Progressive Muscular Atrophy

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KEYWORDS

- Lower motor neuron syndrome
- Lower motor neuron-onset ALS
- PMA
- Progressive muscular atrophy

KEY POINTS

- Progressive muscular atrophy (PMA) is a rare, sporadic, adult-onset motor neuron disease (MND), clinically characterized by isolated lower motor neuron (LMN) features; however, clinically evident upper motor neuron (UMN) signs may emerge in 20% to 30% of patients with the initial diagnosis of PMA within typically 5 years from onset and up to 10 years.
- Subclinical UMN involvement is identified pathologically, radiologically, and neurophysiologically in a substantial number of patients with PMA.
- Imaging and electrophysiologic biomarkers of UMN involvement should be easily accessible in clinical practice. Patients with PMA with subclinical UMN involvement do not fulfill the revised El Escorial criteria to participate in amyotrophic lateral sclerosis (ALS) clinical trials and may follow a different trajectory. Intravenous immunoglobulin (IVIg) therapy is only marginally beneficial in a small subgroup of patients with LMN syndrome without conduction block (CB).
- There continues to be debate regarding whether PMA is a unique variant of MNDs or belongs on an ALS spectrum.

INTRODUCTION

PMA is a rare, sporadic, adult-onset, clinically isolated LMN syndrome due to the degeneration of LMNs, including anterior horn cells and brainstem motor nuclei. It is clinically characterized by progressive flaccid weakness, muscle atrophy, fasciculations, and reduced or absent tendon reflexes. The term PMA was first coined by the French neurologist Aran in 1850 to describe patients with progressive muscle atrophy.
of presumed myopathic cause. Later, Duchenne also claimed the first description of PMA. Therefore, PMA is sometimes referred to as Aran-Duchenne or Duchenne-Aran disease. In 1853, Cruveilhier provided the first evidence of PMA being a neurogenic disorder based on the atrophy of the ventral spinal roots and the motor nerves found on autopsy of Aran’s patients. Nearly 2 decades later, Charcot described the first patients with ALS and highlighted the pathologic differences between PMA and ALS. Charcot concluded that degeneration affected only the LMNs in PMA but affected both LMNs and corticospinal tracts (UMNs) in ALS. At that time, PMA was considered a distinct entity of pure LMN syndrome. PMA can be distinguished from ALS by the absence of clinical evidence of UMN dysfunction (spasticity, hyperreflexia, preserved tendon reflexes in atrophic limbs, pathologic reflexes, and pseudobulbar affect). It has been recognized that a substantial number of patients with the initial diagnosis of PMA progress to a diagnosis of ALS through the development of UMN signs or may have UMN pathology at autopsy despite the absence of clinical UMN features during their lifetime.

Recent studies have shown that patients with PMA often have subclinical UMN involvement identified radiographically or neurophysiologically despite the absence of UMN findings on examination. Mutations in genes responsible for familial ALS (FALS) may also cause clinically isolated LMN syndrome phenotypes, mimicking PMA. Patients with PMA have been considered to have longer life expectancy than patients with ALS, but recent studies show that the difference in life span may not be as long as previously reported. These observations support the notion of PMA belonging to an ALS spectrum rather than being a unique variant of MNDs. However, there remains a significant proportion of patients with PMA who have no clinical or subclinical evidence of UMN dysfunction, supporting the existence of PMA as a separate entity. At present, the term PMA is reserved for sporadic patients with MND with pure LMN findings on examination, who may or may not later develop clinically defined UMN features. Patients who subsequently developed UMN signs are reclassified as having ALS.

There are a limited number of studies dedicated to the epidemiology and natural course of PMA. Most of these studies have grouped patients with PMA with or without later clinical UMN features together. Earlier studies predated the description of multifocal motor neuropathy (MMN) and hereditary MNDs, which may mimic PMA. Several studies suggest the usefulness of ancillary tests to detect subclinical corticospinal tract degeneration, but epidemiologic studies of PMA have not used such testing. These factors affect the interpretation of available studies.

**EPIDEMIOLOGY**

PMA accounts for 2.5% to 11% of MND. Its incidence is estimated at 0.02 per 100,000. PMA is more common in men than in women (male/female ratio, 3:1–7.5:1). Age of onset is generally older than for patients with ALS, with the mean being 63.4 ± 11.7 years. Previous studies report an earlier age of onset, but many of these earlier studies may have included patients with other LMN syndromes mimicking PMA.

**CLINICAL PRESENTATION**

Patients with PMA develop a constellation of LMN features, namely, progressive flaccid weakness, muscle atrophy, fasciculations, and hyporeflexia or areflexia. Weakness and atrophy typically start in distal limb muscles in an asymmetric manner following neuropathy pattern 5 (NP5) and then spreads over months and years. There is a mean delay of approximately 23 months between the onset and the
diagnosis. Symmetric proximal limb weakness (myopathy pattern 1 [MP1]) occurs in only 20% of patients. Bulbar muscles are generally spared at onset but may be involved in up to 40% of patients within a median of 19 months from onset of limb weakness. Patients with bulbar involvement (NP8/MP7) are more likely to progress to ALS or run a relentless course, as seen in ALS. It is uncommon for axial or respiratory muscles (NP8/MP6) to be involved at the onset of PMA.

About 22% to 35% of patients with the initial diagnosis of PMA develop UMN features at a later time. UMN findings mostly emerge within the first 2 years of diagnosis; however, it could range from a half month to 5 years (median, 8.5 months) or even a decade after the onset of LMN weakness. This subset of patients, in fact, has LMN-onset ALS. Patients with LMN-onset ALS have an earlier age of onset compared with patients with PMA who have no UMN signs throughout their clinical course (mean ± standard deviation, 58.8 ± 11.2 vs 64.8 ± 11.7 years). Patients with LMN-onset ALS are more likely to need noninvasive ventilation compared with patients with PMA without subsequent UMN signs (60% vs 30%). A feeding tube is used in a similar proportion (10%–15%) of patients with PMA or LMN-onset ALS.

Cognitive impairment affects about one-third of nondemented patients with ALS and was reported in 8 of 9 nondemented patients with PLS. A neuropsychological study of 12 patients with PMA identified no patients with cognitive dysfunction. Therefore, the cognitive impairment in MND is initially thought to be linked to UMN involvement. A subsequent study identified executive dysfunction in 4 of 23 nondemented patients with PMA; moreover, the degree of UMN involvement in cognitively impaired patients with ALS does not correlate with cognitive dysfunction. Functional MRI showed impaired recruitment of left inferior frontal gyrus in patients with PMA with letter fluency impairment. This impaired prefrontal activation is similar to what is observed in patients with ALS with executive dysfunction.

The rate of progression in patients with PMA varies from slow (over years and decades) to very rapid (months to a year). The median survival duration after onset in patients with PMA is about 12 months longer than in patients with ALS (48.3 vs 36 months). An earlier study estimated the mean survival duration in patients with PMA at 200 months. Survival duration could have been overestimated due to a fewer subjects and the inclusion of other LMN syndromes. The 3-year and 5-year survival rate is 67% to 73.3% and 40.7% to 45%, respectively. There is no significant difference in the survival time between patients with PMA with and without subsequent UMN signs (median, 47.2 vs 63.2 months from onset). However, this could be in part due to the inclusion of patients with radiographic or neurophysiologic evidence of subclinical UMN degenerations in the category of patients with PMA without interval development of UMN signs. Several factors have been shown to be associated with shorter survival, including axial onset, involvement of more segmental regions, ALSFRS-R at diagnosis less than 38, baseline forced vital capacity (FVC) less than 80% of the predicted value, and a sharp decline in FVC within the first 6 months. Patients with PMA who have weakness restricted to distal or proximal muscles for at least 4 years typically have a more favorable prognosis. Restricted arm (brachial amyotrophic diplegia) and leg (leg amyotrophic diplegia) variants carry a more favorable prognosis.

**PATHOPHYSIOLOGY**

Like other sporadic adult-onset MNDs, the pathogenesis of PMA is unknown. Isolated anterior horn cell degeneration has long been thought to be the pathologic hallmark of PMA; however, postmortem studies identified not only LMNs harboring ubiquitinated
inclusion bodies, similar to ALS, but also corticospinal degeneration in 50% to 85% of patients with PMA. These patients with autopsy findings of UMN degeneration have mostly had a rapidly progressive course despite the absence of clinically detectable UMN features antemortem; however, corticospinal tract degeneration has also been reported in patients with PMA with a slow progressive course over 4 to 10 years. The aggregation of macrophages is more sensitive than the presence of myelin pallor in detecting the corticospinal tract pathology. This series of autopsy findings highlights the difficulty in detecting UMN signs in patients with severe LMN weakness. Most inclusion body–containing LMNs are also positive for TAR DNA-binding protein 43 (TDP-43) immunoreactivity, similar to findings in patients with ALS. A recent study has classified PMA into 3 different pathologic conditions: (1) ALS-like pathology (combined UMN and LMN degeneration with TDP-43-positive cytoplasmic inclusions) in 61.5% of patients, (2) isolated LMN degeneration with TDP-43-positive inclusions in 23% of patients, and (3) combined UMN and LMN degeneration with FUS-positive inclusions in 15.5% of patients.

It has long been known that patients with mutations in genes responsible for FALS may present with a familial or sporadic, purely or predominantly LMN syndrome, mimicking PMA. The initial descriptions of such cases were mostly attributed to SOD1 mutations. Mutations in other FALS genes have also been identified in patients with sporadic PMA, including C9orf72 hexanucleotide repeat expansions, ANG, CHMP2B, FUS, and TARDBP. The C9orf72 repeat expansions account for 1.6% of patients with sporadic PMA. About 3% of patients with sporadic PMA carry mutations in ANG, CHMP2B, FUS, SOD1, or TARDBP. Analysis of VCP and TRPV4 mutations in patients with PMA revealed no pathogenic mutations. It is unknown to what extent overlap exists between hereditary adult-onset LMN diseases and PMA with symmetric proximal weakness. The absence of family history does not necessarily exclude hereditary disorders.

DIAGNOSIS

There is no biological marker for the diagnosis of PMA. Diagnosis requires clinical and electrophysiologic features of LMN dysfunction in 2 or more different myotomal distributions (bulbar, cervical, thoracic, and lumbosacral), evidence of disease progression over time, and the exclusion of other LMN syndromes. Needle electromyography (EMG) could help to show fasciculations in deep muscles that are not visible on examination and provide evidence of LMN dysfunction (large polyphasic motor unit potentials with reduced recruitment) in clinically affected and nonaffected areas. Other ancillary tests may be applied to exclude PMA mimickers. PMA should be differentiated from LMN diseases that affect only 1 myotome, either the cervical (flail arm syndrome or brachial amyotrophic diplegia) or the lumbosacral (flail leg syndrome or leg amyotrophic diplegia) area, for at least 1 to 2 years without spreading to other body areas. Patients with flail arm or flail leg syndrome generally have a better prognosis than patients with PMA. PMA is included in the category of suspected ALS according to the 1994 El Escorial criteria; however, this category no longer exists with the 1998 revision of El Escorial criteria. Therefore, patients with PMA have now been excluded from ALS clinical trials and other research studies.

SUBCLINICAL UPPER MOTOR NEURON INVOLVEMENT IN PROGRESSIVE MUSCULAR ATROPHY

PMA is a clinical diagnosis. It encompasses patients with MND with pure LMN signs, some of which may later develop into UMN signs (ALS with LMN onset). Needle EMG
is the only mandatory ancillary test included in the revised El Escorial criteria. It could enhance the detection of LMN dysfunction in clinically unaffected or minimally affected body areas, but it cannot detect subclinical UMN dysfunction. Over the years, several radiologic and neurophysiologic techniques, outline later, have been developed to identify subclinical UMN involvement in patients with MND with clinically isolated LMN dysfunction. However, none of these techniques are included in the revised El Escorial criteria.

**Imaging Biomarkers of Upper Motor Neuron Involvement**

The data on radiographic biomarkers of UMN lesions are inconclusive. Two different techniques have been applied to identify UMN involvement in patients with MND: diffusion tensor MRI and magnetic resonance spectroscopy (MRS).

Diffusion tensor MRI studies of the structural integrity of neuronal fibers showed modest reduction of fractional anisotropy, suggesting axonal degeneration and myelin breakdown in the corticospinal tract in all 12 patients with PMA, suggesting the clinical evidence of UMN lesions in some patients. However, another study showed no significant abnormal fractional anisotropy in 8 patients with PMA. White matter involvement in patients with PMA may be involved beyond the corticospinal tract. Voxel-based analysis identified fractional anisotropy reduction in nonmotor white matter including the prefrontal area.

MRS showed reduced N-acetyl aspartate (NAA) concentration and ratio of NAA to creatine, markers of neuronal health, in the primary motor cortex, suggesting UMN involvement, in about 60% of patients with PMA. The corticospinal tract degeneration was pathologically confirmed when autopsy was available. However, normal results on MRS does not exclude UMN pathology. Another MRS study showed only modest, nonsignificant changes in patients with PMA, which could be due to the slightly different imaging technique.

**Neurophysiologic Biomarkers of Upper Motor Neuron Involvement**

Transcranial magnetic stimulation (TMS) assesses the electrophysiologic integrity of central motor pathways. Prolonged central motor conduction time occurred in 30% to 60% of patients with PMA. A new neurophysiologic technique, β-band intermuscular coherence, has shown to be a reliable marker of UMN degeneration in patients with PLS, a clinically isolated UMN disorder. This technique aims to assess the propagation of oscillatory activity between the motor cortex and the contralateral limb muscles. In a study of patients with PLS with abnormal results on TMS, β-band intermuscular coherence was absent. TMS and β-band intermuscular coherence were normal in patients with PMA in this study.

**DIFFERENTIAL DIAGNOSIS**

Unlike ALS, in which the combination of UMN and LMN signs presents a rather distinctive clinical presentation, PMA can be difficult to distinguish from other LMN syndromes, including disorders affecting motor neurons, motor nerves, neuromuscular junctions, and muscle fibers.

**Motor Neuron Diseases**

Hereditary LMN diseases encompass spinal muscular atrophy (SMA) (MP1 or NP7; Table 1 in Ref. and spinobulbar muscular atrophy (SBMA) (Kennedy disease; MP1 or NP8/MP7). Obviously, positive family history, when present, provides an invaluable clue. SMA and SBMA produce symmetric, predominately proximal weakness (MP1),
which is different from asymmetric distal weakness (NP5), typically seen in PMA. SMA generally presents in young patients, but there is overlap with the age groups in whom PMA is seen. Distal variants of SMA (NP7) have been reported. Although weakness in these patients with distal SMA is predominant distally, it is symmetric. In SBMA, there are additional distinguishing features such as prominent bulbar involvement (NP8/MP7), perioral fasciculations, gynecomastia, testicular atrophy, and subtle sensory abnormalities. In one series, SBMA made up 13% of patients initially misidentified as having ALS. The creatine kinase (CK) levels can be elevated in any chronic MND. HyperCKemia has been observed in about 25% of patients with ALS and 85% of patients with SBMA. CK levels more than 1000 U/L are more common in patients with SBMA than in patients with ALS. The range of CK levels in patients with PMA is unknown. Hexosaminidase A deficiency is a multisystem lysosomal storage disease. Late-onset patients may present with predominant LMN dysfunction, mimicking PMA. Careful neurologic examination may identify, in addition to progressive proximal weakness (MP1), ataxia and in some psychiatric symptoms.

Acquired LMN degeneration can rarely be a result of a paraneoplastic process, a long-term complication of radiotherapy or viral illness. The absence of conventional paraneoplastic antibodies does not exclude a paraneoplastic process. In postradiation LMN syndrome, the onset of weakness may occur months to years, or even decades, after exposure, and can affect any body areas depending on what part of the neuraxis was irradiated. LMN disease due to viral infection (poliovirus, West Nile virus, and enterovirus D68) or poliomyelitis should be considered in patients with febrile illness preceding LMN weakness. Polio survivors may develop progressive weakness years after the initial polio attack in initially affected or nonaffected body areas, so-called postpolio syndrome.

A rather unique motor neuron disorder that is part of the differential diagnosis of PMA is monomelic amyotrophy. In this clinical entity, there is usually weakness and denervation restricted to 1 limb, usually the arm. The contralateral limb may appear unaffected clinically, yet show denervation on needle EMG. Some cases of monomelic amyotrophy are simply early cases of PMA and, with more time, the typical phenotype may become apparent. There are also regional variants of PMA. What has been referred to as monomelic amyotrophy in the literature for the most part is Hirayama disease. Hirayama disease, also referred to as juvenile muscular atrophy of the distal upper extremity, affects mainly young men. The average age of onset is approximately 20 years (13–28 years). Weakness tends to progress over 1 to 4 years and then often plateaus. Hirayama has strong geographic proclivities, occurring most often in parts of India, Japan, and other East Asian countries. Weakness usually involves just 1 upper limb, distally in the C7–T1 myotomes (NP5). Atrophy is typical, and there is more hypothenar than thenar involvement; this is observed both clinically and on nerve conduction studies. Fasciculations and tremor are common. An interesting phenomenon that may be seen is cold paresis wherein cold exposure increases weakness. There may be progression to the contralateral arm, which occurs 20% to 40% of the time and tends to occur within 3 to 4 years (range 2–120 months) after onset in the initial limb. When this occurs, weakness tends to be much less than in the initial limb. More often, needle EMG shows subclinical involvement in the contralateral arm. Hirayama disease has a unique imaging finding consisting of an increase in the posterior epidural space and a compressive flattening of the lower cervical cord due to forward displacement of the cervical dural sac induced by neck flexion. Madras disease is another LMN disorder affecting young adults in India. In contrast to Hirayama disease, patients with Madras disease may have cranial nerve involvement, manifest weakness in multiple limbs, and exhibit UMN findings.
Spinocerebellar ataxias and Creutzfeldt-Jakob disease may rarely mimic PMA due to LMN involvement; however, there are other clinical features pointing away from a purely LMN process in both disorders.

Motor Neuropathies

Probably the most difficult differential diagnosis challenge comes from distinguishing PMA from motor neuropathies. Motor neuropathies could be due to immune-mediated disorder, MMN, or hereditary motor neuropathies (HMNs).

MMN, in most cases, exhibits features that permit clear diagnosis based on the clinical, electrodiagnostic, or laboratory features. MMN typically affects men between ages 30 and 50 years. Weakness commonly involves the upper extremities (NP5) but follows a motor nerve distribution as opposed to a myotomal pattern. Fasciculations may be present, making differentiation from MND difficult. CB has been considered the electrophysiologic hallmark of MMN; however, CB is not necessary for diagnosis. It is often not emphasized, but most patients with MMN, even if they lack CB, have other features of demyelination, such as slow nerve conduction velocity or prolonged distal latencies. IgM antibodies directed against ganglioside-monosialic acid (GM1), when present at a high titer, are specific for MMN. However, GM1 antibodies are identified in only 30% to 50% of patients with MMN. The treatment of MMN is typically IVIg. Cyclophosphamide is also of demonstrated effectiveness but is infrequently used because of morbidity. Corticosteroids and plasmapheresis do not help and make the condition worse in some patients.

The most difficult diagnostic conundrum is posed by cases of MMN that lack clear-cut electrodiagnostic features. In the literature as well as in clinical practice, there is concern about when to consider a trial of immunotherapy (usually IVIg) in patients presenting with an LMN syndrome. A careful review of these reported cases illustrates that IVIg is not warranted in most patients with an LMN syndrome, so liberal use of IVIg brings about expense and risk of complications. The biggest issue with these studies is that patients with high-titer GM1 antibodies, CB, or prolonged F-wave latencies were not excluded. Such patients can be considered to have MMN or demyelinating motor neuropathies and, therefore, warrant treatment with IVIg. Aside from GM1 antibodies and CB, factors that favored a response to IVIg were distal upper limb–onset weakness, normal CK levels, and needle EMG showing denervation only in clinically affected muscles. Important considerations to keep in mind when approaching the electrodiagnosis of MMN have been outlined by Bromberg and Franssen. Imaging studies, MRI or ultrasonography, may help identify patients with MMN, but more studies are needed.

HMNs (NP7) are a rare form of hereditary neuropathies affecting only motor nerves. These can manifest with asymmetric features, but the age of onset is often early enough to steer the clinician toward this diagnosis away from PMA. In addition to HMN, other hereditary neuropathies, such as Charcot-Marie-Tooth disease (CMT; NP7) can mimic PMA. Although most patients with CMT have sensory signs and symptoms, some patients can have purely motor phenotypes but have subtle sensory deficits on examination or nerve conduction studies. Amyloid neuropathy and porphyria-related neuropathy rarely may present with PMA-like phenotype.

More prosaic conditions can be mistaken for PMA, such as radiculopathies. Most commonly, this is cervical spondylotic disease. In this condition, there are usually sensory symptoms and signs but presentation can be purely motor. Cervical spine MRI should facilitate the diagnosis along with needle EMG to show that denervation is restricted to myotomes that could be affected by the abnormal imaging findings.
Neuromuscular Junction Disorders

Myasthenia gravis generally affects oculobulbar (MP5 ocular and NP8/MP7 bulbar) and proximal limb muscles (MP1); however, a subset of patients with isolated limb weakness can sometimes be mistaken as having PMA, especially if weakness is distal (NP7) or asymmetric (NP5). In such cases, routine electrodiagnostic testing may not readily point to a diagnosis of neuromuscular transmission defects, but the absence of denervation on needle EMG would at least direct the clinician away from a diagnosis of PMA. If findings of myopathy are also lacking, then more specialized electrodiagnostic testing, such as repetitive stimulation and single-fiber EMG, can be obtained as can serologic testing for myasthenia gravis antibodies.

Myopathies

Myopathies are more likely to be confused with PMA than with neuromuscular transmission disorders. In older individuals, inclusion body myositis (IBM) should be considered. IBM typically produces asymmetric proximal and distal weakness and muscle atrophy (MP4), mimicking PMA, but fasciculation is absent. Nevertheless, the unique pattern of weakness affecting finger flexors and knee extensors usually guides the clinician to this diagnosis. Similarly, needle EMG findings in IBM usually point to a myopathic process. However, in some patients, there may be neurogenic features, making definitive diagnosis difficult. In selected circumstances, muscle biopsy can help determine whether one is dealing with a myopathic or neurogenic process. The symmetric proximal weakness seen in most cases of polymyositis and dermatomyositis (MP1) should not lend to confusion with PMA, but some patients with myositis may have regional presentations, such as those affecting bulbar and upper body/limb muscles.

There are several genetic distal myopathies and muscular dystrophies (MP2) that could potentially be confused for PMA. However, CK levels in some of these distal muscular dystrophies are markedly elevated. Electrodiagnostic testing should clearly differentiate these myopathic changes from neurogenic features of PMA. In rare circumstances, muscle biopsy can be useful.

MANAGEMENT

The principles of managing the patient with PMA do not differ from those for the patient with ALS. As previously mentioned, patients with PMA are excluded from clinical trials. This area is being carefully reconsidered by the ALS research community.

SUMMARY

PMA poses several difficulties as a diagnostic construct. In clinical practice, 20% to 30% of patients initially identified as having PMA may develop ALS with UMN features, typically within 5 years from onset and up to 10 years, and many more have subclinical UMN involvement. However, there are patients who have a benign clinical course distinctly different from that of ALS. Patients with deficits that remain restricted to upper or lower limbs, brachial amyotrophic diplegia or leg amyotrophic diplegia, generally are grouped into this category. However, clinicians also encounter patients with progressive, asymmetric multilimb weakness who have diseases showing long duration and survival. For such patients, the term PMA remains valuable to emphasize to these patients (and providers) that these individuals do not share the grave prognosis of a typical ALS patient. Another consideration is that the absence of UMN signs can make it difficult to be certain that a patient has PMA as opposed to other LMN
syndromes. Potentially treatable disorders, such as MMN, remain important considerations and may be considered in a small subgroup of cases with distal upper limb-onset weakness, normal CK levels, and needle EMG showing denervation only in clinically affected muscles, but liberal use of treatment trials with IVIg is not appropriate. Last but not least, more clinically accessible means for identifying UMN involvement in patients with PMA are needed.

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