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ORIGINAL ARTICLE

Infantile spinal atrophy: Our experience in the last 25 years☆

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Received 30 January 2014; accepted 25 June 2014
Available online 25 March 2015

KEYWORDS
Spinal muscular atrophy;
Spinal muscular atrophy;
Spinal muscular atrophy with respiratory distress type 1

Abstract
Objectives: To determine the incidence of spinal muscular atrophy (SMA) in our study population and genetic distribution and epidemiological and clinical characteristics and to analyse the level of care and development.
Material and method: Retrospective descriptive study of patients treated in our hospital in the past 25 years (from 1987 to early 2013), with a clinical and neurophysiological diagnosis of SMA.
Results: A total of 37 patients were found, representing an incidence for our reference population and year of 1 case per 10,000 live births. Males predominated (male/female ratio: 1.6/1). The type of SMA diagnosed more frequently was type I (26 cases), followed by type II (9 cases), one case with SMA type III, and one case of spinal muscular atrophy with respiratory distress type 1 (SMARD1). The most frequent genetic alteration was homozygous deletion of exons 7 and 8 of SMN1 gene in 31 cases, while five patients had atypical genetics. The median survival for type I was 8.0 months and 15.8 years for type II.
Conclusions: The incidence in our population remains stable at around 1/10,000. Most cases presented with, predominantly male, typical genetics. In approximately 1/10 patients the genetic alteration was different from the classical one to the SMN gene. The prevalence of AME unrelated SMN gene was 1/37. The level of care has increased in line with social and welfare demands in recent years.

☆ Please cite this article as: Rodríguez AM, Martínez PLM, Fernández JMR, Cardona AU, Antón JM. Atrofia muscular espinal: revisión de nuestra casuística en los últimos 25 años. An Pediatr (Barc). 2015;82:159–165.

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PALABRAS CLAVE
Atrofia muscular espinal;
Atrofia espinal infantil;
Atrofia muscular espinal con distrés respiratorio

Atrofia muscular espinal: revisión de nuestra casuística en los últimos 25 años

Resumen
Objetivos: Conocer la incidencia de la atrofia espinal infantil (AME) en nuestra población y estudiar la distribución genética y las características epidemiológicas y clínicas, el nivel de cuidados y su evolución.
Material y método: Estudio descriptivo retrospectivo de los pacientes atendidos en nuestro hospital en los últimos 25 años (1987–2013), con diagnóstico clínico y neurofisiológico de AME.
Resultados: Se halló a 37 pacientes, lo que supone una incidencia aproximada de 1/10,000 recién nacidos vivos. Predominaba el sexo masculino (relación varón/mujer: 1,6/1). El tipo de AME diagnosticado más frecuentemente fue el tipo I (26 casos), seguido del tipo II (9 casos), un caso de AME tipo III, y otro caso de *spinal muscular atrophy with respiratory distress type 1* (SMARD 1). La alteración genética más frecuente fue la deleción en homocigosis de exones 7 y 8 del gen SMN1, en 31 casos, mientras que 5 pacientes presentaban una genética atípica. La mediana de supervivencia para el tipo I fue de 8,0 meses y de 15,8 años para el tipo II.
Conclusiones: La incidencia en nuestra población permanece estable en torno a 1/10,000. La mayoría de los casos presenta una genética típica con predominio de varones. En aproximadamente 1/10 pacientes la alteración genética fue diferente de la clásica. La prevalencia de AME no relacionadas con el gen SMN fue de 1/37. El nivel de cuidados se ha incrementado en los últimos años, en consonancia con las demandas sociales y asistenciales.

Introduction

Our knowledge of spinal muscular atrophy (SMA) has advanced considerably since the earliest descriptions done by Werdnig, in 1891, and Hoffmann, in 1893. We know that it is due to a defect in the translation of the telomeric survival motor neuron (SMN) protein, which seems to play a role in several essential cellular functions (RNA metabolism, processing, and splicing) and other functions more specifically related to the survival of alpha motor neurons (apoptosis, axonal transport) in the anterior horn of the spinal cord. The SMN protein is encoded by the *SMN1* and *SMN2* genes. The literature describes a worldwide incidence of approximately 1 in 10,000 live births, with 1 out of 40 people being carriers of the disease.

The classical clinical picture of SMA is predominantly proximal muscle weakness and atrophy, with ages of onset and severity that vary depending on the clinical type of SMA. Traditionally, the classification of SMA comprised 3 types: infantile, juvenile, and adult. At present, the International Consensus Statement for Standard Care in SMA[1,2] classifies it into more types based on the age of onset and clinical course, dividing type III into subtypes according to the age of onset. Type IV was added for adult-onset cases, and type 0 for cases with prenatal onset, which result in death within the first weeks of life (Table 1). While there is clinical variability among individuals in each type and up to 25% of the patients cannot be categorised, this classification is useful for clinical practice and prognosis.

The gene involved in SMA, discovered in 1995,[3] is located in the long arm of chromosome 5 (5q11.1-13.3). It has been named *SMN* for ''survival motor neuron''. Humans have two nearly identical copies of this gene that have been called *SMN1* and *SMN2*. They differ in a single nucleotide at the beginning of exon 7 (C in *SMN1* and T in *SMN2*) that is important in the splicing of the SMN RNA. We do not know why this ubiquitous protein causes this highly selective neuronal disease. Deletions in *SMN1* cause SMA. Approximately 95% of SMA patients have homozygous absence of exons 7 and 8 of the *SMN1* gene, and about 5% are compound heterozygous for absence of exons 7 and 8 in one *SMN1* allele and a point mutation in the other. Deletions in the *SMN2* gene do not cause the disease; instead, it is the number of copies of this gene, which may vary, that has an effect on the phenotype and determines the severity of SMA, with a greater number of *SMN2* copies correlating to a milder phenotype, although there are other factors at play.[4,5] In this regard, it has been hypothesised that the disease could be treated with gene therapy by induced overexpression of the *SMN2* gene, and the day when this terrible disease can be mitigated may not be far away.[6,7]Another genetic approach that was successful in an experimental study was the insertion of the *SMN* gene by means of viral vectors in the genome of a mouse model of the disease.[8]

Other forms of disease with clinical features that overlap with SMA, with subtle differences, are associated to different genes. Cases associated with chromosome 11 alterations have been described (spinal muscular atrophy with respiratory distress type 1 [SMARD1])[9,10] as well as cases of early-onset recessive X-linked disease in males (Kennedy's disease).[11,12]

The aim of this study was to determine the present incidence of SMA in our population, its genotype distribution, and its epidemiological and clinical characteristics in the past 25 years in the context of our current knowledge, and to assess the level of care and the outcomes of SMA in our setting based on the international consensus.[1,2]