Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

Growth hormone therapy in pre-pubertal children with Noonan syndrome: first year growth response and comparison with Turner syndrome

J. De Schepper[1], B.J. Otten[5], I. François[2], J.-P. Bourguignon[3], M. Craen[4], I. Van der Burgt[6], G.G. Massa[7]

Departments of Paediatrics, University Hospital of Brussels[1], Leuven[2], Liège[3], and Ghent[4], Belgium, the Departments of Paediatrics[5] and Human Genetics[6], University Hospital of Nijmegen, Nijmegen, and the Bureau of the Dutch Growth Foundation[7], University Hospital of Leiden, The Netherlands.
J. De Schepper, Department of Paediatrics, University Hospital Brussels, Laarbeeklaan 101, B-1090 Brussels, Belgium.

KEYWORDS: Growth hormone therapy, height velocity, Noonan syndrome, Turner syndrome.

ABSTRACT

We studied the growth-promoting effect of treatment with recombinant human growth hormone in 23 pre-pubertal children with Noonan syndrome, aged between 5.4 and 14.3 y, and all with a height < 1.4 SD for Tanner standards. The growth response and skeletal maturation after 1 y of recombinant human growth hormone treatment (0.15 U/kg/day given by daily injection) in the Noonan syndrome patients was compared with the auxological changes observed in a group of 17 girls with Turner syndrome with a comparable age and height deficit who were treated with recombinant human growth hormone in a similar way. During 1 y of treatment, the mean ± SD height velocity increased by 4.0 ± 1.6 cm/y in the Noonan syndrome group and by 3.6 ± 1.3 cm/y in the Turner syndrome group. Height SDS for chronological age in the Noonan syndrome group increased by 0.53 ± 0.46 ($p < 0.001$). In the Noonan syndrome patients the changes in height velocity were positively related to birthweight ($r = 0.48$, $p < 0.05$). The changes in height velocity or height SDS were not related to the age, height deficit or a delay in bone age maturation at start of treatment. In neither the patients with Noonan syndrome nor Turner syndrome was an acceleration of bone maturation found. We conclude that treatment with recombinant human growth hormone in pre-pubertal NS patients induces an increase in height velocity and height SDS comparable to that observed in Turner syndrome girls.

Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

Growth retardation involving both height and weight is a relatively consistent aspect of Noonan syndrome (NS) (1, 2). Adult height averages 162.5 ± 5.4cm in males and 152.7 ± 5.7 in females (2). Phenotypically, NS is strikingly similar to Turner syndrome (TS) and is therefore sometimes called the male TS. In girls with TS, treatment with supraphysiological doses of recombinant human growth hormone (rhGH) results in a clear-cut increase of height velocity and an amelioration of final height (3, 4). The similarity between NS and TS has led to the expectation that rhGH therapy in children with NS might also have a beneficial effect on growth rate and final height.

Most reports on the effect of treatment with rhGH studied small groups of NS patients (5–8) only. Recently, growth hormone treatment data from the national Cooperative Growth Study in the US (150 patients with NS), and from the KIGS database in Europe (55 patients with NS) were published, reporting a significant sustained improvement of growth (9, 10). In the present study, we report first year auxological results of treatment with rhGH in a group of 23 NS children, and compare the data of the NS children with those observed in a group of rhGH-treated TS girls of comparable age and height deficit.

Patients and methods

Twenty-three children with NS (5F, 18M) followed in four university medical centres were included. Diagnosis of NS was made on the presence of typical phenotypic features. Typical facial changes were present in 22 patients, a congenital heart defect (most often pulmonary valve stenosis) in 15, and thorax deformity in 9 patients. Cryptorchidism was noted in 13 of the 18 males. Seven patients had one parent with NS. All patients had a score of ≥ 60 on the score of Duncan et al. (11) and had a normal karyotype. Inclusion criteria were a chronological age of at least 4 y, a height deficit of ≥ 2 SDS for local standards, and a prepubertal status. The study protocol was approved by the local ethics committees, and informed consent was obtained from the parents.

All patients were treated with daily subcutaneous injections of rhGH (Genotropin, Pharmacia & Upjohn, Sweden) at a dose of 0.15 IU/kg per day. The rhGH was given in the evening by means of a commercial pen system (KabiPen, Pharmacia & Upjohn). The calculated doses were rounded to the nearest 0.5 IU and adjusted to body weight every 3 months. No sex steroids were administered during the study period.

Patients were followed-up at 3-monthly intervals. Height was measured with a Harpenden stadiometer. Height SDS was calculated using the reference standards of Tanner et al. (11). Height velocity was calculated over whole year periods and expressed as cm/y. Weight was expressed as body mass index (BMI, weight/length^2). Puberty was assessed according to Tanner (13). At the start and after 1 y, bone age was determined using an X-ray of the left hand and wrist by an experienced observer (JDS) using the method of Greulich and Pyle (14). Biochemical analyses, including total blood count and glucose, haemoglobin-A_{1C}, immunoreactive insulin, free thyroxine and thyroid stimulating hormone, were performed at 3-monthly intervals.

Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

The auxological data of the NS patients were compared with those of a group of 17 girls with TS, who were followed at the same centres and treated in a similar way with daily rhGH (Norditropin, Novo Nordisk, Denmark) injections (15). None of the TS patients showed breast development, or was treated with sex steroids during the study period. Similar surveillance examinations as in NS patients under GH therapy were performed in these TS patients. The TS patients were selected by dose of GH administered and on age range (4–14.7 y) at the start of treatment to be comparable with the NS group studied.

Results are expressed as mean ± SD. Inter-group comparisons were made with the unpaired Student's *t*-test and intra-group comparisons were done with the paired Student's *t*-test. The correlation between various parameters was studied by linear regression analysis. The level of significance was set at $p < 0.05$.

Results

Baseline data are given in **Table 1**. Birthweight and mid-parental height of patients with NS and TS were comparable. At start of treatment, no differences were found between the patient groups for CA, BA, BA delay, height SDS, and height velocity. The BMI, however, was lower in NS patients than in TS patients (15.1 ± 1.0 kg/m^2 vs 17.6 ± 3.1 kg/m^2; $p < 0.01$). There were no differences between NS patients with or without a cardiac anomaly (data not shown).

Table 1. Baseline data (mean ± SD) and auxological data at the start of treatment with rhGH of patients with Noonan syndrome (NS) in comparison to patients with Turner syndrome (TS).

	NS Group (n = 23)	TS Group (n= 17)
Birthweight (g)	2900 ± 694	2837 ± 607
Midparental height (cm)	166.9 ± 7.4	167.1 ± 6.4
Chronological age (y)	9.4 ± 3.0	9.2 ± 3.7
Bone age (y)	7.2 ± 3.4	7.3 ± 3.7
Bone age delay (y)	2.2 ± 1.0	1.9 ± 1.2
Height (cm)	118.5 ± 14.5	115.5 ± 18.0
Height SDS for CA	−2.28 ± 0.68	−2.70 ±0.81
Height SDS for BA	0.04 ± 1.50	−0.58 ± 1.50
Weight (kg)	21.5 ± 5.8	25.0 ± 12.0
Body Mass Index (kg/m^2)	15.1 ± 1.0*	17.6 ± 3.2
Height velocity (cm/y)	4.5 ± 1.0	4.4 ± 1.4

*$p < 0.01$

During the first year of rhGH treatment, height velocity of the NS patients increased from 4.5 ± 1.0 cm/y to 8.5 ± 1.6 cm/y (**Table 2**). The increase in height velocity was comparable with the acceleration observed in TS girls (4.0 ± 1.6 cm/y vs 3.6 ± 1.3 cm/y, respectively). While the height velocity before and during treatment was negatively correlated with age at the start of treatment (*r*

Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

= −0.60, $p < 0.005$ and $r = -0.53$, $p < 0.01$, respectively), the change in height velocity during treatment was not significantly related to age ($r = -0.14$). The increment in height velocity was significantly related to birthweight ($r = 0.48$, $p < 0.05$; **Fig. 1**), but not to any other baseline variables.

Table 2. Auxological data (mean + SD) after 1 y of treatment with rhGH of patients with Noonan syndrome (NS) in comparison to patients with Turner syndrome (TS).

	NS Group ($n = 23$)	TS Group ($n = 17$)
Chronological age (y)	10.3 ± 3.0	10.1 ± 3.7
Bone age (y)	8.3 ± 3.4	8.8 ± 3.3
Bone age delay (y)	2.0 ± 1.0	1.5 ± 1.2
Height (cm)	127.1 ± 13.9	123.6 ± 16.5
Height SDS for CA	−1.78 ± 0.76	−2.11 ± 0.90
Height SDS for BA	0.34 ± 1.50	−0.80 ± 1.26
Weight (kg)	24.8 ± 6.5	−28.4 ± 12.5
Body Mass Index (kg/m^2)	15.1 ± 1.1*	17.7 ± 3.3
Height velocity (cm/y)	8.5 ± 1.5	8.1 ± 1.7

*$p < 0.01$

Fig. 1. Changes in height velocity during the first year of rhGH treatment in patients with Noonan syndrome as a function of birthweight.

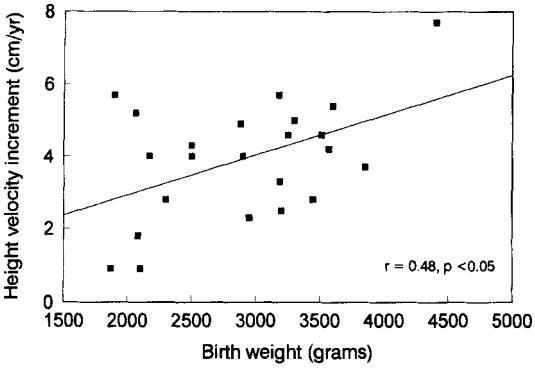
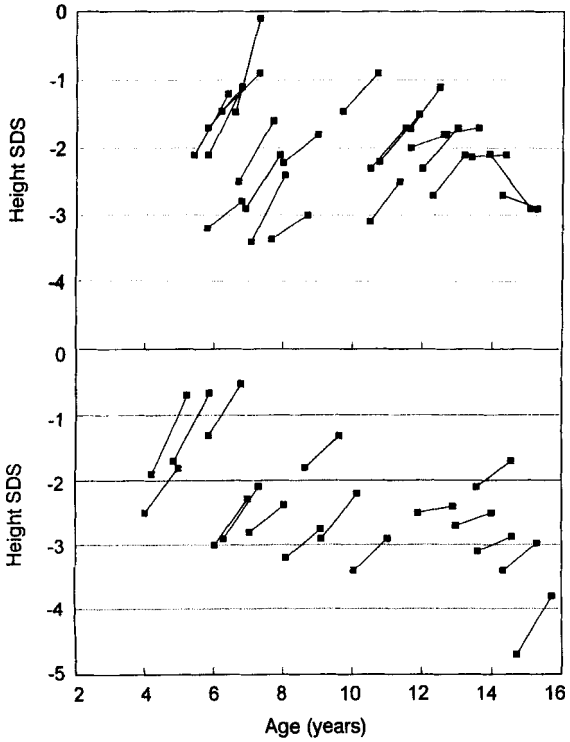


Figure 2 illustrates the changes in height SDS for CA during 1 y of rhGH treatment in patients with NS (upper panel) and TS (lower panel). Mean increase of height SDS for CA was 0.53 ± 0.46 ($p < 0.001$) in the NS patients and 0.59 ± 0.30 ($p < 0.001$) in the TS patients. At treatment start, height SDS for CA was > −2 SD for Tanner standards in 7 NS patients, whereas after 1 y of rhGH treatment 14 had height > −2SD. The patients with NS showed an increase in height SDS for BA of 0.30 ± 0.63 ($p < 0.05$) while height SDS for BA did not change in the TS patients (−0.13 ± 1.13). The changes in height SDS for BA and CA in NS patients were not statistically different from those observed in TS girls. In the NS patient the delta height SDS for BA was inversely related to the initial BA delay ($r = -0.49$, $p < 0.02$). The changes in height SDS for CA or BA were not related to any other baseline variables.

Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

During rhGH therapy, BA in the NS group advanced from 7.2 ± 3.4 y to 8.3 ± 3.4 y and the BA delay did not change. The increase of 1.1 ± 0.4 y in the NS group was comparable to the change in skeletal maturation observed in TS girls (1.4 ± 0.9 y). The changes in skeletal maturation in the NS group were not related to age or any other baseline parameter.

Fig. 2. Changes in height SDS for chronological age during 1 y of rhGH treatment in patients with NS (upper panel) and in girls with TS (lower panel).



During rhGH treatment the NS and TS patients showed a weight gain of 3.4 ± 1.0 kg and 3.4 ± 1.7 kg, respectively. BMI, however, did not change. No differences were observed between NS patients with and without a cardiac anomaly. All patients remained pre-pubertal during the study period.

No side effects were noted during rhGH therapy. No significant changes in chemical and haematological parameters were observed during the first year of treatment. All patients and parents desired to continue the treatment.

Discussion

In this study, we clearly show that daily administration of pharmacological doses of rhGH in pre-pubertal children with NS increases height velocity and height SDS during the first year of treatment, while no acceleration of bone maturation was observed. In addition, we demonstrated that the response to rhGH therapy was comparable to that seen in girls with TS.

Published in : Acta Paediatrica (1997), vol. 68, pp. 943–946
Status : Postprint (Author's version)

Although the prevalence of NS is higher than TS, only few studies on the growth-promoting effect of rhGH in NS have been published. Cianfarani et al. (5) studied three NS children who were treated with human GH in a dose of 0.1 IU/kg/day three times a week for 6–9 months and could not demonstrate any improvement of height velocity. Ahmed et al. (6), in contrast, using the same daily dose but given 6 days a week, observed a significant acceleration of height velocity after 1 y of treatment in five patients. Thomas et al. (7) observed that rhGH treatment in a daily dose of 0.15 IU/kg/day, similar to our dosage regimen, in five NS children, started at a mean age of 3.9 y, resulted in a mean height increase from −3.3 to −2.4 SDS after a mean duration of 2.9 y. The experience from the Kabi International Growth Study (KIGS) of GH treatment in NS showed a significant increase in height SDS in NS patients treated for up to 3y, while the National Cooperative Growth Study in the US reported an increase for up to 4 y with rhGH (9, 10). The response was slightly better than observed in girls with TS. Municchi et al. (8) reported an increase in final height in three NS patients treated with rhGH (0.5 IU/kg/week) for at least 3 y. In line with these data from the literature, we observed an improvement of growth in our patients with NS. Moreover, we clearly demonstrated that the average first year growth response to rhGH treatment in pre-pubertal NS patients was comparable to that observed in TS girls treated with a similar treatment regimen. It remains, however, to be shown whether this treatment during the following years will finally result in an increase in final height, as reported in TS girls (3, 4).

Compared to TS girls, the inter-individual variation in growth response was larger in the patients with NS. This cannot only be explained by the wide age range of the studied patients, since marked changes in height between patients were observed in young as well as older subjects. It is likely that the population of NS children included in this study, despite the fact that they all responded to a NS-specific scoring system, represents a heterogeneous group of disorders with different aetiologies and different growth histories, which might be reflected in disparate growth responses to rhGH administration. In this respect, it is important to remember that we observed a smaller growth response in those NS patients with a smaller birthweight suggesting that the degree of intrauterine growth retardation is one of the factors modulating the response to rhGH therapy.

We found that skeletal maturation advanced slightly but not significantly slower during rhGH treatment in the NS group compared to TS girls. In untreated NS children Greulich and Pyle bone age determinations are, and continue to be, delayed by about 2 y after the age of 5 y compared to the normal population, inducing a delay of epiphyseal closure of about 2 y. In the TS girls, however, this delay in bone age increases steadily from the age of about 12 y, inducing a closure of the epiphyses probably after the age of 19 y (15). We confirmed in our NS group a delay in bone age of about 2.2 y, which did not change during rhGH treatment. All patients remained pre-pubertal during the study period and did not receive sex steroids or other drugs which might have influenced their skeletal maturation.

This similar increment in height and bone age in NS patients makes rhGH treatment encouraging in obtaining a similar final height gain as in TS girls. However, we only showed similarities in the growth-stimulating effect of rhGH therapy between these two groups in pre-pubertal patients. This might not be the case during the pubertal period, since changes in bone age maturation and

growth during the pubertal age period might be different in NS compared to TS patients, who develop spontaneous puberty (16) less frequently. It is clear that long-term studies of rhGH therapy, preferably when final height is reached, are necessary before the full value of rhGH treatment in NS can be assessed, but the first year results presented here are certainly encouraging.

Acknowledgments

We thank members of the Belgian Study Group for Paediatric Endocrinology and the Dutch Growth Hormone Working Group for referring patients. We also thank Pharmacia & Upjohn, Belgium and the Netherlands, and Novo Nordisk, Denmark, for the supply of recombinant human growth hormone.

References

1. Win DR, Keena BA, Hall JG, Allanson IE. Growth curves for height in Noonan syndrome. Clin Genet 1986; 30: 150–3.
2. Ranke MB, Heidemann P. Knupfer C, Enders H, Schmaltz AA, Bierick JR. Noonan syndrome: growth and clinical manifestations in 144 cases. Eur J Paediatr 1988; 148: 220–7.
3. Van den Broeck J, Massa GG, Attanasio A, et al. Final height after long-term growth hormone treatment in Turner syndrome. J Pediatr 1995; 127: 729–35.
4. Nilsson KO, Albertsson-Wikland K, Alm J, et al. Improved final height in girls with Turner's syndrome treated with growth hormone and oxandrolone. J Clin Endocrinol Metab 1996; 81: 635–40.
5. Cianfarani S, Spadoni GL, Finocchi G. Treatment of growth hormone (GH) in 3 cases of Noonan syndrome. Minerva Pediatr 1987; 39: 281–4.
6. Ahmed ML, Foot AB, Edge JA, Lankin VA, Savage MO, Dunger DB. Noonan syndrome: abnormalities of the growth hormone/IGF-I axis and the response to treatment with human biosynthetic growth hormone. Acta Paediatr Scand 1991: 80: 446–50.
7. Thomas BC, Stanhope R. Long-term treatment with growth hormone in Noonan syndrome. Acta Paediatr Scand 1993; 82: 853–8.
8. Municchi G, Pasquino AM, Pucarelli I, Cianfarani S, Passed F. Growth hormone treatment in Noonan syndrome: report of four cases who reached final height. Horm Res 1995; 44: 164–7.
9. Romano AA, Blethen SL, Dana K, Noto RA. Growth hormone treatment in Noonan syndrome: the national cooperative growth study experience. J Pediatr 1996; 128: S18–S21.
10. Kabi International Growth Study. Short stature in Noonan Syndrome: Demography and response to growth hormone treatment in the Kabi International Growth Study. In: Ranke MB, Gunnarsson R, editors. Progress in growth hormone therapy—5 years of KIGS. Mannheim: J & J Verlag, 1994: 206–15.

11. Duncan WJ, Fowler RS, Farkas LG, et al. A comprehensive scoring system for evaluating Noonan syndrome. Am J Med Genet 1981; 10: 37–50.
12. Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children. Arch Dis Child 1966; 41: 454–71.
13. Tanner JM. Growth at adolescence. Oxford: Blackwell, 1962.
14. Greulich WW, Pyle SI. Radiographic atlas of skeletal development of the hand and wrist, 2nd ed. Stanford: Stanford University Press, 1959.
15. De Schepper J, Craen M, Massa G, Heinrichs C, Maes M, Du Caju M, et al. Growth hormone therapy in Turner's syndrome. J Clin Endocrinol Metab 1994; 79: 489–94.
16. Massa G, Vanderschueren-Lodeweyckx M, Malvaux P. Linear growth in patients with Turner syndrome: influence of spontaneous puberty and parental height. Eur J Paediatr 1990; 149: 246–50.