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OPIS PRZYPADKU
CASE REPORT

Floating-Harbor syndrome: A case report of a patient with coexisting pulmonary hypertension

Zespół Floating-Harbor – przypadek pacjenta ze współistniejącym nadciśnieniem płucnym

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ABSTRACT

Floating-Harbor syndrome (FHS) is an extremely rare, genetically determined disorder characterized by intellectual disability, distinctive facial features, and short stature, combined with bone age delay and speech disorders. To date, just over 100 cases of patients with this syndrome have been reported in the literature. Our article describes the case of an 8-year-old boy diagnosed with FHS, who additionally suffers from primary pulmonary hypertension. In the article, we address whether the boy's heart defect and cardiac conditions can be components of a genetic defect. In addition, we address the problem of growth deficiency in patients with FHS and present the results of treatment using recombinant human growth hormone. Given the extremely limited number of reported FHS cases, we believe our contribution will help expand the current understanding of the syndrome and further define its clinical phenotype.

KEYWORDS

pulmonary hypertension, growth deficiency, Floating-Harbor syndrome

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STRESZCZENIE

Zespół Floating-Harbor (*Floating-Harbor syndrome* – FHS) to wyjątkowo rzadkie, uwarunkowane genetycznie schorzenie, charakteryzujące się niepełnosprawnością intelektualną, specyficznymi rysami twarzy i niskim wzrostem, w połączeniu z opóźnieniem wieku kostnego oraz zaburzeniami mowy. Do tej pory w literaturze opisano nieco ponad 100 przypadków pacjentów z tym zespołem. W pracy opisano przypadek 8-letniego chłopca, u którego rozpoznano FHS, a który dodatkowo choruje na nadciśnienie płucne. Starano się odpowiedzieć na pytanie, czy wada serca i schorzenia kardiologiczne u chłopca mogą być składowymi jego wady genetycznej. Ponadto poruszono problem niedoboru wzrostu u pacjentów z FHS i przedstawiono wyniki leczenia rekombinowanym ludzkim hormonem wzrostu. Z uwagi na niezwykle ograniczoną liczbę opisanych przypadków FHS artykuł może się przyczynić do poszerzenia wiedzy na temat zespołu i dokładniej zdefiniować jego fenotyp kliniczny.

SŁOWA KLUCZOWE

nadciśnienie płucne, niedobór wzrostu, zespół Floating-Harbor

INTRODUCTION

Floating-Harbor syndrome (FHS) is a genetically determined, extremely rare disease characterized by facial dysmorphia, mild to moderate intellectual disability, speech impairment, short stature, and bone age delay [1,2,3,4]. The genetic cause of FHS is a heterozygous mutation in the *SRCAP* gene [5,6]. FHS is inherited in an autosomal dominant manner [6]. To date, just over one hundred cases have been described in the medical literature, and current treatment options for the symptoms of this condition are limited [5,7].

The aim of this paper is to present the case of a 8-year-old boy diagnosed with Floating-Harbor syndrome based on clinical presentation and genetic testing. Notably, our patient is also affected by pulmonary hypertension, a comorbidity that has not been previously associated in the literature with FHS. The limited number of documented cases has led to a limited understanding of the disease and poses challenges in the management of affected individuals. We believe that this article may contribute to the knowledge regarding FHS and support physicians in making therapeutic decisions for patients with FHS.

CASE REPORT

Cardiac history

At present, our patient is 8 years and 7 months old. During the first 30 months of life, he received medical care at a foreign center. He was born via caesarean section at 39 weeks gestation, with a birth weight of 3000 g and a length of 48 cm. His Apgar scores were 8, 9, and 10 at 1, 5, and 10 minutes, respectively. On the fourth day of life, a heart murmur was identified on clinical examination. Echocardiographic evaluation revealed a ventricular septal defect (VSD) located near the membranous part of the septum, measuring approximately 7 mm in diameter, with a left-to-right shunt and a peak velocity through the defect of 3 m/s. Despite the presence of a large VSD, the child showed no signs of heart failure during the first three months of life. During that time, his growth and weight gain were appropriate. Follow-up echocardiographic examinations during the first quarter of life continued to show the VSD with a low-pressure gradient across the defect. No aortic coarctation was detected.

In a preoperative evaluation, in addition to the previously described VSD, coarctation of the aorta was identified, with a diameter of 3 mm at the isthmus. At the age of 3 months, the patient underwent a surgery, which included aortic arch reconstruction and closure of the VSD. Following the procedure, the patient developed severe pulmonary hypertension. A lung biopsy was performed on the fifth postoperative day, which ruled out vascular disease. Sildenafil therapy was initiated immediately after surgery and was continued for 12 days. The patient was discharged without a recommendation to continue pharmacological treatment for pulmonary hypertension.

At 15 months of age, cardiac catheterization was performed to assess pulmonary arterial pressure, confirming the presence of severe, non-reactive pulmonary hypertension. The baseline pulmonary vascular resistance was 14 Wood units, decreasing to 9.7 Wood units after a reversal test was performed. Based on these findings, antihypertensive treatment was initiated in the form of sildenafil monotherapy.

After 10 months of treatment, an attempt was made to discontinue the medication. Two months later, the full dose was reinstated based on a follow-up echocardiographic examination.

After the family relocated, the patient – then in his third year of life – was hospitalized at a center in Poland for revaluation of his cardiovascular status. A chest computed tomography scan ruled out any pulmonary causes of pulmonary hypertension. Additionally, another cardiac catheterization was performed, which confirmed non-reactive pulmonary hypertension. Based on these findings, the patient was qualified for a drug program for the treatment of pulmonary hypertension, using sildenafil monotherapy.

At the age of 4.5 years, another cardiac catheterization was performed, which again confirmed severe, non-reactive pulmonary hypertension. The baseline pulmonary vascular resistance was 32.08 Wood units

(indexed: 17.85), which decreased to 9.9 Wood units (indexed: 5.51) after a reversal test. As a result, the treatment was intensified by adding macitentan. The patient remains on dual therapy to this day. The patient does not present any signs of pulmonary hypertension, despite echocardiographic examinations showing otherwise.

History of genetic diagnosis

Since infancy, our patient exhibited distinct physical features, particularly involving the craniofacial area. At the age of six, he was evaluated by a geneticist, who noted mild hypertelorism, the presence of epicanthal folds, a prominent nose, thickened vermilion of the lips, micrognathia, and clinodactyly of the fifth fingers. Based on the characteristic facial appearance, intellectual disability, short stature, hyperactivity, and speech delay, the patient underwent exome sequencing, which was expanded to include a full mitochondrial genome analysis and a panel of known pathogenic variants listed in the ClinVar database located outside of coding sequence. This analysis revealed the *c.7219C>T* variant of the *SRCAP* gene in a heterozygous state, leading to the diagnosis of FHS.

Height and bone age

In addition to his history of cardiac treatment, our patient has been under the care of genetic, metabolic, endocrinological, rheumatological, gastroenterological, and psychiatric clinics since his early stages of life. One of the ongoing issues he faces is growth deficiency. Since the growth monitoring began, his height has consistently been below the 3rd percentile. At 5.5 years of age, his height standard deviation score (SDS) was -4.86, and his bone age was assessed to be 20 months.

Thyroid function tests – including TSH, FT3, and FT4 – were within normal limits, and thyroid ultrasound revealed no abnormalities. Biochemical and hormonal workups, including a glucagon stimulation test for growth hormone (GH) secretion and insulin-like growth factor 1 (IGF-1) measurement, were also within normal ranges. The patient underwent further diagnostic evaluation at the age of 7. At that time, a GH stimulation test using clonidine showed GH levels below 10 ug/L, despite normal IGF-1 and insulin-like growth factor binding protein 3 (IGFBP-3) concentrations. This result, combined with the previously observed low GH response to glucagon stimulation, led to a diagnosis of somatotropic pituitary insufficiency. At the time of writing, GH therapy has been initiated in our patient, though it is still too early to determine whether the treatment will have the desired effect.

DISCUSSION

FHS is an extremely rare and still relatively unknown genetic disorder. According to the literature, there have been no reports of co-occurring congenital heart defects and primary pulmonary hypertension in patients with FHS. Our patient presents with hallmark features of the condition, including short stature, characteristic facial appearance, psychiatric disturbances, and intellectual disability. Additionally, during the neonatal period, he was diagnosed with a congenital heart defect, and shortly thereafter developed severe pulmonary hypertension.

Although the large VSD identified during the first three months of life did not appear to be hemodynamically significant (the child showed no signs of heart failure and exhibited normal weight gain), the undetected coarctation of the aorta in combination with the VSD may have contributed to the early onset of pulmonary hypertension. However, given that the cardiac defect was surgically repaired relatively early, one would expect the hypertension to resolve if it had been purely secondary to the heart defect.

The presence of elevated pulmonary pressures during the first three months of life – reflected in the low gradient across the VSD and the persistence or even progression of pulmonary hypertension – suggests a primary form of pulmonary hypertension coexisting with the congenital heart defect. This raises the question of whether the observed cardiac abnormalities might be connected with the underlying genetic syndrome. Given the small number of reported cases, this possibility cannot be ruled out. Future diagnoses may help clarify the extent to which cardiac involvement is a feature of FHS.

The lack of reported co-occurring congenital heart defects and pulmonary hypertension in FHS may simply reflect the rarity of the condition and the limited number of published cases. The clinical course of our patient may expand the phenotypic characterization of individuals with FHS.

Another therapeutic challenge in patients with FHS is short stature [4,8,9,10]. Several reports have already been published describing the use of recombinant human growth hormone (rhGH) therapy in individuals with this condition [7,8,9,10,11]. In 2021, Bo et al. [8] reported on the outcomes of GH treatment in patients with FHS. According to their findings, among 22 patients who received rhGH, 3 did not achieve satisfactory results, while the remaining 19 showed a measurable increase in height. The patient described in that study also demonstrated positive effects of the therapy after just 6 months of treatment. In 2020, the first study was published describing a female patient

with FHS who underwent long-term treatment with GH – specifically, for a duration of 55 months [7]. As a result of the therapy, her height SDS improved from -3.33 at baseline to -2.7 after nearly five years. The authors acknowledged that the gains were not dramatic, but nonetheless considered the therapy effective in treating growth deficiency in patients with FHS.

It is worth noting that, in both our patient and the individuals described in the above-mentioned studies, birth weight was within the normal range and the growth problems became apparent during infancy.

In summary, most reported cases of rhGH use in FHS patients have shown improvement in height SDS and accelerated growth velocity. However, the number of cases remains too limited to draw definitive conclusions about whether the lack of response in some individuals is due to treatment errors or other, as yet unidentified factors.

CONCLUSIONS

This case highlights the need for broader recognition of possible cardiac involvement in FHS, particularly in the form of congenital heart defects and primary pulmonary hypertension – features that have not yet been documented in association with this rare condition. The coexistence of these findings in our patient suggests the potential for a wider phenotypic spectrum of FHS than currently acknowledged. Additionally, our report supports the consideration of rhGH therapy for managing growth deficiency in these patients, although individual responses may vary. Continued case reporting and clinical follow-up will be essential for refining the understanding and treatment of this complex syndrome.

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Conflict of interest

All authors declare no conflict of interest.

Authors' contribution

Study design – H. Raś, P. Kubicki, M. Greniuk
Manuscript preparation – M. Raś, H. Raś, K. Jankowska
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Final approval of the version to be published – H. Raś, K. Jankowska

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