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GH Deficiency, a Therapeutic Challenge in a Context of Congenital Heart Disease

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Abstract **Case Report**

Growth retardation (GR) has various etiologies including the deficit of growth hormone (GH). In this case, the treatment is a replacement by recombinant hormone (rhGH). In some specific situations, such as congenital heart disease associated with GH deficiency, the treatment may appear debatable, because of a risk of repercussions, particularly on the ventricular wall. We received a young patient with severe GR and interventricular and interauricular communications, with a proved GH deficiency. The possibility of treating by rhGH has been discussed. The situation has been reported to cases of patients with Noonan syndrome, which most often associates a GR with indication for rhGH and congenital heart disease. In this context, many studies have established not only the efficacy but especially cardiac safety of this treatment.

Keywords: Growth retardation; Growth hormone deficiency; congenital heart disease; Recombinant growth hormone.

INTRODUCTION

Growth retardation (GR) is defined as an insufficient growth and development of stature and / or weight corresponding to less than two standard deviations (SD) compared to children of the same age and sex, based on reference tables. A widely recognized and increasingly diagnosed cause is growth hormone (GH) deficiency. It is a well-defined entity and of various etiologies. The treatment is codified and the dose may depend on the etiology. In some particular situations, treatment protocols are poorly referenced. But it is always important to judge the balance between the benefit of treatment and the potential risk, while ensuring regular and close monitoring and follow-up when the situation requires it.

Congenital cardiopathy, by left-right shunt, is a cause of GR, like other chronic diseases. Most often, children recover their growth retardation after the surgical cure of the cardiopathy. When surgery is not urgent or not immediately feasible, the treatment of GR -when GH deficiency is retained-, is based on hormonal substitution, only if it will not aggravate or affect the heart disease.

We report the case of a child with congenital heart disease and severe GR, treated with recombinant GH (rhGH).

OBSERVATION

We received a young boy, who was referred by the pediatric department for the exploration of a severe growth delay. "He arrives on the back of his mother", yet the child were eight years old and four months, contrary to appearances.

During the interrogation, we found out that his parents were consanguineous, no history of incident during pregnancy, no drug intake, and no delay of psychomotor acquisitions. On the other hand, he had a congenital heart disease: atrial and ventricular septal defects. A stagnation weight was observed at 40 days of life, posing, in this context, the diagnosis of congenital heart disease. And at the age of five, the retardation was noted by the family, with no transit disorder, no headache or visual fog, and no signs of other pituitary deficiency.

When examining the child, the weight was 12 kg, less than 3 DS and the height was 90 cm far below 4 DS. His target height, taking into account the size of his parents, was 172 cm. His face was chubby, his palate archival and his feet flat. A micropenis of 3 cm, corresponding to -2DS and a systolic heart murmur.

Biochemically, there were no evidence of malabsorption, including no anemia, normal serum calcium and normal lipid status. Antibodies of celiac disease were negative. The bone age was 3 years below the chronological age. The other biological assessment found was a low IGF1, a normal cortisol rate, thyrotropic axis and prolactin rate. On MRI, anterior pituitary hypoplasia was found, measuring 2 mm and the pituitary stalk was in place. On the cardiac ultrasound, two defects with left-right shunt were found: a perimembranous ventricular defect measuring 5mm and an atrial defect, ostium secundum, measuring 4mm.

The diagnosis of growth retardation by GH deficiency was retained based on: severe GR, chubby face, micropenis, low IGF1 and pituitary hypoplasia.

Thus, treatment with growth hormone (rhGH) was started, at a dose of 0.025 mg / kg / day, accompanied by a therapeutic education for the mother who will perform the injections and be in charge of the follow-up.

Close monitoring of cardiac status by clinical examination and cardiac ultrasound (CUS), as well as other usual monitoring parameters for patients taking recombinant growth hormone (rhGH) is needed. Indeed, clinically, headaches are a sign to look for regularly, as well as areas of lipodystrophy at injection sites. A regular evaluation of the weight and height gain, both to signal the effectiveness of the treatment but also in order to periodically adjust the dose of rhGH treatment. Biologically, an assessment of blood glucose, glycated hemoglobin, blood count, lipid, renal and phosphocalcic status, TSH, T4, and IGF1. Radiologically, an annual bone age can be used to assess ossification stages during treatment.

At the cardiac level, a CUS was performed after one week, then at one month and at three months, with no effect on the size of the cardiac communications or on the ventricular walls.

Thus, the treatment was continued, and the doses were adapted to the weight after 6 months. Indeed, there was a good clinical evolution, with a 2 kg weight and a 2 cm statural gain over this period, with no side effects of the treatment.

DISCUSSION

Recombinant growth hormone (rhGH) has been used for over 30 years, and both its efficacy and its safety in children has been the subject of many studies. In 2001, the GH research company (GRS) came to the conclusion that whenever an indication is made, GH is safe. Follow up is needed, however, including the risk of neoplasia, or the impact on carbohydrate homeostasis [1].

In our case, the issue was in the possibility of treating a child with growth hormone when his heart is carrying atrial and ventricular defects. In the majority of situations, the indication for cardiac surgery, in congenital affections, precedes treatment with recombinant growth hormone (rhGH). In the case of our young patient, it was not urgent and not indicated immediately. Indeed, in most studies, surgery precedes treatment [6], explaining the delay by the cardiopathy and, thus, the surgical cure makes the catch up possible.

Our case could be linked to the situation of patients with Noonan syndrome. Indeed, this syndrome is considered as the first cause of congenital heart disease (after Down syndrome), whose treatment is not always surgical. The GR is found in more than 70% of cases and treated with rhGH. It is caused by either insufficient secretion of GH, neurosecretory dysfunction in GH or resistance to GH [7]. Thus, the question of the impact of growth hormone supply on ventricular development has been raised in this context [2]. However, the safety of the treatment has been proven, especially the cardiovascular one [2].

After treatment with rhGH, there were no significant side effects on the left ventricular size in children with Noonan syndrome [3] at a dose of 0.05 mg / kg / day, even after 5.6 years of follow-up. In another study, there was no impact on the thickness of the ventricular wall in patients taking rhGH at a dose of 0.05 mg / kg / day over a period of one year [4]. A Swedish study had reached the same conclusion [5]. Similarly, data from a large cohort study of children with Noonan Syndrome, published in 2018, demonstrated the safety and absence of any cardiac side effects during treatment with rhGH [8].

Nevertheless, in addition to the usual monitoring parameters of patients treated with recombinant growth hormone, close monitoring by cardiac examination and ultrasound remains necessary in the follow-up of patients with congenital heart disease taking rhGH. The purpose of this monitoring being to look for a possible change in the thickness of the ventricular wall. However, the pace of observation remains discussed. It has to be very close at the beginning, then more and more spaced afterwards: first, a pre-therapeutic evaluation, then an evaluation after two weeks of treatment, then another one after one month and finally every three months.

CONCLUSION

Growth retardation, associated with congenital heart disease, can be explained by the cardiac pathology. In this case, the patient's growth parameters should reach the norms once the surgical cure is performed. However, growth hormone deficiency can be sought and highlighted especially in situations where a heart disease is well tolerated. Thus, treatment is based on recombinant growth hormone. Despite this

particular context, its effectiveness and its cardiovascular safety, especially the absence of repercussions on the thickness of the ventricular wall, have been proved.

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