Adult-onset sporadic progressive muscular atrophy: natural history, diagnosis, and prognostic factors
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The history of progressive muscular atrophy: syndrome or disease?

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Summary
Since its first description more than a century ago, 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 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. Therefore, PMA should be considered as a syndromal subtype within a clinical spectrum of motor neuron diseases.
Early clinical observations
In 1850, a French neurologist Aran described eleven patients with different patterns of progressive muscle weakness and atrophy of the limbs, which he called *atrophie musculaire progressive* [progressive muscular atrophy, PMA]. He speaks of “une maladie non encore décrite du système musculaire” [a not yet described disease of the muscular system]. According to Aran, a striking feature of this condition was,
‘…instead of affecting the whole limb or part of a limb, as seen in other atrophies, it irregularly affects certain muscles, while it spares others’

In the introduction of his article, Aran referred to earlier case reports of patients with a possible similar syndrome described by other authors. However, he was the first to recognize the autonomous disease entity.

After the publication of Aran, Duchenne persistently claimed the first description of PMA. He referred to a report on *progressive muscular atrophy with fatty transformation* dated 1848 or 1849. This report has never been retrieved. However, Duchenne performed electrical stimulation studies on all Aran’s patients and possibly provided him with the data on two of his observations. Although Aran deserves more credit than Duchenne for describing and introducing the concept of PMA, Duchenne was more influential in those days and contemporary neurologists credited both by referring to progressive muscular atrophy as *Aran-Duchenne disease* or *Duchenne-Aran disease.*

According to current standards less than half of Aran’s patients still satisfy a diagnosis of PMA. However, overall, most of the symptoms and the natural course of PMA as described in this landmark article are still valid today, as is exemplified by Aran’s description of one of the essential features of the disease, i.e., fasciculation:
‘It is a unique phenomenon, which consists of isolated involuntary contractions of the muscle fascicles constituting a muscle; in some patients, they are so numerous and so persistent, that the various parts which constitute the muscle seem continuously moving; in others these contractions are so rare, that the affected member needs to be closely looked at for some time.’

Motor neuron degeneration
Both Aran and Duchenne were of the opinion that PMA was a muscle disease, caused by a nutritional disorder which resulted into their fatty degeneration. The first link to a neurogenic cause was established in 1853 with the discovery of atrophy of the anterior spinal roots and the motor nerves innervating the limbs at the autopsy of one of Aran’s patients, the acrobat Lecomte, for which Cruveilhier is to be credited. Cruveilhier speculated about a neural origin, which was independently confirmed by Luys in Paris (1860) and Lockhart Clarke in London, by demonstrating anterior horn cell degeneration in PMA. Also in 1860, Duchenne published a patient with “progressive muscular paralysis of the tongue, lips and palate”, which he called “glosso-labial-laryngeal paralysis” and which was recognized as
progressive bulbar palsy (PBP) at a later time. In 1869, Charcot and Joffroy published the autopsy of “two cases of progressive muscular atrophy with lesions of the gray matter and anterolateral fascicles of the spinal cord”. In this article, they linked clinical amyotrophy to pathology of the anterior horn cells and spastic paresis to corticospinal tract pathology:

‘…, symptoms of progressive muscular atrophy developed in succession. In the final stages of the illness, symptoms of paralysis and spasticity developed, which seem to be linked to the symmetrical sclerosis of the lateral pyramidal tracts. Subsequently…. will spread further….all the way to the gray matter, and at that point, the symptoms of amyotrophy appear.’

In a series of successive works (1870-1874), Charcot gave a further detailed description of this new clinical condition which he called amyotrophic lateral sclerosis (ALS). Charcot introduced a sharp demarcation between ALS and PMA. He stated that in PMA anterior horn cell degeneration was the most fundamental lesion: “primary progressive spinal muscular atrophy.” In ALS, these abnormalities were secondary of nature: “secondary spinal amyotrophy”. He assumed primary pathology of the descending fibers in the lateral columns, subsequently causing degeneration of anterior horn cells.

By the same time ALS was recognized as an autonomous disease entity, various other conditions with a myopathic or neurogenic pathology were designated, including pseudo-hyper trophy paralysis (1853), hereditary muscular atrophy (1875, 1879), progressive myopathy, progressive muscular dystrophy (1884), peripheral neuritis, and syringomyelia (1882). Prior to these descriptions, patients with those conditions probably had been classified as PMA. At the end of the 19th century therefore, “progressive muscular atrophy appeared to disappear from the list of nosological categories.”

Nonetheless, in 1909 Dejerine propagated PMA to be a separate disease entity: “progressive muscular atrophy of Aran-Duchenne due to chronic poliomyelitis”, which was supported by two clinico-pathologic reports demonstrating isolated involvement of anterior horn cells in four patients.

The distinction between PMA and ALS

Following the constellation of the clinical and pathological features of motor neuron degeneration of the lateral fascicles and anterior horn cells in ALS, debate arose whether PMA represented a separate disease entity or formed part of a spectrum including primary lateral sclerosis (PLS) and PBP in addition to ALS.

While Charcot insisted on distinction between PMA and ALS, Dejerine lumped PMA, PBP and ALS as variants of one disease entity. He argued that autopsy findings in these three illnesses were often indistinguishable. Gowers combined PMA, progressive bulbar palsy, and ALS as “Motor Neuron Disease (MND)” in 1899. Other neurologists accepted this integrated viewpoint.
However, the classification of PMA in relation to ALS remained a point of dispute for a long period of time. Contemporary focus on the issue whether they were variants of the same disease or are different disease entities was brought by the writings of Rhein in 1917, summarising the older literature on diverging opinions between neurologists. He concluded “that spinal muscular atrophy and amyotrophic lateral sclerosis are probably one and the same disease in different stages of the same pathological process.”

Strong support for the notion that they represent variants of the same disease came from autopsy series demonstrating corticospinal degeneration in patients with clinically ‘pure’ PMA.

In 1943, Swank and Putnam wrote, ‘…..one might be tempted to conclude that there are two distinct groups of cases in which the condition is diagnosed as progressive muscular atrophy, those with lesions of the pyramidal tracts which produce no signs, or in which the signs are masked by atrophy, and those in which the older methods of investigation have revealed no degeneration of the pyramidal tracts. Under the circumstances it seems expedient to consider progressive muscular atrophy as an incompletely developed phase of amyotrophic lateral sclerosis.’

Their comment on the few examples of ‘pure’ PMA with isolated anterior horn cell involvement post mortem was that “none of these have been studied by means of newer methods.”

The observation that both conditions may appear in one and the same patient during the course of the disease, contributed to “valuable evidence of the concept of ‘motor neuron disease’ by showing transition from one disease to another.”

However, proponents of the opinion that PMA is a separate disease entity pointed out that in some progressive muscular atrophy cases the course of the disease is quite different from that found in ALS and that they “live for years and years, up to 20 and 30 or longer after the initial signs or symptoms appear.”

In 1952, Müller confirmed this observation in patients with progressive spinal muscular atrophy (PSMA), a term he introduced for patients with PMA. Although the majority of his PSMA patients proved to be cases of ALS in the long run, he described slow progression of pure lower motor neuron signs over years and decades in 7 of his patients. He stated that “there is reason to assume that they represent a different morbid state.”

In 1975, Norris emphasized “the real clinical experience with progressive muscular atrophy as a more slowly progressive disorder which spares the upper motor neurons and the bulbar neurons until late in the course, and affects men in higher ratio than amyotrophic lateral sclerosis.”
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Differentiation from other lower motor neuron syndromes

Over the last decades various other lower motor neuron syndromes have been distinguished which can ‘mimic’ PMA in different stages of its course.

In 1959, Hirayama et al reported 12 cases of muscular atrophy of the distal part of the upper extremity, which could be distinguished from classical MND, especially P(S)MA, by the clinical characteristics of juvenile onset, benign course and the restricted localization of muscular atrophy to the forearms, mostly unilateral. The authors proposed to name the condition juvenile muscular atrophy in unilateral upper extremity. When less pronounced contralateral weakness of hand and forearm in about one-third of patients was found, as was observed by others as well, the name of the disease entity was changed into juvenile muscular atrophy of distal upper extremity. Subsequently, descriptions of patients with focal motor neuron syndromes restricted to a particular or single limb, either in geographic clusters or as isolates, began to emerge. These disorders are known under various terms and are currently grouped as benign focal amyotrophy disorders, reflecting their self-limiting nature.

Flail arm syndrome, also called brachial amyotrophic diplegia, is regarded a distinctive variant of MND, characterized by predominant lower motor neuron involvement of both upper limbs, mainly the proximal part and shoulder girdle, and a long disease duration. These terms are synonyms for an older, probably similar condition known as the scapulo-humeral form or Vulpian-Bernardt’s form of ALS.

A variant of chronic anterior horn cell degeneration was described in 1980 by Harding et al. The reported patients demonstrated chronic symmetrical and distal muscle weakness in arms and legs, and both sporadic and hereditary forms were recognized. The authors designated this syndrome as distal spinal muscular atrophy (distal SMA). The hereditary forms have been classified in seven types based on mode of inheritance, age at onset and clinical progression and are also known as hereditary motor neuro(no)pathy (dHMN) or the spinal form of Charcot-Marie-Tooth (CMT).

In 1988 Pestronk et al reported two patients with a progressive purely motor, predominantly distal, asymmetric neuropathy with multifocal persistent conduction blocks on motor but not on sensory nerves. They introduced the term multifocal motor neuropathy (MMN). It was recognized that this presumed immune mediated and possibly treatable disease can clinically mimic PMA and probably accounts for the reported earlier onset of PMA as compared to ALS in previous studies.

Over the last decades, genetic defects in several hereditary forms of lower motor neuron syndromes have been identified. These include mutations in adult-onset forms of hereditary spinal muscular atrophy (SMA type IV) and in X-linked bulbospinal muscular atrophy, also known as Kennedy’s disease. In addition, several mutations in the SOD1-gene have been recognized more recently in patients with familial ALS (FALS), presenting with a predominant lower motor neuron syndrome.
Ongoing controversies
Progressive muscular atrophy (PMA) is defined as (1) a sporadic disease, characterized by (2) progressive muscle weakness and atrophy due to degeneration of anterior horn cells, (3) with onset in adulthood.
In some patients initially labelled with PMA, another diagnosis is established after additional investigations or during follow-up or; e.g. MMN, ALS, focal or segmental form of motor neuron disease.43
The group of patients who continue as PMA may still harbour different conditions. With respect to MMN, recent studies raised the question whether, with modern techniques, MMN and PMA can be distinguished at all times. Conduction block(s), necessary for the diagnosis of MMN, may not be present or recognized in some patients with MMN.51-54 Additionally, positive anti-GM1 titre and high signal intensity on T2-weighted MRI images of the brachial plexus are supportive but not specific for MMN, whereas a negative test has no diagnostic value.55,56 A helpful point to distinguish PMA and MMN clinically is that MMN impairment follows a peripheral nerve distribution, which often distinguishes it from PMA – the latter disease characterized by more diffuse symmetrical weakness associated with severe muscular atrophy.57
It is also unknown to what extent overlap exists between the extremely rare SMA type IV44 and (slowly progressive) PMA. Although clinical presentation in SMA type IV is with symmetrical and predominantly proximal weakness, gene identification is not always possible and some may not have a family history.
Another group of patients presenting with PMA can remain a pure lower motor neuron disease at the clinical level and show a relentless ALS-like course.57 Because more than 50% of these patients reveal UMN pathology at autopsy, this group is usually regarded as a form of ALS.58,59 In addition, familial ALS may present as a lower motor neuron syndrome.47-49 Again, the question is justified whether PMA as a disease entity exists. It is apparent that no single clinical feature or investigational abnormality is diagnostic of PMA. It seems that the early history of PMA repeats itself: the ongoing recognition of other lower motor neuron syndromes will constantly reduce the group of patients previously designated as PMA. In addition, from the group of patients presenting with PMA ultimately a few patients will still show features of a true lower motor neuron disease at the clinical level throughout life. However, the concept of PMA as a subtype within the collective group of motor neuron disorders should be maintained, because it may show a distinction from ALS in terms of natural history. In addition, the differential diagnosis of PMA is distinctive from ALS.45 Both clinical practice and research in MND will benefit from this categorization into subgroups.60
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References
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