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Review article

The wide spectrum of clinical phenotypes of spinal muscular atrophy with respiratory distress type 1: A systematic review

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ABSTRACT

Spinal muscular atrophy with respiratory distress type 1 (SMARD1), also known as distal spinal–muscular atrophy 1 (DSMA10), is an autosomal recessive type of spinal muscular atrophy that is related to mutations in the *IGHMBP2* gene, which encodes for the immunoglobulin μ-binding protein. SMARD1 patients usually present low birth weight, diaphragmatic palsy and distal muscular atrophy. Clinical features are still the most important factor that leads to the diagnosis of SMARD1, due to the fact that *IGHMBP2* gene mutations are characterized by significant phenotypic heterogeneity. In the present review, we will systematically discuss the genetic, clinical and neuropathological features of SMARD1 in order to provide a complete overview of SMARD1 variable clinical presentations and of the most important diagnostic tools which can be used to identify and properly manage affected individuals. This background is crucial also in the perspective of the development of novel therapeutic strategies for this still orphan disorder.

Contents

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1. Introduction

Spinal muscular atrophy with respiratory distress type 1 (SMARD1), also known as distal spinal muscular atrophy 1 (DSMA1) or distal hereditary motor neuronopathy type VI (dHMN6/HMN6), is a rare autosomal recessive disorder that is caused by mutations in the gene *IGHMBP2*. *IGHMBP2* gene is located on the chromosome 11q13, and encodes for the immunoglobulin μ -binding protein 2 which is a ubiquitously expressed ATPase/helicase within the SF1 superfamily [1,2]. The specific role of this protein is still not clear, but it has been suggested that it is involved in ATP-dependent mRNA decay. Mutations in *IGHMBP2* lead to anterior horn motor neuron degeneration, which is at the basis of SMARD1 phenotype. The main features of the disease are represented by a progressive distal symmetrical muscular weakness (particularly at lower limb muscles) and by an irreversible diaphragmatic paralysis that usually requires mechanical ventilation within the first year of life. While the exact prevalence of SMARD1 is not known, diaphragmatic palsy is observed in approximately 1% of patients diagnosed with early onset SMA [3].

SMARD1 is considered a fatal form of infantile motor neuron disease: patients usually die within 13 months of life and only a small number of studies report patients surviving longer [4,5].

It was first identified as an unusual variant of spinal muscular atrophy (SMA) in 1974 [6], was described later in 1989, [7] but it was recognized as a separate clinical entity only in 1996 [3]. Since then, about 60 cases have been described. Clinical features of patients with SMARD1 include low birth weight, feeble cry, weak suck, failure to thrive, and progressive symmetrical muscular weakness along with predominant distal lower limb muscle involvement that can be associated with foot deformities (Fig. 1). The diaphragmatic paralysis arises as dyspnea, with eventration of one or both hemidiaphrgams and ultimately requires permanent respiratory support. Cranial nerve dysfunction is also a late manifestation of the disease, and deep tendon reflexes cannot be elicited in 86% of cases [8]. The autonomic system is also affected: patients show excessive sweating, decreased pain perception, constipation, bladder incontinence and cardiac arrhythmias [5,8]. No effective therapy is available for motor neuron diseases, including SMARD1.

The main clinical, neuropathological, and genetic aspects of SMARD1 are here systematically reviewed, considering all published clinical studies, delineating the natural history of the disorder and genotype–phenotype correlations.

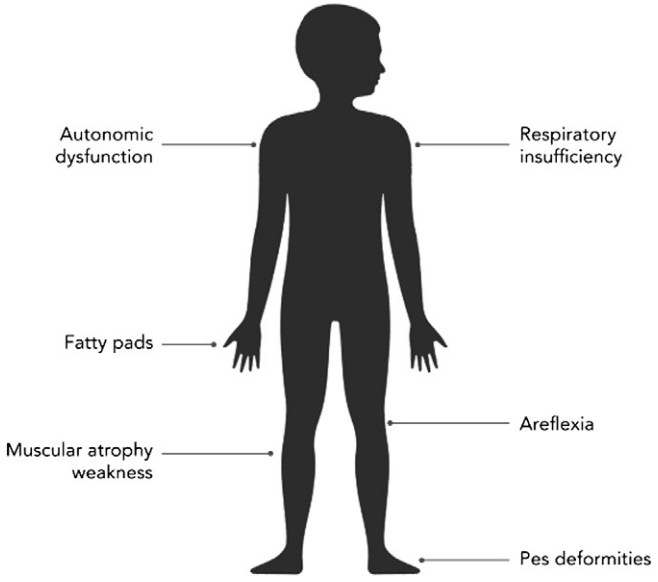

Fig. 1. SMARD1 clinical signs and symptoms.

2. Clinical features

2.1. Classical presentation

2.1.1. Neuromuscular and respiratory features

After the discovery of mutations responsible for the disease, the clinical hallmarks of the disease have become more and more delineated (Table 1). It was reported that SMARD1 can be associated with intrauterine growth delay, prematurity, foot deformities and a weak cry [8,9]. Some patients also presented an involvement of the autonomic and sensory systems [8,9]. Patients with features slightly different from the classical form have also been reported. Indeed, in some children a peculiar absence of the pathological modifications of anterior horn cells has been observed [10].

The natural course of SMARD1 was described in a longitudinal study on 11 infant patients aged between 2 and 14 years which were followed for 7.8 years [11]. A semi-quantitative scoring system was applied to evaluate the specific features of the disease consisting in 10 items that reflected the development of the disease. The monthly sum scores were calculated every year, and the residual enzymatic activity of 6 patients was analyzed. At the end of the observational period, all the children had respiratory distress that required mechanical ventilation—except one girl who regained independent breathing at 4 years of age. All patients showed muscular weakness, with an earlier involvement of the distal limbs and no patient was able to walk; all the patients had autonomic dysfunction; 7 subjects out of 11 had normal facial expression; 4 were able to sit and hold the head; 6 could speak through a speech cannula; and 5 of 10 remained seizure free. The clinical outcome of the patients varied with the score at 3 months of age, which predicted the clinical outcome at 1 and 4 years of age. After a rapid decline of the clinical score during the first 2 years of age, residual capabilities reached a plateau or even improved. A better outcome appeared to be associated with residual enzymatic activity of the IGHMBP2 protein.

Foot deformities (equinovarus feet), fatty pads over the metacarpophalangeal joints, excessive sweating [9,12] and seizures [13] have also been reported. In some patients limb muscle involvement follows early respiratory failure making the clinical diagnosis more challenging. This is the case of an infant, aged one-month, with loud breathing and failure to thrive since birth [14]. He presented inspiratory stridor, weak cry, and hemidiaphragm palsy, but the diagnosis was delayed until the appearance of distal muscle weakness. A nerve conduction study performed at 3 months of age showed low or absent responses and an EMG study displayed significant denervation of the motor neurons of distal upper extremities. Genetic tests confirmed the diagnosis of SMARD1.

Fanos et al. described the first and only case of typical SMARD1 form (confirmed by genetic test) presenting also hepatic and myocardial alteration. Myocardial dysfunction is also present in the nmd mouse, an animal model for human SMARD1; thus it could be valuable to evaluate the hepatic and cardiac involvement in SMARD1 patients [15].

2.2. Atypical clinical presentations

2.2.1. Autonomic deregulation

An important involvement of the autonomic system, especially in an advanced stage of disease has been observed: patients can present excessive sweeting, urinary retention that requires catheterization, constipation, and also cardiac arrhythmia [5,8,16]. However in some reports, the autonomic deregulation is a prominent feature: Nomura et al. described a case of a genetically confirmed SMARD1 in a Japanese girl who presented a severe autonomic paroxysm with hypotension [17]. The patient, born from non-consanguineous parents, had to be treated with mechanical ventilation from the age of two months. At the age of 15 months, studies performed in order to investigate high heart rate variability demonstrated neither a significant parasympathetic nervous activity nor the existence of circadian rhythm. At 16 months, the patient