Effect of Growth Hormone Treatment with Noonan Syndrome: Experience from Kabi International Growth Study (KIGS/ICGS)

Patrick Wilton and Barto Otten on behalf of the International Board of the Kabi International Growth Study

Department of Clinical Research, Peptide Hormones (PW), Stockholm, Sweden and Department of Paediatrics, University Hospital, Sint Radboud (BO), Nijmegen, The Netherlands

Abstract 55 children, 34 males, 21 females, with Noonan syndrome (NS) included in the Kabi Pharmacia International Growth Study were treated with growth hormone (GH) in a median dose of 0.6 IU/kg/week. Median age at start of treatment was 10.6 years and median height standard deviation score (SDS) was -3.1. Pretreatment height velocity was 4.3 cm/year and during the first, second and third years it increased to 7.0, 6.0 and 4.8 cm/year respectively. Projected adult height with Noonan specific standard increased from -0.4 SDS to 0.3 SDS at the end of three years' treatment. No adverse reactions were reported.

Key words: Noonan syndrome, growth hormone, efficacy, safety.

Introduction

NS was differentiated from the Ullrich-Turner syndrome in 1963 by pediatric cardiologists (1). The incidence has been estimated to be around 1/2,500 live births (2). One of the characteristics of NS is short stature. Growth curves describing the natural growth in this syndrome have been published (3, 4). The final height has been reported to be 163 and 153 cms in males and females respectively (4). GH secretion has been reported to be within normal limits but serum concentrations of IGF-I were low (5, 6). Pilot studies have reported

experiences with GH treatment in children with NS (5-10). The Kabi International Growth Study, KIGS, was initiated in 1987 to follow the efficacy and safety of GH treatment in children. The purpose of this paper is to report the outcome of up to six years of GH treatment in 55 children with NS included in the KIGS.

Patients and Methods

Data from 55 patients, 34 males, 21 females given a diagnosis of NS was available. Height and weight SDS were calculated according to the standards of Tanner *et al.* (11) and the Noonan specific standards of Ranke *et al.* (4). Birth weight and length SDS were calculat-

Correspondence: Dr. Patrick Wilton, Pharmacia, Peptide Hormones, 112 87, Stockholm Sweden

ed using the standards of Wälli *et al.* (12). Weight-for-height was calculated as the percentage of ideal weight for a given height at a chronological age among the normal population. Bone age estimations using the standard of Greulich and Pyle (13) were performed by the investigators. Adult height predictions were performed with the method of projected final height (14) using the standards of Ranke *et al.* (4). In the statistical analysis the Kruskal-Wallis test was used.

Results

The auxological characteristics of the patients at start of GH therapy are presented in Table 1. Birth weight and length were within normal limits as was target height. The median age at GH start was 10.6 years. The median height SDS was -3.1 compared to the standard of Tanner and -1.0 compared to the

Table 1 Clinical characteristics at start of GH treatment.

	n	Median	Percentiles	
			10th	90th
Age (years)	55	10.6	4.6	14.9
Bone age (years)	26	7.0	6.0	10.3
Height SDS Tanner	55	-3.1	-4.4	-2.1
Height SDS Noonan	54	-1.0	-2.1	-0.2
Weight-for-height (%)	54	101	89	121
Projected adult height Male	34	-0.30	-1.11	0.40
Projected adult height Female	20	-0.55	-1.89	0.07
Birth weight SDS	43	-0.26	-1.70	1.03
Birth length SDS	23	-0.25	-1.79	1.73
Target height SDS	52	-0.27	-1.32	0.63
GH dose (IU/kg/week)	55	0.61	0.48	1.03

Noonan standard. Individual heights compared to the Noonan specific standard are shown in Fig. 1 and 2 for boys and girls respectively. The median projected adult height was -0.30 in the males and -0.55 in the females.

Bone age was retarded in all investigated children (Fig. 3). GH stimulation test was reported in 46 patients and in 17 the GH peak was below 20 mU/L.

The median dose of GH at start of treatment was 0.6 IU/kg/week and remained rather constant throughout the treatment. Median frequency of injections was six/week.

The auxological data during the first three

Fig. 1 Height in 34 boys with NS at start of GH treatment. Reference according to Tanner 1966.

GH treatment in Noonan Syndrome

Fig. 2 Height in 21 girls with NS at start of GH treatment. Reference according to Tanner 1966.

years of GH treatment are shown in Table 2. The median height velocity was 4.3 cm/year the year before treatment and increased to 7.0, 6.0

Fig. 3 Bone age versus chronological age in 26 patients with NS, line of identity is shown.

and 4.8 cm/year during first three years of treatment (Fig. 4). Eleven children were treated for three years and their median height SDS (Tanner) increased from -2.8 to -2.4 and their projected final height SDS (Ranke) increased from -0.3 to $+0.3$ during the three years of treatment.

No adverse reaction was reported.

Table 2 Auxological characteristics during three years of GH treatment.

	1st year			2nd year			3rd year		
	<i>n</i>	median	(10-90th)	<i>n</i>	median	(10-90th)	<i>n</i>	median	(10-90th)
Height SDS									
Tanner	44	-2.6	(-3.8, -1.9)	24	-2.5	(-3.6, -1.6)	11	-2.4	(-3.7, -1.2)
Noonan	46	-0.8	(-1.8, 0.5)	26	-0.5	(-1.5, 0.7)	11	0.2	(-1.3, 0.7)
Height velocity (cm/year)	46	7.0	(5.4, 9.1)	26	6.0	(3.5, 8.5)	11	4.8	(4.2, 7.7)

Fig. 4 Height velocity (cm/year) at start of treatments and during first four years of GH. Box represents median, 75th and 25th centile. Star represents the mean and vertical lines 10th and 90th centiles.

Discussion

In contrast to Turner syndrome there is no objective method for diagnosing NS. There are however, scoring systems developed for the diagnosis of it (15, 16). The diagnosis of the patients in this report is most probably correct so there must be other reasons for the finding that the height is below what has been reported in this syndrome. The most important reason is likely to be that it is the shortest children who are considered for treatment. Most of the tested patients had a GH response which can be considered normal. Despite this there was a significant growth promoting effect of GH. The increase in height velocity is usually

more pronounced in Turner syndrome during GH treatment compared to the present findings. But the dose of GH used in the Turner syndrome is usually higher than the actual median dose of 0.6 IU/kg/week. With a higher dose of GH, 28 IU/m²/week (corresponding to about 1.0 IU/kg/week) a very good growth response (10 ± 0.5 cm/year) has been reported in 14 children with NS (Dunger, personal communication). The findings in the actual analysis from the KIGS enhance the published suggestion that GH safely increases linear growth in children with NS.

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GH treatment in Noonan Syndrome

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