 42. Veldink JH, van den Berg LH, Wokke JHJ. The future of motor neuron disease - The challenge is in the genes. *J Neurol* 2004;251:491-500.
 43. Echaniz-Laguna A, Guiraud-Chaumeil C, Tranchant C, Reeber A, Melki J, Warter JM. Homozygous exon 7 deletion of the SMN centromeric gene (SMN2): a potential susceptibility factor for adult-onset lower motor neuron disease. *J Neurol* 2002;249:290-293.
 44. Moulard B, Salachas F, Chassande N, et al. Association between centromeric deletions of the SMN gene and sporadic adult-onset lower motor neuron disease. *J Neurol* 1997;244:16-17.
 45. Lefebvre S, Burlet P, Liu Q, et al. Correlation between severity and SMN protein level in spinal muscular atrophy. *Nat Genet* 1997;16:265-269.
 46. Miller RG, Mitchell JD, Lyon M, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS) / motor neuron disease (MND). *Cochrane Database Syst Rev* 2007 Jan 24;(1):CD001447.
 47. Andersen PM, Borasio GD, Dengler R, et al. Good practice in the management of amyotrophic lateral sclerosis: Clinical guidelines. An evidence-based review with good practice points. *EALSC Working Group. Amyotrophic Lateral Sclerosis* 2007;8:195-213.
 48. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with ALS: a randomised controlled trial. *Lancet Neurol* 2006;5:140-147.
 49. Miller RG, Rosenberg JA, Gelinas DF, et al. Practice parameter: the care of the patient with amyotrophic lateral sclerosis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology: ALS Practice Parameters Task Force. *Neurology* 1999;52(7):1311-1323.