

ELECTRONIC LETTER

Is growth hormone treatment beneficial or harmful in Costello syndrome?

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Costello syndrome (CS) was first described by Costello in two unrelated children, in 1971 and 1977.¹ The major manifestations of CS have been summarised as postnatal growth deficiency, developmental delay, relative macrocephaly, coarse face, thick ears, thick lips, depressed nasal bridge with anteverted nares, excess skin, thick palms and soles, short neck, curly hair, nasal papillomata, and sociable personality.²

Recently, it has become apparent that children with CS have an increased risk of malignancy, particularly rhabdomyosarcoma. Rhabdomyosarcoma, predominantly embryonal, has been reported in 10 children, ganglioneuroblastoma in three, bladder carcinoma in two, epithelioma in one, and acoustic neuroma in one adult.³ A further three unpublished cases of rhabdomyosarcoma in children with CS are known to us through the International Costello syndrome support group and a fourth case is included in this report (case 2).

The frequency of tumours in CS has been estimated to be as high as 17%³ and a screening protocol has been proposed. These recommendations for surveillance include three to six monthly abdominal and pelvic ultrasound until the age of 8–10 years, urinary catecholamine analysis every six to 12 months until the age of 5, and annual urine analysis after the age of 10. Whether or not abdominal ultrasound would enable detection of early stage disease in rhabdomyosarcoma with a benefit for both survival and morbidity is unknown. For neuroblastoma, however, data from the general population suggested that screening had no impact on mortality or morbidity and the use of urine analysis in detection of bladder cancer has not been evaluated.⁴ Evaluation of the risks and benefits of the suggested screening regimen in this rare disorder will require in the first instance a network of collaborating geneticists and parents who are willing to allow screening without proven benefits.⁴

Cardiac complications are common in CS. Congenital heart disease, predominantly pulmonary stenosis, occurs in about a third of patients with CS.⁵ Arrhythmias, usually atrial

tachycardias, occur in a third and, of these, a third will have an otherwise normal heart.⁵ A further third of patients with CS have cardiomyopathy, predominantly left ventricular hypertrophy, reported in patients ranging from the first year of life until 27 years. Cardiomyopathy was the only cardiac abnormality in a notable number of the patients reported.⁵

These two important risks to health, the development of malignancy and cardiac hypertrophy, in children and adults with CS have led to concern about the use of growth hormone (GH) in CS.^{3, 5}

Postnatal growth retardation with preservation of head circumference, despite high normal birth weights and normal length at birth, is a consistent feature of CS. It seems unrelated to whether or not adequate nutrition can be maintained in the first years of life when oral feeding is often impossible. Reported adult heights range from 135 to 150 cm. The bone age is delayed in most. Menstruation may not occur and when it does, the onset has varied between the ages of 14 and 18.

There have been few published reports of the use of GH in CS^{6–9} and the evidence for effectiveness in the long term in CS is limited. Partial GH deficiency was reported in a Japanese patient⁶ but treatment with GH using an unspecified dose for several years was reported to have had only limited effect. A good growth response over several years has been reported in two children.^{7, 8}

Bladder carcinoma has occurred in a patient with CS treated with GH.⁹ In this girl, symptomatic hypoglycaemic episodes at the age of 6.5 years were treated with recombinant GH in association with replacement therapy for secondary hypothyroidism. Growth hormone did improve growth rate over the first four years of treatment, but this was not sustained, with her height after seven years of treatment at the age of 14 years 5 months (four months after menarche) being 5 SD below the mean, as it had been when treatment with GH started. She developed multiple papillary transitional bladder carcinomas at the age of 16.

We describe here two patients with CS treated with GH who developed a known complication of CS while on treatment.

CASE 1

The clinical details of the first patient reported on here have already been published (case 1).¹⁰ Nuchal thickening and abnormal hand posture were noted on prenatal ultrasound. She had a large head circumference at birth with a normal birth weight. She fed poorly from the beginning and her extreme feeding difficulty with failure to thrive persisted. Mild pulmonary stenosis was diagnosed in the early postnatal period, after she developed a supraventricular tachycardia. Costello syndrome was diagnosed at 3 months of age on the basis of the characteristic history, facial features, and striking

Key points

- Postnatal growth deficiency is one of the defining characteristics of Costello syndrome (CS).
- There are several reports of growth hormone (GH) treatment of children with CS, with variable outcome. They have an increased risk of both malignancy and hypertrophic cardiomyopathy.
- We describe here two children with CS treated with GH. Progression of cardiomyopathy while on GH treatment occurred in one, and in the other an embryonal rhabdomyosarcoma was diagnosed.
- The use of GH in CS requires further careful study, and should only be undertaken with thorough explanation of the possible risks and close monitoring.

Abbreviations: BMI, body mass index; CS, Costello syndrome; GS, growth hormone; IGF, insulin-like growth factor

excess of palmar skin. Embryonal rhabdomyosarcoma was diagnosed at the age of 2 years 6 months. By the age of 7, she had been successfully treated for recurrence of the rhabdomyosarcoma, which had occurred 22 months after the end of her initial treatment. She had had decompression of a Chiari type I malformation at the age of 4. Despite the use of a therapeutic jacket, she developed a progressive thoracolumbar scoliosis for which a growing rod was inserted.

She was markedly short: at the age of 2.2 years her height SD was -3.6 and her body mass index (BMI) SD was $+1$. Her growth rate over the next five years was extremely slow at 2.9 cm/year (height velocity SD -3.5). Over this time her scoliosis was also increasing. Provocation tests with GH were undertaken at the ages of 2.6 and 4.9 years, on both occasions assessing the GH response to arginine. Peak GH concentration was 39 mU/l at the age of 2.6 years, a value indicative of a normal pituitary reserve of GH, whereas at the age of 4.9 years peak GH concentration was 13 mU/l, consistent with moderate GH deficiency. Insulin-like growth factor-1 (IGF-1) concentration coincident with the normal peak GH at the age of 2.6 years was, however, low at 29.5 ng/ml, and remained low at 55 ng/ml when re-evaluated at the age of 4.6 years (normal range for IGF-1 at 5 years 125–375 ng/ml). All other pituitary function tests were normal. These results were considered to indicate dysfunction within the GH-IGF-1 axis, and in view of the marked short stature and poor growth performance and after detailed discussion of potential side effects, it was decided that she should begin a trial of GH treatment.

When treatment was started, she was aged 7.5 years with a height SD of -6.2 and BMI SD of $+1.2$. Treatment with GH began at a low dose of 20 $\mu\text{g}/\text{kg}/\text{day}$ (replacement dose in GH deficiency 25–35 $\mu\text{g}/\text{kg}/\text{day}$) for 6 weeks and this was increased to 25 $\mu\text{g}/\text{kg}/\text{day}$. Over 10 months on GH treatment, growth velocity was 6.1 cm/year, an increment of 3.2 cm/year over the pretreatment growth rate. Concentrations of IGF-1 remained low, indicating that a dose increase in GH could be tolerated from a metabolic perspective. Weight velocity on GH treatment has slightly decreased from 0.96 kg/year pretreatment to 0.75 kg/year on GH. The parents reported that the patient was more active and had better muscle tone since starting GH.

Regular monitoring with echocardiography has been carried out. At 6 and 9 months a mild left ventricular hypertrophy was documented with normal cardiac function. This had been present and unchanged over several years, and was concentric rather than localised.

On routine echocardiography after three months of GH treatment, progression of the cardiomyopathy was seen. This was confirmed by transoesophageal echocardiography. A sub-aortic tissue projection was found, with significant left ventricular outflow tract obstruction and a gradient of 60 mm Hg. Treatment with propranolol was started. The family did not want to stop treatment with GH. Over the next year, there was no further progression of the cardiomyopathy.

CASE 2

This patient was the child of a healthy 30 year old mother and 51 year old father. At birth, the weight and length were in the normal range. Macrocephaly and coarse facial features were noted. In the neonatal period, he developed supraventricular tachycardia. He subsequently had severe failure to thrive, and the diagnosis of CS was made on the basis of the characteristic history, facial features, hand configuration, and hand posture. Permission to publish photographs has been refused; these have been reviewed by two of us (BK, NP) and the diagnosis confirmed. At the age of 26 months, a large pelvic mass was discovered. Ultrasound imaging of the abdomen showed a retrovesicular mass. Histology was compatible with an embryonal rhabdomyosarcoma. Despite extensive chemotherapy, the tumour progressed rapidly and the patient died

two months later. He had been treated with GH from the age of 12 months at a dose of 0.7 U/kg/week, until the treatment was stopped on the diagnosis of the tumour. Before treatment, on investigation at 8 months of age, his sleeping GH concentration was 6.6 ng/ml, with glucagon stimulation concentrations of 3.5 and 6.8 ng/ml. After giving growth hormone releasing factor, the peak was 40 ng/ml. The IGF-1 concentration was very low at less than 3 ng/ml, but it rose after two months of GH treatment to 17 ng/ml.

DISCUSSION

Children with CS have an appreciable risk of malignancy and a separate and high risk of hypertrophic cardiomyopathy. The occurrence therefore of hypertrophic cardiomyopathy in one child with CS and embryonal rhabdomyosarcoma in another while on GH treatment may be coincidental to GH treatment.

Growth hormone is considered to be potentially mitogenic. Children treated with GH after treatment for the more common types of brain tumour do not seem to be at increased risk of tumour recurrence.¹¹ If CS is, however, a tumour predisposing syndrome, the experience in otherwise normal children may not be reassuring.

Growth hormone is known to stimulate myocardial hypertrophy.¹² Acromegaly results in cardiac hypertrophy that can progress to cardiac failure, the degree of hypertrophy correlating with duration of disease. The hypertrophy, which largely improves with treatment of acromegaly, is thought to be the result of the action of locally produced IGF-1.

Adverse cardiac events have been rare in the National Co-operative Growth Study, monitoring GH treatment in childhood.¹² This large sample has included a few children with pre-existing heart disease, including six with a cardiomyopathy. In a separate study, in 30 children with Noonan syndrome, use of GH was not associated with development of cardiomyopathy,¹³ although all patients had normal hearts before GH treatment.

The experience of GH treatment in the two patients described here suggests that the use of GH in CS should be very carefully monitored and studied. For a rare disorder such as CS, obtaining useful information about the use of GH will require the cooperation of families and their doctors in sharing growth data both with and without GH treatment.

Before treatment with GH is started, the unproven benefits of treatment in the long term should be explained. The possible effects of GH in both increasing malignancy risk and causing progression of cardiomyopathy should be understood. If treatment with GH is undertaken, monitoring should include echocardiography before and during treatment and an abdominal ultrasound as a minimal screen for malignancy should be obtained before treatment is started.

Ultimately, determining whether or not GH treatment is beneficial or harmful in CS may depend on finding the cause of this multifaceted disorder and understanding the biological basis of the risk of malignancy.

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