Clinical Pediatric Endocrinology

Vol.33 / No.3
July 2024
pp 144–150

Case Report

A case of long-term survival of SADDAN treated with growth hormone for marked short stature

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Highlights

- *FGFR3* analysis in the early neonatal period is useful in SADDAN diagnosis.
- GH therapy may contribute to long-term survival of SADDAN patient.

Abstract. Severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN) is a bone dysplasia caused by a pathogenic variant of fibroblast growth factor receptor 3 (*FGFR3*). Pathogenic variants in *FGFR3* also cause thanatophoric dysplasia (TD) and achondroplasia. Although the findings of SADDAN and TD during the fetal and neonatal periods are similar, they differ in their long-term prognoses. We conducted *FGFR3* analysis in one male patient because of the difficulty in differentiating SADDAN from TD during the neonatal period. We found that the patient had a pathogenic variant, p. Lys650Met, which was similar to that previously reported in patients with SADDAN. Reports on long-term survival in patient with SADDAN are scarce, and there have been no reports of treatment with GH. We administered GH therapy for a markedly short stature. After treatment, his height increased by 4 cm each year for 4 years, the frequency of hospitalizations due to respiratory failure decreased, and the health improved. *FGFR3* analysis is useful for diagnosing SADDAN during the early neonatal period. GH therapy may have contributed to the patient's long-term survival.

Key words: SADDAN, long-term survival, *FGFR3*, GH

Received: October 27, 2023 Accepted: February 20, 2024 Advanced Epub: March 10, 2024
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Introduction

Achondroplasia, a common type of human dwarfism, is characterized by short limbs (1, 2). It is reported to occur in approximately 1 in 15,000 to 40,000 live births; more than 90% of cases are sporadic, and more than 97% of patients have a pathogenic variant, p. Gly380Arg, in the transmembrane domain of the fibroblast growth factor receptor 3 (*FGFR3*) gene (1). Pathogenic variants of *FGFR3* also cause hypochondroplasia, thanatophoric dysplasia (TD), severe achondroplasia with developmental delay and acanthosis nigricans (SADDAN), and craniosynostosis disorder (1, 2). The first case of SADDAN was reported in 1999 in four unrelated patients, all of whom had the pathogenic missense variant, p. Lys650Met, in the tyrosine kinase domain of *FGFR3*; to date, it has only been reported in four more patients (3–8). FGFR3 negatively regulates linear bone growth by inhibiting the proliferation of growth plate chondrocytes and terminal differentiation (2). Gain-of-function *FGFR3* variants cause disturbances in bone growth and other symptoms in various tissues (1, 2). Lys650 is located in the activation loop of the *FGFR3* tyrosine kinase domain, and substitution of this amino acid can significantly affect autophosphorylation via constitutive FGFR3 activation (4, 9, 10).

The clinical and radiological features of SADDAN and TD are similar in the fetal and neonatal periods, with overlapping features, including limb shortening and thoracic hypoplasia, which are more severe than those of achondroplasia (1, 2); however, these diseases have different prognoses (1–8, 11). In the neonatal period, the features of SADDAN, such as severe acanthosis nigricans and developmental delay, are not evident, and genetic analysis in the early neonatal period is important for a definitive diagnosis. Kitoh *et al*. reported a case of neonatal death with clinical manifestations of SADDAN and the pathogenic variant, p. Lys650Met, in *FGFR3* as a TD (7) before Bellus' report (3). TD is a more common sporadic lethal form of skeletal dysplasia. Patients with TD usually die of respiratory failure during the neonatal period, although some cases of long-term survival have recently been reported because of advances in modern respiratory care (11). However, 50% of patients with SADDAN die of respiratory failure in the neonatal period or early childhood, whereas the remainder survive into childhood or adulthood. Due to the rarity of this disease, reports on long-term survival of patients are scarce. Three long-term survivors exhibited markedly short stature (3, 4, 8). GH therapy for patients with SADDAN has not yet been reported. We herein describe the long-term survival of a patient with SADDAN who was treated with GH for his marked short stature.

Patient and Methods

Methods

This study was conducted after the patient's parents provided written informed consent. This study was approved by the Ethics Committee of Tohoku University School of Medicine. This was a retrospective chart review. The patients' radiological findings were analyzed using bone radiography, computed tomography (CT), and magnetic resonance imaging (MRI). Genetic analysis was conducted after extracting genomic DNA from the patient's leukocytes; PCR and direct sequencing were performed using standard protocols. The patient's parents were assured in writing that the patient's anonymity and confidentiality would be protected.

Case report

The patient is the first child of nonconsanguineous Japanese parents. Ultrasound findings at 17 wk of gestation indicated that the fetus had short limbs and a small thorax, and the mother was referred to our hospital at 26 wk. Ultrasound examination revealed a large head and short limbs. The biparietal diameter was 81.4 mm (+5.0 SD), and the femoral length was 25.9 mm (−6.6 SD). The thorax was slightly smaller than normal; however, no significant hypoplasia consistent with TD was observed. A CT scan at 27 wk of gestation suggested achondroplasia (**Figs. 1A, B**). The fetus

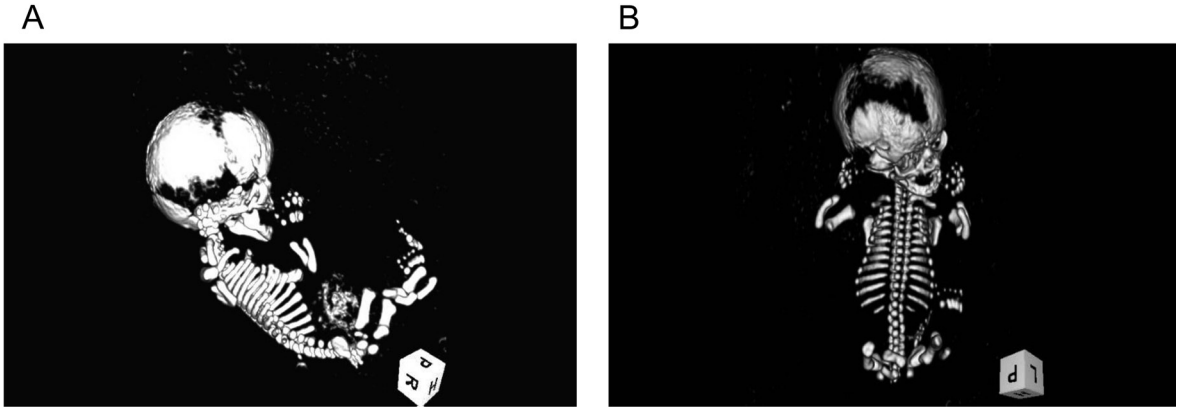

Fig. 1. Fetal CT scan at 27 wk of gestation. (A) Lateral image, (B) frontal image. Skull enlargement, frontal bossing, shortened extremities, small thorax, and pelvic hypoplasia are seen.

doi: 10.1297/cpe.33.2023-0068

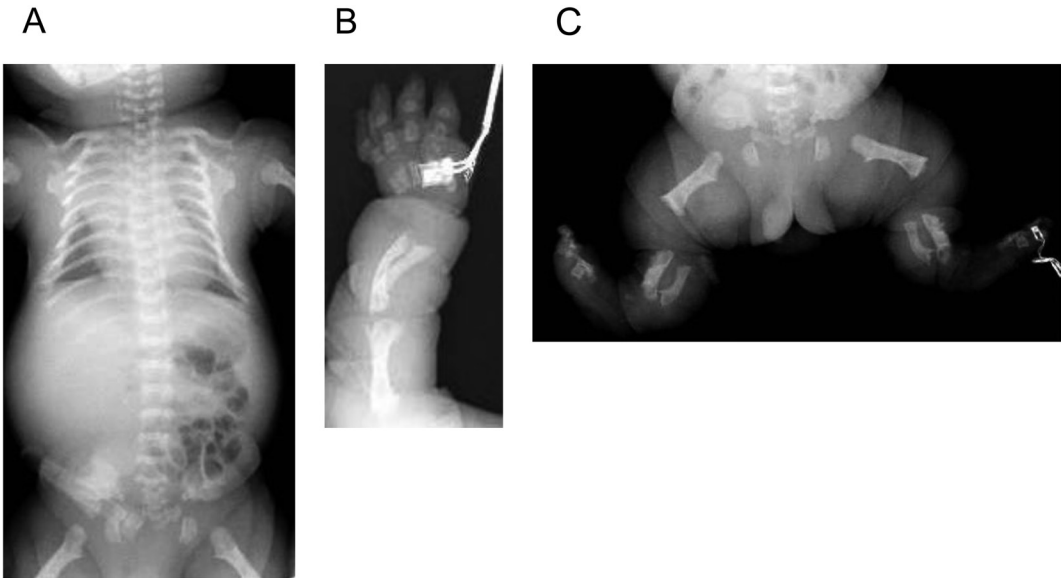

Fig. 2. Bone radiographs at birth. The patient's bone findings are more severe than those normally observed in achondroplasia; the patient also exhibited other unusual bone features. (A) The thorax is slightly smaller, but there is no finding of significant hypoplasia as seen in TD. (B) (C) Shortened extremities, bowing of the tibia and fibula, and pelvic hypoplasia are seen.

was delivered via cesarean section at 38 wk and 2 d of gestation. The Apgar scores were 8 and 9 at 1 and 5 min, respectively. The patient had a large head and markedly short stature. His weight was 3,048 g (+0.59 SD), his length was 40 cm (−3.66 SD), and his head circumference was 39.8 cm (+5.32 SD). The patient exhibited marked limb shortening with excess skin, lower leg deformity, and frontal bossing. Bone radiographys revealed that his symptoms were more severe than those associated with achondroplasia (**Figs. 2A–C**). He was admitted to the Neonatal Intensive Care Unit and received oxygen, but did not require ventilator support throughout the neonatal period. His symptoms were more severe than those of achondroplasia, but not as severe as those of TD. Therefore, TD or SADDAN, a severe form of achondroplasia, was suspected. *FGFR3* analysis revealed a pathogenic variant, c. 1949 A > T, p. Lys650Met, in the tyrosine kinase domain of *FGFR3* (NM_000142.5), previously reported in patients with SADDAN (**Fig. 3**). Cranial and spinal MRI findings at 1 mo indicated upper cervical spinal cord compression with ventricular enlargement and narrowing of the foramen magnum (**Figs. 4A, B**). From 2 mo, he exhibited acanthosis nigricans in the nipples, axilla, and external genital area, which gradually spread all over the body (**Figs. 5A, B**). At 2.5 mo, the patient was discharged and started on home oxygen therapy. At 4 mo of age, he presented with frequent vomiting and the setting sun sign. A head CT scan revealed progressive hydrocephalus; thus, a VP shunt was placed (**Fig. 4C**). He was prone to vomiting, and his limbs had poor mobility. At 9 mo, the patient underwent foramen magnum occipitalis decompression, after which his symptoms improved. He was often hospitalized during infancy because of respiratory

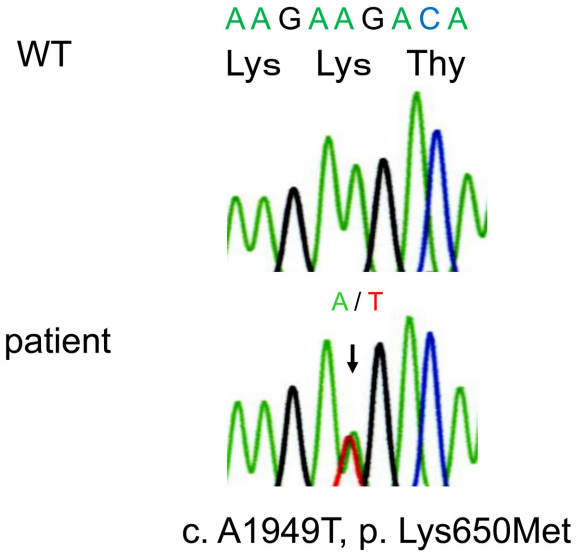

Fig. 3. Polymerase chain reaction-direct sequencing analysis of *FGFR3* in the patient. The chromatogram shows transition to heterozygous A to T at nucleotide position 1949, predicted to result in lysine to methionine substitution at codon 650. The arrow pointing downward indicates the mutated nucleotide.

infections and gastroenteritis. He experienced his first seizure at the age of 1 yr, and phenobarbital was administered. Based on echocardiography, the patient was diagnosed with mild pulmonary hypertension and was administered beraprost sodium. When he was hospitalized at 1 yr and 5 mo of age, he developed status epilepticus, required ventilatory management, and underwent a tracheostomy. Electroencephalography

doi: 10.1297/cpe.33.2023-0068

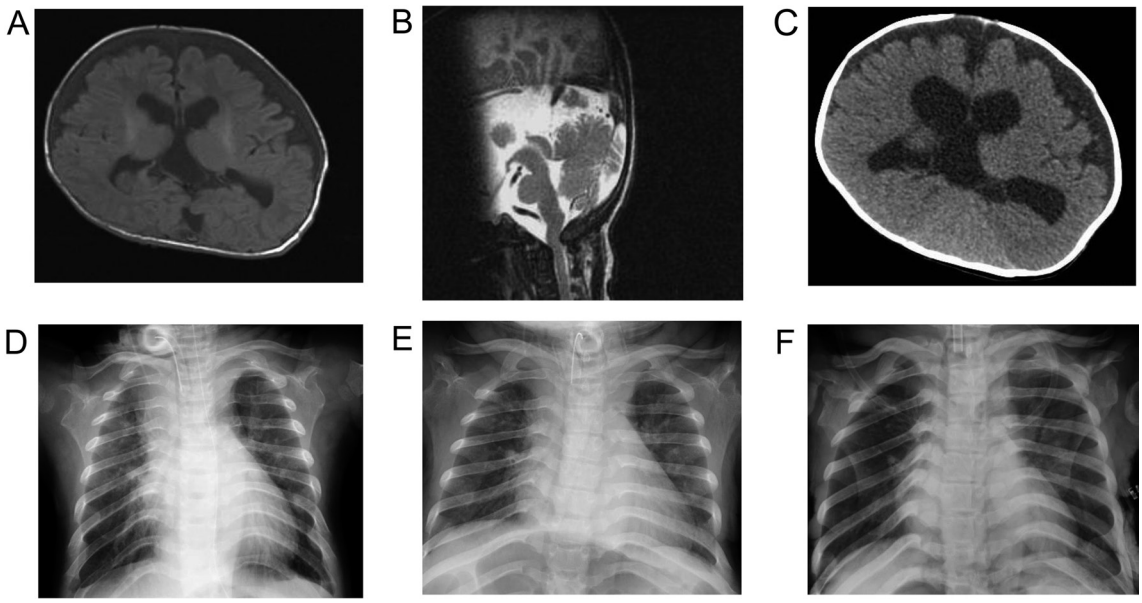

Fig. 4. (A) (B) Cranial and spinal MRI findings at 1 month. Upper cervical spinal cord compression with ventricular enlargement and narrowing of the foramen magnum are seen. (C) At 4 mo, a cranial CT scan shows progressive hydrocephalus. Chest radiographs after initiation of GH treatment, (D) at 6 yr 1 mo, (E) at 12 yr 1 mp, and (F) at 17 yr 8 mo, respectively.

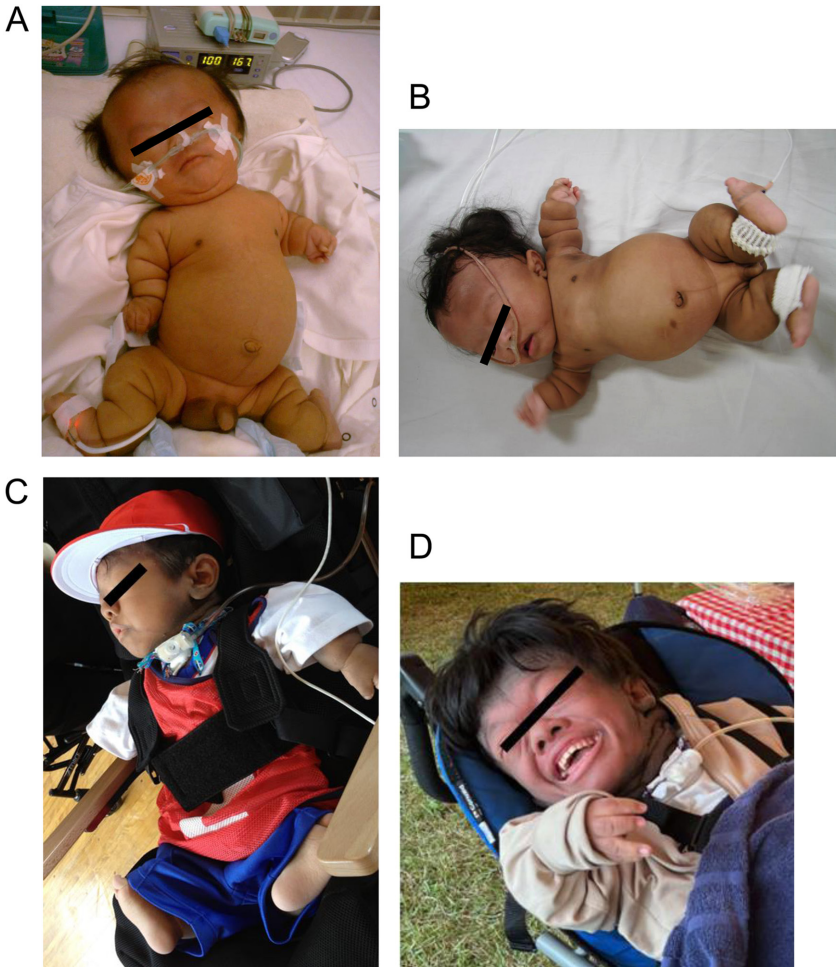

Fig. 5. Clinical photo of the patient. (A) At 2 mo, (B) at 9 mo. He showed acanthosis nigricans in the nipples, axilla, and external genital area, which gradually spread throughout the body. (C) At 7 yr, (D) At 17 yr. He cannot sit, stand, or walk, but can turn over, eat without the feeding tube, and smile, and he attends a supportive high school with his mother's assistance.

doi: 10.1297/cpe.33.2023-0068

revealed no evident epileptic discharges; thus, the diagnosis was symptomatic epilepsy. Subsequently, the patient was weaned from ventilatory management but continued on home oxygen therapy. An intelligence test conducted at 1 yr and 7 mo revealed an overall developmental index of 25, equivalent to that of a 4.8-mo-old child. At age 3, GH therapy was initiated because of his markedly short stature. GH was administered according to the ACH treatment protocol, but no GH stimulation tests were performed. The initial GH dose was 0.23 mg/kg/wk, subsequently increasing to 0.35 mg/kg/wk. The patient's height increased by 4 cm each year until he reached 7 yr of age (**Table 1** and **Fig. 6**). His IGF-1 level began at 24.7 ng/mL and increased to 115.6 ng/mL after 3 yr and 10 mo. Subsequently, IGF-1 level remained sufficient until the end of GH administration.

Table 1. Height and chest circumference from the start of GH treatment to 10 years later

	3 yr 0 mo	7 yr 0 mo	10 yr 0 mo	13 yr 2 mo
Height (cm)	61.3	77	83	90
Chest circumference (cm)	40.9	50	57	60.3

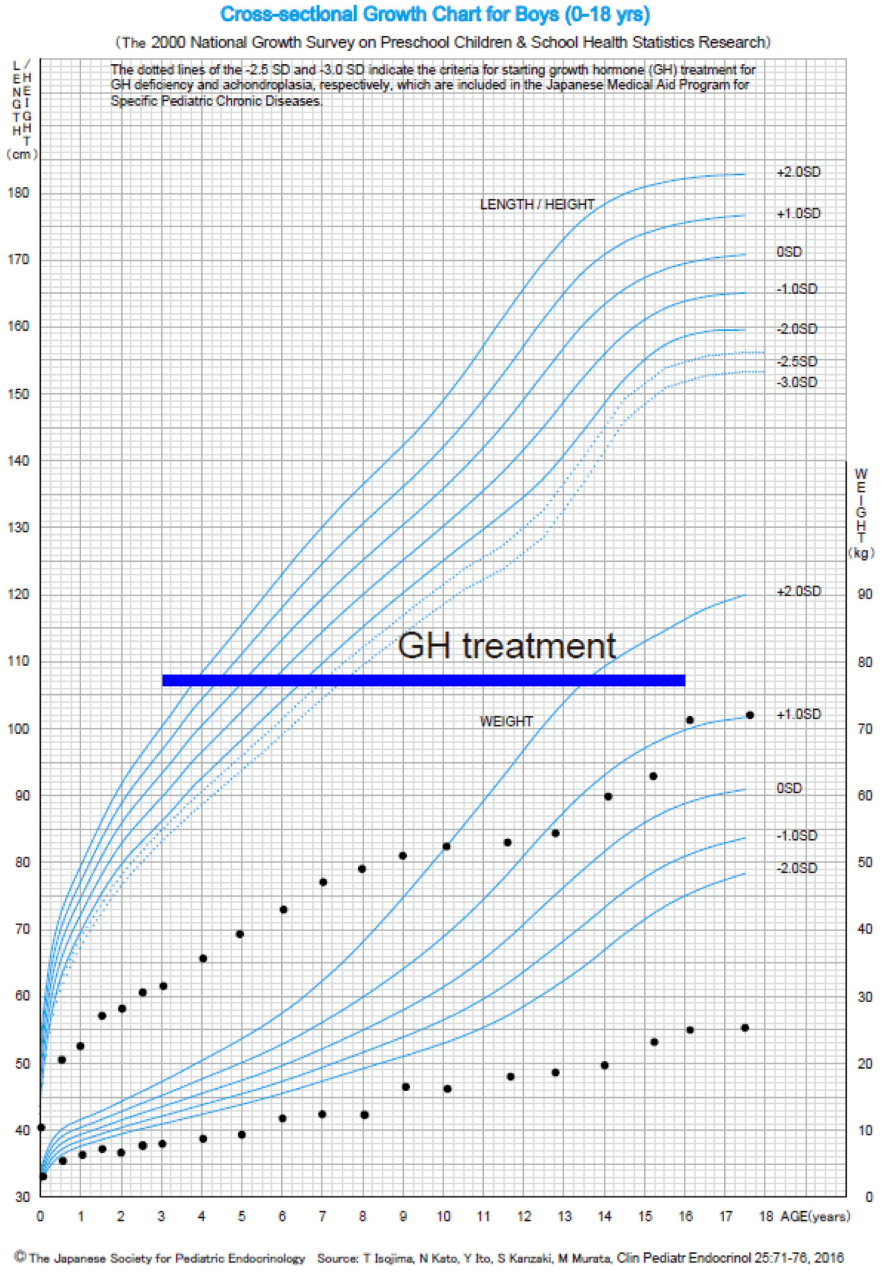

Fig. 6. Growth charts of our patient. GH treatment was started at the age of 3 and continued until the age of 16.

doi: 10.1297/cpe.33.2023-0068

During the 4 yr, his chest circumference increased by approximately 10 cm, and he could live without oxygen therapy (**Table 1**). After starting GH therapy, the frequency of hospitalization due to respiratory infections decreased, and his health improved. In the neonatal period, his thorax was hypoplastic and bell-shaped but became larger as he grew (**Figs. 1 and 4**). His pulmonary hypertension progressively improved and beraprost treatment was discontinued at 12 yr of age. Although his age at puberty onset was later than average, LH and testosterone levels were found at 13 yr and 1 mo and 13 yr and 10 mo, respectively, with a gradual increase in both. His external genitalia had developed into an adult male shape by the age of 17 yr. At present, the patient is 18 yr old and 102 cm tall. Although he cannot sit, stand, or walk, he can turn over, eat without a feeding tube, and smile; he attends a supportive high school with his mother's assistance (**Figs. 5C, D**). Respiratory function tests could not be performed due to severe developmental delay; however, after GH treatment, his chest circumference measurements and chest radiograph findings have improved, hospitalizations for respiratory symptoms have decreased, and his general condition remains good.

Discussion

We confirmed the diagnosis of SADDAN, which is difficult to differentiate from TD during the neonatal period, using genetic testing. After GH therapy, the patient reached adulthood and survived for an extended period without ventilatory management.

To the best of our knowledge, only eight cases of SADDAN have been reported worldwide to date, and reports on long-term survival remain scarce. In most neonatal-to-infant mortality cases, the cause of death was respiratory failure (**Table 2** and **Table 3**) (3–8). Reports on GH therapy in patients with SADDAN are lacking. Recombinant human GH has been reported as a treatment method for short stature in achondroplasia (12–14). Increased growth during the early phases of GH therapy is reported in patients with achondroplasia and hypochondroplasia. In one study, patients receiving GH therapy for an average of 2.6 yr gained an average of 0.7 SD in height (13). Hertel *et al.* reported that 35 patients with achondroplasia gained an average of 1.0 SD in height after 5 yr of GH therapy (14). Our patient, however, gained 0.84 SD in height after 4 yr of GH therapy. The adult height of our patient was 102 cm. After GH therapy, the frequency of hospitalization for respiratory infections decreased, and the patient was able to live a healthy life. In achondroplasia, the chest has small dimensions, which decreases tidal volume (12). However, the effect of GH therapy on thoracic hypoplasia remains unclear. Since GH therapy is effective for growth disturbances caused by *FGFR3* abnormalities, it may also be effective for thoracic hypoplasia caused by these abnormalities. Improvement in thoracic hypoplasia may positively impact brain development through improved oxygenation and reduced respiratory failure due to

Table 2. Characteristics of cases of death from neonatal to early childhood

	Kitoh *et al.* (1998)	Bellus *et al.* (1999)		Zankl *et al.* (2008)
Sex	F	F	F	M
Death of age	2 d	6 h	5 yr	21 d
Cause of death	Respiratory failure	Respiratory failure	NR	Respiratory failure
Height at birth (cm)	NR	43	NR	47
Head circumference at birth (cm)	41.5	40.3	37.5	38.7
Apgar score	4,8	7,9	2,8	5,8
Thoracic hypoplasia	yes	yes	yes	yes
Early respiratory failure	yes	yes	yes	yes

NR; not reported.

Table 3. Characteristics of cases reaching final height

	Bellus *et al.* (1999)		Adachi (2008)	This case
Sex	M	F	F	M
Final height (cm)	104	103.6	117	102
Age at time of report (yr)	30	16	36	17
Height at birth (cm)	48.3	46	NR	40
Head circumference at birth (cm)	40.6	NR	NR	39.8
Apgar score	NR	NR	8,9	8,9
Thoracic hypoplasia	yes	NR	yes	yes
Early respiratory distress	yes	yes	no	yes
Intellectual disability	Severe	Moderate-severe	Severe	Severe
Hydrocephalus	yes	yes	yes	yes

NR; not reported.

doi: 10.1297/cpe.33.2023-0068

increased tidal volume. Thus, GH therapy may have contributed to the long-term survival of this patient.

Further accumulation of cases is necessary to elucidate the various manifestations and pathophysiology of SADDAN.

Conclusions

Genetic analysis early in the neonatal period is useful in children suspected of having *FGFR3* abnormalities, in whom differential diagnosis is difficult. Thus, GH therapy may contribute to the growth and long-term survival of patients with SADDAN.

Conflict of interests: Ikuma Fujiwara received a research grant for a clinical trial from Pfizer, and the other authors have no conflicts of interest to declare.

Acknowledgments

We thank the patient and his family for their participation in this study. We would also like to thank Tadashi Matsuda for the clinical support. Finally, we thank Yoichi Matsubara and Gen Nishimura for their diagnostic support.

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