A Case of Schinzel-Giedion Syndrome

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ABSTRACT

Schinzel-Giedion syndrome (SGS) is a rare malformation syndrome characterized by severe midface retraction, multiple congenital malformations including hydronephrosis, congenital heart defect, skeletal anomalies and hypertrichosis, and a higher prevalence of tumors. We experienced a case of a male newborn with SGS showing midface retraction with infraorbital deep groove, hydronephrosis, bilateral hydronephrosis, and hypotonia. At the age of 2 months, hepatosplenogmegaly with unknown cause appeared. There was no evidence of hepatoblastoma in abdominal computed tomography. SGS is known to have an autosomal recessive inheritance pattern. Recently, it has been suggested that de novo mutations of SETBP1 causes SGS. However, there has been no report regarding the genetic analysis of SGS in the Korean population. We first sequenced the exones using array CGH and SETBP1 gene analysis in Korea. However, no specific gene mutation was apparent.

Key Words: Newborn, Seizures, Outcome, Risk factor

INTRODUCTION

Schinzel-Giedion syndrome (SGS) is a rare malformation syndrome characterized by severe midface retraction, multiple congenital malformations including hydronephrosis, congenital heart defect, skeletal anomalies and hypertrichosis, and a higher prevalence of tumors. Approximately 46 cases have been reported since a brother and sister with this disorder were described in 1978. In our knowledge, two cases have been reported since 2000 in Korean population. Since the specific gene and chromosome has not yet been identified, diagnosis is strictly based on clinical findings and radiographs. SGS is postulated to have an autosomal recessive inheritance pattern. Recently, it has been suggested that de novo mutations of SETBP1 cause SGS. Although little is known about the function of SETBP1, it might be associated with bone development and specific pediatric cancer. However, there is no report regarding the genetic analysis of SGS in the Korean population. We sequenced the exones using array CGH and SETBP1 gene analysis in the present case, involving a neonate with SGS.
CASE REPORT

A 2-days-old male patient was referred to our hospital because of weak crying and problem with feeding. The patient had been born at 40 weeks gestation by cesarean delivery and weighed 3,400 g at birth. The patient was the first baby of nonconsanguineous parents. The patient’s mother was a 30-years-old female. Gross bilateral hydronephrosis and cerebral ventriculomegaly were detected by prenatal ultrasonography at 36 weeks gestation. There was no family history of congenital major malformations. Apgar scores were 8 and 10 at 1 and 5 min, respectively. The patient presented with coarse facial features with protruding forehead, infraorbital deep groove, and a figure-8-shaped face. The ears were low set with protruding lobules. In addition, hypospadia was observed on genital examination (Fig. 1). A feeding problem was evident and a nasogastric tube was required for nutrition. Postnatal renal sonography showed bilateral hydronephrosis with grade II-III. Voiding cystogram and diuresis renogram showed no abnormal findings. Broad ribs were seen on chest radiographs (Fig. 2). However, skeletal radiology showed no abnormal findings such as mesomelic shortening of the long bones. Both echocardiography and brain magnetic resonance imaging revealed no abnormal findings. Screening for metabolic diseases was unremarkable. The patient’s karyotype was 46 XY. Also, array comparative genomic hybridization was normal. SGS was suspected based on the distinctive facial features, hypospadia, hydronephrosis, and clinical course such as the feeding problem. The patient was discharged while having tubal feeding at 26-days-of-age. However, the patient was readmitted because of febrile condition at 40-days-of-age. During hospitalization, seizure developed at 47-days-of-age. The seizure was a tonic and/or clonic type, and was refractory to anticonvulsants. The interictal electroencephalogram during sleep was markedly abnormal due to discontinuous background activity for patient age, abnormal sleep activity, and focal interictal epileptiform discharge over the left central, right temporal and left frontal areas. At the age of 2 months, hepatosplenomegaly and thrombocytopenia appeared and progressed (Fig. 3). There was no evidence of hepatoblastoma in abdominal computed tomography. Although principal tests concerning platelet profile such as anti-platelet antibody and platelet-associated IgG were done to ascertain the cause of thrombocytopenia, all tests were negative. The range of thrombocytopenia was 72-74×10^9/L and persisted about 2 months. At the age of 4 months during hospitalization, the patient died because of sudden respiratory failure. Unfortunately an autopsy could not be performed. We sequenced the exones using array CGH and SETBP1 gene in our patient. According to Hoischen et al, all mutations of the SETBP1 gene in their patients

Fig. 1. Physical examnination revealed distinctive infraorbital groove, abnormal lobules and hypospadia.

Fig. 2. Chest radiography shows wide ribs.
were revealed in exon 4. Therefore, direct sequencing of exon 4 was accomplished using author-designed primer pairs as previously described by Hoischen et al. However, we found no mutations in our patient.

**DISCUSSION**

SGS is thought to have an autosomal recessive inheritance pattern on the basis of some affected siblings with normal parents. However, alternative hypotheses such as microdeletion, microduplication, or heterozygous de novo mutations in a single gene must be considered because the recurrence of this syndrome was rare in the aforementioned siblings and because the disease phenotype occurs sporadically in almost all subjects.

Metabolic abnormality has been raised as the most likely cause by many. Facial features, progressive gingival hypertrophy, occasional hepatomegaly, and dysostosis suggest substrate accumulation and could be associated with a metabolic defect. Unlike previous reported cases in Korean population, our patient showed progressive hepatosplenomegaly and thrombocytopenia with unknown cause, which might support the view that SGS may be a metabolic disorder. However, consistent with previous reported cases, no metabolic and biochemical abnormalities were recognized in our patient.

Several attempts have been made to investigate SGS gene mutations by using of array comparative genomic hybridization (CGH). However, no information on cause of SGS based on array CGH has been forthcoming, including the present patient.

Recently, it was suggested that de novo mutations of SETBP1 cause SGS. Hoischen et al sequenced the exons of four affected cases with SGS and found heterozygous de novo variants in SETBP1 in all four. Although little is known about the function of SETBP1, it might be associated with bone development and specific pediatric cancer. However, there has been no report regarding the genetic analysis of SGS in the Korean population. We sequenced exons to detect de novo mutations using SETBP1 gene analysis in our patient. However, no specific gene mutation was apparent.

**REFERENCES**

Schinzel-Giedion 증후군 1례

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Schinzel–Giedion syndrome (SGS)는 특이적인 얼굴 모양과 심장기형, 신장 및 골격계 기형 등 여러가지 선천성 기형을 나타내는 증후군이다. 저자들은 midface retraction, infraorbital deep groove를 보이는 얼굴 모양과 요도하열, 양측 수신증과 근긴장도 저하등의 임상 소견을 보이는 SGS 환자 1례를 경험하였다. 이 질환은 상염색체 열성 유전 방식을 취하는 것으로 알려져 있으나 최근 SETBP1의 돌연변이에 발생한다고 보고되기도 하였다. 이에 본 저자들은 국내에서 처음으로 SGS 환자를 대상으로 array CGH와 SETBP1 gene 분석을 시행하였다. 그러나 특이한 유전학적 변이 소견은 명백하지 않았다.