CASE REPORT

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A Rare Cause of Proportional Short Stature and Puberty Precocity: Floating-Harbor Syndrome

Duygu Çetinkaya[1], Gönül Büyükyılmaz[2], Esra Kılıç[1]

[1]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Pediatric Genetics, Ankara, Türkiye
[2]University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Pediatric Endocrinology, Ankara, Türkiye

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What is already known on this topic?

Floating-Harbor syndrome is a rare autosomal dominant disorder caused by heterozygous SNF2-associated CREB-binding protein activator protein gene mutations. It is characterized by distinctive craniofacial features, proportionate short stature, delayed bone age, and expressive language delay. However, phenotypic variability may complicate diagnosis, requiring careful clinical and molecular evaluation.

What this study adds?

This study presents a clinically and molecularly confirmed case of Floating-Harbor syndrome, highlighting its characteristic phenotype. It underscores that in patients with short stature and delayed bone age, careful assessment of dysmorphic features is crucial for differential diagnosis, contributing to improved recognition and expanding the clinical spectrum of this rare disorder.

ABSTRACT

Floating-Harbor syndrome is a sporadic, autosomal dominantly-inherited, malformation syndrome characterized by typical craniofacial findings, proportional short stature, significantly delayed bone age, delayed expressive language, delayed speech, and normal head circumference. It is caused by heterozygous mutations in the *SNF2-associated CBP activator protein* gene (*SRCAP*) located on chromosome 16. Here, we report a 9.3 years old male patient who presented to the pediatric genetics outpatient clinic with retardation in early developmental stages, dysmorphic facial features, and short stature. A triangular face, short filtrum, posteriorly rotated ear, deep-set eyes, bulbous nose, prominent columella, and low hairline are unique facial features in the syndrome. He also has short stature, significant retardation in bone age, and retardation in expressive language, all suggesting Floating-Harbor syndrome. The diagnosis was confirmed through molecular testing which revealed a

Corresponding Author: Duygu Çetinkaya, University of Health Sciences Türkiye, Ankara Bilkent City Hospital, Clinic of Pediatric Genetics, Ankara, Türkiye
E-mail: drduygukose@gmail.com **ORCID:** orcid.org/0009-0003-0499-7207
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heterozygous c.7330C>T p.(Arg2444Ter) pathogenic variant in exon 34, of the *SRCAP* gene. Floating-Harbor syndrome should be remembered in the differential diagnosis of patients evaluated for short stature and learning disability with its unique facial features. By reporting a new case of Floating-Harbor syndrome our aim was to expand the clinical and molecular spectrum in this rare syndrome and increase diagnostic awareness for pediatric endocrinology practitioners.

Keywords: Floating-Harbor syndrome, *SRCAP* gene, short stature

Introduction

Floating-Harbor syndrome (FHS) is a rare, hereditary syndrome, characterized by a head circumference in the normal range, low birth weight, proportional short stature, delayed speech, retarded expressive language, and significant retardation in bone age with typical facial features. FHS was first reported in 1973-1974 (1,2). The unique facial features of patients may become less distinctive with age (3). In addition, microcephaly, trigonocephaly, dental problems, abnormal EEG, late-onset hypertension, cone-shaped epiphysis, and Perthes disease may accompany the syndrome (4). FHS occurs due to heterozygous mutations in the *SNF2-associated CBP activator protein* gene (*SRCAP*). *SRCAP* is a 43.2 Kb gene consisting of 34 exons in the 16p11.2 region. It encodes the SNF2-associated CREBBP activator protein. This protein has ATPase activity. It is responsible for cell growth and division by increasing CREB-binding protein (CBP) transcription (5). Here, a boy with FHS who presented to the pediatric genetics outpatient clinic with speech disorder and dysmorphic features and was diagnosed through clinical findings will be reported.

Patient and Methods

A 9-year and 4-month-old male patient was referred to the pediatric genetics outpatient clinic due to delays in early developmental milestones, dysmorphic facial features, and short stature. He was born via Cesarean section at 40 weeks of gestation with a birth weight of 3000 grams [-1.2 standard deviation score (SDS)]. He is the fifth child of healthy, non-consanguineous parents. There is no history of special infant care. On initial physical examination, his weight was 23 kg (-1.6 SDS), height was 118 cm (-2.66 SDS), body mass index (BMI) was 0.01 SDS, arm span was 111 cm, and head circumference was 52 cm (-0.81 SDS). The pubertal examination was normal, with Tanner stage 1, but bone age was approximately 4 years as assessed by X-ray (Figure 1d). The dysmorphic evaluation revealed a triangular face, deep-set eyes, prominent nasal root, low-set ears, bulbous nose, low-hanging columella, and short philtrum (Figure 1a-c). Developmentally, the patient began walking at 1.5 years of age and talking at three years of age. He exhibited significant expressive language delays and shy behavior. Initial hematologic, biochemical, and metabolic parameters were within normal limits. At 10 years and 3 months of age, the patient was evaluated by the pediatric endocrinology department due to short stature and early puberty. Physical examination revealed a weight of 28.8 kg (-0.86 SDS), height of 126.8 cm (-1.9 SDS), BMI of 0.66 SDS, and arm span of 124 cm. Annual growth was 8.8 cm, with an increase in height velocity. Bone age was 6 years (Figure 1e), showing a 2-year increase within 1 year. Testicular volume was 8-10 cc, appropriate for his age. Endocrinological evaluation showed follicle-stimulating hormone (6) level of 2.2 U/L (reference range: 0.3-10.1), luteinizing hormone level of 2.2 U/L (reference range: <6), and testosterone level of 1.02 µg/L. Insulin-like growth factor-1

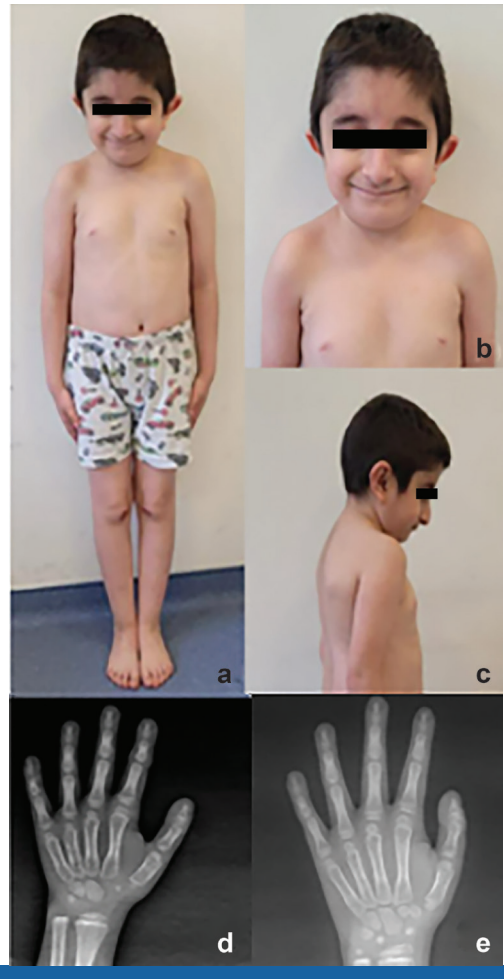

Figure 1. a) Nine years 4 months old male patient. **b** and **c)** Dysmorphologic evaluation triangular face, deep-set eyes, low-set ear, bulbous nose, low hanging columella, short filtrum. d) Bone age consistent with 3 years 6 months. e) Bone age consistent with 6 years

(IGF-1) level was 157 µg/L (reference range: 63-271), and IGF binding protein 3 level was 7.6 (reference range: 2.4-8.4), both within normal ranges. Pituitary and brain magnetic resonance imaging were normal, and follow-up was conducted for early and rapid puberty. Echocardiography and abdominal ultrasound screening showed no major organ abnormalities. Hearing test results were normal, and the ophthalmology department followed the patient for esotropia with corrective glasses. Psychometric evaluation using the Wechsler Intelligence Scale for Children identified mild to moderate intellectual disability. The patient is receiving special education for cognitive and speech delays.

Karyotype analysis revealed a normal 46, XY result. Microarray analysis showed no pathogenic copy number variations [Illumina Infinium CytoSNP 850K "Infinium CytoSNP-850K BeadChip (Illumina, Inc., San Diego, CA, USA)]. Fragile X gene DNA analysis with triplet primer polymerase chain reaction identified 56 CGG repeats, placing the patient in the Fragile X premutation range. Due to the clinical presentation and dysmorphic features suggestive of FHS, sequencing of the *SRCAP* gene was performed. Next Generation Sequencing (NGS) of the *SRCAP* gene revealed a heterozygous c.7330C>T p.(Arg2444Ter) variant in exon 34, which is predicted to cause premature protein termination. This variant is classified as pathogenic according to ACMG-AMP criteria (7). Verification with Sanger sequencing confirmed the presence of this variant in the patient in the heterozygous state. This variant was not detected in the Sanger sequencing of the parents, thus it is interpreted as a disease-causing, *de novo* mutation.

Discussion

FHS is a very rare malformation syndrome with autosomal dominant inheritance characterized by short stature, typical facial features, and significant delay in bone age (1). A total of 100 cases of this extremely rare syndrome have been reported (8). It occurs because of mutations in the *SRCAP* gene located on chromosome 16. The *SRCAP* gene encodes the SNF2-related CREB binding protein. This protein has a role in the activation of the *CREBBP* (CREB binding protein) gene, which is involved in the exchange of histone dimers in the nucleosome and provides transcriptional regulation by remodeling chromatin. CREB binding protein, the protein encoded by the *CREBBP* gene, is involved in cell proliferation and normal growth (9,10). The mutations reported so far are especially clustered in the 34th exon and the variant in our patient was also located in the 34th exon (11). There is no known genotype-phenotype relationship in the reported cases. In the series of 13 cases reported by Hood et al. (12), six patients had the same variant that was present in our patient. Syndrome-specific facial features are the most important differential diagnostic step in FHS (13). Our patient exhibited typical facial features of the syndrome with a triangular face, prominent nasal root, inferiorly located columella, thin upper lip vermillion, and deeply set eyes. Low birth weight has been reported in FHS but it is not characteristic of this syndrome. Our patient was born at 40 weeks with a birth weight of 3000 g (-1.2 SDS). The patient had a normal birth weight based on anthropometric measurements at birth. Thirteen out of 49 (26.5%) patients with FHS were reported to have a birth weight below -2 SDS (11). Short stature is the cardinal sign of FHS, but may vary somewhat in patients with FHS. The exact mechanism by which *SRCAP* mutations cause short stature has not been fully elucidated. It is thought that anomalies that cause irregularity in chondrocyte proliferation and maturation may affect the growth phenotype of patients with FHS by causing a delay in long-bone development (14). It has also been reported that short stature may be associated with growth hormone (GH) deficiency, GH neurosecretory dysfunction, and IGF-1 signaling defects (15). In a series of 52 patients reported from two previous studies, the maximum height in girls was 20th percentile and the majority of the cases were located between -2 and -4 SDS. In boys, the maximum height was 25th percentile and two adults were -4 SDS for height (11). In another study, the heights of 13 patients ranged between -4.3 SDS and -0.6 SDS (12). When the growth parameters of previously reported patients were analyzed, it was reported that head circumference for height was within the normal range (11). Similarly, the presented patient's height was -2.2 SDS and head circumference was 0.81 SDS in the normal range. GH may be one of the treatment alternatives in FHS (16,17). In a study evaluating 22 cases of FHS who received GH treatment, most showed accelerated growth and improved height SDS (15). However, as the IGF-1 level of our patient fell within the normal range for his age, GH treatment was not considered. He is being monitored for potential GH therapy based on an ongoing assessment of his growth rate.

Significant delay in bone age, which is one of the essential features of FHS, was reported in all patients in the series of 13 cases (14). Although there is a significant delay in bone age (≥2 SD below the mean), normalization in bone age is expected between the ages of six and 12 years. The chronological age of our patient was 9 years and 4 months but his bone age was only 3 years and 6 months (12). Interestingly, in the follow-up, a 3-year improvement in bone age was detected in 1 year. This rapid change may also be due to our patient's fast puberty. Puberty precocity is among the features reported in patients with FHS and, again, the underlying mechanism is still unknown (16). Cases have been reported in which GnRH analog treatment was started due to early puberty, and bone maturation was successfully suppressed (18). In the case described by Stagi et al. (18), it was reported that adult height of -1.2 SDS was achieved with both GH and GnRHa treatments. In the presented case, an early and fast puberty was detected and GnRHa treatment will be planned according to the follow-up.

Expressive language delay is another major finding of the syndrome and our patient was receiving speech therapy due to significant delay in expressive language (13). In one study, the frequency of attention deficit hyperactivity disorder was reported to be 28% and in another study, the frequency of behavioral problems was reported to be 60%. In keeping with this, the presented patient was being treated for attention deficit hyperactivity disorder but had no behavioral problems (9,11,12,16). In our patient, premutation was detected with 54 repeats in the CGG 3-repeat analysis for Fragile X syndrome, but we diagnosed FHS with further molecular analysis because of dysmorphic facial finding and short stature. The patient being a Fragile X premutation carrier could potentially affect their behavioral phenotype and intellectual disability profile. In a study of 52 cases, although at least one major organ anomaly was found in 33 of the patients diagnosed with FHS, no specific anomaly was reported to be associated with it, and our patient had no major organ anomaly (11).

FHS must be distinguished from other genetic conditions with short stature. Rubinstein-Taybi syndrome was ruled out due to the absence of its characteristic features and organ anomalies. Silver-Russell syndrome was unlikely because the patient's head circumference and birth weight were normal. 3M syndrome was excluded as the patient did not have the typical skeletal features and had developmental delays. SHORT syndrome was not considered due to the lack of associated symptoms, such as hearing loss and joint laxity. Aarskog syndrome was also excluded because the patient's facial features did not match those of the syndrome.

Conclusion

In conclusion, FHS should be considered in the differential diagnosis of patients being investigated for short stature and learning disability, especially when exhibiting characteristic facial features. Although the presented patient was found to be a premutation carrier on Fragile X analysis carried out for a learning disability, he was diagnosed with FHS with a molecular examination performed because of his characteristic facial findings. Herein, we report a new case of FHS who was diagnosed after evaluation for short stature, precocious puberty, and dysmorphic facial features. We hope to increase the awareness of rare genetic diseases among pediatric endocrinology practitioners who may encounter undiagnosed FHS because of the short stature and or markedly delayed bone age.

Ethics

Informed Consent: Written informed consent was obtained from the family of the patient for publication of this report.

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Footnotes

Authorship Contributions

Surgical and Medical Practices: Duygu Çetinkaya, Gönül Büyükyılmaz, Esra Kılıç, Concept: Duygu Çetinkaya, Esra Kılıç, Design: Duygu Çetinkaya, Gönül Büyükyılmaz, Esra Kılıç, Data Collection and Processing: Duygu Çetinkaya, Esra Kılıç, Analysis or Interpretation: Duygu Çetinkaya, Literature Search: Duygu Çetinkaya, Gönül Büyükyılmaz, Writing: Duygu Çetinkaya, Gönül Büyükyılmaz, Esra Kılıç.

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