SPINAL MUSCULAR ATROPHY FROM NORTHERN IRAN: A CLINICAL AND GENETIC SPECTRUM OF TEN PATIENTS

M.R. Salehi Omran MD [1],
A. Ghabeli Juibary MD [2]

Abstract

Objective

Autosomal recessive spinal muscular atrophy (SMA) is, after cystic fibrosis, the second most common fatal monogenic disorder and the second most common hereditary neuromuscular disease after duchenne dystrophy. The disease is characterized by degeneration of anterior horn cells leading to progressive paralysis with muscular atrophy. Depending on the clinical type (Werdnig-Hoffmann = type I, intermediate form = type II, Kugelberg-Welander = type III), some workers also have delineated an adult form of SMA (SMA type 4). SMA causes early death or increasing disability in childhood. The aim of this investigation was to describe the clinical findings of patients with spinal muscular atrophy (SMA) with survival motor neuron (SMN) gene deletion.

Materials & methods

This is a descriptive study conducted on 10 patients of SMA, confirmed by deletion of the SMN gene. All 10 patients had symmetrical muscle weakness, which was diffuse in those with onset of symptoms up to 1 months of age, and either proximal or predominant in lower limbs.

Frequency determination of positive clinical and laboratory data was done according to revised diagnostic criteria

Results

It was found that all patients with SMA had homozygous deletions of exons 7 and 8 of the survival motor neuron 1 (SMN1) gene, which is one of the candidate genes identified within 5q13. Fasciculations, atrophy and decreased DTR were frequent findings. Laboratory metabolic tests and all brain CT scans were normal. EMG and NCV findings, all showed normal motor and Sensory NCV and denervation of muscles of upper and lower extremities were compatible with a diagnosis of spinal muscular atrophy.

Conclusion

Our results confirm that SMN1 copy number analysis is an important parameter for identification of couples at risk of having a child affected with SMA and reduces unwarranted prenatal diagnosis for SMA.

Keywords: Spinal muscular atrophy, SMN Gene, clinical findings, EMG, NCV

1. Pediatric Neurologist,Babol University of Medical Sciences
2.General Physician

Corresponding Author:
M.R. Salehi Omran MD
Amirkola pediatric hospital
E-mail: salehiomran@yahoo.com

Introduction

In children the most common entity affecting the motor neuron in the brain stem and spinal cord is SMA, with a prevalence of 1 in 10,000 live births and a carrier frequency of approximately 1 in 50 (1); proximal spinal muscular atrophy (SMA)

represents the second most common fatal autosomal recessive disorder after cystic fibrosis (2) and the second most common hereditary neuromuscular disease after duchenne dystrophy. SMA is characterized by the degeneration of anterior horn cells of the spinal cord, resulting in progressive weakness. The condition is clinically heterogeneous and has been divided into four subtypes according to age of onset and clinical severity (3). About 10% of infants with SMA type 1 are born with arthrogryposis , and this may indicate the severe fetal form recently designated type 0 (4,5). Molecular genetic analysis has mapped all four forms of childhood and adult SMA to chromosome 5q11.2-q13.3, suggesting that they are allelic disorders.

In a majority of normal individuals, survival motor neuron (SMN) genes are present in at least one telomeric (SMN1) and one centromeric (SMN2) copy per chromosome. However, 26% of all normal chromosomes 5 lack the SMN2 copy of the gene. The two SMN genes are highly homologous but a single nucleotide variation in exon 7 of SMN1 and SMN2 genes is responsible for functional differences (6). The majority of SMA patients, irrespective of their clinical types, have homozygous deletion of the SMN1 gene (7). In addition intragenic mutations have been identified in most of the patients who have only one copy of SMN1 gene, confirming the involvement of SMN1 in the pathogenesis of SMA (8). Normal individuals with one copy of the SMN1 gene are carriers for this autosomal recessive disorder.

The single nucleotide differences in exons 7 and 8 are used to distinguish SMN1 and SMN2 in diagnostic and prenatal testing for SMA (9,10). Although this methodology can detect homozygous absence of SMN1, it cannot differentiate the presence of one copy from two or more copies of SMN1. In recent years, molecular diagnostic testing for SMN1 copy number by dosage analysis has been developed (11,12), and is used to determine the carrier status for SMA in the majority of cases.

Material and Methods

Subjects

Detailed clinical history and pedigree was drawn for all cases and their families. Clinical examinations of patients and family members were carried out in the neurology outpatient department of the Amirkola pediatric hospital. Informed consents were obtained for all participants, following genetic counseling. Eventually ten children, four female and 6 male, were included in the study.

Results

Mean age at time of diagnosis of the 10 infants was 4 months. All had symmetrical muscle weakness, which was diffuse in those with onset of symptoms up to 1 month of age, and either proximal or predominant in lower limbs .It was found that all patients with SMA had homozygous deletions of exons 7 and 8 of the survival motor neuron 1 (SMN1) gene, i.e. one of the candidate genes identified within 5q13. Fasciculations, atrophy and decreased DTR were frequent findings.Laboratory metabolic tests and all brain CT scans were normal. EMG and NCV findings, all showed normal motor and sensory nerve conduction velocity (SNCV) and denervation of muscles of upper and lower extremities that were compatible with a diagnosis of spinal muscular atrophy.

Discussion

Ten samples were analyzed by quantitative PCR to determine the number of SMN1 gene copies present, and all of these were found to have one SMN1 gene copy. A previous study reported that 94.3% of normal individuals had two SMN1 copies and 2.1%, 0.7% and 2.9% had three, four and one copy (ies), respectively [13]. Only one SMN1 gene copy is sufficient for normal functioning in an individual, as all parents with one copy of the SMN1 gene are asymptomatic.

From our small group of SMA cases, parents of confirmed SMA patients were obligate carriers of the disease, which was confirmed by SMA carrier testing; however, parents of children with SMA may not always be carriers as de-novo deletions of the SMN1 gene occurs in more than 2% of patients, with SMA (12,14). Presence of de-novo deletion in the family lowers the recurrence risk for couples from 25% to the risk of a second de-novo mutation which is very low. Knowledge of the carrier status of parents of affected children is useful for determining if a de-novo mutation has occurred and establishing the couple's future risk of having an affected

child. If the parents are found to be carriers, then carrier testing can be offered to the siblings of the parents, who also have a 50% risk of being a carrier for SMA (1).

The most severe form of SMA occurs at birth or in early infancy and in Iran this may be difficult for primary care providers to diagnose. No data are available on the population prevalence of SMA and the status of diagnosis of SMA from Iran, due to the limited number of centers and the high cost and complexity of the molecular genetic test. Hence unfortunately in many cases the child usually expires before the diagnosis is confirmed and the parents refer with a history of a previous child's death with symptoms consistent with SMA. In absence of a sample for molecular genetic testing for SMA, the information obtained by SMN1 copy number analysis for the parents can be utilized to confirm the diagnosis for the deceased child and to offer prenatal diagnosis for future pregnancies. The presence of one copy of the SMN1 gene in the parents will confirm their carrier status and prenatal diagnosis can definitely be advised in subsequent pregnancies. Our results confirm that SMN1 copy number analysis is an important parameter for identification of couples at risk for having a child affected with SMA and reduces unwarranted birth of children with dignosis of SMA. Copy number analysis is also useful in the setting of clinically suspected SMA with a negative diagnostic SMA test.

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