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

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of presumed myopathic cause.[1] 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.[1] 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.[2]

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.[3–8] Mutations in genes responsible for familial ALS (FALS) may also cause clinically isolated LMN syndrome phenotypes, mimicking PMA.[9–12] 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.[13–15] 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.[13,15–18] Its incidence is estimated at 0.02 per 100,000.[13] PMA is more common in men than in women (male/female ratio, 3:1–7.5:1).[13,15] Age of onset is generally older than for patients with ALS, with the mean being 63.4 $\pm$ 11.7 years.[15] Previous studies report an earlier age of onset, but many of these earlier studies may have included patients with other LMN syndromes mimicking PMA.[13]

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 starts in distal limb muscles in an asymmetric manner following neuropathy pattern 5 (NP5)[19] and then spreads over months and years. There is a mean delay of approximately 23 months between the onset and the