Childs Nerv Syst (2013) 29:525–529
DOI 10.1007/s00381-013-2047-2

BRIEF COMMUNICATION

Distinct neurological features in a patient with Schinzel–Giedion syndrome caused by a recurrent *SETBP1* mutation

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Received: 1 November 2012 / Accepted: 31 January 2013 / Published online: 12 February 2013

Abstract
Introduction Schinzel–Giedion syndrome (SGS) is a rare multiple congenital malformation syndrome defined by characteristic facial features, profound developmental delay, severe growth failure, and multiple congenital anomalies. Most individuals affected by SGS die in early childhood mainly because of progressive neurodegeneration and respiratory failure. The causative gene of SGS, *SETBP1*, was identified, but there are few reports of SGS with molecular confirmation worldwide.
Patient and method In this study, we present a 10-month-old boy presenting with SGS complicated by epilepsy and profound developmental delay.
Results Typical facial features, multiple anomalies, and associated neurological findings suggested a clinical diagnosis of SGS. Unusually in our patient, generalized tonic seizure occurred and has been controlled well by combined antiepileptic therapy during 7 months of follow-up. Electroencephalography findings were compatible with partial seizures, and ventriculomegaly, thinning of the corpus callosum, and delayed myelination were identified on brain MR images. *SETBP1* mutational analysis revealed the presence of a recurrent mutation, p.Gly870Ser. Thus, the diagnosis of our patient was molecularly confirmed as SGS.
Conclusions Although this syndrome is extremely rare, it is important to consider SGS in the differential diagnosis of infantile-onset epilepsy with progressive neurodevelopmental retardation, especially in patients with multiple anomalies and facial dysmorphism.

Keywords Schinzel–Giedion syndrome · Dysmorphism · Neurodegeneration · Epilepsy · Growth failure

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Introduction

Schinzel–Giedion syndrome (SGS, MIM#269150) is an extremely rare multiple congenital malformation syndrome characterized by midfacial retraction, hypertrichosis, congenital heart defects, urogenital malformations, and multiple skeletal abnormalities including short and sclerotic skull base, short neck, talipes equinovarus, postaxial polydactyly, as well as profound developmental delay and epilepsy. Almost half of the patients with SGS die within the first 2 years of life and the main causes of death are epilepsy, respiratory failure, and infection [16]. Moreover, an increased prevalence of embryonal tumors, including hepatoblastoma and sacrococcygeal teratoma has been reported in SGS [3, 12].

In 2010, the gene responsible for SGS was identified via exome sequencing. Heterozygous de novo mutations in the SET binding protein 1 (*SETBP1*) gene are the genetic cause of SGS [6]. However, the function of *SETBP1* and the pathogenesis of this syndrome remain poorly understood. To date, only 14 patients have been confirmed as having SGS with *SETBP1* mutations using molecular genetic methods [6, 15]. Herein, we present a boy with SGS resulting from a *SETBP1*mutation who manifested epilepsy and developmental delay with typical facial features and multiple congenital anomalies.

Case report

A 3-month-old Korean boy was referred to the Seoul National University Children's Hospital for the evaluation of multiple congenital anomalies and seizures. He was the second baby in the family and the parents and his 3-year-old sister were healthy. The patient was delivered by cesarean section because of mild polyhydramnios and breech presentation, his birth weight was 2.9 kg (10th–50th percentile), and the length at birth was 47.0 cm (10th–50th percentile) at the 37th week of gestation. On prenatal ultrasonography, bilateral hydronephrosis was observed, and bilateral congenital talipes equinovarus was suspected. After birth, facial dysmorphism, generalized hypertrichosis, bilateral congenital talipes equinovarus, poor sucking power, and noisy respiration were identified, and the patient was admitted to the neonatal intensive care unit in a regional hospital. During the 18 days of the first admission, gavage feeding combined with oral sucking training had been performed because of feeding difficulty. A tendon-release operation was performed and casts were applied to both lower extremities. Chromosome analysis and neonatal screening for inborn errors of metabolism revealed a normal male karyotype (46,XY) and no abnormal results. To rule out Cornelia de Lange syndrome, *NIPBL* gene analysis was performed; no pathologic mutation was identified.

At the initial examination at our hospital, his weight (5.5 kg), height (59.6 cm), and head circumference (36 cm) were lower than the third percentile. He had coarse facial features, including a widely open anterior fontanelle, hypertrichosis, frontal bossing, midface hypoplasia, low-set dysplastic ears, micrognathia with a high arched palate, hypertelorism, and exophthalmos of both eyes (Fig. 1a). Hypospadia was also evident, although both testes were palpable in the scrotum. He made a snoring-like sound during inspiration but had no respiratory insufficiency. Laryngoscopic examination revealed a low-set soft palate with micrognathia, which might have been the cause of the

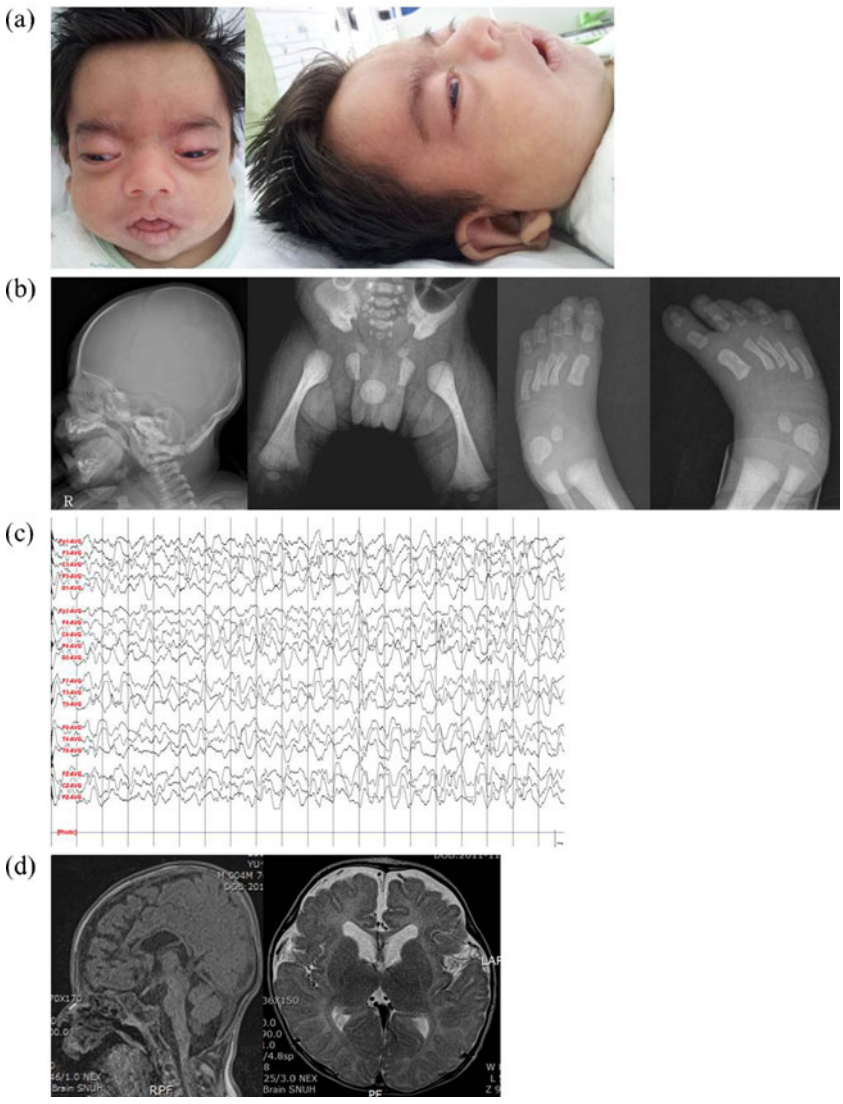

Fig. 1 **a** Facial appearance showing hypertrichosis, a prominent forehead, midface retraction, orbital hypertelorism with exophthalmos, a protruding tongue, and low-set ears with dysplastic lobules. **b** Plain radiographs showing the wide occipital synchondrosis, bowed femora with distal widening, and talipes deformities in both feet. **c** Electroencephalographic findings revealing high-amplitude and irregular 1–2-Hz delta slowings on the whole background activity and occasional spike discharges in the left central or right central to parietal regions (C3-AVG, C4-AVG, P4-AVG). **d** T1-weighted sagittal MR image of the brain showing thinning of the corpus callosum without brainstem or cerebellar abnormality and T2-weighted transverse MR image of the brain showing enlargement of the ventricles and myelination delay without polymicrogyria or cortical atrophy

oropharyngeal stridor. He showed clinodactyly of the third and fourth fingers of the left hand; however, joint contractures and mesomelic brachymelia were absent. Plain radiographs showed widening and subtle bowing of both femora, bowing of both tibiae, talipes deformities in both feet, hypoplastic pubic bones, hypoplasia of distal phalanges, broad ribs, a deep short base of the skull, a sclerotic skull base, and wide occipital synchondrosis (Fig. 1b). Bilateral hydronephrosis with mild pelvicalyceal dilatation and a visible distal ureter were detected using abdominal ultrasonography. However, there was no evidence of vesicoureteral reflux on voiding cystourethrography. Echocardiography showed only a small persistent foramen ovale.

At the age of 2 months, the patient experienced generalized tonic convulsions for less than 1 min several times a day with a frequency of 1 or 2 days per week. However, the initial interictal electroencephalography (EEG) was normal, and we did not prescribe any medication. Two weeks after the first seizure, he revisited the neurology clinic because of increased frequency and intensity of seizures, which were clustered generalized tonic seizures with eyelid fluttering. Repeat EEG revealed high-amplitude and irregular 1–2-Hz delta slowings on the whole background activity and occasional spike discharges in the left central or right central to parietal regions (Fig. 1c). Phenobarbital was loaded and levetiracetam was administered, and the patient has had no seizure recurrence up during the 7 months of follow-up. Brain MRI revealed enlargement of both ventricles, thinning of the corpus callosum, and delayed myelination (Fig. 1d). On neurological examination, his motor tone was decreased with absence of deep tendon reflexes and his spontaneous activity was definitely decreased. He also had bilateral optic disc pallor and reduced response in both ears, with 35 dB for the right side and 40 dB for the left side, on audiometry. There was no remarkable finding on laboratory studies, including thyroid function test, serum amino acids and urine organic acid analyses, and urine mucopolysaccharidosis screening.

SGS was suspected based on medical history and the findings at physical examination. Direct sequencing analysis of exon 4 of the *SETBP1* gene was performed, as a molecular genetic confirmation of SGS [6]. The primer sequences used were as described previously. A previously reported heterozygous mutation in exon 4, c.2608G>A (p.Gly870Ser), was detected (Fig. 2). We also performed a genetic analysis using the DNA of both his parents and found that they carried the wild-type allele. The patient was confirmed as a de novo case. He is now 10 months of age and his seizures have been controlled well; however, the patient exhibits no developmental progression and has poor gastrointestinal motility with vomiting.

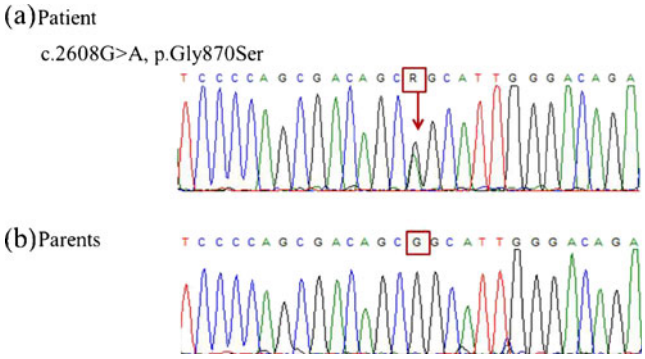

Fig. 2 Partial genomic DNA sequence of the *SETBP1* gene in the patient and his parents. **a** The patient exhibited a missense mutation, c.2608G>A (p.Gly870Ser), whereas **b** his unaffected parents carried the wild-type allele

Discussion

The *SETBP1* gene is located on chromosome 18q21.1 and encodes a protein of 1,542 amino acids and 170 kDa [9]. This gene is ubiquitously expressed throughout the body [14], which is consistent with the multisystemic involvement observed in SGS. The protein product of *SETBP1* binds to another protein called SET, but the physiological function and the molecular mechanism of the SETBP1 protein remain unknown [9]. Only five mutations in *SETBP1* have been identified in patients with SGS. All mutations detected to date in SGS patients clustered to one highly conserved 11-bp region of exon 4 [6, 15]. Although the specific function of the *SETBP1* gene and the effects of the mutations identified in SGS remain unknown, the first report of *SETBP1* mutations in SGS suggested that the mutations identified might result in SGS phenotypes via gain-of-function or dominant negative effects [6]. Another previous study also supported this hypothesis, because patients with haploinsufficiency or loss-of-function mutations in *SETBP1* exhibited a mild phenotype that was distinct from SGS [4].

Until the identification of *SETBP1* as a causative gene in SGS, the diagnosis of the disease was based on clinical characteristics. Our case was consistent with a diagnosis of SGS based on typical craniofacial features, skeletal anomalies, urogenital malformations, and profound neurodevelopmental delay with epilepsy. The craniofacial features of SGS include a large anterior fontanelle, a prominent forehead, midface retraction, hypertelorism, low-set dysplastic ears, and a short and upturned nose [6, 10]. A sclerotic skull base, wide occipital synchondrosis, broad ribs, widening of distal femora or proximal humeri, bowing of tibiae, hypoplastic distal phalanges, and talipes deformities are associated skeletal malformations [1]. Genital anomalies and hydronephrosis with or without vesicoureteral reflux

have been reported frequently [10, 16], and hearing and vision impairment can accompany the symptoms [6, 16]. Embryonal tumors, including hepatoblastoma and sacrococcygeal teratoma, are occasionally reported in SGS patients [2, 11].

The clinical features of our patient are listed in Table 1. The mutation identified in our patient, c.2608G>A (p.Gly870Ser), was previously reported in 3 of the 14 patients with molecularly confirmed SGS [6, 15]: two were Thai and one was Caucasian, and all three patients exhibited typical clinical features, including neurodevelopmental delay and epilepsy [6, 15].

Central nervous system involvement in SGS appears as a prominent feature of the disease. Intractable epilepsy, neurological deterioration, cortical blindness, spasticity, and hyperreflexia can be associated with this syndrome. Serial MRI studies of the brain showed progressive and diffuse degeneration of the peripheral white matter and the cortical gray matter, delayed myelination, and ventriculomegaly [13, 17]. Agenesis or hypoplasia of the corpus callosum, choroid plexus cysts, and periventricular cysts are repeatedly observed findings in brain imaging [7, 8, 13, 17]; our patient also showed ventriculomegaly, thinning of the corpus callosum, and delayed myelination. Epilepsy is a common manifestation of SGS (present in 73–92 %) patients clinically diagnosed with SGS and is usually intractable [5, 16]. Thirteen out of 14 (93 %) patients reported as having *SETBP1* mutations also had clinical seizures [6, 15]. However, few studies on the type and the course of epilepsy and related EEG abnormalities have been reported because of the rarity of this syndrome. Among the reported epileptic SGS patients [5], one-third exhibited seizures starting in the neonatal period and another one-third exhibited seizures starting after the neonatal period. The type of convulsions at onset in SGS patients is heterogeneous and includes tonic, tonic–clonic, myoclonic, or partial motor seizure and infantile spasms. EEG findings associated with SGS mainly consist of multifocal spikes or hypsarrhythmia [5], and infantile spasms have been a most frequently reported type of epilepsy shown in 25 % of epileptic SGS patients [5]. In addition, some patients exhibit evolution from another type of epilepsy to infantile spasms and the recently reported early myoclonic encephalopathy with burst suppression, which was refractory to conventional treatments, such as ACTH, a ketogenic diet, and various antiepileptic drugs [10, 17]. In contrast, our patient started having seizures at the age of 2 months and the type of epilepsy was generalized tonic seizure which was unusual in SGS. His EEG findings were compatible with partial seizures as distinct from multifocal spikes or hypsarrhythmia. Although a long-term EEG follow-up and a careful observation of seizure pattern evolution are required, epilepsy has been controlled well by combined therapy with phenobarbital and levetiracetam and has not been recurred or progressed in our patient.

Here, we report a patient with SGS resulting from a *SETBP1* mutation who showed typical clinical phenotypes, including neurodevelopmental delay and epilepsy. If diagnosed in the early stages, possible life-threatening malformations or complications can be managed properly. Moreover, the natural history and pathogenesis of SGS need to be further studied to provide appropriate management and genetic counseling to these patients.

Table 1 Major clinical findings in reported SGS patients with mutations in *SETBP1*

	p.Gly870Ser (n=4)				The other mutations (n=11) in Ref. [6]	Published cases without mutation confirmation in Ref. [1, 10, 16]
	Present case	Reported patient 1 in Ref. [6]	Reported patient 2 in Ref. [15]	Reported patient 3 in Ref. [15]		
Gender	M	F	M	M	M/F=6:5	M/F=18:17
Neurodevelopmental delay	+	+	+	+	10/11	24/25
Seizure	+	+	+	+	10/11	22/24
Vision impairment	–	+	–	Unknown	7/11	
Hearing impairment	+	+	+	Unknown	4/11	4/5
Typical craniofacial features	+	+	+	+	11/11	35/35
Genital anomaly	+	+	+	+	11/11	27/28
Hydronephrosis or vesicoureteral reflux	+	+	+	+	11/11	31/35
Cardiac defect	–	+	Unknown	–	6/11	11/27
Skeletal malformations	+	+	+	+	9/11	28/39
Choanal stenosis	–	–	–	–	4/11	8/26

Ref. reference

Acknowledgments We express our gratitude to the patient and his family for their participation in this study. This study was supported by a grant from the Korean Health Technology R&D Project, Ministry of Health and Welfare, Republic of Korea (A120099).

Conflict of interest The authors report no conflicts of interest concerning the materials and methods used in this study or findings specified in this paper.

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