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RESEARCH ARTICLE

A RARE CASE OF SPINAL MUSCULAR ATROPHY

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ABSTRACT

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. It is classified into three groups according to the age of onset and progression of weakness. SMA I, II, III & IV. Type I being most serious form & type III being the mildest form & Type IV being adult onset disease. Here we present you a case who presented with similar history and examination for which genome analysis was done and confirmed the diagnosis of SMA.

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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 (Lawton *et al*., 2014). 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. In addition to these classical SMA types, unusual SMA variants have been described (Kocova *et al*., 2014). 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. 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 (Fraidakis *et al*., 2012). The aim of this study is to review SMA clinical and molecular manifestations.

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CASE REPORT

A 3 months old male baby, third child of consanguineous parents, presented with history of cough, breathing difficulty and fever of 3days 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 at age of 4months cause not known. The second child was healthy. During pregnancy, fetal movements were reduced from 32 weeks of gestation. There was no history of polyhydramnios. 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 in drawing 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

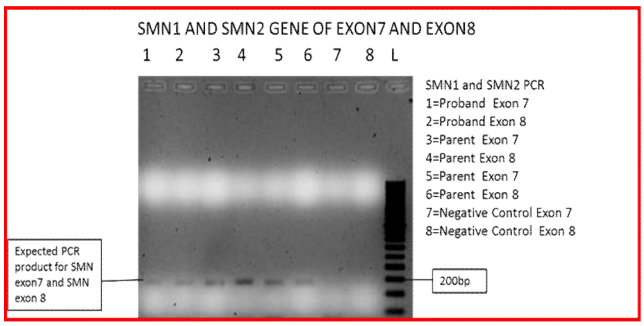
absence of deep tendon reflexes. Investigations revealed abnormal arterial blood gases suggestive of respiratory failure. Electro-diagnostic studies showed a neurogenic pattern supporting the diagnosis of SMA. The child was started on supportive care, antibiotics and mechanical ventilation. Molecular genetic analysis was carried out as follows.

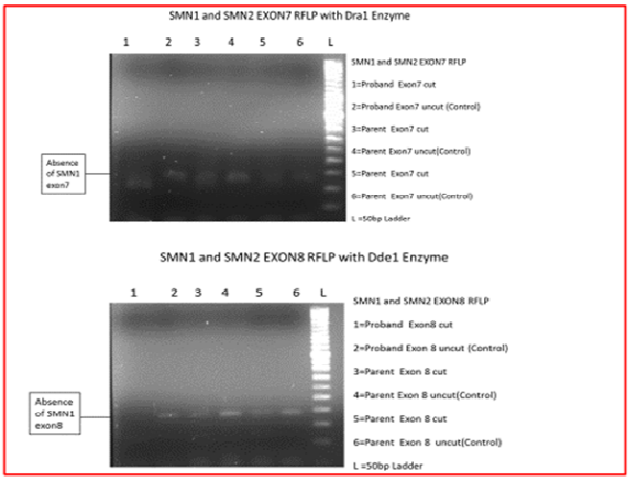
METHODS

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. The digested products were then analysed in a 10% PAGE (Polyacrylamide gel and photographed by a Bio-Rad Gel Doc XR+ System with Image Lab softwareelectrophoresis)

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 asthe 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.





DISCUSSION

Spinal muscular atrophy (SMA) is a genetic disorder which affect nervous system and is characterized with progressive distal motor neuron weakness. SMA is a hereditary (autosomal recessive) neuromuscular disease which leads to paralysis and death in childhood.[5] Four form of SMA were identified; type zero is the fetus form of disease which causes death in early infancy. 1) Type I: Infantile (Werdnig-Hoffmann disease). 2) Type II: Intermediate (Dubowitz disease). 3) Type III: Juvenile (Kugelberg–Welander disease). 4) Type IV: adult onset (Fraidakis *et al*., 2012). Spinal Muscular Atrophy Spinal muscular atrophy with respiratory distress type 1 (SMARD1) is a type of distal spinal muscular atrophy with diaphragm involvement; its clinical manifestation varies in different patients. Infants had severe symptoms from birth with frog like position or bell shaped deformity in chest. Foot deformities and contractures are common in SMARD1 patients (AlSaman, 2010). Disease pathology base is anterior horn motor neuron degeneration like SMA, and it is also an autosomal recessive disorder. SMARD1 is a rare condition and there are about 100 case report of this condition from all around the world. The survival motor neuron (SMN) protein level reduces in patients with SMA (Kuźma-Kozakiewicz *et al*., 2013). Two different genes code survival motor neuron protein in human genome. In SMA patients have homozygous changes of SMN1 with at least unique copy of SMN2. Genetic changes in chromosome 5 q 13 (mutation, deletion, or rearrangement) are responsible for SMA. More than (95%) of children with SMA have homozygous deletion of SMN I gene axons 7 and 8 (Majid *et al*., 2012). Other patients might have changes in SMN II gene. Spinal muscular atrophy is the second common neuromuscular disease after Duchenne muscular dystrophy (DMD) and its incidence is one in every 10000-25000 birth (Martinez *et al*., 2012). SMA mortality and morbidity depends on the age at disease onset. Early onset form of SMA such as type zero and Iare mortal in (95%) of cases (MacLeod *et al*., 2009). Pulmonary complications like respiratory failure and infections are the most common cause of death. Males were affected in type I and II in comparison with females individuals. Consanguineous marriages are frequent in Iranian population, so it is estimated that SMA prevalence might be higher in our country (Devriendt *et al*., 2011). Skeletal and intercostal muscles denervation lead to weakness, hypotony, hyporeflexia, respiratory failure, atrophy and paralysis in patients with SMA. Manifestations are prominent in proximal muscle of lower extremities. Children who suffer from spinal muscular atrophy show no sign of central nervous system involvement; loss of muscle tone (hypotony) poor sucking reflex, and floppy baby are the most common presentation in acute infantile form of SMA (Korinthenberg, 2004). Mean survival life is estimated about 6 months in this children and death happens due to Respiratory failure. Chronic infantile form manifestations are developmental motor lag, difficulties in standing or walking. Patients might survive for 30 years (Kizilates *et al*., 2005). Respiratory infections cause death in this type of SMA. Chronic juvenile type (Kugelberg–Welander disease) occurs after 18 months old and most of them have normal life span. Motor skills might disrupt in some cases. Type IV is similar to type III, and disease is benign (Pavone *et al*., 2004).

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. 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. 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 (MacLeod *et al*., 2009). Devriendt K *et al* reported a neonate who presented with foetal hypokinesia and signs of SMA at birth with deletions of both exon 7 of the SMN gene and exon 5 of the NAIP gene. 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 (DevriendtK *et al*., 2006). Korinthenberg *et al*. documented three siblings who presented with asphyxia, generalized weakness, facial weakness and external ophthalmoplegia in the new born period; they were found to be absent for the SMN gene (Korinthenberg *et al*., 2004).

Pavone P, *et al* reported a case of SMA with respiratory failure being ventilator dependent at birth. The diagnosis was made by genetic analysis. 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 (Pavone *et al*., 2004). 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). Prenatal analysis of SMN gene is useful for prenatal diagnosis of SMA when a positive family history is present. The diagnostic criteria for SMA do not include antenatal presentation; however, there have been case reports of in utero onset SMA (Fraidakis *et al*., 2012). Although hypoxia is the most common cause of reduced foetal 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 paediatricians 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.

Conclusion

Spinal muscular atrophy is a neuromuscular disorder of paediatrics interest which has no cure yet and need a multidisciplinary diagnostic and therapeutic approach in order to slow muscle atrophy and preserve essential life function such as swallowing, breathing and locomotion. The various pattern of symptoms and the lack of expertise in this area for many healthcare professionals lead to a frequent diagnostic delay of SMA, even if awareness of SMA is recently increasing. The diagnostic “odyssey” from the time first symptoms are noticed to a confirmed genetic diagnosis of SMA puts patients and caregivers through physical and mental stress and deny the possibility of early intervention. In this work we present a case of SMA early recognized and diagnosed since a detailed clinical and neurological examination and underline the importance of a correct diagnostic approach in order to ensure disease issues to a specific follow up route.

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