

A Case of Spinal Muscular Atrophy Type 1 in a Filipino Infant

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ABSTRACT

We present a case of a 7-month-old Filipino who manifested with generalized muscle atrophy and areflexia. She had weak gag reflex and tongue fasciculations. She eventually developed feeding difficulty and recurrent pneumonia. Laboratory work-up showed a slightly elevated serum creatinine kinase (CK) and myopathic changes on electromyography and nerve conduction velocity (EMG-NCV) studies. Genetic study confirmed that the patient was homozygous for deletions on exons 7 and 8 of the survival motor neuron (SMN) 1 gene. Carrier testing on both parents revealed that only the mother was a confirmed carrier of the SMN1 gene deletion. The challenges for genetic counseling in this case are discussed.

Key Words: Spinal Muscular Atrophy, SMA, SMN gene, SMN1 gene

Introduction

Spinal muscular atrophies are a group of diseases characterized by degeneration and loss of the anterior horn cells in the spinal cord, and occasionally in the brainstem.¹ The clinical picture includes muscle weakness and atrophy, with intact sensory neurons and pyramidal tract. The estimated incidence is 1 in 10,000 among Caucasians.² An International SMA Consortium meeting in 1992 and 1998 have led to the proposal of a classification based on age of onset, severity of progression, distribution of weakness, additional features, and the different modes of inheritance.³ The severe form, SMA Type I, has its onset ranging from prenatally to 6 months of age, usually with symmetrical, proximal muscle weakness of the trunk and limbs, tongue fasciculations, delayed motor milestones (never able to sit with support), and often do not survive beyond 2 years of age.^{2,3} Children with SMA Type II, the intermediate form, start having symptoms before 18 months of age, with similar

muscle weakness and tongue fasciculations like type I, delayed milestones (unable to stand or walk without assistance), but these patients can survive into adolescence or adulthood.^{2,3} Type III is a mild form whose onset is after 18 months, again with similar proximal weakness and tongue fasciculations as the other types, and they are expected to be able to walk and to have normal life expectancy.^{2,3} Adult SMA, or Type IV, have symptoms after 20 or 30 years of age.³ Diagnosis is established by showing the absence or deletion of the telomeric copy of the survival motor neuron gene (SMN^T or SMN1) located on the chromosome 5q.^{1,2,3} Rarely, there may be point mutations on the SMN gene or it may be a case of Non-5q SMA.^{1,2,3}

In the Philippines, most cases are diagnosed clinically and only supported by neurophysiologic studies and muscle biopsy. The Philippine Pediatric Society ICD-10 Registry of Childhood Diseases reported only 5 cases of SMA and related syndromes (ICD-10 Code: G12) out of 1,350,090 hospital discharges submitted by the accredited training hospitals all over the country as of October 2011 data.⁴

This paper aims to present a case of SMA in a Filipino infant, confirmed by molecular studies, and with carrier testing done on both parents.

Clinical Report

The patient was the product of a non-consanguineous marriage and delivered to a 28-year-old G2P1(1001) mother who had an uncomplicated prenatal history. Birth history was uneventful. She was delivered full term, weighing 2.84 kg, with good tone, strong cry and good suck. At 3 months of age, she had poor head control and poor tone. At 5 months of age, she started to have feeding problems and recurrent pneumonia. She was eventually admitted at the age of 7 months due to failure to feed and respiratory difficulty.

Language and personal-social developmental milestones were achieved at the expected ages. A review of the family history revealed a paternal cousin with motor delay but details were not well known to the parents. The patient's older sibling is normal.

Physical examination on admission showed an awake, febrile infant, in respiratory distress. She had a high-arched palate, bell-shaped chest and exhibited abdominal breathing. There were no dysmorphic features. Neurologic examination demonstrated an infant with good eye contact and conjugate eye movements. She had poor suck, weak

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cry, weak gag reflex, drooling of saliva, and tongue fasciculations. She had generalized muscle atrophy, frog-posture, and marked hypotonia (both axial and appendicular). She would slip through on vertical suspension and droop over the examining hand on horizontal suspension, with head lag on traction maneuver. She had generalized, symmetrical weakness, predominantly involving the proximal muscles. Deep tendon reflexes were absent. The rest of the physical and neurologic examinations were normal.

She was worked up and treated for pneumonia. Chest x-ray showed bibasal consolidation/segmental atelectatic changes. There was metabolic acidosis with hypoxemia on ABG. Tracheal aspirate culture grew *Klebsiella pneumoniae*, which was sensitive to the patient's antibiotic regimen.

The infant was also worked up for SMA. Her serum total CK (201 IU/L) was only around 1.5x elevated. There were myopathic changes (fibrillations and polyphasic waves on all extremities) on EMG-NCV with more involvement of the proximal muscles. Blood samples were sent to KK Women's and Children's Hospital in Singapore for diagnostic genetic testing for SMA. PCR amplification of SMN1 gene exons 7 and 8 were done. The patient had a homozygous deletion for both exons, confirming the diagnosis. Carrier testing on both parents (where the number of SMN1 gene copies was determined) was also done. It showed that the mother was a confirmed carrier, with only one copy of SMN 1 gene. The father, however, showed two copies of SMN 1 gene.

During hospitalization, the patient was intubated and hooked to a mechanical ventilator. Several attempts at weaning her from mechanical ventilator failed due to poor respiratory muscle function. Genetic counseling was offered and, the parents were appraised regarding their child's condition and prognosis. Options were discussed regarding the chronic management of the disorder. Parents decided to bring the patient home without supplemental oxygen. She eventually expired 3 hours after discharge.

Discussion

The patient's clinical presentation conformed to the modified diagnostic criteria for SMA Type 1 described in the 59th ENMC International workshop on SMA.³ These include age of onset (less than 6 months), symmetrical proximal muscle weakness rather than distal, tongue fasciculations, inability to sit without support, CK being only slightly elevated, and abnormal activities on EMG/NCV. Muscle biopsy was not done on this patient but biopsy of a patient with SMA will show groups of atrophic fibers of both types.^{3,5} DNA testing is now recommended for suspected cases of SMA because it is non-invasive.^{3,6}

Prognosis for SMA type 1 was said to be less than 2 years of age.^{2,3} Our patient survived up to the age of 7 months. Treatment is primarily supportive. A study on the

survival pattern of SMA patients conducted by Chung et al. showed that 72% of their 22 SMA type 1 patients had died, due to cardio-respiratory failure.⁷ Non-invasive ventilatory support is one option that has prolonged the lifespan in some patients,^{8,9} but this was not done in our case.

There is a paucity of reports regarding SMA in general among Filipinos. Majority of the SMA type 1 patients from Singapore,⁸ Malaysia,⁹ and Vietnam¹⁰ had deletions on exons 7 and 8, similar to the finding in our case.

Although recognized to be an autosomal recessive condition, carrier testing is recommended for parents of diagnosed cases because of the impact on genetic counselling. The challenges in the interpretation of SMA carrier test results are demonstrated in the following scenarios: 1) the carrier may have two SMN1 gene copies on 1 chromosome and none on the other ("the so-called 2+0 genotype"); 2) the carrier may have one normal SMN1 allele and a mutation in the other allele; 3) a de novo deletions may have occurred, requiring only one parent to be a carrier.^{10,11} Such de novo changes occur in 2% to 3% of SMA patients.³ On the other hand, the 2+0 genotype or cis configuration of SMN1 genes are seen in 3-4% of individuals.^{3,11,12} Given these potential difficulties, SMA carrier testing, when available, is recommended. Because the patient's father was not a carrier of a deletion, the scenarios enumerated previously are entirely possible in this case being presented. Linkage analysis would help determine if this was a case of de novo deletion or of two SMN1 copies on one chromosome. A study by Smith et al. on screening for carriers of SMA gave the recommendation of a combination of SMN dosage and linkage analysis, plus genetic risk assessment.¹³ Such risk assessments rely on published data like carrier frequencies for specific populations. The often quoted carrier frequency of SMA among Caucasians is 1 in 50² but this may not hold true for Filipinos. Risk assessment also involves calculations such as the Bayesian analysis.¹³ Aside from carrier frequency, the analysis would also take into account the fact that the first child of this couple is normal. Unfortunately, Bayesian analysis was not done in this family's case. The worst case scenario of a 25% recurrence risk was discussed with the family, following the autosomal recessive mode of inheritance.

Summary

DNA testing confirmed the diagnosis of SMA type 1 in a Filipino infant. The result was a homozygous deletion of exons 7 and 8 of the SMN1 gene. Carrier testing showed a mother with only 1 copy of the SMN1 gene while the father had 2 copies. Such results present challenges in the genetic counselling of SMA.

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