A case of Sotos syndrome presented with end-stage renal disease due to the posterior urethral valve

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Sotos syndrome (SS, OMIM 117550) is characterized by prenatal and postnatal overgrowth with multiple congenital anomalies. However, there have been few cases of growth retardation caused by renal failure from infancy. We report a case of dysplasia of the bilateral kidneys with renal failure and poor postnatal growth. A 2-month-old boy visited the emergency room owing to poor oral intake and abdominal distension. He was born at the gestational age of 38 weeks with a birth weight of 4,180 g. After birth, he had feeding difficulty and abdominal distension. Upon physical examination, his height and weight were in less than the 3rd percentile, while his head circumference was in the 50th percentile on the growth curve. He also showed a broad and protruding forehead and high hairline. Blood laboratory tests showed severe azotemia; emergent hemodialysis was needed. Abdominal ultrasonography revealed bilateral renal dysplasia with multiple cysts and diffuse bladder wall thickening. A posterior urethral valve was suggested based on vesicoureterography and abdominal magnetic resonance findings. Results of a colon study to rule out congenital megacolon did not reveal any specific findings. The conventional karyotype of the patient was 46, XY. Array comparative genomic hybridization study revealed a chromosome 5q35 microdeletion including the *NSD1* gene, based on which SS was diagnosed. We describe a case of SS presenting with end stage renal disease due to posterior urethral valve. The typical somatic overgrowth of SS in the postnatal period was not observed due to chronic renal failure that started in the neonatal period.

Key words: *NSD1*, Overgrowth, Sotos syndrome, Posterior urethral valve, Chronic kidney failure.

Introduction

Sotos syndrome (SS, OMIM 117550) is an autosomal dominantly inherited congenital malformation syndrome characterized by four cardinal features: pre- and postnatal overgrowth, typical facial dysmorphism, macrocephaly, and variable degrees of mental retardation [1]. SS patients sometimes

show additional clinical features including neonatal jaundice, congenital heart defects, brain anomalies, neonatal hypotonia, skeletal anomalies, and increased incidence of malignancy [2]. Among them, genitourinary defects such as vesico-ureteral reflux, multiple renal cysts, unilateral renal aplasia, and hypoplasia have been associated with about 15% of SS patients, with vesico-ureteral reflux being the most commonly observed [2].

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Kurotaki et al. [3] reported a *de novo* translocation t(5,8)(q35;q24.1) in SS that bisected the *NSD1* (nuclear receptor-binding SET domain containing protein) gene on chromosome 5q35.3. Several other groups have also confirmed that alterations in *NSD1* cause SS. In Japan and Korea, microdeletion of chromosome 5q35 is the most common cause of SS [4]. However, 5q35 microdeletions are uncommon in Caucasian populations, accounting for only 10% of affected individuals [5]. The phenotypes of SS patients with *NSD1* intragenic mutations and of those with 5q35 microdeletion differ since some of the features of SS, such as overgrowth and learning disability, are attributable to *NSD1*, whereas others, such as cardiac and renal anomalies, are more commonly associated with the deletion of neighboring genes in the 5q35 region rather than *NSD1* itself [4].

Since the first description by Sotos et al. in 1964 (quoted from reference [1]), hundreds of cases of SS have been reported to date, with an estimated incidence of 1/15,000–1/20,000 [6]. However, the prevalence of SS in Korea has not yet been reported, and there have only been seven reports of the disease in Korea [6–12]. Previous studies have reported that only a few patients presented with mild hydronephrosis with or without vesico-ureteral reflux. There have been no reports of SS with end stage renal disease requiring hemodialysis due to posterior urethral valve in Korea.

In this report, we describe the first patient with 5q35 microdeletion who required renal replacement therapy at the age of 2 months due to end stage renal disease.

Case

A 2-month-old boy visited the emergency room of our hospital due to poor oral intake and abdominal distension. The patient was born by caesarian section performed at a local hospital at 38+0 weeks of gestation with a birth weight of 4,180 g (>97th percentile) and length of 52 cm (75th percentile). He was the parents' first child. Oligohydramnios was observed during pregnancy, and fetal ultrasonography revealed a distended fetal bladder and abdomen. Amniocentesis was performed at 18 weeks of gestation, at which time a normal male karyotype, 46, XY, was revealed by chromosomal analysis of the amniotic cells. At the age of 14 days, he showed poor sucking power and difficulty feeding with abdominal distension and visited another hospital where he was admitted for 25 days. Blood laboratory findings showed elevated levels of blood urea

nitrogen (83.9 mg/dL), serum creatinine (9.93 mg/dL), and uric acid (12.8 mg/dL). The karyotype of peripheral blood leukocytes was 46, XY. Abdominal sonography revealed multiple cysts in both kidneys, and renal cortical uptake of both kidneys was not visualized on dimercaptosuccinic acid scan. Abdominal distension and feeding intolerance persisted. Therefore, a colon study was performed; however, there was no evidence of Hirschsprung's disease.

Upon the first visit to our hospital, the patient's body length was 52.8 cm (<3rd percentile), with a weight of 3.95 kg (<3rd percentile) and head circumference of 37 cm (50th percentile). He had a blood pressure of 69/41 mmHg, pulse rate of 122 beats/min, respiratory rate of 48 breaths/min, and body temperature of 37°C. The patient had a long face with a broad and prominent forehead, pointed chin, and down-slanted eyes. He also showed a high arched palate and pectus excavatum deformity of the thorax. The left testis was undescended, and generalized hypotonia was found upon neurologic examination. Although a cardiac murmur was not audible, a small muscular ventricular septal defect (2.5 mm in size) was detected by echocardiography. In the laboratory findings, elevated levels of blood urea nitrogen of 63 mg/dL and serum creatinine of 6.20 mg/dL were noted. Therefore, emergent hemodialysis was performed. Urine analysis performed to evaluate tubular function showed N-acetyl- β -glucosaminidase (NAG) levels of 1.6 mg/dL (0.3–11.5 IU/L), NAG/creatinine of 37.1 IU/g-Cr (0–5.6 IU/g-Cr), and tubular reabsorption of phosphate of 85% (>85%), based on which combined renal tubulopathy was suspected.

Vesicoureterography was performed to identify the cause of neonatal onset renal failure, and dilatation of the bladder neck and posterior urethra were observed, causing urethral obstruction to be suspected (Fig. 1A). Abdominal magnetic resonance (MR) images also revealed bilaterally tortuously dilated ureters and multiple small cysts in both kidneys (Fig. 1B). Brain MR images showed only mild ventriculomegaly.

Based on the facial dysmorphism and congenital anomalies of multiple organs, we decided to perform an additional array comparative genomic hybridization analysis. The results showed a 1.85 Mb deletion on chromosome 5q35.2q35.3, harboring *NSD1* (Fig. 2A). Fluorescence *in situ* hybridization analysis was performed for confirmation of the deletion (Fig. 2B), and the diagnosis of SS caused by 5q35 microdeletion was made.

Renal replacement therapy using regular hemodialysis (3 times a week) was performed for end stage renal failure, and the blood urea nitrogen was decreased. The patient is now 24 months old, and catch-up of growth in both height (82.5 cm,

Fig. 1. (A) Vesicoureterography showed linear filling defects (arrow) between the dilated bladder neck and posterior urethra. The dilated posterior urethra was funnel-shaped, and the bladder wall was thickened. (B) Tortuous and dilated ureters (arrows) in both sides and a thickened bladder wall were observed in the abdominal magnetic resonance images of the patient. Bilateral small-sized kidneys with multiple small cysts can also be seen.

Fig. 2. Results of aCGH (A) and FISH (B) analyses revealed a 1.85 Mb deletion in 5q35.2q35.3. aCGH, array comparative genomic hybridization; FISH, fluorescence *in situ* hybridization.

5th–10th percentile) and weight (10.6 kg, 5th–10th percentile) was observed with renal replacement therapy. Macrocephaly with a head circumference of 48 cm (50th–75th percentile) was evident. In addition, his developmental milestones are generally delayed. He can control his head perfectly and roll over to both sides, but he cannot sit alone at the age of 24 months. Regular hemodialysis was changed to peritoneal dialysis at the age of 17 months, and rehabilitation therapy has been continued to date.

Discussion

Our patient showed the characteristic facial features of SS including frontal bossing, antimongoloid slant of the palpebral fissures, sparseness of hair in the frontoparietal region, high anterior hairline, and prominent and pointed jaw, as previously described [1]. In particular, macrosomia and macrocephaly

are considered cardinal manifestations that can be important clues for the clinical diagnosis of SS [1]. The patient herein was born large for his gestational age with a large head, and this finding had persisted since the initial antenatal sonographic examination. Additionally, the patient's birth weight was over the 97th percentile for his age and gender. However, upon admission to our hospital at the age of 2 months, his length was only 52.8 cm (<3rd percentile), weight was only 3.95 kg (<3rd percentile), and head circumference was 37 cm (50th percentile). These observations might be associated with rapid progression of chronic renal failure after birth. SS patients also usually have abnormal neurologic manifestations such as developmental delays, hypotonia, myoclonus, and seizures [2]. The majority of SS patients have various degrees of developmental delay. Walking and speech development are generally delayed, and most patients have various degrees of intellectual disabilities with intelligence quotients ranging from below 30 to above 100 [5]. In addition, seizures have been reported in up to 50% of SS patients [1]. Consistent with previous studies, hypotonia and seizure-like movements were observed in the patient, accompanied by developmental delays in motor and neuropsychological function.

The pectus excavatum presented in the patient is also a common feature of SS, though the thoracic wall anomalies observed are not a cardinal feature. Thoracic wall anomalies such as pectus excavatum are seen in 2-5% of individuals with SS [13]. About 20% of SS patients have cardiac anomalies, of which atrial septal defects and patent ductus arteriosus are most common [13]. The patient examined herein also had a ventricular septal defect. In addition, the patient had difficulty feeding, with abdominal distension and defecation difficulty that mimicked Hirschsprung's disease in the neonatal period. Early feeding difficulty is a common gastrointestinal symptom, along with neonatal jaundice. The frequency of gastrointestinal symptoms observed in SS patients is unclear. However, a previous study reported that about 40% of SS patients required tube feeding during infancy due to feeding difficulty [1].

Genitourinary anomalies associated with SS were identified in 19% of patients and can be accompanied by duplex or vesico-ureteric reflux, pelvo-ureteric junction obstruction, and cystic kidneys [14]. However, vesico-ureteric reflux is the most common urogenital problem in SS [4], and unilateral renal agenesis is often observed [5,15]. There were no abnormal kidney findings detected by antenatal sonography in the patient. However, renal sonography performed due to the finding of azotemia in laboratory tests showed bilateral renal dysplasia

and multiple cortical cysts, suggesting a posterior urethral valve at the age of 2 months. Although there was one report of a Japanese patient who had multiple dysplastic renal cysts in the unilateral kidney, the other kidney was normal, making renal replacement therapy unnecessary [4]. In the patient herein, bilateral renal dysplasia due to posterior urethral valve was observed, which may have caused chronic renal failure to start during the fetal period. During pregnancy, oligohydramnios had been noted. This finding also suggested that bilateral renal dysplasia and renal function deterioration had started at that time [16]. Therefore, renal replacement therapy was required at the age of 2 months. Although SS is commonly accompanied by urogenital anomalies, severe bilateral renal dysplasia and rapid progression to end-stage renal disease caused by posterior urethral valve is quite rare.

NSD1 on chromosome 5q35 is the main causative gene of SS [5] and is expressed in several tissues including the brain, kidney, skeletal muscle, spleen, lung, and thymus [17]. The haploinsufficiency of *NSD1* occurs in 60-90% of clinically diagnosed SS patients and can be transmitted in an autosomal dominant fashion, but over 95% of patients gain SS from *de novo* mutation without any family history [6]. *NSD1* abnormalities include microdeletion of 5q35 and intragenic mutations within the *NSD1* gene [6]. 5q35 microdeletion encompassing *NSD1* is more common (approximately 50%) than *NSD1* intragenic mutation in Japanese patients with SS; however, less than 10% of non-Japanese patients show 5q35 microdeletion [18]. A previous report documenting Korean patients with SS indicated that 53% of patients had a 5q35 microdeletion, which was consistent with the findings of Japanese studies [12]. The patient herein was also diagnosed as having SS caused by 5q35 microdeletion. In previous studies, some genotype-phenotype correlations have been suggested. The frequency of cardiac and urogenital malformations in the 5q35 deletion group was reported to be more common than in the *NSD1* intragenic mutation group [4,5]. Saugier-Verber et al. [19] described 116 patients with *NSD1* alterations, in which a significantly higher frequency of cardiac (37.5% vs. 8%) and renal (50% vs. 12%) malformations were observed in the 5q35 deletion group than in the group with the *NSD1* intragenic mutation. The patient herein also had a 5q35 microdeletion with both cardiac and urologic anomalies.

Here, we reported the first case of an infant with SS presenting with severe uremia associated with chronic renal failure. At diagnosis, the patient showed lower body weight and short stature due to chronic renal failure, even though he had SS.

Therefore, if patients have a history of relative macrocephaly, high birth weight, and long birth length, SS should not be excluded for differential diagnosis of multiple congenital malformation syndrome.

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