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Spinal Muscular Atrophy Type 1 Presented with Clinical Sepsis: A Case Report and Review of Literature

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ABSTRACT

Background and Objective: Spinal muscular atrophy (SMA) type 1 is an autosomal recessive degenerative disease presenting early in life and progressing into neonatal and infancy. It is caused by a loss of function of the gene for surviving motor neuron 1, leading to degeneration of the anterior horn cells of the spinal cord and consequent to progressive muscle weakness and atrophy. The aim of this case report is to report an infant with SMA type 1which was presented with clinical sepsis.

Case Report: This study reports a 1.5 months old male infant presenting with floppy limbs, poor nutrition, inadequate weight gain, and respiratory distress. The infant had tachypnea with paradoxical breathing, hypotonia, tongue fasciculations, bilateral wrist contractures, and absent deep tendon reflexes. He was tested for SMA by multiplex ligation-dependent probe amplification (MLPA). Reports were positive for a homozygous mutation of the SMN1 gene in exon 7 and exon 8, confirming the diagnosis of SMA type 1.

Conclusion: SMA can be confused with neonatal sepsis due to similar clinical presentation; a high level of suspicion is required in children with respiratory distress in early infancy. It is important to alert clinicians to this differential diagnosis in children with failure to thrive, respiratory failure, and progressive muscle weakness, as the care of these patients presents unique challenges and ethical dilemmas.

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Introduction

Spinal muscular atrophy (SMA) type 1 is an autosomal recessive degenerative disease. The incidence of SMA is reported as 1:6,000 to 1:10,000 live births. In a recent study, the carrier frequency of Indian ethnicity was stated to be 1 in 38 [1]. A homozygous deletion in the survival motor neuron 1 (SMN1) gene on chromosome 5q13 results in a deficiency of the survival motor neuron (SMN) protein. This mutation results in the loss of α-motor neurons of the anterior horn cells, weakening the bulbar and respiratory muscles and ultimately leading to respiratory failure [2]. The first cases of SMA were described by Werdnig and Hoffmann in 1891 and 1893, hence it is also called 'Werdnig-Hoffmann disease'. The severity and age of the disease depend on the phenotypes of SMA, with three major types. Type 1 SMA is the most severe with early onset at 6 months of life. Type 2 SMA is less severe and occurs between 6 and 18 months of age, while type 3 SMA occurs in adolescence. As in our case, the child had Werdnig-Hoffmann disease (SMA type I).

To date, there is no curative treatment for this disease, and treatment consists mainly of multidisciplinary supportive care. Many neonates with feeding difficulties and respiratory problems are misdiagnosed as septicemia because they have too little experience and are unaware of the disease. It is important to make physicians aware of this life-threatening disease and to offer genetic counselling to parents so they can better understand the disease and plan for its future. Though not a rare clinical entity, SMA is usually missed or diagnosed late due to lack of knowledge in clinicians. Therefore, we are reporting this case of an infant presenting in early life as sepsis.

Case Report

A 45-day-old male presented to the Pediatric Intensive Care Unit with respiratory distress, poor feeding, and inadequate weight gain. He was a firstborn child by normal vaginal delivery to unrelated parents. The ultrasounds done in the 5th and 7th month of gestation were normal and revealed adequate liquor. The antenatal and perinatal periods were uneventful. There was no need for resuscitation and he cried immediately at birth. He was born with a birth weight of 2.7kg and passed meconium and urine at 8hrs and 12hrs respectively. There was a history of hospitalization for poor feeding and late-onset sepsis at 30 Days of life for which he received antibiotics. On admission, respiratory rate was 68 /min, SpO2= 97%, and heart rate=108/min. The infant had intercostal, and subcostal retractions with nasal flare. A respiratory system examination showed a bell-shaped chest with crackles in bilateral basal areas. On central nervous system examination, he was conscious and alert. He had frog-leg posture in the supine position, complete head lag, slipping through, and a rag-doll appearance. Power was 3/5 at hip joints, knee joints, and elbow joints. The bilateral wrist joints had contractures (arthrogryposis). Deep tendon reflexes were absent and plantar reflex was normal. Oral examination showed tongue fasciculations. Cardiovascular and abdominal examinations were normal.

His complete blood count showed hemoglobin=10.5 gm/dL, white blood cell counts=8,500/mm3, platelet counts=6,67,000/mm3, MCV=93/fl, Polymorphs=47% and Lymphocytes=46%. His blood gas analysis and serum lactate were normal. Renal and Liver function tests were normal. Chest radiography revealed no abnormalities. When sepsis was clinically suspected, Inj. ampicillin (100 mg/kg/day) and Inj. gentamicin were started empirically and later Inj. gentamycin (7.5 mg/kg/day) was continued because Staphylococcus capitis was detected in the blood culture. Because of persistent hypotension and respiratory distress, the child was examined: creatinine kinase= 35U/L, serum sodium=138 mEq/L, serum potassium= 5.4 mEq/L, serum calcium= 9.7 mg/dL. His 2D echocardiography was normal. Karyotype showed 46 XY with no numerical aberration. SMA was tested for carrier by multiplex ligation-dependent probe amplification (MLPA). Reports were positive for a homozygous mutation of the SMN1 gene in exon 7 and exon 8, confirming the diagnosis of SMA type 1.

The infant was continued on respiratory supportive therapy along with tube feeding and physiotherapy. During his hospital stay, he

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developed respiratory failure and needed positive pressure ventilation. Eventually, he required mechanical ventilator support and succumbed to his illness on day 94 of life. Parents were counselled and evaluated for carrier state. Molecular analysis of the parents revealed that the father was a carrier and had single copies of SMN1 Exon 7 and exon 8 with zero copies of SMN2 and the mother was normal with two copies of SMN1 exon 7, three of SMN1 exon 8, three of SMN2 exon 7 and two of SMN2 exon 8. Consent was obtained from parents before writing this case report.

Discussion

This SMA is the most common genetic cause of infant mortality affecting 1 in 10,000 live births. It is characterized by the weakness of proximal muscles with greater involvement of the lower extremities. In severe cases, bulbar and respiratory muscle weakness are particularly seen with sparing of facial and ocular muscles. Type 1 SMA being the most common form, represent approximately 45%-60% of cases with onset between 0-6 months. Children affected with Type 1 SMA show a bell-shaped chest deformity and tongue fasciculations. These children usually do not achieve the ability to sit independently. Most type 1 patients have one or two copies of SMN 2 [3]. Table 1 illustrates the phenotypic overlap of our patient with previously reported cases of SMA type 1 [4, 5, 6, 7, 8].

In recent times, a detailed study of a gene for SMA has been possible. Gene therapy with RNA-based modulation of SMN-2, stem cell transplantation and SMN-independent pathways targeting muscle enhancement and actin dynamics are under study. Currently, two drugs Nusinersen and Risdiplam are available. These drugs work on the principle of increasing the SMN protein production and improvement of motor functions with some improvement in respiratory impairment and hence, improving survival [9, 10]. However, the high cost and non-availability of these drugs to the masses pose a great barrier to the successful treatment of SMA. Therefore, for the majority of patients, mainly supportive care by multidisciplinary teams with the aim of reducing the risk of infections, aspiration, and appropriate airway-secretion clearance techniques are the mainstay of treatment. Feeding is an essential component of the care of these children and can be managed by nasogastric tube feeding. Caring for children affected by SMA type 1 is challenging for both clinicians and parents. Awareness of this disorder is important for timely detection and for genetic counseling of parents. Moreover, many times type 1 SMA presents a particular challenge for clinicians in many cases and can lead to ethical dilemmas.

Table 1. Common characteristics in cases with SMA type I

Patient Characteristics	Park et al (n=14)	Madakshira et al (n=1)	Behera et al (n=1)	Cobben et al (n=34)	Malerba et al (n=1)	Current case (n=1)
Male Gender	8/14	1/1	1/1	22/34	1/1	1/1
GA * (weeks)	39	NA **	34	NA	40	38
Consanguinity	NA	1/1	1/1	4/34	0/1	1/1
Affected sibling	NA	1/1	1/1	3/34	0/1	0/1
Significant perinatal history	NA	0/1	1/1	NA	1/1	0/1
Age of Presentation (months)	3	2	0	1	5	1.5
Age at diagnosis (months)	4.0	Post-mortem	NA	NA	9	2.5
Head control	4/14	0/1	NA	6/34	0/1	0/1
Hypotonia, tongue fasciculation, absent Reflexes	NA	1/1	1/1	NA	1/1	1/1
Bell shaped chest	NA	1/1	0/1	0/1	1/1	1/1
Arthrogryposis	NA	0/1	1/1	1/1	1/1	1/1
Infection setting	NA	1/1	0/1	NA	1/1	1/1
Artificial feeding	8/14	1/1	1/1	NA	1/1	1/1
Respiratory support	8/14	1/1	1/1	31/34	1/1	1/1
Genetic testing	13/14	1/1	1/1	34/34	1/1	1/1

* GA- Gestational age
** NA- Not applicable

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Conclusion

A high level of clinical suspicion is needed for the diagnosis of SMA. In the absence of modest treatment options, it is important to correctly diagnose SMA and make educate parents about available options for the care of affected children and genetic counselling before the next pregnancy. If more cases are reported, this can help physicians diagnose SMA early and offer genetic counselling to families for future pregnancies.

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Ethical approval

Ethical approval is not required as per the institutional policy. An informed written consent was obtained from the parents for writing and publication of the case report.

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Conflict of interest

There was no conflict of interest.

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