Spinal Muscular Atrophies

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KEYWORDS

- Spinal muscular atrophy • 5q SMA • Non-5q SMAs
- Survival of motor neuron protein • Werdnig-Hoffmann disease • Dubowitz disease
- Kugelberg-Welander disease

KEY POINTS

- Spinal muscular atrophies (SMAs) are hereditary degenerative disorders of lower motor neurons associated with progressive muscle weakness and atrophy.
- SMA subtypes are classified by severity of weakness: type I nonsitters, type II sitters, type III walkers, and type IV adult-onset patients with mild phenotype.
- The survival of motor neuron (SMN) gene is present in 2 copies on each chromosome 5, designated *SMN1* and *SMN2*. A majority of cases are caused by homozygous deletions of exon 7 of the telomeric *SMN1* gene on chromosome 5q.
- An approximate inverse correlation exists between *SMN2* gene copy number, which varies normally in the population, the level of SMN protein, and severity of disease; however, the role of the SMN protein is still under active investigation.
- No cure exists for SMA. Treatment consists of multidisciplinary management of symptoms. Trials are under way to identify agents for therapy.

INTRODUCTION

Spinal muscular atrophies (SMAs) are genetic disorders clinically characterized by progressive muscle weakness and atrophy associated with degeneration of spinal and, in the most severely affected patients, lower bulbar motor neurons. Classic proximal SMA, the most common form of SMA and the leading genetic cause of infant mortality, seems to be found in practically all populations, but it is diagnosed more frequently in infants and children than in adults. The severe form of SMA was first described in the early 1890s by clinician Guido Werdnig[1] of the University of Graz, Austria, and physician Johann Hoffmann[2] of Heidelberg, Germany. Their reports described the neuromuscular phenotype of the disease and the associated loss of anterior horn cells in the spinal cord.

Disclosures: Dr. Darras receives research support from PTC Therapeutics and ISIS Pharmaceuticals.
This article was funded in part by the SMA Foundation (New York, NY).
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Pediatr Clin N Am 62 (2015) 743–766
http://dx.doi.org/10.1016/j.pcl.2015.03.010 **pediatric.theclinics.com**
0031-3955/15/$ – see front matter

SMA results from homozygous deletions or mutations involving the "survival of motor neuron" (SMN) gene at locus 5q13. The *SMN* gene is present in 2 copies on each chromosome 5, designated *SMN1* and *SMN2*, forming an inverted duplication (**Fig. 1**). *SMN2* is differentiated from *SMN1* by 5 nucleotide changes that do not change amino acids. The crucial single nucleotide change in *SMN2* creates an exonic splicing suppressor in exon 7 that leads to exclusion of exon 7 in most transcripts[3]; thus, the duplicated (*SMN2*) gene produces less functional SMN protein. Most patients with 5q proximal recessive SMA harbor homozygous deletions involving exon 7 of the *SMN1* gene but maintain at least 1 copy of *SMN2*. An approximate correlation exists between *SMN2* gene copy number, which varies normally in the population, the level of SMN protein, and severity of disease; however, the role of the SMN protein is still under active investigation. Modifying genes that serve other roles in motor neuron function seem present as well. SMA may involve dysfunction of more than lower motor neurons, with abnormalities of the neuromuscular junction noted in animal models and abnormal muscle development in the most severely affected patients. There are also many other types of SMA, known as non-5q SMAs, which are related to mutations in various genes expressed in a wide range of tissues, including the nervous system.

EPIDEMIOLOGY

The incidence of SMA has been estimated at 1 in 6000 to 11,000 live births[4–7] or approximately 7.8 to 10 per 100,000 live births[8–10] and at 4.1 per 100,000 live births for type I SMA.[8] The estimated panethnic disease frequency is approximately 1 in 11,000.[7] The carrier frequency for mutations in the *SMN1* gene has been estimated from 1:38 to 1:70. Despite the high carrier frequency, the incidence of SMA is lower than expected. It has been postulated that this may reflect that some fetuses have a 0/0 SMN1/SMN2 genotype (ie, no SMN protein is present at all), which is known in other species to be embryonic lethal.[11]

CLINICAL CHARACTERISTICS

Although most patients with SMA have deletions or mutations involving the *SMN1* gene, a range of phenotypic severity permits division into 4 broad clinical subtypes. It is recognized that the subtypes represent a phenotypic continuum extending from the very severe, with onset in utero, to the very mild, with onset during adulthood; there is also a spectrum of severity within each of these groups (**Table 1**).[12,13] For the purposes of clinical classification or of guidelines developed for standards of care, the maximal functional status achieved approach, which classifies type I patients as nonsitters, type II patients as sitters, and type III patients as walkers, has been used.[14,15] Patients with a mild phenotype and onset during middle or late age are classified as type IV. The age at onset is also considered in the classification but because of potential overlap between subtypes and the difficulty in accurately determining the onset of symptoms, it has not been considered as the sole determinant of disease subtype.

Type I Spinal Muscular Atrophy

After the initial description of infantile SMA by Werdnig and Hoffmann in the early 1890s and further descriptions made by Sylvestre in 1899[16] and Beevor in 1902,[17] infantile or type I SMA was described again in detail, both clinically and pathologically, by Randolph Byers and Betty Banker at Boston Children's Hospital in 1961.[18] Patients with type I SMA, also known as Werdnig-Hoffmann disease, present between birth and 6 months of age. Type I SMA has been further subdivided into 3 groups: type IA (or type 0 in certain reports[19]) with onset in utero and presentation at birth, type