

Growth and somatomedin responses to growth hormone in Down's syndrome

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SUMMARY Five growth retarded children with Down's syndrome, three girls and two boys aged between 3½ and 6½ years with trisomy 21, were treated with human growth hormone for six months. Before treatment the growth hormone response to sleep and insulin-arginine load, as well as serum concentrations of insulin, thyroid hormones, and cortisol was found to be in the normal range. During the treatment with human growth hormone the growth velocity increased in all the children with Down's syndrome from 2.3–2.8 cm to 3.3–5.8 cm per six months. The serum concentrations of immunoreactive insulin like growth factor 1 (IGF-1) were low before treatment and increased during the treatment with human growth hormone. The serum concentrations of immunoreactive insulin like growth factor 2 (IGF-2), which were within the normal range, however, increased during treatment with human growth hormone. Children with Down's syndrome respond to treatment with human growth hormone, with an increase in both growth velocity and serum somatomedin concentrations.

Growth retardation and development of presenile dementia are characteristic features of Down's syndrome. Even if the basic defect, trisomy for chromosome 21, is well defined, little is known about the mechanisms causing growth retardation, mental retardation, and the other abnormalities.

Somatomedins have been proposed as regulating growth, including brain growth,¹ and being altered in mental retardation due to disturbances in brain development.² Several studies have examined the role of somatomedins in Down's syndrome.^{3–5} Patients with Down's syndrome show a deficiency in serum insulin like growth factor 1 (IGF-1). This growth hormone dependent somatomedin fails to rise during childhood and remains at a low concentration throughout life.³ The serum concentration of insulin like growth factor 2 (IGF-2) in patients with Down's syndrome is, however, within the normal range,⁵ and the receptors for somatomedins and insulin in fetuses with Down's syndrome have been found to be normal.⁴ Determination of serum somatomedins by a radioreceptorassay proposed to detect a fetal form of somatomedin showed scarcely detectable concentrations in fetuses with Down's syndrome,⁶ but raised concentrations throughout postnatal life.³ A delayed maturation and incomplete switching from production of a fetal form of

somatomedin to the IGF-1 regulated by growth hormone was suggested in patients with Down's syndrome.

Growth becomes dependent on growth hormone during the first year of life. At this time growth hormone begins to regulate the production of somatomedin.⁷ The concentration of growth hormone has been reported to be in the normal range in patients with Down's syndrome.⁸ Some trials with treatment with growth hormone in patients with Down's syndrome have been performed. However, these studies used animal growth hormone and even a peroral route for administration, and thus the results are inconclusive.⁹ The current belief therefore is that children with Down's syndrome do not respond to human growth hormone.

The aim of this investigation was to study if somatomedin concentrations, especially IGF-1, and growth velocity in children with Down's syndrome substantially increased on treatment with standard dosages of parenterally given human growth hormone.

Methods

Subjects (Table 1). Five children, three girls and two boys of ages 3½ and 6½ years with trisomy 21, but

without clinically important congenital malformation, were chosen. None were malnourished or had any deviation in dietary habit or food preferences. They were all cared for by their biological parents. None of them had had any severe infectious disease or had been taking any drug during the last year before or during the treatment with human growth hormone. All had profound growth retardation with a height >3 SD below the mean according to the Swedish standard,¹⁰ but they did not deviate further from the -3 SD channel of the growth chart the last year before treatment. The parents were all of normal height, except for the mother of case 4, who was 1.50 m.

Laboratory investigations before treatment with human growth hormone. Glucose clearance after intravenous glucose load (0.3 g/kg birthweight) was within the normal range in all cases (half life 28–54 minutes). Thyroid hormone assays (thyroid stimulating hormone, triiodothyronine, and thyroxine) were all within normal reference limits. Plasma cortisol concentration was measured after insulin stimulation and was found to be within normal limits in all cases (660–1100 nmol/l (23.9–39.8 μ g/100 ml)).

Concentrations of immunoreactive growth hormone were determined by a radioimmunosorbent

technique¹¹ using human pituitary growth hormone (Kabi AB, Stockholm) for labelling and rabbit antihuman pituitary growth hormone. The results were expressed in μ g/l using the World Health Organisation International Reference Preparation of Growth Hormone, 66/217, as a reference.¹¹ The secretion of growth hormone was evaluated during sleep and after an arginine-insulin load. Four of the children showed a peak value of at least 16 μ g/l in one of the tests; case 4 had a maximal peak value of 8.8 μ g/l (Table 2).

Somatomedin assays. The concentrations of somatomedins were determined by two radioimmunoassays. The radioimmunoassay for IGF-1, which allows determination in whole serum, has been described previously.¹² This assay measures predominantly IGF-1, and IGF-2 crossreacts only 1%. The arbitrary local reference serum used as standard contained 180 ng of IGF-1/ml.

The radioimmunoassay for IGF-2, with sepharose coupled antibodies and pure IGF-2 as ligand was used.¹³ The crossreaction of IGF-1 varied between 8 and 10%. The immunoreactive IGF-2 values are given for acid ethanol extracted serum. The results are expressed in ng equivalents of IGF-2 and corrected for the crossreaction of IGF-1. The

Table 1 Clinical characteristics of five children with Down's syndrome with growth retardation, before and after six months' treatment with 0.5 U/kg/week of human growth hormone

Case no	Before or after treatment	Sex	Age (yrs, months)	Skeletal age (Greulich-Pyle) (yrs)	Weight (kg)	Height (m)	Height (Swedish standard) (SD)	Growth over six months (10^{-2} m)	Mental development (Griffiths' scale) (quotients)
1	Before	F	6.6	4.5	14.7	0.952	-5.0	2.8	34
	After		7.1	5.0	15.3	1.001	-4.0	5.1	34
2	Before	M	5.0	3.5	13.5	0.930	-4.0	2.5	60
	After		5.5	4.0	14.5	0.972	-3.5	4.3	60
3	Before	F	5.6	3.0	18.0	0.978	-4.0	2.8	40
	After		6.1	3.5	18.0	1.010	-3.5	4.2	40
4	Before	M	4.1	3.5	15.4	0.873	-4.0	2.3	52
	After		4.6	4.5	15.4	0.909	-4.0	3.6	55
5	Before	F	3.4	2.0	13.4	0.870	-3.0	2.3	59
	After		3.9	2.5	15.2	0.928	-1.5	5.8	60

Table 2 Concentrations of plasma growth hormone (μ g/l) during sleep and the insulin-arginine loading test in five patients with Down's syndrome, before treatment with growth hormone

Case no	Sleep test Time (mins)					Insulin-arginine loading test Time (mins)						
	0	30	60	90	120	0	30	60	90	120	150	180
1	55.0	25.0	12.4	4.8	9.3	2.3	3.2	16.7	6.4	13.8	16.5	13.0
2	16.7	6.4	3.3	1.7	2.7	4.2	1.5	1.9	3.3	9.7	13.7	13.2
3	5.2	2.2	3.5	1.5		2.1	7.1	1.4	9.5	12.3	11.4	19.9
4		6.2	8.8	8.6	5.4		1.9	4.4	5.4	3.4		
5		9.6	4.7	2.7	6.0	11.8	5.7	11.8	18.4	7.9	16.5	20.0

arbitrary local reference serum used as standard was shown to contain 980 ng of IGF-2/ml after correction for its content of IGF-1.

Growth hormone loading test. A daily dose of 0.08 U/kg body weight of human growth hormone (Crescormon, KabiVitrum) was administered subcutaneously at 1900 during 10 days in hospital, according to Rudman *et al.*¹⁴ Serum immunoreactive IGF-1 and IGF-2 concentrations were determined by radioimmunoassay on 0, 5, and 10 days of the human growth hormone loading test. All serum samples were immediately frozen at -20°C until assayed.

Growth hormone treatment. After the human growth hormone loading test the children with Down's syndrome were treated at home with 0.5 U/kg week of human growth hormone (Crescormon, KabiVitrum), divided into three doses given at bedtime. Height and weight measurements were performed monthly by the same physician, and the average of three readings was recorded at each visit. Height was measured on a Stadiometer mounted on a wall. Blood samples for somatomedin assays were drawn once monthly between 0930 and 1100. Before and after the six months of treatment with human growth hormone, examinations of the mental development according to Griffiths' mental development scale¹⁵ and of the skeletal maturation according to the method of Greulich and Pyle¹⁶ were performed.

Results were expressed as mean \pm 1 standard deviation (SD). Because of the small number of patients no significance test was performed.

Results

Growth and development. All the patients increased their growth velocity during treatment with human growth hormone (Table 1). The increase of the growth velocity ranged from roughly 50% to 200%. The growth velocity during treatment ranged between 3.3 and 5.8 cm each six months (mean (SD) 4.5 (1.0) cm) compared with 2.3–2.8 cm (2.5 (0.3) cm) before treatment and 1.5–4.0 cm (2.6 (1.0) cm) after treatment (Fig. 1). The skeletal maturation of the children with Down's syndrome was retarded by about one and a half years, according to the method of Greulich and Pyle,¹⁶ both before and after treatment with human growth hormone (Table 1). Quotients according to Griffiths' mental development scale¹⁵ before and after treatment with human growth hormone did not show any differences.

Serum somatomedins. In all the patients the serum

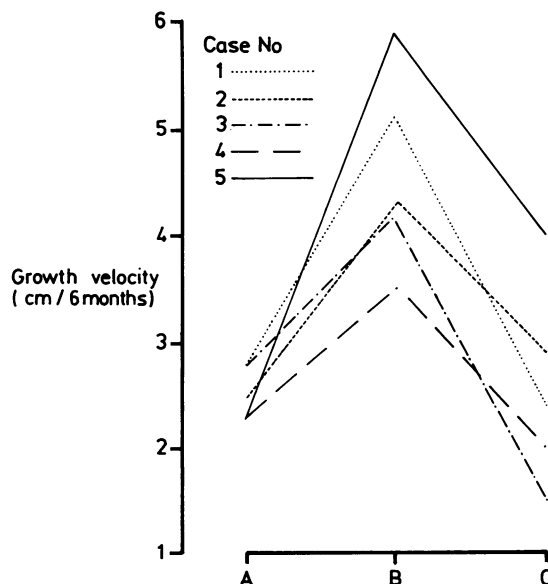


Fig. 1 Growth (cm) during six month periods in five children with Down's syndrome (A) before; (B) during; and (C) after six months' treatment with 0.5 U/kg/week human growth hormone.

concentration of immunoreactive IGF-1 increased during the ten days of loading with human growth hormone (Fig. 2). The increase from concentration before treatment ranged from 46% to 234%. Concentrations before treatment (62.3 (17.5) ng/ml) were low and ranged between -2 and -1 SD below the normal concentration in children of this age (2–4 years: 121 (38) ng/ml; 4–6 years: 126 (64) ng/ml).¹⁷ The mean immunoreactive IGF-1 concentration increased to normal (125.6 (48.3) ng/ml) after 10 days of treatment and ranged from -1 to $+1.5$ SD of the control value. During the six months of treatment with human growth hormone the concentrations remained above that before treatment in all patients (Fig. 3). The increases in serum immunoreactive IGF-1 concentrations six months after the start of treatment with human growth hormone ranged from 37% to 224% of the concentrations before treatment. The maximal concentration during treatment of one patient (case 5) was even greater than $+3$ SD above mean for age.

In all patients the serum concentrations of immunoreactive IGF-2 increased during the loading test (Fig. 2). The increases from values before treatment ranged from 30% to 108%. Concentrations before treatment lay between -2 SD and -1 SD below the mean in normal adults (606 (158) ng/ml¹³) and after 10 days of treatment between -1

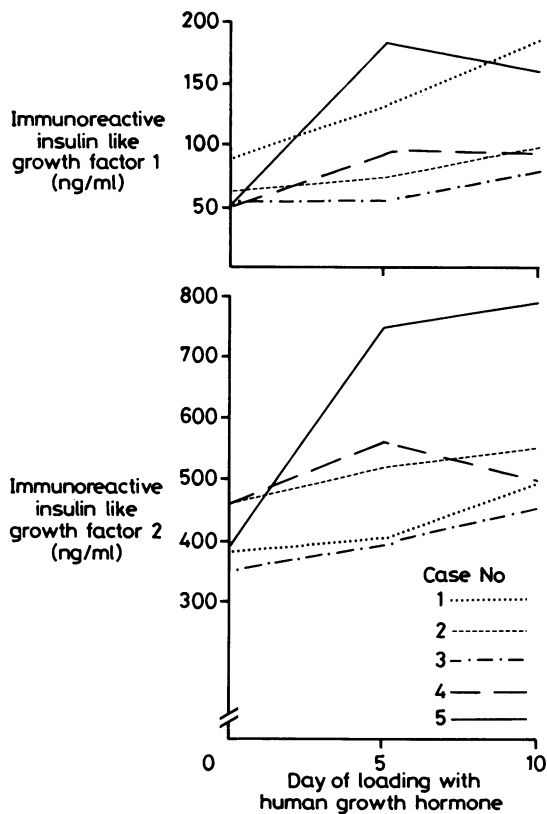


Fig. 2 Serum somatomedins (ng/ml) determined by radioimmunoassays for IGF-1 (upper panel) and IGF-2 (lower panel) during 10 days of human growth hormone loading (0.08 U/kg/day) in five children with Down's syndrome. Serum immunoreactive IGF-1 and IGF-2 concentrations were determined on 0, 5, and 10 days of the human growth hormone loading test.

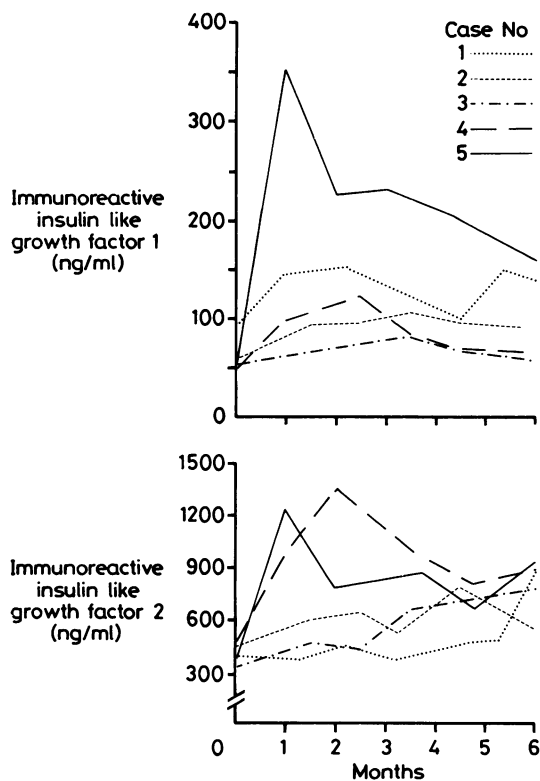


Fig. 3 Serum somatomedins (ng/ml) determined by radioimmunoassays of IGF-1 (upper panel) and IGF-2 (lower panel) during six months' treatment with 0.5 U/kg/week human growth hormone in five children with Down's syndrome. Serum immunoreactive IGF-1 and IGF-2 concentrations were determined monthly from months 0-6 of treatment.

and +1.5 SD. The immunoreactive IGF-2 concentrations remained raised during treatment (Fig. 3), and in two patients (cases 4 and 5) the maximum concentrations during treatment were increased to more than +3 SD from normal. The increases in serum immunoreactive IGF-2 concentrations at the end of the six months' treatment with human growth hormone ranged between 15% and 176% of the concentrations before treatment.

There were great individual variations both in the time of occurrence of the peaks and in the magnitude of immunoreactive IGF-1 and IGF-2 responses to treatment with human growth hormone (Fig. 3). Comparison of individual responses (Figs. 1 and 3) showed a relation between maximal responses of immunoreactive IGF-1 and increase in growth velocity.

Discussion

Earlier studies have shown that, similar to pygmies,¹⁸ children with Down's syndrome have a selective deficiency of serum IGF-1 concentrations.^{3, 5} From the present results it is clear that children with Down's syndrome respond to treatment with human growth hormone. The growth velocity increased considerably during the six months of treatment in all the patients. This is remarkable, as the growth velocity before treatment was within the normal range for healthy children at this age and height. Skeletal retardation was observed in the present patients. There was no difference between the skeletal retardation before and after treatment, crudely indicating that no acceleration of the maturation accompanied the growth spurt. The

concentrations of the IGF-1 like peptide determined by radioimmunoassay were low before treatment in all the patients and increased after 10 days of loading with human growth hormone to normal for this age group. Although the IGF-2 values were within the normal range, immunoreactive IGF-2 concentrations also increased promptly on treatment. The individual increases in these children with Down's syndrome suggested a relation between growth velocity and the growth hormone dependent somatomedin IGF-1.

Although the present findings suggest deficiency of growth hormone, children with Down's syndrome seem to have reasonable endogenous growth hormone concentrations, as evaluated from two accepted clinical standard test procedures in the present patients, as well as from earlier reports.⁸ Hayek and Peake¹⁹ classified children with short stature into three groups. Group 1 comprised the children deficient in growth hormone and groups 2 and 3 both comprised children with normal serum growth hormone concentrations and low somatomedin C (IGF-1) concentrations. The children of group 2 responded with increased velocity of growth and increased concentrations of somatomedin treatment with human growth hormone, while the children of group 3—that is, the Laron dwarfs—with a growth hormone receptor failure²⁰ did not respond at all. Patients with Down's syndrome, thus, could be classified in group 2. Before a partial growth hormone insufficiency can be eliminated in patients with Down's syndrome, however, further studies will be required to determine their pattern of secretion of growth hormone over 24 hours to evaluate a possible 'relative' growth hormone deficiency.

This study shows that children with Down's syndrome increase their growth velocity during six months' treatment with human growth hormone, but does by no means prove that short term (or long term) treatment with human growth hormone increases final height in these children. Even if the delay in skeletal maturation during the six months was unchanged, it has to be considered that skeletal maturation as measured by most routine methods is very crude, while in the long run increased growth and maturation could well be parallel. After treatment growth velocity essentially returned to values before treatment.

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