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Good growth response to growth hormone treatment in the ring chromosome 15 syndrome

M Nuutinen, K Kouvalainen, M Knip

Abstract

Ring chromosome 15 syndrome is a rare condition in which severe growth retardation is a major finding. We report a 4 year old boy with the karyotype 46,XY, r(15)(p11.2q26.2) whom we have treated with recombinant human growth hormone (GH) for two years. During the first year of treatment, the insulin-like growth factor I increased from subnormal 4·2 nmol/l to normal 13·8 nmol/l and the insulin-like growth factor binding protein 3 levels increased from 2·6 to 3·8 mg/l, whereas high binding protein 1 concentrations normalised from 52·0 to 16·7 µg/l. During the two years of treatment his relative height improved from −6·2 SD to −4·4 SD and the predicted adult height from 159·6 cm to 163·5 cm. Owing to the good growth response, we have decided to continue GH treatment.

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Ring chromosome 15 is a rare condition resulting from breakage and closure of chromosomal material leading to a ring formation and loss of genetic material.[1 2] According to Butler *et al*[2] 27 cases had been published by 1988. Since then six new cases have been described.[3–7] Severe growth retardation is a major and constant finding in this syndrome,[2] but no reports on GH treatment have been published. We report here a 4 year old boy whom we have treated with recombinant human GH for two years in order to test whether he would benefit from GH therapy. A remarkable acceleration in growth velocity, as well as a substantial increase in relative height and predicted adult height was observed. During the first year of treatment, we repeatedly measured the circulating concentrations of IGF-I, IGFBP-1 and IGFBP-3.[8 9]

Case report

The proband's karyotype was 46,XY, r(15)(p11.2q26.2). At birth the boy was small for gestational age (40 weeks, 2310 g, 43·0 cm), and his relative height was −4·0 SD. A chromosome analysis was therefore performed, and the diagnosis was made in the neonatal period. Failure to grow was the main symptom from birth, and at the age of 7 months his relative height was −6·2 SD and relative weight approximately 78%. He also presented several other (9/13) features typical of the ring chromosome 15 syndrome (table 1).

Peak GH response to clonidine stimulation was good (35·6 µg/l) at the age of 2 years 3 months, but low (5·3 µg/l) in response to insulin induced hypoglycaemia (lowest blood glucose 1·5 mmol/l). Other possible causes for growth retardation (coeliac disease, hypothyroidism) were excluded.

At the age of 2 years 3 months, his GP bone age was 1 year (−3·2 SD), height 70·2 cm (−6·2 SD), weight 6·3 kg (77%), sitting height 41·7 cm (59·4%), and treatment with recombinant human GH (Saizen, Serono) at a daily dose of 1 unit sc was started. His relative height and predicted adult height improved continuously on GH therapy. During the two years of treatment his growth velocity increased from 5·9 cm/year to 8·5 cm/year, that is, by 44% and his relative height improved by 1·8 SD, that is to −4·4 SD (table 2). His predicted adult height assessed according to the Roche-Wainer-Thissen method (RWT)[10] increased during the same time from 159·6 cm to 163·5 cm (table 2). His relative sitting height remained normal. During the two year treatment his GP bone age advanced by one year (table 2).

In response to GH treatment the IGF-I doubled in one month from a starting level of 4·2 nmol/l to 8·3 nmol/l (table 2). The increase continued, subsequently reaching a level of 13·8 nmol/l after treatment for one year. The IGFBP-3 concentration was within the normal range before treatment, but increased by 66% over the first month of therapy. Thereafter the levels remained higher than the initial one. The pretreatment IGFBP-1 level was raised but normalised during treatment.

Discussion

Our case had nine of the 13 main features (table 1) of the ring chromosome 15 syndrome.[2] He was diagnosed very early, since a sample

Table 1 Main clinical features and their frequency in the ring chromosome 15 syndrome according to Butler et al[2] and their manifestations in our case

Clinical feature	*Frequency (%)*	*Our case*
Growth retardation	100	+
Mental retardation (variable)	95	Slight?
Microcephaly	88	+
Hypertelorism	46	−
Triangular face	42	+
Delayed bone age	75	+
Brachydactyly	44	+
Speech delay	39	+
Frontal bossing	36	+
Anomalous ears	30	−
Café au lait spots	30	+
Cryptorchidism	30	−
Cardiac anomalies	30	−

Department of Paediatrics, University of Oulu, Kajaanintie 52, FIN-90220 Oulu, Finland
M Nuutinen
K Kouvalainen
M Knip

Correspondence to:
Dr Nuutinen.

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Table 2 Growth parameters, IGF-I, IGFBP-1, and IGFBP-3 concentrations during GH treatment started at the age of 2 years. Age related reference values for IGF-1, IGFBP-1, and IGFBP-3 from our own laboratory (range, n = 10) are given in parentheses under each parameter

Age (y)	Height cm	Height SD	Growth velocity (cm/y)	Weight g	Weight %	GP bone age y	GP bone age SD	Predicted adult height (cm)	IGF-1 (4·4–15·0) (nmol/l)	IGFBP-1 (3·8–19·0) (μg/l)	IGFBP-3 (1·5–4·3) (mg/l)
2·24	70·2	−6·2	5·9	6300	77	1·0	−3·2	159·6	4·2	52·6	2·6
2·32	71·2	−6·0	12·5	6570	77	—	—	—	8·3	4·1	4·3
2·47	72·7	−5·8	10·9	6695	76	—	—	—	10·3	5·5	3·5
2·70	75·2	−5·5	10·9	6940	72	1·25	−3·1	161·9	10·0	12·0	3·6
3·24	80·0	−5·0	9·8	7850	74	1·5	−3·2	162·6	13·8	16·7	3·8
4·19	86·8	−4·4	8·5	9100	73	2·0	−3·5	163·5	—	—	—

Predicted adult height was assessed according to Roche-Wainer-Thissen method.[10]

for chromosome analysis was taken at the age of a few days because of intrauterine growth retardation. The average age at diagnosis has been reported to be 8·1 years.[2]

In our case, peak GH response to clonidine stimulation was normal but was low in response to insulin induced hypoglycaemia. Only in the case described by Kitatani *et al*[5] have GH responses been reported. They observed a normal GH response to the combined arginine-insulin test on three occasions in their case.

It has been suggested that the decreased viability of fibroblasts obtained from these patients could be an in vitro reflection of growth failure.[3] Recently, it was suggested that distal deletion of the long arm of chromosome 15 is associated with loss of an IGF-I receptor gene copy which may lead to an abnormal number or structure of the receptors resulting in severe intrauterine growth retardation and postnatal growth failure.[6] Tamura *et al*[11] reported similar results in a patient with features of Russell-Silver syndrome and assigned the IGF-I receptor gene to 15q26.3. However, intensive molecular genetic analysis of 15q→qter markers has shown that the cause of growth retardation in ring 15 syndrome or Russell-Silver syndrome is not always the loss of genetic material on the distal long arm of chromosome 15.[12 13] Our results, showing a low IFG-I level before GH treatment, do not support a loss of the IGF-I receptor gene in the present case, since IGF-I receptor defects are associated with normal or increased IGF-I concentrations.

As far as we know, there have been no previous reports published on the results of GH therapy in the ring chromosome 15 syndrome. Our results suggest that GH therapy improves growth and predicted final height considerably in this syndrome, and we have therefore decided to continue treatment. This seems to be justified, since growth retardation is severe in most cases and may complicate everyday activities of these patients as adults.[17] However, the decision on possible GH treatment should be made taking into account the complete spectrum of symptoms, for example, the degree of mental retardation, characteristic of this syndrome.

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