Spinal Muscular Atrophy

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KEYWORDS

• Spinal muscular atrophy • Motor neuron • Survival motor neuron gene • *SMN1* • *SMN2*

KEY POINTS

- Spinal muscular atrophy (SMA) is the most common genetic cause of infant mortality and is characterized by proximal muscular weakness.
- Humans have 2 nearly identical inverted SMN genes (*SMN1* and *SMN2*) on chromosome 5q13 and homozygous deletion of the SMN1 gene results in SMA.
- The *SMN2* gene produces mostly a shortened, unstable SMN messenger RNA (mRNA) and, through alternative splicing, a relatively small amount of full-length, functional SMN mRNA.
- The *SMN2* gene copy number is a good prognostic biomarker of SMA clinical severity.
- Clinical management of SMA is supportive; however, current and planned clinical trials designed to increase SMN expression levels in motor neurons hold great promise.

INCIDENCE

The incidence of SMA is 1 in 11,000 live births.[1]

PREVALENCE

The prevalence of the carrier state is approximately 1 in 54.[1]

SEVERITY

The clinical severity of spinal muscular atrophy (SMA) correlates inversely with *SMN2* gene copy number and varies from an extreme weakness and paraplegia of infancy to a mild proximal weakness of adulthood.

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NATURAL HISTORY

The natural history of SMA is complex and variable. For this reason, clinical subgroups have been defined based upon best motor function attainment during development. Type 1 SMA infants never sit independently. Type 2 SMA children sit at some point during their childhood, but never walk independently. Type 3 SMA children and adults are able to walk independently at some point in their childhood.

INTRODUCTION

The term "spinal muscular atrophy (SMA)" refers to a group of genetic disorders all characterized by degeneration of anterior horn cells and resultant muscle atrophy and weakness. The most common SMA, accounting for more than 95% of cases, is an autosomal-recessive disorder that results from a homozygous deletion or mutation in the 5q13 survival of motor neuron (*SMN1*) gene. In a large, multiethnic study to test the feasibility of high-throughput genetic testing for SMA carriers, the overall carrier frequency was 1 in 54 with an incidence of 1 in 11,000 live births.[1] The severity of SMA is highly variable and the clinical features can be classified into 4 main phenotypes on the basis of age of onset and maximum motor function achieved.[2] There is no cure for SMA; however, an understanding of the molecular genetics of SMA has led to the development of preclinical models and numerous potential therapeutic approaches.[3–5] There is great excitement in the SMA field because these therapeutic approaches have recently entered early phase clinical trials.

Paired with the excitement of an active therapeutic pipeline has been a focus on understanding the natural history of this disorder as well as early diagnosis and clinical intervention. This has led to the development of clinical standards of care.[6,7] The natural history of the most severe form of SMA (type 1) has been the subject of particular attention and is characterized by a rapid loss of motor and respiratory function in the first year of life.[8] Studies have shown that survival beyond 1 year in these infants can be improved to 70% or more with proactive use of noninvasive ventilatory support and enteral feeding.[9–11] In contrast, studies on the natural history of the milder forms of SMA (types 2 and 3) have shown little decrease in motor and respiratory function during the course of a single year.[12,13]

This article focuses on the clinical manifestations of SMA and how it relates to the molecular genetics and pathogenesis of the disease. We discuss genetic testing and review the clinical management of SMA with particular attention to aspects of care and methods of assessment that can be used in clinical practice and as clinical trial outcome measures. We also review current therapeutic approaches and highlight current controversies in clinical management, newborn screening, and clinical trial design.

CLINICAL FEATURES

The predominant clinical features of SMA are muscle weakness and atrophy. Weakness is usually symmetric, with proximal muscles more affected than distal groups as in NP7.[14] Over the last 125 years, reports detailing the clinical manifestations and wide range of clinical severity have all recognized and emphasized the seminal pathology as anterior horn cell degeneration, as well as the pertinent clinical features of symmetric, proximal predominant extremity weakness that also affects axial, intercostal, and bulbar musculature.[15] The multiple described phenotypes were eventually formalized into a classification scheme at an International Consortium on Spinal Muscular Atrophy sponsored by the Muscular Dystrophy Association in 1991.[16] This