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Short Communication

WERDNIG-HOFFMANN DISEASE (SPINAL MUSCULAR ATROPHY TYPE I VERY SEVERE FORM) - A CASE REPORT

[a]Krishnappa, J., [b]Harsha Vardhana, S., [b]Prabhakara, S., [b]Divya Chidambaram

[a]Department of Paediatrics, R.L. Jalappa Hospital, SDUMC, Tamaka, Kolar.

[b]Department of Research & Development, Genome Laboratory, SDUAHER, Tamaka, Kolar. India.

ABSTRACT

Spinal muscular atrophies are a group of autosomal recessive neuro-degenerative disorders affecting anterior horn cells of spinal cord and motor cells of cranial nerve nuclei. Depending on the age of onset and severity these disorders are classified as type I (Werdnig-Hoffmanns disease), type II and type III SMA. We report a severe form of SMA type I presenting with generalised hypotonia, reduced spontaneous movements, absence of DTR and signs of aspiration pneumonia with respiratory failure. The child was ventilated and treated with supportive care but expired after 3 days.

KEY WORDS: Spinal muscular atropy, Neurodegenerative, Werdnig-Hoffmanns

INTRODUCTION

Spinal muscular atrophies are a group of autosomal recessive degenerative diseases primarily affecting the anterior horn cells of the spinal cord and the motor cells of the cranial nerve nuclei. Incidence is of approximately 1 in 6,000 to 10,000 live births and a carrier frequency of about 1 in 50.[1] Depending on the age of onset and severity spinal muscular atropy (SMA) is classified into 3 major groups. SMA type I (Werdnig-Hoffmann Disease) are more severely affected and usually have symptoms before 6 months of age and die within 1-2 years as a result of respiratory insufficiency. Type II patients have a milder presentation usually presenting between 6 to 18 months of age and may survive up to adolescence. Type III SMA (Kugelberg-Welander Disease) is the mildest form and usually manifests after 12-24 months of age.[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]

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.[3] Type 0 is rare and accounts for less than 1% of all types of SMA. 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.[3,4,5,6]

CASE REPORT

A 2 months old male baby, third child of consanguineous parents, presented with history of cough, breathing difficulty and fever of 3 days duration. There was no history of unconsciousness or convulsions. The child had reduced activity since birth, hurried respiration and admitted to different hospitals for the respiratory symptoms. The first child died of pneumonia at the age of two and half months. The second child was healthy. During pregnancy, fetal movements were reduced from 32 weeks of gestation. There was no history of polyhydraminous. He was born at term with a birth weight of 2.5 kgs. On examination, the heart rate was 160/min, respiratory rate was 70/min, SPo2 80% at room air. Chest indrawing was present. Respiratory examination revealed bilateral crepitations; cardiovascular examination and per abdominal examination was within normal limits. Central nervous system examination revealed conscious baby with generalised hypotonia, paucity of spontaneous movements and absence of deep tendon reflexes. Investigations revealed abnormal arterial blood gases suggestive of respiratory failure. Electro-diagnostic studies showed a neurogenic pattern supporting the diagnosis of SMA. The child was started on supportive care, antibiotics and mechanical ventilation. Molecular genetic analysis was carried out as follows.

METHODS

DNA Isolation

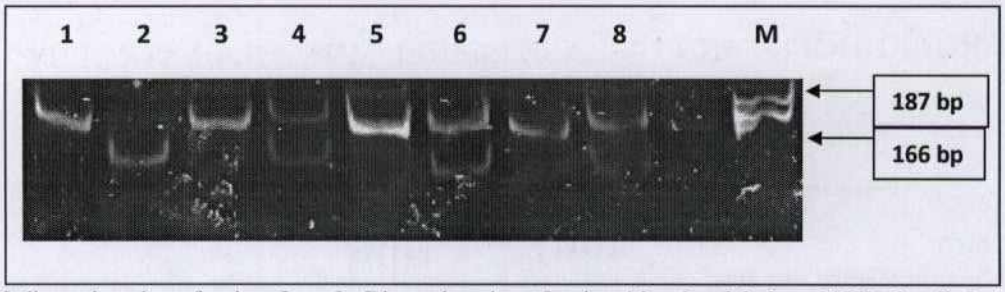
Three ml of blood each was collected in EDTA vacutainers from the patient, his father and mother for DNA isolation. Written consent was obtained. DNA was extracted from blood by the standard salting out method.[7] 2 µl of the dissolved DNA was added to each 25 µl PCR reaction.

Molecular analysis of SMN gene

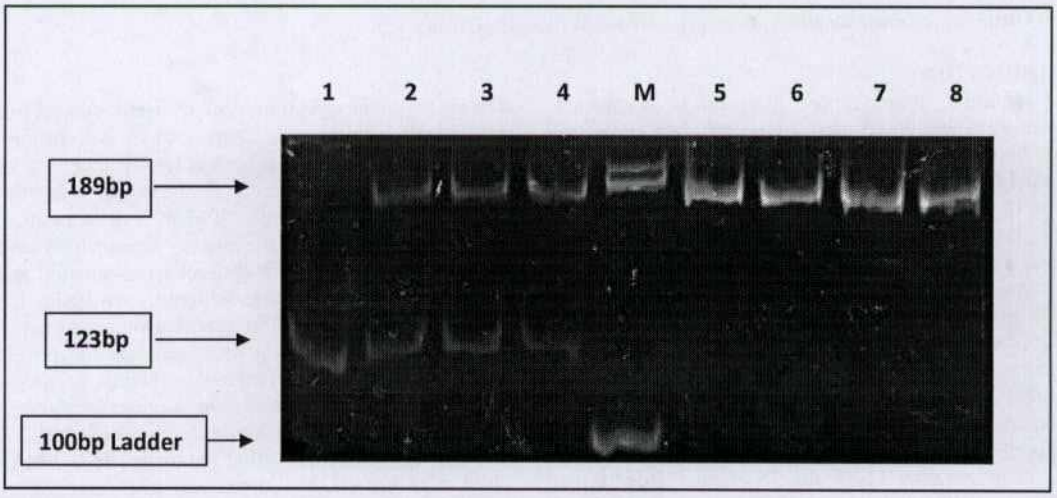
All three samples were tested for homozygous deletion of exons 7 and 8 of SMN1 gene by a Polymerase Chain Reaction – Restriction Fragment Length Polymorphism (PCR – RFLP) method.[8] The digested products were then analysed in a 10% PAGE (Polyacrylamide gel electrophoresis) and photographed by a Bio-Rad Gel Doc XR+ System with Image Lab software.

RESULTS

The exon 7 amplified product digested with *Dra I* gave three products (187 bp, 166 bp and 21 bp) on PAGE; the 21 bp product runs out of the gel (Fig 1). The exon 8 amplified product digested with *Dde I* also gave three products (189bp, 123bp and 66bp) in the control as well as the father and mother of the patient (Fig 2). In Fig. 2, the 66bp product has run out of the gel and hence, is not seen. The absence of the 187 bp band and the 189 bp band in both the exon digested products shows SMN1 deletion in this patient.



Lane 1 - Undigested product of patient; Lane 2 - Digested product of patient (**showing deletion of 187bp band**); Lane 3 - Undigested product of patient's father; Lane 4 - Digested product of patient's father; Lane 5 - Undigested product of patient's mother; Lane 6 - Digested product of patient's mother; Lane 7 - Undigested product of Control; Lane 8 - Digested product of Control; M – 100bp Ladder.



Lane 1 – Digested product of patient (**showing deletion of 189bp band**); Lane 2 – Digested product of patient's father; Lane 3 – Digested product of patient's mother; Lane 4 – Digested product of control; M – 100bp Ladder; Lane 5 - Undigested product of patient; Lane 6 - Undigested product of patient's father; Lane 7 - Undigested product of patient's mother; Lane 8 - Undigested product of control.

DISCUSSION

Spinal muscular atrophy is the second most common lethal autosomal recessive disease in humans after cystic fibrosis and the most common fatal neuromuscular disease diagnosed in children. Although hypoxia is the most common cause of reduced foetal movements, rarer causes should be considered if there is a significant family history. To date, it is not known with certainty whether this subgroup represent a distinct entity or is merely the severe end of the classic SMA type 1. Duobowitz 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 type I.[3] Pavone et al, reported a case of SMA with respiratory failure being ventilator dependent at birth, diagnosed with genetic analysis.[5] MacLeod et al reported 5 cases of neonatal onset SMA presenting with diminished fetal movements in utero, asphyxia or severe weakness at birth. Three of their patients needed immediate resuscitation and ventilatory support. Exons 7 and 8 of SMA gene are absent in all cases and 4 had deletions in NAIP gene.[4]

Barzegar Mohammad et al reported 3 cases with prenatal onset severe SMA with respiratory problems and need lifelong ventilatory support. 2 of 3 had reduced fetal movements and absent copies of exons 7 and 8 of SMN gene and exon 5 of NAIP gene.[9] Devriendt et al reported a case of fetal hypokinesia and signs of SMA at birth and concluded that NAIP gene played a major role in modifying the severity of phenotype.[10]

Prenatal diagnosis of SMN gene is useful when there is a family history of SMA. The diagnostic criteria for SMA do not include antenatal presentation. However, there have been case reports of in utero onset SMA.[11,12] SMA type 1 usually presents itself at birth or the early days of life may be difficult to diagnose by primary care providers. Proper diagnosis maybe required or needs high index of suspicion or understanding of clinical features. SMA should be kept in mind in the differential diagnosis of severe generalised hypotonia and severe respiratory distress at birth or the neonatal period, in patients with bright expression.

This case demonstrates classical presentation of very severe type 1 SMA due to age of onset and severity of weakness. The literature search reveals very little documentation of clinical course and outcome of type 1 SMA. In our rural Medical College, we confirmed the diagnosis by genetic analysis which is confirmatory.

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