Clinical Case Reports

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CASE REPORT

Genetic and prenatal findings in two Japanese patients with Schinzel–Giedion syndrome

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Key Clinical Message

We report two Japanese patients with Schinzel–Giedion syndrome. When polyhydramnios is observed, additional fetal findings such as overlapping fingers, hydrocephalus, hydronephrosis, and very characteristic facial appearance comprising high, prominent forehead, hypertelorism, and depressed nasal root may suggest Schinzel–Giedion syndrome.

Keywords

Mutation, prenatal diagnosis, Schinzel–Giedion syndrome, SETBP1

Introduction

Schinzel–Giedion midface retraction syndrome (SGS; MIM%269150) is a recognizable malformation syndrome characterized by severe psychomotor retardation, seizures, distinctive facial features, and multiple congenital anomalies in the cardiac, genitourinary, renal, skeletal, and central nervous systems. The highly characteristic facial appearance consists of high, prominent forehead, low nasal root, ocular hypertelorism, midface hypoplasia, and low-set ears [5, 7, 10]. A higher risk of embryonal tumors, particularly malignant sacrococcygeal teratoma, has been noted in patients with this syndrome in comparison with the normal population [8]. The prognosis of patients with SGS is poor, and most patients die during early childhood. The disease phenotype occurs sporadically in most cases, suggesting the involvement of an autosomal dominant mutation in a single gene [1]. Hoischen et al. [2] recently sequenced the exomes of four unrelated patients with SGS and found heterozygous de novo mutations in *SETBP1*.

We report herein the cases of two unrelated Japanese patients with SGS. One patient developed sacrococcygeal tumor, and prenatal findings were available for the other.

Case Reports

Patient 1, a male infant, was born to unrelated healthy Japanese parents. The father was 34 years old and the mother 30 years old when he was born. Two older sisters, 14 and 7 years old, and a 6-year-old brother were phenotypically normal. At 29 weeks of gestation, ultrasound examination showed excess amniotic fluid. The male infant was delivered at 39 weeks and 1 day of gestation, weighing 3185 g and with a length of 48 cm.

Serial apneic attacks were noted during early infancy, and he developed infantile spasms by 1 year old. Abnormalities were identified on electroencephalography, and antiepileptic agents were administered. At 14-month old, he was referred to Tenshi Hospital for surgical treatment of a tumor developing in the sacrococcygeal region. At that time, serious psychomotor retardation was evident. He could not sit, turn over, or even suck milk. Distinctive dysmorphic features were evident, including prominent forehead, hypertelorism, shallow orbits, thick eyebrows, long eyelashes, depressed nasal root, upturned nostrils, low-set ears, hypospadias, right undescended testis, and overlapping fingers. Further examinations revealed atrophy of bilateral optic nerves, bilateral sensorineural deafness, broad ribs, and bilateral hydronephrosis (Fig. 1). The tumor was removed surgically at 16-month old, and histological analysis revealed malignant teratoma. DNA was extracted from peripheral lymphocytes, and the *SETBP1* coding sequence was determined according to standard protocols. A heterozygous guanine-to-adenine missense mutation was found at position 2602, predicting an amino acid substitution (D868N). The patient died at 2 years and 9 months old due to generalized metastasis of malignant teratoma.

Patient 2, a female infant, was born to unrelated healthy Japanese parents. The father was 25 years old and the mother 24 years old when she was born. At 28 weeks of gestation, the mother was sent to our hospital after esophageal atresia was suspected in the fetus. Excess amniotic fluid, hydrocephalus, bilateral hydronephrosis, overlapping fingers and toes, high prominent forehead, hypertelorism, and depressed nasal root were observed in the fetus on ultrasonography (Fig. 2A–C). The female infant was delivered at 37 weeks and 4 days of gestation, weighing 3106 g and with a length of 47 cm. Soon after birth, she developed respiratory difficulty due to middle airway obstruction attributed to the posteriorly placed tongue and narrow nasal cavity. Esophageal atresia was not found on nasogastric tube examination. The patient showed a characteristic facial appearance with high prominent forehead, hypertelorism, upturned nostrils, midface hypoplasia, depressed nasal root, and micrognathia (Fig. 2D). She also had a large fontanel, malformed auricles, low-set ears, and overlapping fingers and

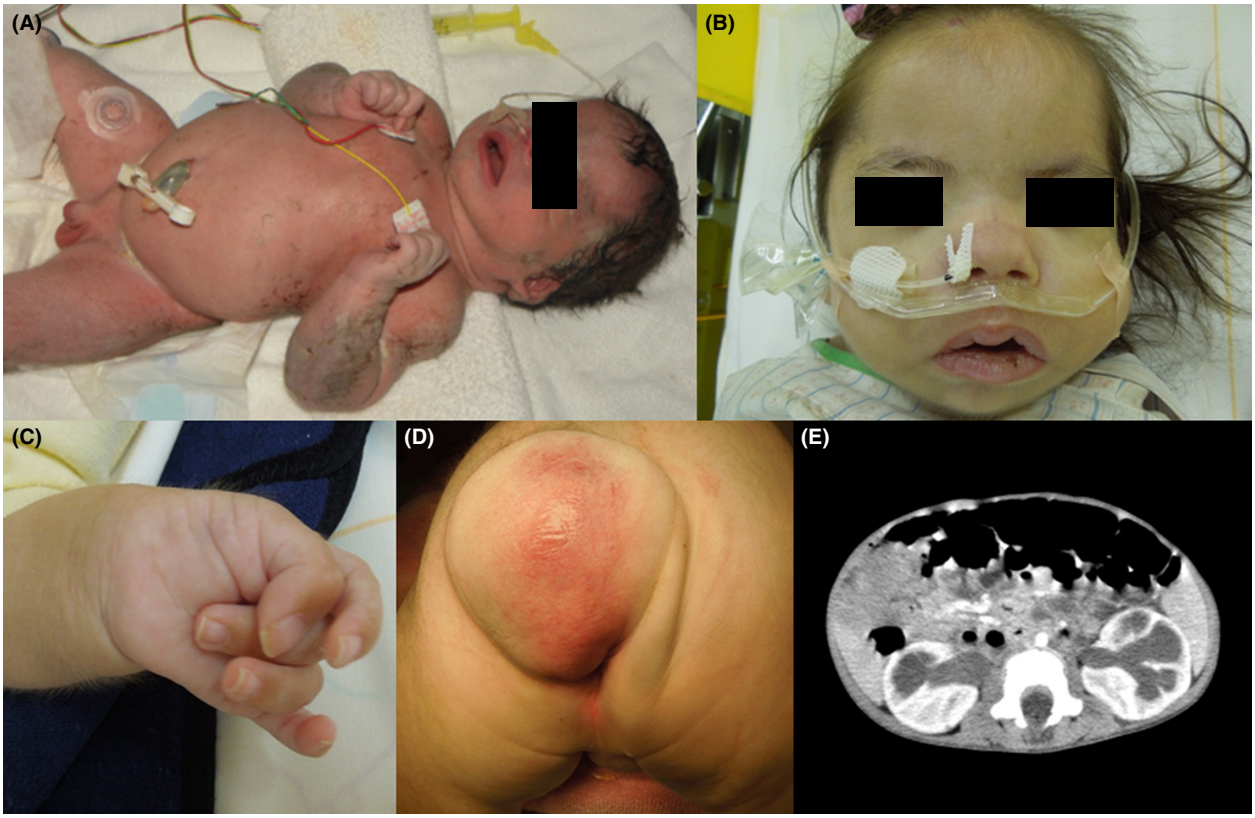

Figure 1. Patient 1. General appearance just after birth (A), facies (B), overlapping fingers (C), tumor in the sacrococcygeal region (D), and bilateral hydronephrosis (E). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833.

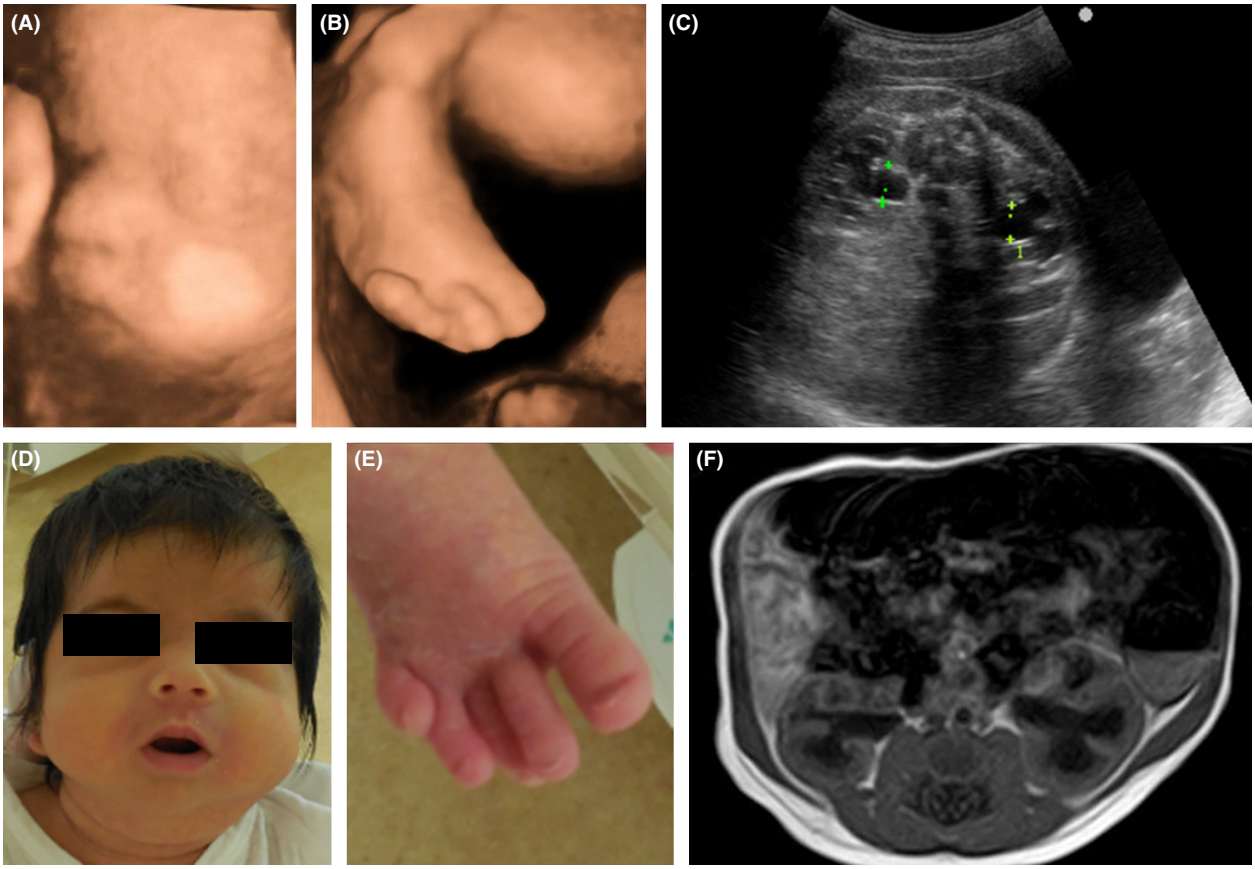

Figure 2. Patient 2. Ultrasonography at 30 weeks of gestation (A–C) and postnatal images (D–F). Facial appearance (A, D), overlapping toes (B, E), and bilateral hydronephrosis (C, F). Color figure can be viewed in the online issue, which is available at http://onlinelibrary.wiley.com/journal/10.1002/(ISSN)1552-4833.

toes (Fig. 2E). By 17 days after birth, her respiration had improved and oral milk feeding was started. Further examinations revealed mild hydrocephalus, hydronephrosis (Fig. 2F), normal heart structure, and normal external genitalia. No neoplasia was detected before she left our hospital at 30 days old. Peripheral blood was withdrawn for chromosomal and DNA examinations. GTG-banded chromosome examination revealed 46,XX. *SETBP1* coding sequence analysis revealed a heterozygous guanine-to-adenine missense mutation at position 2608, predicting amino acid substitution (G870S).

This research was prospectively reviewed and approved by the Committee for Genetic Testing and Counseling at Tenshi Hospital in Japan.

Discussion

Among the 17 individuals with SGS tested with *SETBP1* sequencing to date, 16 have shown heterozygous mutations in a highly conserved 11-bp exonic region [2, 3, 6, 12]. These mutations predicted substitutions at amino acid 868 in five patients, amino acid 870 in five, and amino acid 871 in six. The mutations identified in our patients, namely D868N and G870S, were both recurrent [2, 12].

Patient 1 was diagnosed with SGS at 14 months of age. The typical clinical features met the diagnostic criteria proposed by Lehman et al. [5].

Prior to delivery, polyhydramnios was noted with Patient 1. Among nine SGS patients for whom prenatal findings were reported, polyhydramnios was observed in two and fetal hydronephrosis in six [3, 4, 6, 7, 9, 11, 13]. Polyhydramnios is caused by excess production of amniotic fluid or poor swallowing of amniotic fluid by the fetus. Obstructive disorders of the upper digestive tract such as esophageal atresia and duodenal atresia may cause polyhydramnios, as might neuromuscular disorders that cause impaired swallowing of amniotic fluid. After birth, hydronephrosis was observed in 14 of 16 SGS cases reviewed by Labrune et al. [4] and all 10 of the cases described by Okamoto et al. [7]. Prenatal ultrasonography thus predicted hydronephrosis in six of the nine fetuses

for which findings have been reported. Touge et al. [13] reported that many SGS patients displayed several types of urinary tract anomalies, such as pyeloureteral junction stenosis, ureterovesical junction stenosis, and vesicoureteral reflux. These anomalies caused hydronephrosis with or without hydroureter. Interestingly, two patients were recorded as having polyhydramnios along with hydronephrosis on prenatal ultrasonography [3, 11]. In those fetuses, urine volume should theoretically have been reduced, but other mechanisms such as impaired swallowing function might have resulted in increased amounts of amniotic fluid. A combination of polyhydramnios, overlapping fingers, hydrocephalus, and hydronephrosis on prenatal ultrasonography may represent strong evidence for the prenatal diagnosis of SGS and other malformation syndromes including trisomy 18. In Patient 2 in this report, findings from prenatal ultrasonography matched those found in typical SGS infants. In particular, the facial appearance on three-dimensional ultrasonography was typical of SGS and differed from that of trisomy 18 (Fig. 2A).

When polyhydramnios is observed, additional fetal findings such as overlapping fingers, hydrocephalus, hydronephrosis, and a typical facial appearance with high, prominent forehead, hypertelorism, and depressed nasal root may suggest SGS. Prenatal diagnosis of SGS is noteworthy in providing advance notice of serious clinical problems in the neonatal period and allowing planning for appropriate management of the affected infant.

Conflict of Interest

None declared.

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