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Motor neuron diseases

Adult-onset spinal muscular atrophy: An update

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ABSTRACT

Spinal muscular atrophy (SMA) refers to a group of disorders affecting lower motor neurons. The age of onset of these disorders is variable, ranging from the neonatal period to adulthood. Over the last few years, there has been enormous progress in the description of new genes and phenotypes that throw new light on the molecular pathways involved in motor neuron degeneration. Advances in our understanding of the pathophysiology of the most frequent forms, SMA linked to *SMN1* gene mutations and Kennedy disease, has led to the development of therapeutic strategies currently being tested in clinical trials. This report provides a general overview of the clinical features and pathophysiological mechanisms in adult-onset genetic SMA disorders in which the causative gene has been identified (*SMN1*-related SMA, Kennedy disease, *CHCHD10*, *TRPV4*, *DYNC1H1* and *BICD2*). Sporadic lower motor neuron disease, also known as progressive muscular atrophy (PMA), is also discussed. The finding of TDP-43 aggregates in immunohistochemical studies of PMA strongly supports the idea that it is a phenotypic variant of amyotrophic lateral sclerosis (ALS).

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1. Introduction

The term 'spinal muscular atrophy' (SMA) refers to a group of diverse genetic disorders that affect the spinal and bulbar lower motor neurons. Several forms of SMA have been described in association with different gene mutations and significant phenotypic variability.

The most frequent form of SMA is the autosomal-recessive proximal SMA, or *SMN1*-linked SMA. Severe forms of this disease typically have neonatal or infantile onset. However, milder phenotype variants can be diagnosed in adulthood. Promising results from recent research studies could lead to significant therapeutic progress in this disease.

The second most common genetic disorder affecting lower motor neurons is Kennedy disease (KD), or spinal and bulbar muscular atrophy (SBMA). A better understanding of the complex molecular pathways implicated in such motor neuron damage has revealed several lines of potential therapeutic strategies that are currently under investigation.

The number of causative genes associated with rare forms of autosomal-dominant SMA has increased exponentially over the past few years due to next-generation sequencing technologies. Clinical heterogeneity within the same family

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has also contributed to expansion of the phenotypic spectrum associated with these genes. Despite their low prevalence, functional studies exploring the impact of gene mutations involved in these rare disorders are crucial for unraveling the mechanisms behind motor neuron degeneration.

The present review discusses only the adult-onset SMA conditions with predominantly proximal lower motor neuron syndromes, and excludes the clinical entities exclusively affecting infants, including lethal infantile SMA with arthrogryposis, SMA with progressive myoclonic epilepsy and pontocerebellar hypoplasia with infantile SMA. SMA conditions of predominantly distal involvement, which largely overlap with distal hereditary motor neuropathies, have already been extensively covered by Devic et al. [1].

2. SMA secondary to *SMN1* gene mutations

This form of SMA is due to homozygous deletion or mutation of the survival motor neuron 1 (*SMN1*) gene [2]. Its frequency is approximately 1/11,000 births, and it is the most common genetic cause of death in infants [3].

2.1. *Clinical features*

The clinical features associated with this disorder are muscle weakness and atrophy with a predominantly proximal muscle distribution. Lower limbs are more involved than upper limbs. Bulbar and respiratory weakness is seen in patients with more severe disease.

SMN1-linked SMA is classified into distinct clinical phenotypes based on the highest level of motor function achieved and age at disease onset. The clinical spectrum ranges from the most severe phenotype (type 1 SMA) to milder clinical forms (type 4 SMA) [3].

Type 1 SMA (Werdnig–Hoffmann disease) is the most common and severe form, representing about 45% of SMA cases. In classic terms, these patients develop, before the age of 6 months, severe hypotonia, symmetrical flaccid paralysis, respiratory distress, weak cry and poor feeding. Oculomotor and facial muscles are spared. Tongue fasciculations are common. By definition, the ability to sit independently is never achieved, and most patients die before the age of 2 years.

Type 2 SMA is characterized by a disease onset between 6 and 18 months. This disorder represents about 20% of SMA cases. Patients achieve the ability to sit unsupported, but these children never stand or walk independently. Examination demonstrates predominantly proximal weakness with more severe involvement of the lower limbs. Fine tremor is often observed, mainly in distal limbs. Tongue atrophy and fasciculations are characteristic, and impaired swallowing and ventilatory insufficiency are frequent (Fig. 1). Early scoliosis is present in all patients and contributes to the restrictive ventilatory deficit. However, progress in mechanical ventilation techniques has enabled the majority of patients to survive into adulthood.

Type 3 SMA (Kugelberg–Welander disease) affects around 30% of SMA patients. These patients are able to walk without support. They are subdivided into SMA type 3a, with disease onset before the age of 3 years, and a milder form, SMA type 3b, with onset after the age of 3. Patients usually present with proximal lower-limb weakness, and have difficulty climbing stairs and a waddling gait. Some patients need wheelchair assistance in childhood, whereas others preserve the ability to walk into adulthood.

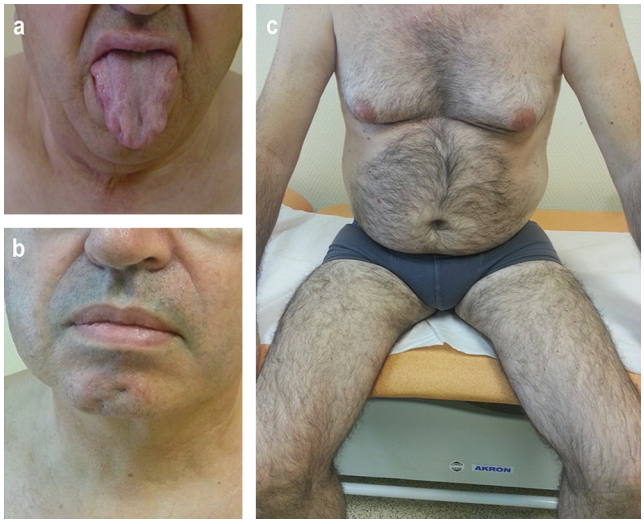

Fig. 1 – a: tongue atrophy; b: chin atrophy; and c: gynecomastia and thigh atrophy.

Type 4 SMA describes patients with an adult onset ($>$ 18 years) and represents $<$ 5% of cases. Patients remain ambulant as adults and, in the majority of cases, have no need of respiratory assistance.

The differential diagnosis with limb-girdle muscle disease, especially Becker dystrophinopathy, may be difficult based on clinical grounds due to their overlapping clinical phenotypes. Electromyography (EMG) and muscle biopsy are useful tools, permitting identification of a neurogenic profile. Muscle magnetic resonance imaging (MRI) can provide additional information to help guide the diagnosis. In a recent study, Durmus et al. [4] identified a selective pattern of muscle involvement in 25 patients with a genetically proven type 3b SMA that was distinct from the profile found in Becker muscular dystrophy. Unlike the latter, severe triceps and iliopsoas involvement, but relative preservation of biceps and gluteus maximus, were associated with the type 3b SMA group.

Besides contributing to the differential diagnosis, electrophysiological and imaging studies have a potential role in identifying biomarkers of clinical evolution. Recently, El Mendili et al. [5] investigated the profile of spinal cord atrophy in 18 SMA patients with quantitative MRI. Cross-sectional area measurements revealed a significant cord atrophy gradient mainly located between C3 and C6 vertebral levels, with maximum involvement at the C4–C5 level. Quantification of spinal cord atrophy could be a potential biomarker of motor neuron loss, although longitudinal studies are needed to evaluate the sensitivity of this tool for changes over time. Electrophysiological studies could provide further quantitative parameters of potential interest, including non-invasive biomarkers for therapeutic trials. Compound muscle action potential (CMAP) amplitude correlates with clinical severity,

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