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Case Report

CASE REPORT

Severe short stature and Wolf-Hirschhorn syndrome: response to growth hormone in two cases without growth hormone deficiency

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Abstract

Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder occurring in approximately 1/50 000 births, with marked pre- and postnatal growth failure. WHS results from the hemizygous deletion encompassing the 4p16.3 region. This report of two children with WHS shows that growth hormone treatment in selected children with WHS and severe short stature may have a substantial effect on long-term growth.

INTRODUCTION

Wolf-Hirschhorn syndrome (WHS) is a rare congenital disorder occurring in approximately 1/50 000 births, with a 2 : 1 female-to-male predominance [1]. It results from the hemizygous deletion encompassing the 4p16.3 region. It is estimated to be *de novo* in 50–60% of cases, with the rest due to an unbalanced translocation [2]. This critical region of 4p16.3 has been localized to an interval of 300–600 kb [3], involving genes that are believed to play an important role in DNA repair [4, 5]. The severity of WHS is directly related to the extent of the deletion; mild WHS has a 3- to 5-Mb deletion, classic WHS has a moderate size deletion of 5–18 Mb, and severe WHS is seen with deletions >22 Mb [6].

The typical craniofacial phenotype is described as a 'Greek warrior helmet appearance' with hypertelorism, a prominent glabella, broad nasal bridge, microcephaly and micrognathia. Classically, children with WHS show developmental delay with hypotonia and seizures, with marked pre- and postnatal growth retardation [1]. Given the often extreme short stature, children with WHS would be potentially eligible for treatment with exogenous growth hormone (GH) in many countries [7]. We report the response to GH in childhood of two unrelated cases without GH deficiency.

CASE 1

Case 1 was born from non-consanguineous parents (mid-parental height 75th percentile) at 36 weeks, and birth weight of 1745 kg (–2.7 SDS). She had ongoing poor growth, moderate developmental delay and developed generalized seizures at the age of 18 months, and started on anti-convulsants. Investigations included normal karyotype (46XX), GH testing (peak GH 35 µg/l; normal >7 µg/l) and unremarkable metabolic evaluation. Microarray confirmed a 3.7-Mb deletion in the region of 4p16.2-p16.3. She had absent middle phalanges of the third and fifth toes bilaterally. At 3.5 years of age, her height was –4.6 SDS, BMI –4.0 SDS and siting height –5.1 SDS, with a bone age of 1.2 years. GH was started at 4 years of age (Figure 1), and was associated with

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increased height to –3.5 and –2.5 SDS after 1 and 2 years, respectively, and at 9.5 years, –1.64 SDS (5th percentile). GH was stopped by the parents at 9.5 years; this was followed by a marked deceleration of growth.

CASE 2

Case 2 was born from non-consanguineous parents (mid-parental height 50%) at 36 weeks, and birth weight of 1867 kg (–2.1 SDS). She had a single kidney on ultrasound and a cleft palate. She had ongoing poor growth and was gastrostomy fed at 2 years of age with little effect on growth. She developed moderate developmental delay and also generalized seizures at ~18 months, and started on anti-convulsants. Investigations included normal karyotype (46XX), GH testing (peak GH 15 µg/l) and general screen. WHS was confirmed with a FISH probe showing a 4p16.3 deletion. Her father had a balanced translocation t(4;14). At 2.6 years of age, her height was –3.4 SDS and BMI –4.8 SDS. She had facial features of WHS and a bone age of 2.0 years. GH was started at 3.3 years of age (Figure 2), and was associated with an increase in height to –2.5 and –2.1 SDS after 1 and 2 years, respectively. At 6.8 years of age, her height is –2.1 SDS.

There have been no complications of GH treatment and no increase in seizures in either case.

DISCUSSION

Children with idiopathic short stature and poor growth in New Zealand are eligible for publically funded treatment with GH in the same dose as used in these cases. In a systematic audit of

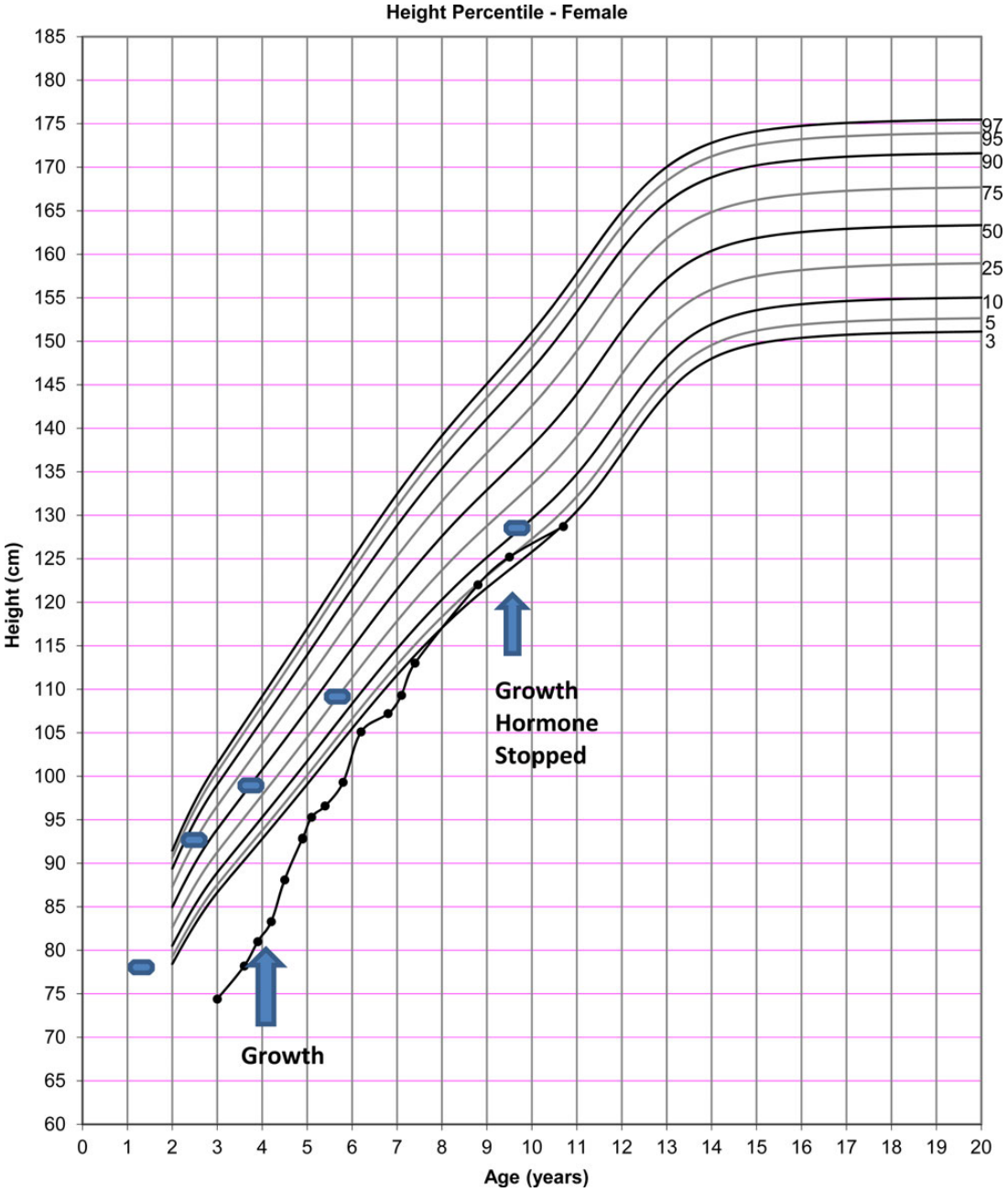

Figure 1: Height during GH therapy in Case 1, blue boxes represent bone age.

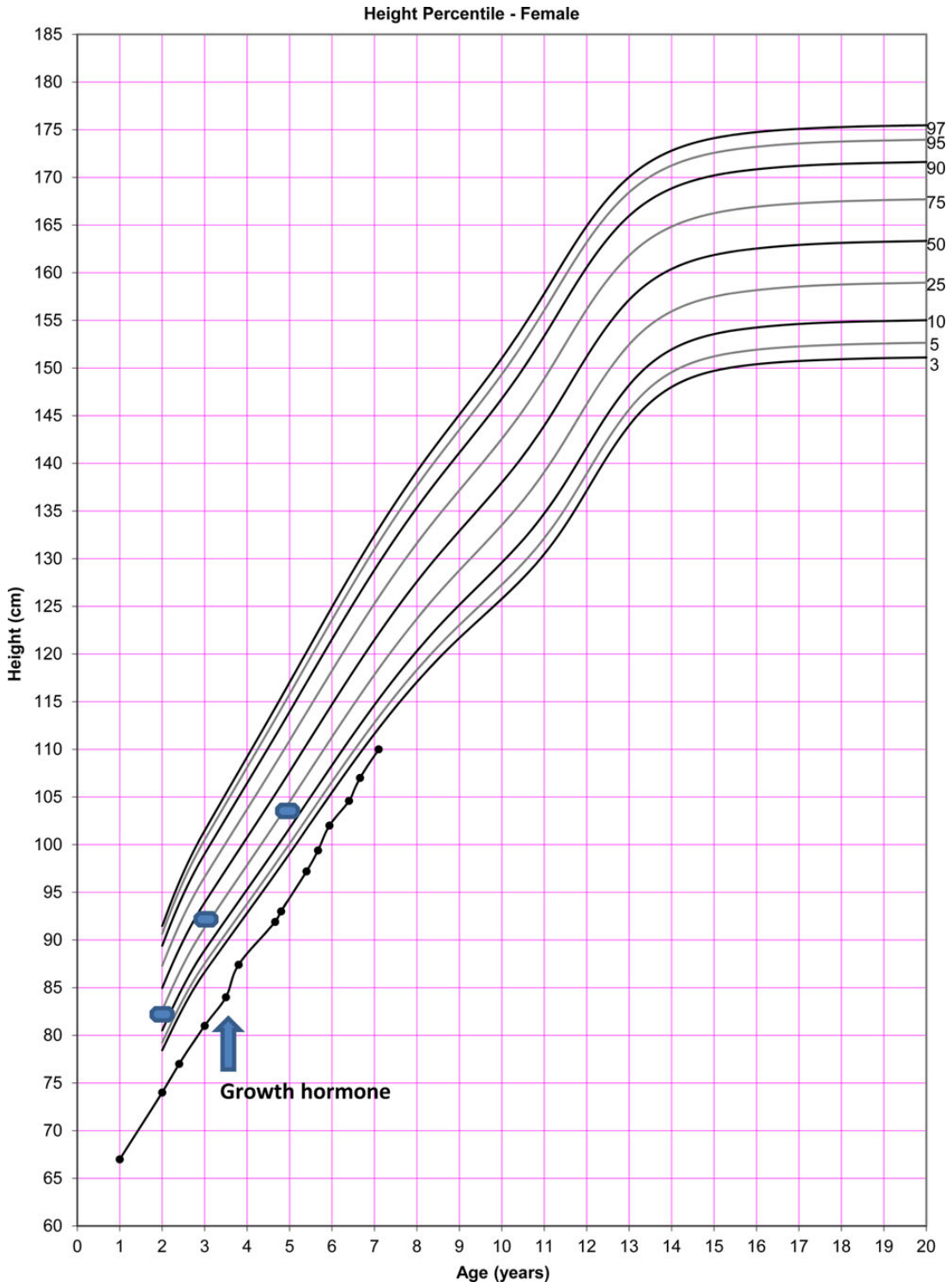

Figure 2: Height during GH therapy in Case 2, blue boxes represent bone age.

non-syndromic, GH-sufficient children, the median increase for height was +0.46 SDS (interquartile range 0.19, 0.76) in the first year of treatment [7]. The present two cases show that GH treatment of WHS in childhood can achieve a similar or potentially even greater acceleration of growth. Indeed, Case 1 showed continuing improvement in height into the normal range. Although there is one published case of WHS suggesting possible partial GH deficiency, with a borderline GH level (peak GH 7.8 ng/ml and normal for laboratory >10 ng/ml) with a low IGF-1 level (35 µg/l) [8], in both the present cases, GH responses were unequivocally normal.

These cases add to the very limited published experience, suggesting that GH therapy for WHS is associated with sustained acceleration of growth during childhood [9–11]. We were able to

identify only one previous case for which the response was described in detail. In that case that had normal GH testing and low normal level of IGF-1. She was treated with GH from 6 years of age for 4 years, her height increased from −5.3 SDS to −1.8 SDS. However, her predicted adult height only increased by 4 cm to 153.1 due to skeletal maturation [11]. This response is highly similar in case 1.

In conclusion, these cases suggest that, in selected children with WHS and severe short stature, GH therapy may have a substantial effect on long-term growth.

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CONFLICT OF INTEREST STATEMENT

None declared.

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