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CASE REPORT

A Case of Floating-Harbor Syndrome with "Growth and Language Development Delay" as Its Clinical Manifestation

Yi-Can Yang[1], Qiong Tang[1], Li-Juan Yan[1], Shi-Bin Zhang[2], Xiao-Min Ye[1], Dai Gong[1], Li Zou[1], Xiang-Lan Wen[1]

[1]Department of Children Health Care Center, Zhuzhou Hospital Affiliated to Xiangya Medical College, Central South University, Zhuzhou City, Hunan Province, 412007, People's Republic of China; [2]Department of Pediatrics, Zhuzhou Hospital Affiliated to Xiangya Medical College, Central South University, Zhuzhou City, Hunan Province, 412007, People's Republic of China

Correspondence: Xiang-Lan Wen, Department of Children Health Care Center, Zhuzhou Hospital Affiliated to Xiangya Medical College, Central South University, No. 116 of Changjiang South Road, Tianyuan District, Zhuzhou City, Hunan Province, 412007, People's Republic of China, Tel/Fax +8673128561905, Email wenxianglianwxl@126.com

Background: Floating-Harbor syndrome (FHS) is a rare autosomal dominant inherited disease characterized primarily by short stature, delayed language development, and typical facial features. There are currently few case reports, diagnoses and treatments for these syndromes at home and abroad.

Case Description: This study reports a case of a boy with "growth and language development delay" as the predominant clinical manifestation. FHS was clinically diagnosed based on his growth hormone (GH) deficiency, significant bone age delay, left testicular hydrocele, and the whole exon gene in peripheral blood, which indicated heterozygous mutation of SRCAP gene. Following the treatment with recombinant human GH (rhGH), the child exhibited height increase benefits, and his articulation improved after language therapy.

Conclusion: Genetic testing facilitates early detection, diagnosis, and treatment of the FHS. Additionally, treatment with rhGH effectively increases the height of these children, and language rehabilitation is especially important for their language development.

Keywords: Floating-Harbor syndrome, language development, growth and development, rhGH, language rehabilitation

Introduction

Floating-Harbor syndrome (FHS) is a rare autosomal dominant inherited disease characterized by short stature, delayed skeletal development, poor language expression, and typical facial features such as a triangular face, a wide nasal columella, long eyelashes, sunken eyes, a flat midface, and a thin upper lip, etc.[1] FHS is caused by mutations in the SRCAP gene, which encodes for the SNF-2-related CREBBP activating protein.[2] There are currently a paucity of cases of FHS reported in China, and fewer treatments are available for these children. Scarcity of the disease lead to poor understanding of the disease and case reports concerning treating this disease may enhance the awareness of the disease. This article describes a male child with FHS whose growth and language development are primarily delayed. The treatment with rhGH and language rehabilitation resulted in a satisfactory increase in height, while the effect of language therapy was improved in comparison to previous studies. In addition, we examined the relevant literature both domestically and internationally to help more clinicians understand this syndrome.

General Data

The boy, aged 5 years and 10 months, was admitted to the Children's Health Department of our hospital due to "slow height and weight gain and slow language development since childhood". The child was gravida 2, para 1, born at 39+ weeks of gestation, had a birth weight of 2.8 kg, and measured 48 cm at birth. The Apgar score was unknown. At birth, there was no asphyxia, birth injury, deformity, rescue, or other high-risk diseases. Two days after his birth, the child was admitted to our

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hospital's Neonatology Department due to "neonatal hyperbilirubinemia" and was discharged after his condition improved. The mother had "oligohydramnios and hypothyroidism" during her pregnancy. She began taking "levothyroxine" around her the seventh month of pregnancy. The mother had no high-risk factors of smoking, alcoholism, hypertension, or diabetes during pregnancy. The child was mixed-fed following birth. Due to his recurring eczema on the back and constipation, allergy testing was performed at two months of age and revealed a milk protein allergy. At 1 year of age, the child was fed complete amino acid milk powder and added complementary food. Compared to children of the same age, gross motor development did not appear to be delayed. The child was able to lift his head at the age of 2 months, roll over at the age of 4 months, sit at the age of 6 months, and walk independently at the age of 1 year. The child had a poor physique and suffered from recurrent colds and pneumonia. There was no history of hepatitis, tuberculosis, or other infectious diseases; there was no history of surgical trauma or blood transfusion. The child only received vaccines against Bacillus Calmette-Guérin and hepatitis B without other vaccines. The relationship within the family was harmonious; the parents were not consanguineous. The father is 164 cm tall; the mother is 162 cm tall; and the genetic height is 169.5 cm. The boy's 10-month-old brother is currently in good health and shows no signs of developmental delay. Both grandparents have diminutive statures. Deny the family history of inherited metabolic diseases, as well as the history of infectious diseases and diseases with similar symptoms. This child's height and weight have shown slow growth in comparison to other children of the same age and gender since birth. Physical examination on admission: The height was 104 cm, the weight was 14.65 kg (lower than the 3rd percentile of children of the same age and gender), and the body mass index was 13.6. Clear mind, acceptable disposition, malnourished appearance, naive face, small face, pointed jawline, thin upper lip, sunken eyes, irregular teeth, crossbite, and short fifth toe. The entire epidermis lacks yellow staining, edema, hirsutism, milk coffee spots, and pigmented nevi. Small superficial lymph nodes. No pharyngeal congestion, tonsil enlargement, thyroid enlargement, or nodule. There was no chicken breast, no special cardiopulmonary examination, a soft abdomen, and no palpable liver or spleen under the ribs. No significant abnormalities were observed in the spine. Normal proportion of upper and lower parts. There is no obvious abnormality in the nervous system. The light transmission test of the left scrotum is positive, and the testis is palpable. The right scrotum and testis are devoid of any abnormalities. The patient was diagnosed with FHS based on the detection of the entire exon gene in peripheral blood and the presence of clinical symptoms and signs. Due to food allergies including "milk, eggs, and carrots", the child currently consumes 100–200 mL of amino acid formula milk powder per day, and the variety and quantity of edible foods are limited. At the age of 2 years and 2 months, the child underwent a GH examination at a different hospital due to "developmental delay". GH deficiency was identified using growth hormone stimulation test. The specific method is to combinedly use arginine and L-dopa to stimulate the synthesis of growth hormone in children, and then take vein blood every half hour to determine the concentration of GH. If the GH peak is greater than 10 ng/mL, it indicates that the GH secretion in children is normal, on the contrary, it indicates that the GH secretion is insufficient in the child. The child had a deficiency of 4.71 ng/mL in GH. Normal values were determined for alpha-fetoprotein, carcinoembryonic antigen, adrenocorticotropic hormone, 25-hydroxyvitamin D, thyroid function, basal levels of sex hormone, and renal function. The age of the bones was noticeably delayed (approximately 1.3 years). A color doppler ultrasound of the scrotum showed a left testicular hydrocele. Cardiac color doppler ultrasound, double kidney and adrenal color doppler ultrasound, and head magnetic resonance imaging all revealed no abnormalities. The whole exon gene in peripheral blood indicated a SRCAP gene mutation, as indicated by NM_006662.2: exon34: c.7219C>T, heterozygous mutation. The child was able to shout "Mom and Dad" at 2 years of age. He can articulate lengthy sentences, recite ancient poems, sing songs, and understand basic instructions. However, the child's pronunciation has always been unclear, although others can comprehend him. The child sleeps poorly, exercises moderately and has normal urination and defecation. We provide rhGH treatment (GenSci, Jilin, China; 0.2 mg/kg; 1/week) and speech therapy in consideration of the child's primarily delayed growth and language development. The child has been receiving treatment with rhGH but has discontinued the medication due to recurring fever and congestion. The parents stopped rhGH therapy for fear of affecting the therapeutic effect by fever and congestion. As shown in Table 1, the child received intermittent treatment with rhGH for a total of 3 years and 8 months. As a result, the child's height increased by 25.8 cm (the standard deviation score (SDS) of height increased from −4.2 to −3.16), the weight increased by 6.35 kg (SDS of weight increased from −11.95 to −2.89), and the body mass index remained essentially the same. Meanwhile, the rate of bone age maturation did not significantly accelerate (bone age increased by 1.6 years during 3 years and 8 months). We observed excellent efficacy in the treatment

Table 1 Follow-Up of the Child Before and After Treatment with Growth Hormone

Age	Height (cm)	Weight (kg)	Height SDS	BMI		Bone Age	
2 years and 2 months	78.2	8.3	−3.4	13.6		1.3 years	
3 years and 3 months	84.5	10.0	−3.74	14.0	6.3cm/y		The child discontinued the drug for 8.5 months due to recurrent cough and fever.
3 years and 8 months	88.6	10.25	−3.38	13.1	4.1cm/5m		
4 years and 1 month	91.4	10.85	−3.41	13.0	2.8cm/5m		
4 years and 9 months	94.6	12.1	−3.55	13.5	3.2cm/8m		The child had recurrent fever and discontinued the drug for 4 months.
5 years and 1 month	98	12.7	−3.23	13.2	3.4cm/4m		
5 years and 5 months	99.9	13.25	−3.16	13.3	1.9cm/4m		
5 years and 10 months	104	14.65	−2.76	13.5	4.1cm/5m	2.9 years	

with rhGH, which can accelerate the rate of height, reaching approximately 0.8 cm monthly during the period of monitoring with fewer missed injections and no significant adverse reactions. Since the child was over 2 years old, the child has received irregular language rehabilitation in rehabilitation institutions, and his speech articulation has improved compared to before. Currently, the child can sing, although with an incorrect tone, narrate short stories and recount daily events, count and make simple calculations up to 5 and comprehend instructions from adults. The child's language development is equivalent to that of children aged 3.5 to 4 years and 11 months by S-S method. Furthermore, we observed that he progressively developed inattention, as reported by kindergarten teachers who noticed his difficulty sitting still and desire to move about the classroom. The English letter cancellation test showed a brain working ability index of 6.04 (a brain ability index below 37 indicates poor attention). Currently, the child is still undergoing treatment and follow-up.

Discussion

FHS, also referred to as Pelletier-Leisti syndrome, is a rare sporadic autosomal dominant inheritable disease. The primary clinical features of these children include short stature (generally less than −4 to −6SD), delayed bone age, skeletal deformities, language retardation, and typical facial features, such as a triangular face, rotated ears, sunken eyes, long eyelashes, a garlic nose, a wide nasal columella, thin lips, and a flat mouth. Some children may suffer from conductive hearing loss, recurrent otitis media attacks, hyperopia, strabismus, a short neck, a low posterior hairline, and a short fifth toe.[3] A small percentage of children may also have an atrial septal defect, median heart, aortic stenosis, left superior vena cava remnant, umbilical hernia, inguinal hernia, hypospadias, cryptorchidism, unilateral renal pelvis ureter, posterior urethral valve, etc. 2The first case of FHS with bilateral cleft lips was reported by Ko et al.[2] According to Seifert et al, patients with FHS may exhibit behavioral abnormalities during preadolescence, adolescence, and adulthood, such as attention deficit hyperactivity syndrome, compulsive behavior, anxiety, and sleep disorders, among others.[4] In addition to the typical symptoms described above, we recently observed the child's inattention, as reported by his kindergarten teachers, who noticed his difficulty sitting still and desire to move about the classroom. The English letter cancellation test revealed a brain working ability index of 6.04 (a brain ability index below 37 indicates inadequate attention), which was also consistent with previous literature reports.

The SRCAP gene mutation is the most common cause of FHS. According to some studies, more than 40 types of mutations in the SRCAP gene have been identified in FHS.[5] The SRCAP gene is located on chromosome 16p11.2 and is composed of 34 exons. It encodes the SNF-2-related CREBBP activating protein that plays a crucial role in regulating cell division, DNA repair, differentiation, cell death, and tumor suppression.[6] The majority of gene mutations in children with FHS occurred in exon 34 nonsense mutations and frameshift mutations, with only two cases of exon 33 nonsense mutations and one case of exon 5 nonsense mutations.[5,7] Consistent with previous reports, the c.7219C>T mutation in exon 34 of the SRCAP gene was found in the male child reported in this paper. Due to the scarcity of the disease, how mutations in the SRCAP gene lead to FHS is poorly understood.

Short stature is the most prominent feature of FHS. These children are generally born with normal length and weight, and their growth is sluggish from infancy. The interference with the specific part of the GH-IGF-1 growth axis in children with FHS is currently unclear. Studies indicate that the syndrome may be caused by a defect in the downstream signaling pathway of IGF-1, as opposed to decreased secretion and/or activity of growth hormone or IGF-1.[8] Furthermore, studies have indicated that decreased growth hormone secretion or activity typically does not result in prenatal fetal growth restriction, whereas decreased IGF-1 secretion or activity is associated with prenatal fetal growth restriction or microcephaly.[1] In our case, the child has a growth hormone deficiency along with the normal range of birth length and weight, which is consistent with the study. Regrettably, the IGF-1 level was not measured prior to initiating rhGH in children. However, the treatment showed a relatively positive effect on height with the use of rhGH. It is unclear whether the short stature is related to IGF-1 or its downstream signal abnormality. Although more than 100 cases of FHS have been diagnosed, only a small number of children have been treated with rhGH, and there are inconsistent reports regarding the effectiveness of this treatment in children with FHS.[9] Including our case, a total of 23 children with FHS have been treated for height with rhGH to date. Most children respond well to growth hormone treatment, but three children exhibit poor sensitivity to rhGH, and there are a few cases of precocious puberty leading to accelerated bone age and the need for combined use of hormone inhibitors to promote height. During rhGH, we observed a height increase rate of approximately 0.8 cm monthly in the child reported in this case, with fewer missed injections, which indicated that the treatment effect of rhGH treatment on height was relatively excellent. Delayed skeletal maturation is also one of the characteristics of children with FHS. Wiltshire and Lacombe et al reported that most children with FHS had delayed bone age before the age of six.[10,11] According to Lacombe and De Benedetto et al, children with FHS between the ages of 6 and 12 still had delayed bone age.[11,12] In contrast, Nagasaki et al found that some children with FHS may experience accelerated bone age maturation following a period of skeletal delay, even reaching or exceeding the actual living age.[13] In our case, the child is currently still under six years of age, and his bone age lagged significantly compared to his actual living age both before and after treatment with rhGH. This finding aligns with previous reports. Additionally, we observed that the bone age of this child did not show significant acceleration in maturation during the treatment with rhGH. Over a period of 3 years and 8 months, his bone age increased by approximately 1.6 years. The reason for the bone age delay in this child is unknown and may be associated with a defect in a particular link of the GH-IGF-1 growth axis or malnutrition. We will also continue to treat and monitor the child to determine if there is a possibility of accelerated bone maturation. Deficiency in GH in the child may account for the therapeutic effect of rhGH. However, the role of rhGH in children with FHS need more study.

Despite the fact that language development delay is one of the characteristics of FHS, little is known about the specific language development and treatment of children with this disorder. Language development consists primarily of the development of language comprehension ability, language expression ability, and speech development. Children with FHS are primarily affected by a delay in the development of language expression, and other language development abnormalities include high pitch, nasal sound, speech development defects, and oral motor dysfunction. Angelillo et al reported a case of a boy with FHS who had borderline mental delay and language retardation. After four years of language rehabilitation and recurrent evaluation, the language function was significantly enhanced.[14,15] Hersh et al reported a case of a 12-year-old and 2-month-old girl with FHS.[16] After receiving special education, despite an ongoing language development delay and abnormal nasal sounds, her language and communication skills improved. Ala-Mello et al reported a case of a boy with FHS who had attended a special school.[17] After undergoing speech treatment, attention deficit became his primary concern, and his high pitch, nasal tone, and weak voice were no longer as pronounced, and he was even able to attend regular classes. The 2-year-old child in this circumstance can only shout “Mom and Dad”. His pronunciation remained unclear, but he was able to comprehend simple instructions, indicating abnormalities in language expression and speech development, but his language understanding ability was acceptable. Due to financial constraints in the family, the child’s parents have been attending language rehabilitation at free rehabilitation institutions. Currently, the child can communicate in simple sentences, narrate short stories, and recount daily events. There has been a slight improvement in pronunciation and articulation compared to before. Although the mentioned child with FHS still has a language developmental delay after undergoing language therapy, significant improvement in language development has been observed compared to before treatment. This demonstrates the utmost significance of language rehabilitation training for children with FHS. Studies have shown that almost all children with FHS have limited maxillary mobility,

which may be the cause of their delayed language development. The specific causes and molecular mechanisms underlying delayed language development in children with FHS remain unclear, and more research is still required. Meanwhile, we observed that the child progressively began to exhibit signs of attention deficit, which means that there is a need to include attention training in his rehabilitation program, and it also reminds us to consider the possibility of additional developmental behavioral abnormalities.

GH is a peptide hormone secreted by the anterior pituitary, which can promote growth of bone, internal organs and the whole body, promote protein synthesis, and affect fat and mineral metabolism. GH exists in the cerebral cortex, hypothalamus, cerebellum, hippocampus, spinal cord, neuroretina and so on, and plays an important role in the structural development, proliferation and differentiation of the nervous system, axonal dendrite growth, synaptic signal transmission, neuroprotection, nerve regeneration, cognition, and behavior.[18] GH receptors, GH effector cells and IGF-1 receptors are widely distributed in the central nervous system, which indicates that GH and IGF-1 are also involved in central nervous system activities. Hu et al founded that GH deficiency affects somatosensory, motor and cerebellar development and may lead to behavioral problems in children.[19] In addition, studies at home and abroad have shown that GH treatment can improve the daily living skills, communication ability and cognition of children with FHS. rhGH treatment and language rehabilitation training may interact to enhance language function in patients with FHS.

This article describes a case of FHS, characterized by delayed growth and language development. We discovered that treatment with rhGH and language rehabilitation yielded promising results. However, the long-term safety and efficacy of using rhGH in children is still being debated, and the specific reasons and molecular mechanisms underlying language development delay in these children are unknown, necessitating additional research by clinical and basic medical physicians.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

This study was conducted with approval from the Ethics Committee of Zhuzhou Hospital Affiliated to Xiangya Medical College, Central South University (ZZCHEC2021121-01). This study was conducted in accordance with the declaration of Helsinki. Written informed consent was obtained from the participant's guardian.

Consent for Publication

All patient guardians signed a document of informed consent for specificity of details.

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Disclosure

The authors declare that they have no competing interests in this work.

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