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Growth and Clinical Characteristics of Children with Floating-Harbor Syndrome: Analysis of Current Original Data and a Review of the Literature

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Keywords
Floating-Harbor syndrome · SRCAP · Short stature · Growth · Growth hormone therapy

Abstract
Background: Floating-Harbor syndrome (FHS) is a rare condition characterized by dysmorphic facial features, short stature, and expressive language delay. ***Objective:*** The aim of this study was to describe a cohort of patients with FHS and review the literature about the response to recombinant human growth hormone (rhGH) therapy. ***Methods:*** Anthropometric and laboratory data from 7 patients with FHS were described. The molecular diagnosis was established by multigene analysis. Moreover, we reviewed the literature concerning patients with FHS treated with rhGH. ***Results:*** All 7 patients were born small for gestational age. At first evaluation, 6 patients had a height standard deviation score (SDS) ≤−2 and 1 had short stature in relation to their target height. Bone age was usually delayed, which rapidly advanced during puberty. Nonspecific skeletal abnormalities were frequently noticed, and normal to elevated plasma IGF-I levels were observed in all except 1 patient with growth hormone deficiency. Information about 20 patients with FHS treated with rhGH was analyzed (4 from our cohort and 16 from the literature). The median height changes during the treatment period (approx. 2.9 years) were 1.1 SDS (range from −0.4 to 3.1). Nontreated patients had an adult height SDS of −4.1 ± 1.2 (n = 10) versus −2.6 ± 0.8 SDS (n = 7, p 0.012) for treated patients. ***Conclusion:*** We observed a laboratory profile com-

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patible with IGF-1 insensitivity in some patients with FHS. Nevertheless, our study suggests that children with FHS may be considered as candidates for rhGH therapy. Further studies are necessary to establish the real benefit and safety of rhGH therapy in these patients.

Introduction

Floating-Harbor syndrome (FHS; OMIM No. 136140) is a rare genetic disorder characterized by short stature with delayed bone age (BA), expressive-language deficits, and a distinctive facial appearance with triangular face, long eyelashes, deep-set eyes, broad and bulbous nose, low-hanging columella, short philtrum, and also a wide mouth with a thin vermilion border of the upper lip [1–3]. Additional features have already been described, such as hearing loss, skeletal features, congenital heart defects, and hydronephrosis [1, 2]; nevertheless, the typical facial gestalt is essential for a clinical diagnosis of FHS.

FHS is caused by heterozygous truncating variants in the final exons (34 and 33) of *SRCAP* (SNF2-related CBP activator protein) [1, 3–5], that presumably escape from nonsense-mediated mRNA decay, indicating a dominant-negative effect of the truncated proteins [3, 6, 7]. *SRCAP* plays crucial roles in fundamental cellular pathways, such as chromatin remodeling, gene expression, DNA damage response, and cell division [3, 7].

The exact mechanism behind the growth impairment caused by *SRCAP* mutations is not completely elucidated. Case report studies have proposed the association of FHS with growth hormone (GH) deficiency [8], GH neurosecretory dysfunction [9], and a defect in IGF-1 signaling [10]. It is also suggested that patients with FHS could have a disturbance in chondrocytes proliferation and differentiation [7]. As with other rare growth disorders [11–13], recombinant human GH (rhGH) has been proposed to improve height in patients with FHS. The response to GH treatment has been described in a few case reports or patient series, usually with a variable growth response [4, 7–10, 14–16].

Herein, we describe the diagnostic processes of 7 patients with FHS from a single tertiary center specialized in growth disorders. All patients had a positive identification of a pathogenic *SRCAP* variant and were anthropometrically and hormonally evaluated. Additionally, we describe the clinical characteristics, including the response to rhGH therapy, in 4 of our patients and review the literature on this subject.

Methods

Subjects and Study Protocol

This is an observational study in which we selected all 7 patients with an FHS diagnosis from a specialized outpatient clinic for growth disorders. We collected data from medical records regarding birth weight and length; measurements of weight (measured on an electronic scale), sitting height, and standing height (mean of three measurements on a calibrated stadiometer to the nearest 0.1 cm). These results were converted to a standard deviation score (SDS) using a gender-specific normative [17]. The target height was calculated ([father's height + mother's height ± 13 cm]/2) and expressed as the SDS [17]. Short stature was defined as a height SDS ≤–2 or a parental height corrected SDS ≤–1.6 [18].

Left hand and wrist x-rays for BA determination were assessed by the method of Greulich and Pyle [19]. Serum insulin-like growth factor 1 (IGF-1) and insulin-like growth factor-binding protein 3 (IGFBP-3) were measured in 6/7 patients using a chemiluminescent immunometric assay (IMMULITE®, Diagnostic Products Corp., Los Angeles, CA, USA). The values of IGF-1 and IGFBP-3 serum concentrations were transformed into SDS according to the established reference ranges of the assay for gender and chronological age [20]. All patients were evaluated by a clinical score to identify IGF-1 insensitivity. This clinical score comprised data about birth weight/length, height SDS, head circumference SDS, and IGF-1 levels [21].

Provocative tests for GH release with clonidine or insulin tolerance test were performed in 3 patients. The diagnosis of GH deficiency (GHD) was considered in patients who had two provocative testing with GH peak <5 μg/L (Immunodiagnostic Systems Holdings PLC, Tyne and Wear, UK) [22]. Additionally, all patients underwent a routine laboratory evaluation for children with growth disorders [23].

Four patients received GH therapy and 1 of them was treated in combination with a GnRH analog to extend the growth period. rhGH was administered subcutaneously at a mean dose of 50 μg/kg/day, which was adjusted according to weight at each visit. All children were evaluated at baseline and every 4 months during rhGH treatment. The height velocity (cm/year) for the year prior to rhGH and the height velocity over the first year of treatment were calculated.

Targeted Panel and Exome Sequencing

Genomic DNA was isolated from peripheral blood leukocytes from all patients using standard procedures. The diagnosis of FHS was confirmed by target panel sequencing in 5 patients and by whole exome sequencing (WES) in 2. We used a customized target panel sequencing (Agilent SureSelect XT assay; Agilent Technologies, Santa Clara, CA, USA) that included 388 genes associated with short stature, including *SRCAP* [24]. For WES, a library was prepared according to Sure Select Human All Exon V6 (Agilent Technologies). For the targeted gene panel, sequencing was performed on an Illumina NextSeq 500 (Illumina, San Diego, CA, USA) and for exome a HiSeq 2500 (Illumina) platform was used, both in paired-end mode. In-house bioinformatics analysis was performed as previously reported [25]. The sequences were aligned with the human reference assembly (GRCh37/hg19). Analysis of results followed a flow established by the laboratory. Patients with a clinical diagnosis of FHS were directly screened for variants at the *SRCAP* gene. Patients without clinical recognition were filtered for rare variants (MAF <0.1%) in public international databases (gnomAD; http://gnomad.broadinstitute.org), a national database

Table 1. Clinical characteristics and genetic evaluation of patients with FHS

Patient No.	1	2	3	4	5	6	7
SRCAP mutation	c.7330C>T; p.Arg2444*	c.7227dupA; p.Ala2409fs	c.7303C>T; p.Arg2435*	c.7262dupG; p.Arg2421fs	c.7684G>T; p.Glu2562*	c.7330C>T; p.Arg2444*	c.7330C>T; p.Arg2444*
Diagnosis	clinical	clinical	clinical	clinical	clinical	after WES	after WES
Sex	M	M	F	M	M	M	F
Gestational age, weeks	38.3	32	39	39.6	39.2	39	39.2
Birth weight SDS	–1.6	–2.2	–0.6	–2.7	–1.2	–1.4	–2.6
Birth length SDS	–2.2	–0.2	–2.2	–3.2	–3.6	–2.5	NA
Birth HC SDS							
Target height SDS	0.4	NA	–0.6	–1.9	0.3	–1.0	–1.8
CA, years	2.2	4.3	3.2	7.4	13.7	5.3	9.0
BA – CA, years	–2.1	NA	–1.2	–4.4	2.3	–1.6	–1.1
Height SDS	–1.4	–4.4	–3.8	–3.3	–2.0	–2.4	–2.7
SH:H SDS	0.8	NA	–0.2	–1.3	NA	0.2	0.1
BMI SDS	–1.3	–0.1	–2.1	0.6	–0.6	3.4	–0.3
HC SDS	–2.0	–0.8	–1.8	–0.9	–1.9	–1.4	–2.0
Age at puberty, years	9.4	11.0	prepuberty	9.8	<12	10	8.5
Adult height, cm	NA	141	NA	NA	150	NA	147
IGF1R clinical score[a]	3	2	3	3	1	1	4
Typical face	+	+	+	+	+	No	+
Language delay	+	+	+	+	+	+	+
Intellectual disability	borderline normal	mild	borderline normal	mild	mild	severe	mild
Behavior disorders	attention deficit	attention deficit, hyperactivity	–	attention deficit, hyperactivity	–	–	–
Skeletal abnormalities	–	shortening of the 5th metacarpal, pectus excavatum, hyperlordosis, spina bifida	–	shortening of the 5th metacarpal pectus excavatum	shortening of the 5th metacarpal	shortening of the 5th metacarpal, cone-shaped epiphyses	shortening of the 2nd and 5th metacarpal lumbosacral interbody fusion
Other findings	short neck, interatrial	short neck, varicocele, lateral asymmetry, accessory spleen, myopia, hypothyroidism	arachnoid cyst, preauricular appendix	hydrocele, cryptorchidism, hearing loss	Raynaud's phenomenon, hydrocele, inguinal hernia, hearing loss	cleft palate, seizures, central hypothyroidism, asthma, intestinal constipation	microcephaly, cleft palate, adenoid hypertrophy
GH peak, μg/L[b]	11.5	NA	NA	7.7	19.0	1.2	NA
IGF-1 SDS[c]	0.3	–0.9	1.6	2.1	NA	–1.8	4.2
IGFBP3 SDS[c]	1.7	–0.4	2.1	1.4	NA	–1.4	1.3
GH treatment	Yes	no	yes	yes	no	no	yes
Growth rate before treatment, cm/year	3.5	–	6	4.6	–	–	5.9
Growth rate in 1st year of treatment, cm/year	8.2	–	8.5	6.5	–	–	6.4[d]
Δ height SDS in 1st year of treatment	+0.7	–	+0.5	+0.3	–	–	+0.2[d]
IGF1 SDS[c] during rhGH treatment	1.7	–	3.3	2.6	–	–	3.9[d]
IGFBP3 SDS[c] during rhGH treatment	1.7	–	3.2	1.1	–	–	1.2

Reference sequence *SRCAP*: NM_006662.2. SDS, standard deviation score; CA, chronological age; BA, bone age; SH:H, sitting height:height; BMI, body mass index; HC, head circumference; IGF1, insulin growth factor type 1; IGFBP3, IGF binding protein type 3; M, male; F, female; NA, not available; WES, whole exome sequencing.

[a] Clinical score to IGF-1 insensitivity; a positive score of 3 or more of the criteria indicates the necessity for *IGF1R* analysis [21].

[b] After clonidine stimulation test and/or insulin tolerance test.

[c] Laboratory reference values for sex and age.

[d] rhGH and GnRHa treatment.

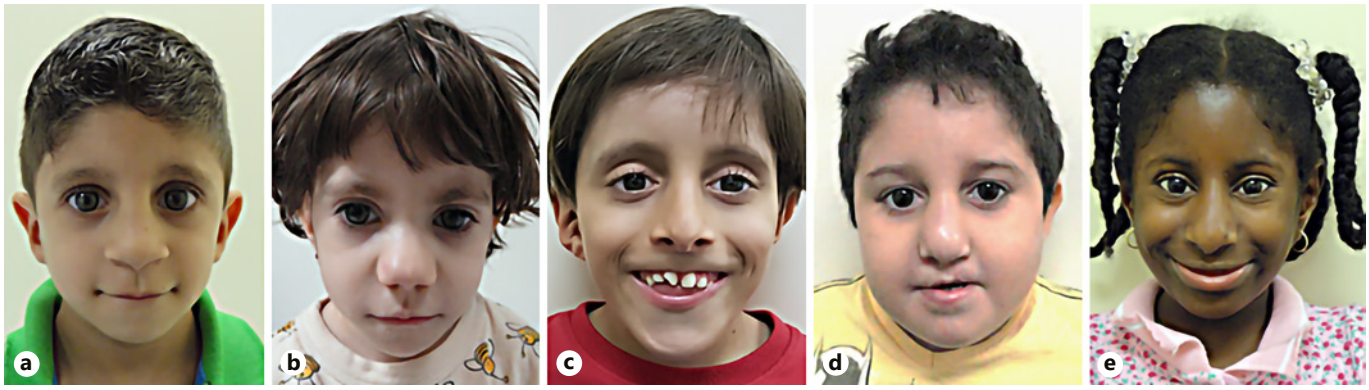

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Fig. 1. a–e The distinctive facial dysmorphisms of patients with FHS: triangular face, long eyelashes, deep-set eyes, broad and bulbous nose, low-hanging columella, short philtrum, and wide mouth with a thin vermilion border of the upper lip (the patients' parents provided written informed consent to use these images).

(ABraOM; http://abraom.ib.usp.br/), and in-house databases. Variants in the exonic and consensus splice site were selected, and the potential to be pathogenic was assessed by multiple in silico programs [24]. According to the possible model of inheritance of the family, we screened for recessive, dominant, or X-linked variants. Gene function assessment was made by OMIM and PubMed. Variants of interest were segregated in family by Sanger sequencing to validate the variants identified. All variants were classified following the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) variant pathogenicity guidelines [26].

Literature Review

We searched the PubMed database for all studies evaluating rhGH treatment in patients with FHS until July 2019 using the following criteria: (1) published in English, and (2) containing enough information about the growth and response to rhGH treatment used in the study. We used the following search terms: Floating-Harbor syndrome AND (growth impairment OR growth restriction OR growth retardation OR height OR dwarfism OR dwarf) AND (growth hormone). Furthermore, we manually searched the reference lists of every primary study for additional information.

Statistical Analysis

Descriptive and comparative statistical analyses between variables were conducted by using SigmaStat version 3.5 (SPSS Inc., San Jose, CA, USA). Differences between groups were tested by *t* test or Kruskal-Walls and Fisher exact tests, as appropriate. Statistical significance was assumed for $p < 0.05$.

Results

Diagnosis of FHS

We enrolled 7 patients with FHS (5 male) evaluated from 2003 to 2019. All patients were referred to our medical service due to short stature and dysmorphic features without a clinical diagnosis in the primary health service. Five participants had specific dysmorphic features that facilitated the clinical recognition of FHS (Table 1, patients 1–5; Fig. 1a–c), and in those cases the molecular diagnosis was confirmed by analysis of *SRCAP* by customized target panel sequencing. Two patients were not clinically recognized due to nonspecific signs (Table 1, patients 6–7; Fig. 1d–e). One patient had midline defects and epilepsy, which are not commonly associated with the FHS phenotype. Another patient was clinically diagnosed first as having IGF-1 insensitivity due to prenatal short stature, microcephaly, and elevated IGF-1 levels. In these 2 patients the diagnoses were obtained through WES. All patients revealed previously described heterozygous de novo mutations in exon 34 of the *SRCAP* gene. In 3 patients we found the most common recurrent variant associated with FHS (c.7330C>T; p.Arg2444*) [1–3], and in the other 4 patients we identified different variants causing a premature stop codon (Table 1).

Clinical Characteristics of Patients with FHS

The mean age at first evaluation was 6.4 years (range 2.2–13.7). All patients were born small for gestational age (SGA): 5 were SGA for length; 2 were SGA for weight, and 1 for both. Six patients had a height SDS ≤–2 at the time of initial evaluation, whereas 1 was 1.8 SDS below his target height. BA was delayed in all but 1 patient at the first evaluation and nonspecific skeletal abnormalities were observed in 5 out of 7 of our patients (Table 1). The patient who had advanced BA was the one evaluated at the oldest age and Tanner stage 4 of puberty (Table 1). The puberty development appeared to be normal among these patients (Table 1). A rapid advance in BA was observed in 4 of our patients during follow-up in puberty (Fig. 2a).

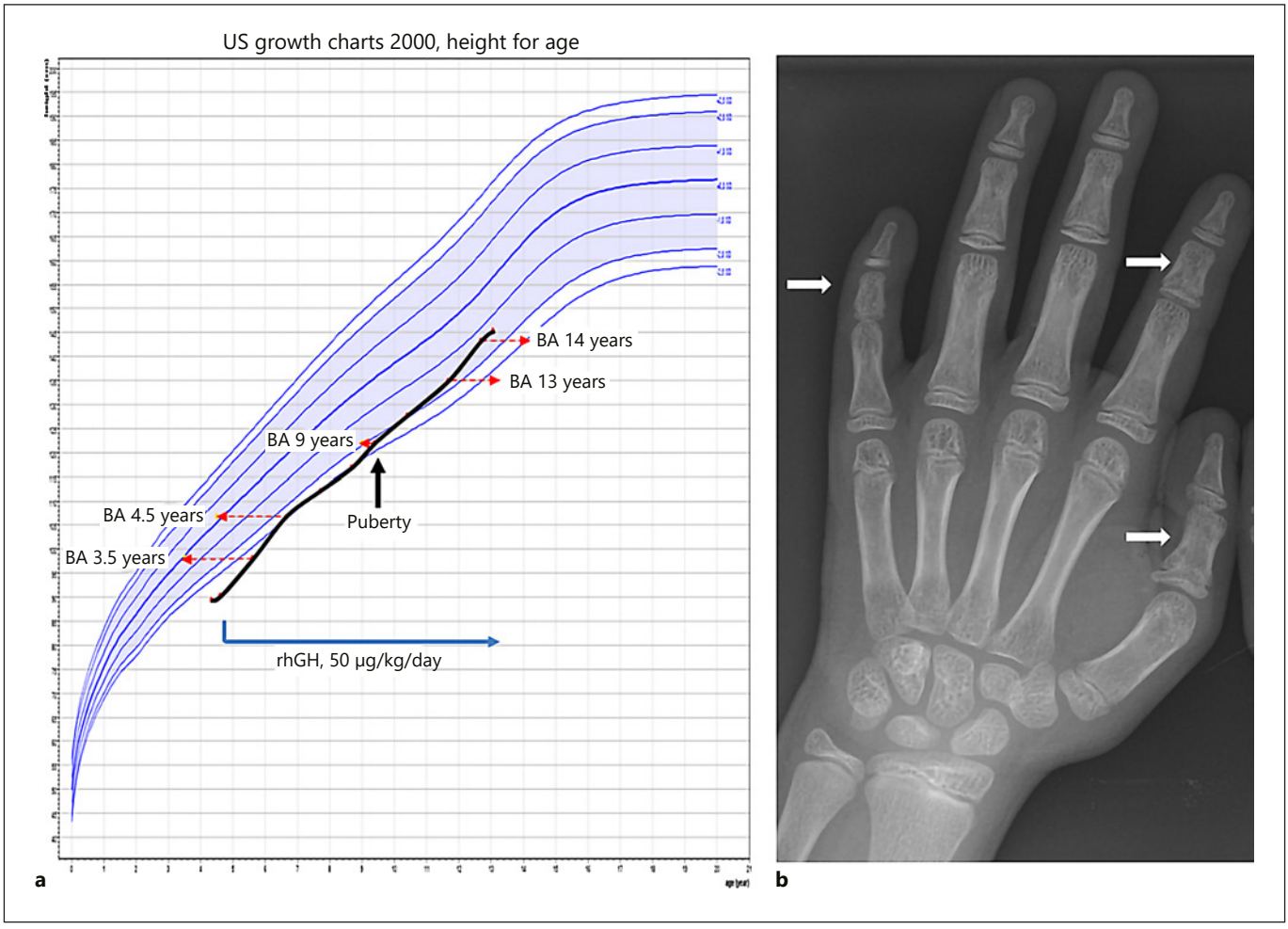

Fig. 2. a Growth chart of a patient with FHS plotted on the CDC reference chart. Red arrows indicate BA, the horizontal blue line indicates rhGH treatment. **b** X-ray image showing some skeletal findings among patients with FHS: shortening of the 5th metacarpal and cone-shaped epiphyses (arrows).

Four patients were submitted to a GH stimulation test (clonidine in 3 and insulin tolerance test in 1; Table 1). Three of them had normal GH values and 1 patient was diagnosed with GHD (GH peak 1.2 µg/L). This patient had midline defects (cleft palate), central hypothyroidism, and the lowest IGF-1 levels (–1.8 SDS) observed in our cohort of FHS and a normal hypothalamic-pituitary MRI. Another patient had primary hypothyroidism (TSH 14 µU/mL, with normal free T4), thyroid hypoplasia detected by thyroid ultrasound, and negative thyroid antibodies. Five patients presented mild skeletal findings, mainly shortening of the 5th metacarpal (Fig. 2b).

Four of our patients with FHS were treated with rhGH. A sustained elevated IGF-1 SDS ≥2 was observed in 4 out of 6 patients, in 2 of them even before rhGH treatment (Fig. 2; Table 2). Four of 7 of our patients with FHS fulfilled the clinical criteria to IGF-1 insensitivity.

Analysis of GH Treatment in Patients with FHS

Reviewing the literature, we identified 75 studies about FHS in the PubMed database (from 1975 until July 2019). However, only 8 described the growth response to rhGH treatment with enough minimum data (Table 2), providing a total of 20 patients with FHS treated with rhGH (16 from the literature database and 4 from our own cohort) [4, 7–10, 14–16]. Three patients were reported as GHD and 1 was classified as an indeterminate case (he had only one GH stimulate test) [8, 9, 16]. Among these 20 patients, 3 were treated concomitantly with a GnRH analog to extend the growth period [8, 14]. The rhGH dose

Table 2. Response to GH treatment in patients with FHS

Sex	AIG/ SGA	Age at start of rhGH, years	Height SDS	rhGH dose, μg/kg/day	Treatment time, years	Age at last assessment, years	Height at last assessment – SDS	Δ height SDS	TH SDS	Reference No.
F	SGA	2	–3.0	40	3.6	8.9	–0.9	+2.1	1.8	15
F	SGA	9.1	–2.9	33	1.5	10.6	–1.9	+1.0	1.0	9
F	SGA	10.1	–2.2	23	NA	17.6	–1.2[b, c]	+1.0	1.2	14
F	AIG	5.3	–3.8	35	2.1	7.5	–2.2[c]	+1.6	–0.8	8
F	SGA	3.5	–3.1	25→50	3	6.5	–2.5	+0.6	0.1	10
M[a]	SGA	10	–4.6	33	2	14	–3.6	+1.0	NA	7
F[a]	SGA	2	–2.5	NA	3	10.5	–2	+0.5	NA	4
F[a]	AIG	2	–3.2	NA	9	22	–1.8[b]	+1.4	NA	4
F[a]	AIG	5.3	–3.4	NA	NA	10	–1.7	+1.7	NA	4
M	NA	5.2	–4.5	50	1	NA	–4.4	+0.1	–0.3	16
M	SGA	4.8	–4.1	39→46	4.1	NA	–2.5	+1.6	–0.7	16
F	NA	5	–3.8	56	1.6	NA	–3.5	+1.8	0.6	16
M	AIG	6.5	–5.3	66	4.3	NA	–3.8	+2.7	–1.6	16
M	NA	5.1	–4.5	46→56	4.3	NA	–3.3	+1.2	NA	16
F	NA	1.5	–4.2	43→66	2.2	NA	–2.9	+3.1	–0.4	16
F	AIG	1.2	–4.2	41	0.3	NA	–3.8	+0.4	–1.0	16
M[a]	SGA	4.9	–3.1	50	8.1	13.0	–1.1	+2.0	0.4	Patient 1[d]
F[a]	SGA	4.2	–3.4	50	2.8	7.0	–2.6	+0.8	–0.6	Patient 3[d]
M[a]	SGA	7.9	–3.0	50	2.5	10.4	–2.0	+1.0	–1.9	Patient 4[d]
F[a]	SGA	10.4	–2.1	50	4.1	15.4	–2.5[b, c]	–0.4	–1.8	Patient 7[d]
Median		5	–3.4	–	2.9	10.5	–2.5	+1.1	–0.4	–

F, female; M, male; AIG, adequate for gestational age; SGA, small for gestational age; rhGH, recombinant human growth hormone; TH, target height.
[a] Diagnosis confirmed by genetic findings.
[b] Adult height.
[c] Use of GnRH analog and rhGH.
[d] Case reported in the present study.

ranged from 23 to 66 μg/kg/day and the treatment period varied from 0.2 to 9 years. The median height change during the treatment period (2.9 years) was 1.1 SDS (–0.4 to 3.1; Fig. 3a). IGF-1 levels during rhGH therapy were reported in only 6 patients; 3 of them had elevated IGF-1 (>2 SDS) during treatment (Fig. 3b).

Data about adult height of patients with FHS were available in 35 published cases and in 2 of our subjects [1–4, 7, 14, 27–30]. In 18 individuals, the provided information was not clear about patients who had undergone rhGH treatment or not. Among patients with enough information, the nontreated group had an adult height SDS of –4.1 ± 1.2 (n = 10) versus –2.6 ± 0.8 SDS (n = 7, p = 0.012) for the treated group.

Discussion

Short stature is one of the major clinical criteria for the diagnosis of FHS; our patients were born SGA and did not demonstrate catch-up growth. The diagnosis is also based on distinctive facial features and expressive-language deficits [1, 2]. Five out of 7 of our patients were clinically diagnosed with FHS, including 3 young patients (age 2.2–4.3 years; Table 1) where the recognition of typical facial features was important (Fig. 1). However, the clinical diagnosis of FHS is expected to be more challenging outside specialized centers, due to the rarity of this condition and the overlapping features with several other syndromic growth disorders [31–34]. Additionally, the facial phenotype and speech or language disorders are more difficult to notice among young patients. For these reasons a multigene sequencing analysis using WES or targeted panel sequencing is helpful to establish the diagnosis.

This is highlighted by one of our patients who presented with microcephaly and short stature with high basal IGF-1 levels. This case was formerly diagnosed as resistance to IGF-1 that was excluded by a normal *IGF1R* sequencing. Only after WES was the diagnosis revealed as FHS. In our study, it was observed that some patients had normal or upper-limit IGF-1 basal levels. Indeed, 4 out of

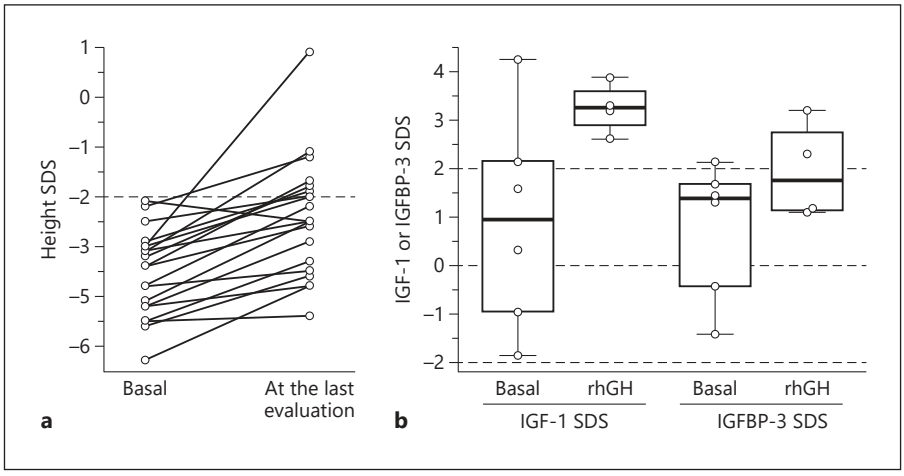

Fig. 3. a Individual height SDS change from the first to the last evaluation in patients with FHS treated with rhGH. **b** Box plot indicating the variation of IGF-1 values before and during rhGH treatment.

7 of our patients with FHS fulfilled the clinical criteria that indicated *IGF1R* analysis [21]. Defects in the *IGF1R* are considered one of the differential diagnoses of FHS, and it is suggested that an impairment of the IGF-1 signaling pathway exists in these patients [10]. Several of our patients fit the clinical criteria observed in patients with partial IGF-1 insensitivity (short stature, microcephaly, high IGF-1 SDS) [21]. For this reason, we recommend a multigene sequencing panel that includes *SRCAP* for patients suspected for IGF-1 insensitivity who have a normal *IGF1R* sequencing.

The other patient diagnosed by WES had a midline defect, central hypothyroidism, and GHD, associated with normal neuroimaging, which prevent the clinical recognition of FHS. The association of FHS and isolated GHD was reported in 2 additional cases in the literature [8, 16] and, similar to our patient, none of them had a structural hypothalamic-pituitary defect. Another study suggested the presence of GH neurosecretory dysfunction among FHS patients because of low serum IGF-1 values, variable GH responsiveness during provocative testing, and a good response to GH treatment [9]. However, this biochemical phenotype is clearly not reflective of all patients with FHS who appear to have a variety of mechanisms involved in their growth disturbance. Furthermore, as the studies were conducted over 25 years, the methodology and the cut-off levels/normal values for the GH provocation test changed during these years. Considering the cut-off level of <5 ng/mL of GH peak for GHD, only 1 patient from all cohorts could be diagnosed with GHD.

We and others observed some nonspecific skeletal abnormalities, such as brachydactyly and early epiphyseal fusions with cone-shaped epiphyses, which indicate dysregulated chondrocyte proliferation and/or maturation and support the idea that direct effects on growth cartilage may influence the growth phenotype of these patients [1, 2, 7]. It is proposed to be due to the interaction of *SRCAP* with several signaling pathways, including cAMP-mediated G protein-coupled receptor signaling, which are associated with some skeletal malformations [7]. Moreover, all our prepubertal patients, who initially had delayed BA, presented with rapidly progressing bone maturation during puberty. This finding may suggest accelerated senescence of growth cartilage and clinically indicated that the delayed BA will not translate into additional time to restore the adult height. The pubertal timing and progression are appropriate in most patients [1, 14], but precocious puberty was previously reported in 1 case [14].

Nowadays, a growing number of studies have demonstrated the use of rhGH therapy to improve the growth velocity and increase the height of syndromic short stature patients, usually under the approved clinical indication of being short secondary to being born SGA [11–13]. Regarding the impact of rhGH therapy in patients with FHS, beyond our 4 patients described in this study, an additional 16 patients were reported in the literature [4, 7–10, 14–16]. This was a heterogenous group, with a variable period and dose of treatment. Furthermore, patients began the treatment at different ages and puberty stages. Despite this limitation, most of these patients increased growth velocity and had an improvement in height SDS. During rhGH therapy, the IGF-1 levels remained in the normal or upper limit of normal ranges in all our patients, suggesting a good sensitivity to GH. Adult height after

rhGH therapy was reported in 7 patients with FHS, with only 2 of them reaching a normal adult height (height SDS of –1.2 and –1.8). Besides that, the mean adult height among treated patients was significantly higher than among not treated patients (–4.1 vs. –2.6 SDS), indicating that rhGH therapy could be a good option to improve the linear growth of patients with FHS.

In conclusion, patients with distinctive facial features, language deficits, and short stature are the most suspect patients for FHS. These patients should be referred to a specialized growth center. However, the rarity and variability in the phenotype of patients with FHS makes it challenging to recognize clinically. In this scenario, a multigene analysis must be considered to clarify the diagnosis, especially among patients born SGA with persistent short stature and normal or upper limit IGF-1 basal levels. The mechanism involved in the growth impairment of patients with FHS is still unknown. There is a wide range of biochemical and radiological manifestations in FHS. Further studies are necessary to clarify the longitudinal growth pattern and the real effectiveness and safety of rhGH therapy in these patients. Because FHS is a very rare syndrome, it is difficult to conduct a large randomized study, and little information about long-term treatment with rhGH has been reported so far. International multicenter studies will be important, especially in rare diseases such as FHS, to provide information with a better level of evidence.

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Statement of Ethics

This study was approved by the local medical ethics committee. The patients and/or guardians gave their written informed consent.

Disclosure Statement

The authors declare that they have no competing interests.

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Author Contributions

All authors made substantive intellectual contributions to the present submitted study. T.K.H. contributed to conception and design, acquisition of data, analysis, and interpretation of data. B.L.F.; A.D.; M.F.A.F., and A.M.L. contributed to the genetic analysis, interpretation of data, and reviewed the manuscript. R.H.; E.V.A.A.; G.A.V.; D.R.B.; C.A.K., and A.C.M. contributed to acquisition of data and reviewed the manuscript. A.A.L.J. had substantial contributions to conception and design, acquisition of data, analysis and interpretation of data, and reviewed the manuscript.

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