Sotos Syndrome with Co-Morbid Polycystic Kidney Disease: A Case Report

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Abstract

Sotos syndrome is a genetic condition characterized by excessive growth both prenatally and postnatally, macrocephaly, distinctive facial gestalt, various degrees of learning difficulty and additional clinical features. We report a case on a 14-month-old male infant with the clinical diagnosis of Sotos syndrome, who was also found to have polycystic kidneys that were first detected by renal sonography at the age of 4 months. This association has been reported only once previously in a patient with Sotos syndrome where autosomal dominant polycystic kidney disease segregated independently in the family. We discuss the possible urogenital findings in Sotos syndrome as well as the association between this syndrome and polycystic kidney disease.

Keywords: Sotos syndrome; Renal cysts; Urogenital anomalies

Introduction

Sotos syndrome is a genetic condition characterized by excessive growth both prenatally and postnatally, macrocephaly, distinctive facial gestalt, various degrees of learning difficulty and additional clinical features [1,2]. The findings present in ≥15% of cases include advanced bone age, cranial CT or MRI abnormalities, neonatal hypotonia, poor feeding in infancy, seizures, scoliosis, cardiac anomalies, renal anomalies and other findings [1-3]. Various urogenital anomalies have been described in Sotos syndrome [1,4], however, the association of Sotos syndrome and renal cystic disease is not known. We report a case of polycystic kidney disease in a patient with Sotos syndrome.

Patient Report

A 14-month old boy was referred for evaluation in our genetic clinic due to dysmorphic features and polycystic kidney disease. His non-consanguineous parents are of Jewish-Uzbek origin and this boy is their first and only child. The mother, aged 26 years, is healthy, and the father, aged 33 years, has psoriatic arthritis. During the pregnancy the mother was treated with aspirin. She had a history of three previous spontaneous abortions. From 30 weeks of pregnancy she had premature contractions and was treated with nifedipine. A glucose challenge test was normal, and fetal sonography follow-up was also normal. The boy was born at 32 weeks gestation by vaginal delivery; birth weight was 2360 grams (+2.5SD) and head circumference 31.5 centimeters (85th centile). The Apgar score was 8 at 1 min and 8 at 5 min. Due to peripheral edema and echymoses observed soon after birth, especially in the upper part of the body, he was hospitalized in the neonatal intensive care unit. His blood pressure at admission was 92/53, heart rate was 112 beats per minute. During the first few days of life he lost 20% of his weight and developed acute renal failure, with an increase in the creatinine level up to 2.1 mg/dL, urea was 57 mg/dL. He was also found to have hyperkalemia, hyponatremia and microscopic hematuria. He was treated with K-exalate, IV NaCl 0.9%+ Glucose 5%, and albumin. Normalization of blood electrolytes was achieved and the creatinine level decreased to 0.9 mg/dL. The clinical and laboratory findings were compatible with post-ischemic acute tubular necrosis. Renal sonography showed normal parenchymal structure and echogenicity, and normal flow in the renal blood vessels. Brain sonography showed bilateral subependymal bleeding (grade 1). Hearing test, Brain Stem Response Audiometry (BERA) and echocardiography were normal.

On follow-up he was found to have global developmental delay (motor, speech, communication). He was treated by physiotherapy from the age of 6 months. Evaluation in the neurology clinic revealed increased tonus of all four limbs and axial hypotonicity. Blood count, biochemistry profile, CPK, pyruvate, lactate, ammonia, plasma amino acids and Very Long Chain Fatty Acids (VLCAF) were all normal. Electroencephalogram (EEG) was normal. Brain MRI at the age of 10 months showed hyperintensity of the white matter and extra-ventricular obstructive hydrocephalus. The corpus callosum was somewhat thin, without evidence of brain dysplasia or heterotopia. X-ray of the lumbar and sacral spine was normal. Serology for TORCH was negative. Ophthalmologic examination including fundoscopy at the age of 10 months was normal. On abdominal sonography at the age of 4 months the length of the right kidney was found to be 5.7 cm., while that of the left kidney was 7 cm. Parenchyma with mild diffuse hyperechogenicity of the cortex was also found. There was a 2 mm diameter cyst in the right kidney and another same diameter in the left kidney. There were also many other smaller cysts in both kidneys, and the collecting system and urinary bladder were normal. The rest of the abdominal viscera were also normal. Repeated renal sonography at the ages of 7 and 11 months showed the same findings (Figure 1a). Renal sonography of both parents was normal. On follow-up at the age of 20 months, renal function tests and urinalysis were normal.

Evaluation in our genetics clinic at the age of 14 months revealed physical findings and dysmorphic features compatible with the diagnosis of Sotos syndrome (Figure 1b): the head circumference was 50.3 cm. (2 SD above the mean). The mother’s head circumference was 55.7 cm. (60th centile) and the father’s was 55.5 cm. (40th centile). The child’s height was 83 cm. (90th centile) and weight 12.5 kg (95th centile). The head was dolichocephalic with a broad forehead; he was somewhat thin, without evidence of brain dysplasia or heterotopia. Ophthalmologic examination including fundoscopy at the age of 10 months was normal. On abdominal sonography at the age of 4 months the length of the right kidney was found to be 5.7 cm., while that of the left kidney was 7 cm. Parenchyma with mild diffuse hyperechogenicity of the cortex was also found. There was a 2 mm diameter cyst in the right kidney and another same diameter in the left kidney. There were also many other smaller cysts in both kidneys, and the collecting system and urinary bladder were normal. The rest of the abdominal viscera were also normal. Repeated renal sonography at the ages of 7 and 11 months showed the same findings (Figure 1a). Renal sonography of both parents was normal. On follow-up at the age of 20 months, renal function tests and urinalysis were normal.

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hypo pigmentation were observed over the central area of the chest, in the left antecubital area expanding to the flexor region of the left arm, and on the left buttock. The distribution was patchy with irregular margins. We re-examined him at the age of 20 months and the findings were as follows: head circumference was 52 cm (2 SD above the mean), height 93.5 cm (95th centile), and weight 15.2 Kg (98th centile). His hand lengths were: right 12.1 cm (+3SD) and left 12.3 cm (+3SD), and foot lengths were: right 15.8 cm (+3SD) and left 16.3 cm (+3SD). An X-ray of the left hand showed normal structure and shape of bones and the bone age was compatible with 2 years. The family refused molecular analysis both for Sotos syndrome (NSD1) and autosomal dominant Polycystic Kidney Disease (PKD1 and PKD2).

Discussion

Urogenital abnormalities were present in seven out of eight (88%) of a group of Japanese patients with Sotos syndrome [5]. In the American and European literature, urogenital anomalies have also been reported, although the incidence was lower. Cases of urogenital disorders accompanying Sotos syndrome are summarized in Table 1 [1,4]. There is a well known association between renal cysts and certain genetic syndromes such as tuberous sclerosis, Von Hippel-Lindau disease, medullary sponge kidney and orofaciodigital syndrome type 1 [6,7]. Cefel et al. [8] reported a case of Sotos syndrome presenting with chronic renal failure due to autosomal dominant polycystic kidney disease (ADPKD) in a 22-year-old male patient [8]. Ultrasonographic examination of the patient, his father, brother and sister revealed polycystic kidneys, indicating that polycystic kidney disease segregated as an independent trait in this family. However, renal failure was present only in the patient with Sotos syndrome, who also had considerably larger cysts (7-8 cm) than other family members (<1 cm). The authors suggested that the underlying mechanism responsible for the somatic overgrowth in Sotos syndrome may also be linked with the development of larger cysts and earlier onset of renal failure in ADPKD [8].

Our patient presented with polycystic kidney disease, which was first diagnosed at the age of 4 months. Renal US in both the parents was normal. It is most likely that the polycystic kidneys found in our patient are part of his Sotos syndrome. However, the possibility of incomplete penetrance due to young parental age or autosomal dominant polycystic kidney disease with a de novo mutation cannot be excluded. In affected individuals with autosomal dominant polycystic kidney disease renal cysts present with increasing frequency with age. More than 90% of affected individuals will demonstrate cystic abnormalities by 20 years of age. Some patients have early onset of the disease (in utero or in the first year of life). The reason for early onset is not known [9]. De novo mutations occur in about 10% of affected individuals with autosomal dominant polycystic kidney disease [7]. It should be emphasized that although the diagnosis of Sotos syndrome is mainly based on clinical signs (accelerated growth, acromegalic appearance, mental retardation and various organ abnormalities), the diagnosis of sporadic APDKD in a child would be more complex. It is difficult to identify a polycystic kidney in absence of a positive family history and without performing the genetic analysis. It is also reasonable to think that the acute tubular necrosis, occurred at birth, would have caused the damage to the tubular epithelium and facilitated the cysts formation. Therefore, a longer follow up or the genetic tests are required to confirm the APDKD diagnosis [10].

Conclusions

This is the first report of polycystic kidney disease in a patient with Sotos syndrome and no family history of autosomal dominant polycystic kidney disease. We suggest that every patient with Sotos syndrome should undergo repeated sonographic evaluation in order to exclude progressive renal cystic disease.

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Table 1: Urogenital anomalies reported in association with Sotos syndrome (adapted from Baujat and Cormier-Daire, 2007, and Visser and Matsumoto, 2003).

| Renal                          | Hydronephrosis | Hypoplastic kidneys | Renal agenesis | Double collecting system | Chronic renal failure | Polycystic kidney |
|-------------------------------|----------------|---------------------|----------------|--------------------------|----------------------|-------------------|
| Bladder/ureter/urethra         | Vesioucretral reflux | Bladder diverticulum/nodule | Hypospadias  |
| Testis                        | Cryptorchidism | Testis redux        |

Figure 1: A- Sonography of right kidney performed at the age of 11 months demonstrating multiple tiny cysts, two of which are shown in the image (arrows); B- the child’s face.