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Case Report
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Silver–Russell Syndrome in a Newborn, with the Phenotype of Potter Sequence and Renal Malformations

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Abstract

Characteristics of Silver-Russell syndrome (SRS) include prenatal or postnatal growth retardation, body asymmetry, and relative macrocephaly at birth. The case patient was diagnosed with SRS, showing Potter sequence as a kidney anomaly at birth, growth retardation, and body asymmetry during growth. Kidney anomaly is not included in the diagnostic criteria for SRS. Since imprinting disorder can have multi loci mutation, genetic testing is required even if the NH-CSS score is low.

Keywords: Kidney; Phenotype; Silver-Russell syndrome

Introduction

A fetus may develop when there is very little amniotic fluid in the uterus (in utero), leading to pregnancy and a rare condition named Potter syndrome [1]. The amniotic fluid supports, cushions, and protects a developing fetus. When there is very little amniotic fluid, normal pressure exerted on the fetus during pregnancy can cause adverse physical features, such as abnormal facial features or skeletal abnormalities. When oligo-anhydramnios develops in the early stages of pregnancy, the lungs become underdeveloped (pulmonary hypoplasia) and lead to severe breathing difficulties. Oligohydramnios is the cause of Potter syndrome, but many factors can cause oligohydramnios. It can occur due to following renal diseases: Bilateral Renal Agenesis (BRA), atresia of the ureter or urethra that causes an obstruction of the urinary tract, polycystic or multicystic kidney diseases, renal hypoplasia [2,3].

Silver–Russell Syndrome (SRS, OMIM #180860, also known as Russell–Silver Syndrome, RSS) is a rare condition, which causes prenatal and postnatal growth retardation [4,5]. Currently, the clinical diagnosis of SRS is based on a combination of characteristic features. Molecular testing can confirm the diagnosis of SRS in around 60% of patients [6]. The clinical diagnosis of SRS is confirmed when a patient scores at least four out of six in the Netchine-Harbison Clinical Scoring System (NH-CSS). The physical characteristics of SRS are as follows: (i) Prenatal growth retardation, (ii) postnatal growth retardation, (iii) relative macrocephaly at birth, (iv) a protruding forehead, (v) body asymmetry, (vi) feeding difficulties, and/or a (vii) a low body mass index (BMI) [7]. The most common underlying molecular mechanisms of SRS are the loss of methylation on chromosome 11p15 (11p15 LOM; it occurs in 30% to 60% of patients) and maternal uniparental disomy of chromosome 7 (upd(7)mat; it occurs in ~5% to 10% of patients) [8,9]. And SRS is imprinting disorder. Imprinting disorders (IDs) are a group of congenital diseases characterized by overlapping clinical features affecting growth, development and metabolism, and common molecular disturbances, affecting genomically imprinted chromosomal regions and genes [3]. Imprinting disorders: a group of congenital disorders with overlapping patterns of molecular changes affecting imprinted loci.

Here, we report a case of SRS; this patient was born with the phenotype of Potter sequence and renal malformations. The study was approved by the Jeju National University Hospital, and written informed consent was obtained from the patient's parents.

Case Presentation

A 34-year-old woman, gravid 2, para 2, was transferred to our hospital at 25 6/7 weeks of pregnancy because she was diagnosed with oligohydramnios, and her fetus had severely restricted growth with no visible kidney in right renal fossa. We antenatally diagnosed the fetus with Potter syndrome. She had no family history, past medical history, or medication history.

At 35 4/5 weeks of pregnancy, a cesarean section was performed on the woman as she presented

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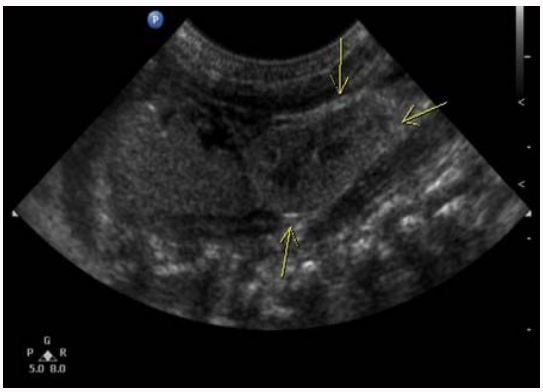

Figure 1: Kidney sonography at birth. (Right kidney is not visible. Hypoplastic left kidney whose size is 2.09 cm and a rotational variation in the left renal fossa with poor corticomedullary differentiation).

a fetal breech. A female newborn was delivered; the infant had a cleft palate, and her left lower leg was shorter than the right lower leg. She showed pronounced underweight and short stature (weight 1340 g, – 3.06 SD; length 34 cm, – 4.62 SD) and relative macrocephaly (head circumference, 31.5 cm, – 0.29 SD).

Her Apgar scores were 5 at 1 min and 8 at 5 min after birth. Soon after her birth, it was found that the baby had tachypnea, with SpO_2 values of 50%. Therefore, a Continuous Positive Airway Pressure (CPAP) was applied to her nose in the neonatal intensive care unit. She was intubated endotracheally, and she received an artificial pulmonary surfactant. Moreover, a High-Frequency Oscillatory Ventilator (HFOV) was connected to her because her gradually increased oxygen demand could be suspicious of pulmonary hypoplasia associated with oligohydramnios. In fact, the chest X-ray showed an increased haziness in both the lungs and pneumomediastinum. The findings of laboratory reports, which were obtained on day 3 of hospital stay, were as follows: White Blood Cells (WBC), 15,800/μL (segmental neutrophil 46%, lymphocyte 36.3%); hemoglobin, 15.4 g/dL; hematocrit, 42%, Platelets (PLT) 308,000/μL; albumin, 3.2 g/dL; total protein, 5.3 g/dL; total bilirubin, 5.9 mg/dL; aspartate aminotransferase, 38 IU/L, alanine aminotransferase, 8 IU/L; blood urea nitrogen, 32.3 mg/dL; Creatinine (Cr), 1.9 mg/dL; sodium, 136 mmol/L; potassium, 5.8 mmol/L; calcium, 9.0 mg/dL; phosphorus, 8.6 mg/dL; uric acid, 5.0 mg/dL; and Parathyroid Hormone (PTH), 289.6 pg/ml. By performing ultrasonography of the kidney, we found that the right kidney was not visible, and the left kidney was hypoplastic with a size of 2.09 cm (Figure 1). Moreover, a rotational variation was observed in the left renal fossa. By performing X-ray of hips, we found that the ossific nucleus of the femur's head was not visible and the left femur was relatively shorter in length. By performing an ultrasonography of hips, we detected the deficient bony acetabulum had an alpha angle of 46° when subjected to stress in the left hip joint. This indicates the occurrence of Developmental Dyplasia of the Hip (DDH) in the newborn.

It was confirmed that the newborn had Potter sequence, chronic kidney disease, and DDH; however, her urination was normal and pneumomediastinum gradually improved with medical intervention. On day 6 of hospital stay, she received synchronized intermittent mechanical ventilation from HFOV. On day 7 of hospital stay, the ventilator was weaned off from the newborn. Renal replacement therapy was not provided despite azotemia. Nevertheless, the oral intake of the newborn had increased. Finally, the patient was

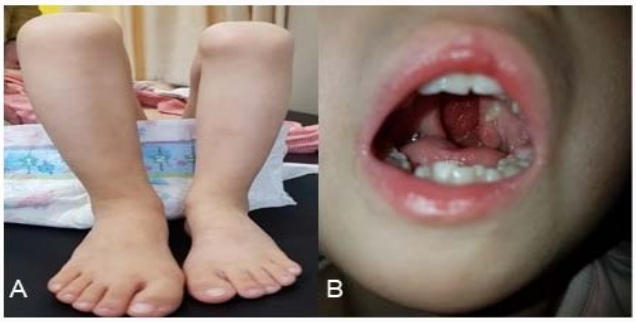

Figure 2: A) At 24 months, limb asymmetry. B) At 24 months, the presence of a cleft palate.

discharged at 3 months of age. (Weight 2720 g, – 5.97 SD; height 46.5 cm, – 6.32 SD; head circumference 35.8 cm, -3.01 SD).

At 24 months of age, the weight gain of the infant was insufficient, and she also did not catch up on growth (Figure 2). (Weight 5.5 kg, – 6.63 SD; height 74.1 cm, – 3.60 SD; head circumference 43.5 cm, -2.64 SD) Therefore, genetic testing was performed at the hospital. Hypomethylation was detected in the H19-Differentially Methylated Region (DMR), and the diagnosis of RSS was confirmed in the patient.

She is currently receiving growth hormones, has undergone cleft palate surgery, and is scheduled to be operated on at an orthopedic clinic due to a difference in low limbs of more than 2 cm.

Discussion

The well-known features of SRS are as follows: Small for gestational age, postnatal growth failure, and relative macrocephaly at birth, protruding forehead, body asymmetry, and feeding difficulty. In addition, various clinical symptoms may also be present in the patient. In this study, the patient was Small for Gestational Age (SGA) due to Intrauterine Growth Restrictions (IUGR) and the development of Potter sequence, which included clinical features such as oligohydoramnios and renal hypoplasia. The most common cause of Potter sequence is kidney abnormality, and this patient had hypoplastic kidney. Her left kidney size was also small in size. However, even after rectifying azotemia, she could not catch up with growth and her body asymmetry worsened with age. Although feeding difficulties were not observed, she had a protruding forehead, a triangular face, a delay in speech, and motor delay. In addition, cleft palate was also observed in the baby. According to NH-CSS classification, since it is based on growth status after 24 months, we subsequently performed genetic testing on patients who did not catch up with growth to diagnose SRS.

Kidney problems are uncommon among the clinical feature of SRS. According to a study published by Haslam structural abnormalities of kidney were observed in 5 cases. This study also included cases of horse shoe kidney, renal tubular acidosis, and chronic kidney disease [10]. Walking compared ICR1 hypomethylation and mUPD7, identifying horseshoe kidney and unilateral kidney hypoplasia only in mUPD7 patients [11].

However, ours is the first case of Potter sequence. The consensus statement of SRS was published in 2017. In this statement, kidney problem was not included as an additional clinical feature of SRS [12].

However, a characteristic kidney problem may occur due to following reasons: Firstly, the molecular finding of the patient

may include hypomethylation of H19/IGF2 IG-DMR gene, which results in reduced expression of paternal IGF2 and an increased expression of maternal H19. This causes growth restriction of the patient. However, previous studies have reported about numerous Copy Number Variants (CNVs) associated with 11p15.5 region; the phenotype is dependent on the size of CNVs, their location, and their parental origin [13,14].

Therefore, there is a possibility that various undisclosed phenotypes appear, depending on the location or size of CNVs involved.

Second, in a study conducted by Eggerman multi-locus genetic testing was performed on 571 SRS subjects [15]. This study showed that 7.1% of SRS children were diagnosed with ICR1 hypomethylation and other genetic mutations. A considerable number of 11p15-associated imprinting disorder patients show additional molecular findings. In addition, the various phenotypes may be shown depending on additional molecular findings.

Although ICR1 hypomethylation was detected in our patient, multi-locus genetic testing was not performed on our patient.

In addition, according to Schwaibold [16], there are cases in which SRS and Sotos syndrome are diagnosed simultaneously. According to the article, this patient was determined through genetic testing, and although Sotos syndrome is an overgrowth syndrome, the child was severely short stature, and it was mentioned that further research is needed on the mechanism. Therefore, we only conducted SRS genetic testing for our case patient, but we cannot exclude the possibility of accompanying genetic diseases.

We reported the first case of an SRS patient with Potter sequence. The study has a limitation as we only identified the hypomethylation of 11p15. Even if NH-CSS scoring is low, genetic testing should be performed by consistent follow-up of patients, and it should be noted that various phenotypes may be shown in the imprinting disorder. In addition, individual genetic testing for accompanying diseases should be considered.

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