

Case Report

VERY SEVERE SPINAL MUSCULAR ATROPHY (TYPE 0): A REPORT OF THREE CASES

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Abstract

Objective

We describe three patients with very severe Spinal Muscular Atrophy (SMA) presented with reduced fetal movement in utero, profound hypotonia, severe weakness and respiratory insufficiency at birth. In all infants, electrodiagnostic studies were compatible with a neurogenic pattern. In genetic studies, all cases had homozygous deletions of exons 7 and 8 of Survival Motor Neuron (SMN) and exon 5 of Neuronal Apoptosis Inhibitory Protein (NAIP) gene. SMA should be considered in the differential diagnosis of reduced fetal movement and respiratory insufficiency at birth.

Keywords: Spinal muscular atrophy, survival motor neuron gene, neonate

Introduction

Spinal Muscular Atrophy (SMA) is an autosomal recessive disease characterized by degeneration of anterior horn cells of the spinal cord leading to progressive symmetrical weakness and atrophy of the proximal muscles (1). Clinically affected patients are classified into three or four groups according to the age of onset and progression of weakness. Children with type I SMA are the most severely affected ones and they usually have symptoms before 6 months of age. These patients are unable to sit and usually die within 1-2 years as a result of respiratory insufficiency. Type II patients have a milder presentation and survive into adolescence but they are unable to stand without support. Type III SMA is the mildest form (1). These three types are allelic and the majority are caused by homozygous deletions of the Survival Motor Neuron (SMN) gene localized on chromosome region 5q13 (2). In addition to these classical SMA types, unusual SMA variants have been described (3-5). Dubowitz described a new form of SMA called type 0 with intrauterine onset, leading to profound hypotonia, facial weakness, a progressive and early fatal course and death within the first 3 months (6). These infants present with asphyxia or severe respiratory distress in the neonatal period as a result of muscular weakness and usually need immediate intubation and artificial ventilation (6-9). This case study describes three patients with neonatal onset SMA. The patients presented with particularly severe forms of SMA with profound weakness and unusually severe respiratory distress at birth and all of them were ventilator dependent until death.

Case report

Case 1: This male infant was the third child born to consanguineous parents. The first child died of pneumonia at the age of 6 months. The second child was a

healthy baby. During pregnancy, fetal movements were absent from 32 weeks of gestation. There was no polyhydraminous. He was born at term with a birth weight of 3.3 Kg. The Apgar score was 8-9. There were no spontaneous respiratory movements and he was immediately intubated and ventilated artificially. He was referred to NICU on suspicion of respiratory distress syndrome. He was hypotonic with absent neonatal reflexes. On the 4th day of admission, he was examined by a pediatric neurologist. On this visit, he was ventilator dependent, alert and responsive to tactile stimuli; he opened his eyes in response to painful stimuli and had a weak cry. Deep tendon reflexes (DTRs) were absent. Electrodiagnostic studies showed a neurogenic pattern supporting the diagnosis of SMA. Molecular genetic analysis revealed the homozygous absence of exons 7 and 8 of the Survival Motor Neuron (SMN) gene. Analysis of exon 5 of the NAIP gene detected a homozygous deletion. The baby died immediately after mechanical ventilation was discontinued at the request of his parents on the 25th day of life. Subsequent pregnancy resulted in a healthy baby.

Case 2: This male infant was the first child born to unrelated parents. The pregnancy was unremarkable but the mother felt that fetal movements were reduced from 34 weeks of gestation. He was born by spontaneous vaginal delivery at 38 weeks of gestation, weighing 2.95 kg. He did not make any respiratory efforts, requiring intubation and mechanical ventilation at birth. Serum creatine kinase level was slightly elevated and tensilon test was normal. He had a bright normal expression with few spontaneous movements, a weak cry and absent DTRs. His molecular genetic analysis and electrodiagnostic studies were similar to case 1. He died 38 days after admission when respiratory support was withdrawn at the request of the parents. The mother's next pregnancy was terminated because genetic studies of the fetus in the 10th week of gestation were compatible with SMA.

Case 3: This female baby was the first child of a 23-year-old healthy mother with an uneventful pregnancy. She was born by elective cesarean section at 39 weeks of gestation weighing 3.2 kg. She presented with asphyxia at birth and needed resuscitation and intubation and ventilator support. The baby was referred to NICU on

suspicion of hypoxic ischemic encephalopathy (HIE). Brain sonography and CT scan were not remarkable. She was noted to be hypotonic with absent DTRs and spontaneous movements of the limbs. She had a bell shaped chest and tongue fasciculation and opened her eyes in response to painful stimuli. Her genetic analysis and electrodiagnostic studies were similar to case 1. On the 23th day of life, ventilatory support was electively withdrawn at the request of the parents.

Discussion

Although a substantial proportion of severe SMA (type 1) patients may have a prenatal onset, spinal muscular atrophy is rarely symptomatic in the first few days after birth and when there is an early onset, it has a lethal course with respiratory problems and lifelong need to mechanical respiratory support (10). MacLeod MJ et al. reported five cases of neonatal onset SMA with a history of diminished fetal movements in utero, presenting with asphyxia or severe weakness at birth. Three of their patients needed resuscitation and intubation and ventilatory support. Exons 7 and 8 of SMN gene were absent in all cases and four of the patients had deletions in NAIP gene (7). Two out of our three cases had reduced fetal movements and all of them had absent copies of exons 7 and 8 of the SMN gene and exon 5 of the NAIP gene.

Devriendt K et al reported a neonate who presented with fetal hypokinesia and signs of SMA at birth with deletions of both exon 7 of the SMN gene and exon 5 of the NAIP gene (11). They concluded that NAIP gene played a major role in modifying the severity of the phenotype. In all our patients, deletion of the exon 5 of the NAIP gene was noted.

Korinthenberg et al. documented three siblings who presented with asphyxia, generalized weakness, facial weakness and external ophthalmoplegia in the newborn period; they were found to be absent for the SMN gene (12).

Pavone P, et al reported a case of SMA with respiratory failure being ventilator dependent at birth. The diagnosis was made by genetic analysis (8).

To date, it is not known with certainty whether this subgroup represents a distinct entity or is merely the severe end of the classic SMA type 1. Dubowitz explains

that from a classification point of view, the more severe cases with prenatal onset and intrauterine death or with severe asphyxia at birth and early neonatal death fit into the category of "very severe" SMA (type 0) as an extension to previous severe SMA (type1) (6).

Prenatal analysis of SMN gene is useful for prenatal diagnosis of SMA when a positive family history is present (12). However, none of our patients had a documented family history of SMA. The diagnostic criteria for SMA do not include antenatal presentation (14); however, there have been case reports of in utero onset SMA (10,15).

Although hypoxia is the most common cause of reduced fetal movements, rarer causes should be considered if there is a significant family history.

The most severe type of SMA presents itself at birth or in the early days of life which may be difficult for primary care providers or pediatricians to diagnose. Proper diagnosis of this disorder needs a high index of suspicion and understanding of clinical signs and symptoms. SMA should be kept in mind in the differential diagnosis for unexplained severe generalized hypotonia and severe respiratory distress immediately after birth in the neonates, notably in patients with a bright expression and alert disposition.

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