A Case of Smith–Magenis Syndrome with Multiple Organ Malformations

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ABSTRACT

Smith–Magenis syndrome (SMS) is a genetic disease caused by microdeletion of p11.2 in chromosome 17. SMS patients have characteristic facial features and accompanying congenital malformations involving the brain, cardiovascular system, and urinary tract. Compared with the distinctive facial characteristics, organ malformations are less common. Several cases of SMS with tetralogy of Fallot have been reported in Korea, none of which were accompanied by other organ malformations. We present the first case report in Korea of an SMS patient with malformations of the brain, heart, and urinary tract.

Key words: Smith–Magenis syndrome, Tetralogy of Fallot, Cisterna magna, Renal agenesis

INTRODUCTION

Smith–Magenis syndrome (SMS) is a rare genetic disease. The incidence of SMS is about 1 in 25,000 children, and characteristically presents with a number of congenital malformations. SMS is caused by autosomal variant partial loss of p11.2 in chromosome 17. SMS patients have characteristic features including a broad square face, projecting forehead, and flat nasal bridge; they also present with congenital malformations involving the brain, cardiovascular system, and urinary tract, in addition to curvature of the spine, mental retardation, and hypotonia. 1

Although multi-organ malformation is a characteristic feature of SMS, organ malformations are less common than the facial and physical abnormalities. 2-5 Over 80-90% of SMS patients have characteristic facial features, whereas organ malformations including cardiac, renal, and central nervous system abnormalities occur in only 30-40% of SMS patients. Only 6 SMS cases have been reported in Korea. 6-9 Although a few SMS cases have presented with tetralogy of Fallot (TOF), none had more than 2 congenital malformations. In the current case, we report on an SMS patient with brain, heart, and urinary tract malformations. This is the first SMS case with multiple organ malformations reported in Korea.
CASE REPORT

1. History and physical examination at birth

The mother was a 31-year-old gravida 1, para 0 when the infant was born. Unique hereditary disease was unknown in the family history, but the mother had polyhydramnios. A fetal sonogram at gestational age 31 weeks showed mega cisterna magna and right renal dysplasia. The infant was born at gestational age 37 weeks with Apgar scores 8 at 1 min and 9 at 5 min after delivery. Vital signs were stable at birth, activity and crying were good, and she was transferred to the nursery. At birth, her body weight was 2.75 kg (10-50th percentile), height was 48 cm (50th percentile), and head circumference was 32.5 cm (10-50th percentile). Murmur was not clearly auscultated at the initial physical examination and the unique appearances of SMS (i.e., broad square face, dysplasia of midline face, projecting forehead, and limb malformations) were not observed.

2. Clinical course

At 4-5 h after birth, oxygen saturation decreased to 60-80% with frequent apneic episodes, and a pansystolic murmur was auscultated at the left upper border of the sternum. After transfer to the neonatal intensive care unit (NICU), we applied 3-5 L/min oxygen for sustained oxygen saturation of 90-95%. With supportive care, the infant maintained an oxygen saturation of 90% or higher. After 3 days of NICU care, she remained stable without supplemental oxygen and was discharged after a week of hospitalization without apnea or feeding problems.

3. Evaluation

There were no specific findings in the complete blood cell count, arterial blood gas analysis, blood chemistry including electrolytes and urinalysis. A subsequent metabolic screening test showed normal findings. Initial chest X-ray showed boot-shaped cardiomegaly with a cardiothoracic ratio of 0.58. On day 2, we found TOF on the echocardiogram, and brain magnetic resonance imaging (MRI) showed mega cisterna magna (Figure 1). On day 3, a kidney sonogram showed agenesis of the right kidney and a left kidney of normal size. A dimercaptosuccinic acid scan on day 6 showed no contrast enhancement in the right kidney (Figure 2). To confirm the genetic problem that induced multiple anomalies in this infant, karyotype analysis was conducted and the result showed 46, XX, del (17) (p11.2p11.2), a finding consistent with SMS (Figure 3).

4. Follow-up

After discharge, the infant was followed up in outpatient clinics. When she visited our clinic at 1 month of age, she had the characteristic appearance found in SMS: a wide flat face, drooping mouth, protruding jaw, and short fingers and toes. Because she had difficulty with bottle feeding, gavage feeding...
was initiated. Despite this, she had poor growth; at 65 days, she weighed 3.7 kg (<3rd percentile), her height was 54.5 cm (10th percentile), and her head circumference was 35 cm (<3rd percentile). Developmental delay was observed at age 65 days, including absence of a social smile and head lagging. At 80 days, she presented with fever, cough, and breathing difficulties with cyanosis due to respiratory syncytial virus infection, and was hospitalized for treatment. After that, she suffered frequent respiratory infections and was repeatedly treated in the outpatient clinic and with hospitalization. We followed her until age 6 months, at which time she still showed head lagging and developmental delay. TOF was not yet corrected.

Considering her medical condition, her treatment plan was as follows. Surgery for TOF would be performed at age 1 year, when hemodynamic status would be stable. As her left single kidney was functioning properly, routine urinalysis and renal function tests were planned. Her last renal function test and urinalysis were normal and there was no urinary tract infections to this point. Due to concerns over psychomotor, language, and intellectual development, she was scheduled for growth and developmental checkups at 1-3-month intervals. A rehabilitation doctor was consulted to implement appropriate treatment methods and establish a time line.

**DISCUSSION**

SMS patients have characteristic facial features including a broad square face, midline facial dysplasia, projecting forehead, prominent jaw, flat skull, flat nasal bridge, and drooping mouth; they may also have other physical characteristics such as chronic otitis media, hearing impairment, strabismus and myopia, hoarseness, and short fingers and toes. Furthermore, they may have multiple organ malformations involving the brain, heart, and urinary tract, in addition to curvature of the spine. They may show various degrees of mental retardation and the typical intelligence quotient (IQ) is within the range of 40-54. These patients show normal weight, height, and head circumference at birth but their growth decreases in early infancy. Meanwhile, their face develops characteristic features and they fail to thrive due to feeding problems. Sleep disorders appear around the age of 9 months, and muscle tone hypotrophy is present during infancy. When they reach early childhood, the distinctive facial shape becomes more evident, and developmental language delay, hearing impairment, and behavior problems such as self-injury are observed.

Even though multi-organ malformation is a typical feature of SMS, organ malformations are less common compared with the facial and physical abnormalities. Over 80-90% of SMS patients have brachycephaly, a broad square face, and midface hypoplasia. Dental anomalies are present in more than 90% of
SMS patients and include tooth agenesis and taurodontism. Otolaryngologic problems such as frequent ear infections (80-90%), hearing loss (60-70%), and hoarse voice (>80%) are common. Ophthalmologic abnormalities include myopia (50-60%), iris anomalies (50-60%), and strabismus (50-80%). Skeletal features consist of short stature (>70%), brachydactyly (>80%), and scoliosis (40-70%). Meanwhile, a heart defect is observed in only 30-40% of SMS patients, a renal/genitourinary abnormality in 15-30%, and seizures in less than 30%.

In 1986, Smith and Magenis first described the condition, and several SMS cases have been reported outside Korea. Thus far, there have been 6 reported SMS cases in Korea. Among these, 3 patients showed characteristic facial and other physical SMS features without other organ malformations, and another 3 patients had characteristic SMS appearance with TOF. No previously reported case had accompanying organ malformations other than TOF. As the current patient had mega cisterna magna, TOF, and agenesis of the right kidney, this is the first report in Korea of an SMS patient with organ anomalies other than TOF. This patient was diagnosed in the neonatal period, and thus also represents the earliest diagnosis of SMS in Korea. The youngest previous diagnosis of SMS in Korea was at age 4 months.

In the current case, SMS was not suspected at birth because the infant did not show the characteristic physical features. However, while assessing her combined multi-organ malformations, we suspected a genetic disease underlying her medical condition, and chromosomal testing led us to diagnose SMS at an early age. Because many SMS cases are not diagnosed on conventional karyotype analysis, ongoing observation and assessment will help clinicians identify the hidden characteristic features of SMS. In addition, those with normal karyotype may benefit from fluorescence in situ hybridization (FISH) or microarray-based comparative genomic hybridization (array CGH).

Unlike Down and Turner syndromes that are well known, SMS is rare, and also involves a number of complex malformations and mental retardation. If clinicians fully understand the clinical features of SMS, earlier diagnosis may be facilitated. When an infant has TOF, hypotonia, and other organ malformations, there are many syndromes to consider (including cri-du-Chat syndrome, Noonan syndrome, and velocardiofacial syndrome). Based on our experience, SMS should also be considered.

REFERENCES