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ABSTRACT... Introduction: Spinal Muscular Atrophy (SMA) consists of three types of disease including Werdnig Hoffman (SMA type1) which is an autosomal recessive degenerative motor neuron disease. These patients have abnormality in motor function of the muscles and will die in the first few years of life. The genetic locuses of all three types of SMA are on the chromosome numbers and a deletion in locus 5q11-q13 will result in a variety of this disease. Case Report: heterozygous twin infants (boy and girl) were born from relative parents admitted to the hospital, one in three days after another, with upper respiratory tract infection, respiratory distress and coughing. They were hypotonic and had tongue fasciculation. They were intubated and ventilated in the PICU. SMA was suspected because of the general muscular weakness; therefore, biopsy and neurophysiologic studies were performed. Quadriceps muscle biopsy showed fascicular atrophy of muscle fibers and in genetic analysis of SMN1 gene in twin homozygous deletion of the SMN1 gene at exon 7 was found. They became ventilator dependent and suffered respiratory failure and two weeks after their admissions in hospital, and with three day interval, died. Conclusions: it seems prudent to perform genetic assessments before having children in the parents who are close relatives especially after having one affected child.

Key words: Spinal Muscular Atrophy-twins-Genetic

INTRODUCTION

Spinal Muscular Atrophy (SMA) are degenerative diseases of motor neurons that begin in fetal life and continue to progress in infancy and childhood². SMA occurs in 1/6000 to 1/20000 birth with approximately 1/40 to 1/50 people being carriers of these genetic disease⁵. SMA (type 1) affects approximately 1/10000 live birth with a carrier frequency of 1/50 in USA⁶.

Most cases are inherited as an autosomal recessive trait².

The genetic locus for all 3 of the common forms of SMA is on chromosome 5, a deletion or mutations 5q11-q13 locus, indicating that they are variants of the same disease rather than different diseases², and a determined gene called survival motor neuron1 (SMN1) is identified. Deletions or mutation in the SMN1 gene substantially decrease expression of the SMN protein.

If the SMN1 gene has reduced or no function, then the motor neuron in the spinal cord and brain stem do not survive, and gradually die off^{4,6}. Each individual has 2 SMN genes, deletion or mutation of two genes which are next to each other on the locus 5 results in W.H, SMN1 and SMN2 or Neuronic Apoptosis Inhabitant Gene (NAIP) which shows the severity of disease. More than 95% of SMA cases have a homozygous disruption in the SMN1 gene on chromosome 5q, cause by deletion or rearrangement⁶. Clinical manifestations include severe.

Hypotonia and frog-leg position, generalized weakness, thin muscular mass, absent deep tendon reflexes, fasciculation of the tongue, respiratory failure and death.

Different types of SMA are as the follows:

1. SMA type1 (Werdnig Hoffman) for onset of symptoms before age 6- months old.
2. SMA type2-onset of symptom 6-18- months-old
3. SMA type 3 (Kugelberg-Welander disease)-

onset of symptoms after age 18 months^{1,2}.

DIAGNOSIS

The simplest, most definitive diagnostic test is molecular genetic marker in blood for the SMN gene. Muscle biopsy reveals a characteristic pattern of prenatal that is not like that of mature muscle.

CASE REPORT

Heterozygous twin infants (boy and girl) were born from relative parents admitted to the hospital, one in two days after another, with upper respiratory tract infection, respiratory distress and coughing. They were intubated and ventilated in the PICU following severe respiratory distress and respiratory acidosis.

They were born by cesarean section in 36 weeks of pregnancy, fed via breastfeeding and had appropriate vaccination history. Parents were relatives and there was no history of abortion or infant death in the family.

CASE 1

70-day-old Male infant, second twin, and birth weight was 2200 gram. On examination he was awake, hypotonic and was unable to hold his head. Fontanel wasn't bulge. He had respiratory distress, intercostals retraction and tachypnea (respiratory rate =81) when he admitted to hospital. Heart sounds were normal. There were wheezing and ronchi on both lungs. There was no organomegaly in abdominal examination. On neurologic examination there was tongue fasciculation and deep tendon reflexes were absent. Sensory exams were normal. Body temperature was 37centigrade degrees axillary.

Laboratory Results

WBC 8400 (pnm 65 -lymph 35)
 BUN 12 Creatinine 0.5
 Na 140 K 4.2
 BS 34 Ca 9.4
 ESR 8 CRP negative
 LDH 795 IU/L Lactate 13 mg/dl
 Ammoniac serum 0.6 micro g/ml
 Serum .chromatography Normal pattern
 U. Reducing Substance Negative
 Sugar .chromatography Normal pattern

ABG (pH= 7.26 Pco2 =59.
 Hco3 =27 Po2=87
 O2 Sat =98%) Chest X Ray
 Lt Lung Pneumonia

CASE 2

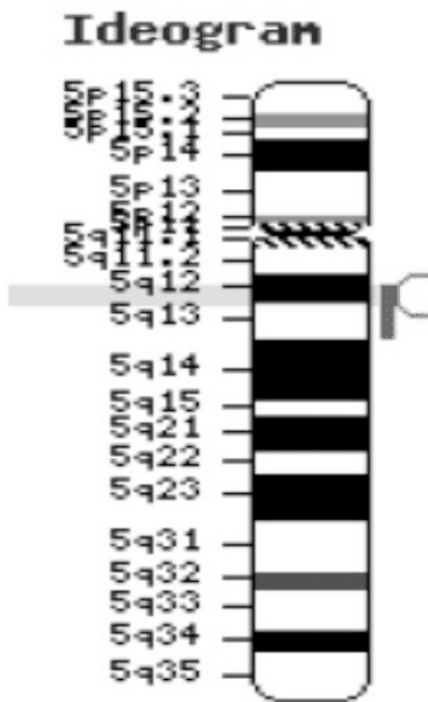
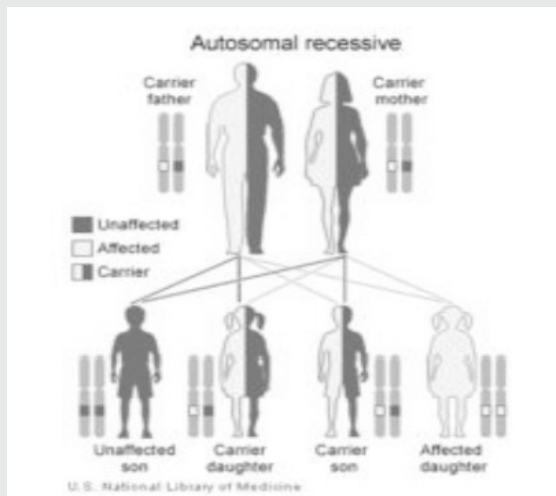
73-day-old female infant, first twin, and birth weight was 2700 gram. She had respiratory distress, coughing and intercostal retraction at the admission. In the examination; she was awake, floppy and unable to hold her head. Fontanele wasn't bulging, heart sounds were normal, respiratory rate was 84, and there were ronchi on both lungs. In abdominal examination there was no organomegaly. She was hypotonic. In neurologic examination; there was tongue fasciculation and deep tendon reflexes were absent. Sensory exams were normal.

Laboratory Results

WBC 9500 (pnm 63 Lymph 37)
 BUN 6 Creatinine 0.5
 Lactate 10mg/dl BS 26 Ca 9.6
 Na 137 K 4.1
 ESR 9 CRP Negative
 LDH 890 Ammoniac 0.4 micro g/ml
 B/C negative U.A and U.C negative
 ABG (pH = 7.21 Pco2 =64
 Hco3 =24 Po2=83
 O2sat=96.1) Chest X Ray=Interstitial pneumonia
 U. Reducing Substance Negative
 Sugar Chromatography Normal pattern
 Serum .chromatography Normal pattern

Both infants were intubated under mechanical ventilation in PICU.

They became ventilator –dependent and weaning was impossible during the next few days. According to the physical examination, SMA (Werdnig Hoffman) was probable so quadriceps muscle biopsy was performed for both of them. Degeneration and loss of spinal motor neurons with a neurogenic pattern of muscle morphology was reported .Serum Ck was normal. There was fibrillation and muscle denervation in EMG. The exon 7 and exon 8 of SMN1 genes were screened in twins and



results showed homozygous deletion of the SMN1 gene at exon7.

After two weeks in the PICU, they suffered respiratory failure and with a three day interval, they had cardiopulmonary arrest and cardiopulmonary resuscitation wasn't successful, they both passed away.

DISCUSSION

Werdnig Hoffman is a rare autosomal recessive disease resulting from abnormality in motor neurons. This abnormality is caused by mutation in two SMN1 genes in chromosomal locus 5q11-q13 .There is another gene named SMN2 which can show the severity of disease being both parents heterozygotes, chance of having affected child in each pregnancy is 25 percent. It seems that SMN1 and SMN2, the involving genes in this disease, encode a protein that is essential for proper function of motor neurons. Mutated SMN1 produces a protein which does not have proper function and mutated SMN2 produces a protein which only partially affects on the function of motor neurons. SMN 2 depletion is more common in Werdnig Hoffman(SMN type1)in comparison with two other types of SMN. The less SMN2 gene (NAIP) is affected, in these two cases, the parents were relatives, the twins were dizygotes and both parents transmitted the abnormal genes to the twins .Sex of twins didn't play any role. It is highly recommended that the next child need prenatal diagnosis for SMA.

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