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Defective Growth Hormone (GH) Secretion and Short-Term Treatment in Noonan Syndrome

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Abstract : Auxological and endocrine data from 12 prepubertal children (3 males, 9 females) with Noonan syndrome (NS) were compared with those of 15 children with constitutional short stature (CSS), 20 children with partial GH deficiency (GHD), and 6 children with Turner syndrome (TS). Four children with NS were treated with human growth hormone (hGH) (n = 4) (25 units/m^2 week, divided on daily s.c. doses). In children with NS, the peak serum GH response to clonidine (5.4 ± 2.7 ug/L) and glucagon (7.4 ± 3.4 ug/L) were significantly lower than those for children with CSS (14.8 ± 3.4 and 12.8 ± 2.8 ug/L respectively). Nine out of the 12 (75%) children with NS did not mount normal GH peak (10 ug/L or more) after provocation. The 12-h integrated GH secretion in the 3 children with NS who had normal GH response to provocation (2.7 ± 0.7 ug/L) was markedly lower compared to that for children with CSS (6.7 ± 1.2 ug/L). The serum insulin-like growth factor-1 (IGF-I) concentrations were lower in children with NS (67 ± 32 ng/ml) vs CSS (165 ± 35 ng/ml), but not different from those for GHD children (59 ± 33 ng/ml). In 4 children with NS, hGH therapy for a year increased height growth velocity from 4.1 ± 0.3 cm/yr to 7.4 ± 0.6 cm/yr and height standard deviation score (Ht SDS) from -2.2 ± 0.6 to -1.45 ± 0.3. This growth acceleration was accompanied by an increase in IGF-I concentration (from 52 ± 21 ng/ml to 89 ± 25 ng/ml). In summary, these results prove a defect of the GH secretion in children with NS and suggest that GH therapy has an important role in the management of their short stature. **(Indian J Pediatr 1998; 65 : 741-749)**

Key words : *Noonan syndrome; Growth; Gonadotrophins; Sex steroids.*

Noonan syndrome (NS) remains a clinical diagnosis that designates individuals with a characteristic facies and body habitus, congenital heart disease, and growth retardation[1]. The frequency in the population may be as high as 1/1000[2].

One of the relatively consistent aspects of NS is growth retardation involving both height and weight. The majority of the affected patients have true short stature (less than 3rd percentile) or fall within the lower range of normal[1,3]. Length and weight at birth are almost invariably normal[1]. Thereafter, short stature occurs uniformly among these patients independent of chronological age[4,6]. Noonan specific growth charts have been developed[4,5]. Growth retardation may be due to multiple factors including the unknown primary defect in the syndrome, congenital heart disease, endocrine disturbance or unexplained failure to thrive[17-13]. Delayed puberty, a feature of the disease, might contribute to the slow linear growth[5].

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Few studies investigated the growth hormone (GH) insulin-like growth factor-1 (IGF-1) axis in NS. Ahmed *et al*[14] reported low plasma IGF-1 concentration despite normal GH response to chemical provocation in 6 children with NS. However, two of these children had abnormal overnight GH secretory profiles. Tanaka *et al*[15] described GH neurosecretory dysfunction in a 16 year old boy with NS characterized by low amplitude and small number of GH secretory bursts during 12-h nocturnal GH sampling. In addition, short term GH therapy (1-year) significantly increased linear growth and increased circulating IGF-1 concentrations in these children supporting the possibility of defective GH-/IGF-1 axis[14-17].

We studied the auxologic and endocrine data from 12 children with NS and presented the results of treatment with human GH (n = 4) and compared these data with those of 20 children with partial GH deficiency (height < 3rd percentile, 15 children with constitutional short stature (CSS) (height < 3rd percentile for age and normal GH response to chemical provocation) and 6 children with Turner syndrome (TS).

MATERIALS AND METHODS

Twelve prepubertal children with NS, 3 males and 9 females (mean age 8 ± 4.1 years) and a body mass index (BMI) of (15 ± 2.4), were studied. All were assigned from the Dysmorphology outpatient clinic of the Royal Hospital, Muscat, Oman. All had features of Noonans syndrome including : hypertolerism, with downward slanted palpebral fissure (12/12), epicanthic folds, ptosis, depressed nasal base, low-set ears, down-turned corner of the mouth, micrognathia, deeply grooved philtrum with high peaks (11/12), low posterior hair line, webbed neck (7/12), pectus excavatum, cubitus valgus (6/12), congenital pulmonary stenosis (7/12), cryptorchidism (2/3) and mild mental retardation (5/12). Fifteen age matched children with CSS (Ht SDS < -2 for age), 20 children with partial GH deficiency (peak GH response to provocation > 7 and < 10 ug/L), and 6 girls with TS (Karyotype 45-X) were used as controls for the growth and endocrine functions. All the children included in the study had normal renal, hepatic and thyroid functions and normal hemogram. Informed consents were obtained from the parents of all the children, and when appropriate, from the children before inclusion in the study. The following were obtained from the files and during examination : (a) chronological age, (b) height (cm) at the time of diagnosis and subsequently at yearly intervals. For each subject the Ht SDS was calculated according to the formula Ht SDS = (X1 - X2)/SD where X2 and SD are age matched population mean height and SD respectively and X1 is the subject height. The height growth velocity (GV) (cm/yr) was calculated for the whole year. Normal population data were according to Tanner *et al*[18]. The BMI were calculated according to the formula BMI = weight (kg)/height (m^2) and bone age determined according to the atlas of Gruelich and Pyle. None of the children had history of intrauterine growth retardation, any other systemic or endocrine disease, or central nervous system irradiation.

Children were primed with ethinyl estradiol for two days before studying their GH response to provocation. After an overnight fast a venous blood sample was withdrawn through a polyethylene catheter inserted in a forearm vein. The serum was

separated by centrifugation and kept frozen at -20°C until analyzed for GH, IGF-I, FT4, TSH and 8-AM cortisol by radioimmunometric assay. After obtaining basal samples, clonidine HCl (0.15 mg/m^2 surface area) was given orally and blood samples obtained at 30, 60, 90, and 120 mins after the oral dose for measurement of GH concentrations. On the next morning and after an overnight fast, glucagon 0.1 mg/kg was injected i.m. and blood collected before and at 30 minute-intervals for 2.5 hours for measurement of GH.

Nocturnal GH secretion (12-h integrated nocturnal GH concentrations) was determined in the three children with NS who had normal GH response to provocation. On the evening of the day of admission an iv. cannulae were placed in the antecubital fossa of the non-dominant arm at least an hour before withdrawing the first sample. An initial blood sample was taken at 2000-h; successive samples were taken at 20 min intervals thereafter, for 12 hours. Blood was collected into tubes and immediately separated and serum stored at -20°C. During sample periods subjects remained recumbent and were allowed to sleep and sit up for drinking water ad lib.

Four children with NS and ten with GH deficiency were treated with human GH (25 units/m^2/week, s.c., divided on daily doses given at night). Ten children with partial GH deficiency did not receive GH for economic reasons. All the subjects were seen at 3-months and GH dose adjusted based on surface area. The height growth velocity (GV) was calculated from the height at the beginning and end of the year of therapy. The actual time interval of measurement was between 0.96 and 1.04 years. Circulating IGF-1, FT4 and TSH concentrations were remeasured after one year of including them in the study.

GnRH test was performed in all the children with NS above the age of 9 years (4 females and 1 male) and their serum sex steroid concentration determined. HCG (1000 μ/day i.m. for 3 days) test was performed in a 16-year old male with NS and bilateral cryptorchidism and his testosterone concentration measured before and on the fourth day.

Human GH and IGF-I concentrations were measured by immunoradiometric assay, employing reagents purchased from Nichols Institute (San Juan Capistrano, CA). Intra and interassay coefficients of variation (C.V.) were 2.6% and 6.8% respectively for GH and 7.8% and 11% respectively for IGF-I. All samples from all the patients were assayed simultaneously. FT4, TSH and cortisol were measured using Amerlex-RIA kits, Kodak Clinical Diagnostics, Amersham, UK. LH and FSH levels were measured using immunoradiometric assay kit (Radium, Pomezia, Rome, Italy). The mean intra and interassay CVs were 4.8% and 7.8% respectively. Estradiol and total testosterone were measured by solid I (125) RIA supplied by Diagnostic Product Corp. (Los Angeles, CA). The mean intra and inter CVs were 4.6% and 7.2% respectively for estradiol and 4.1% and 8% respectively for testosterone.

Data are presented as mean ± SD. ANOVA test was used to compare analyte concentrations in the different groups when the data were normally distributed and Wilcoxon test was used when the data were not normally distributed. Paired Student 't' test was used to analyze changes in each group before vs after one year.

RESULTS

Auxological and hormonal data for chil-

dren with NS are presented in Table 1. Ht SDS ranged between - 1.2 and -2.7 with a mean of -2 ± 0.48. GH responses to provocation with clonidine (5.4 ± 2.7 ug/L) and glucagon (7.4 ± 3.4 ug/l) were subnormal. In nine out of the twelve patients GH peak response to provocation was less than 10 ug/L. Circulating IGF-1 concentrations (66.8 ± 32.3 ng/ml) were significantly lower compared with the lab range for their age and pubertal stage (normal range 110-470 ng/ml). Their thyroid functions and 8-AM cortisol concentration were normal.

Table 2 compares linear growth before treatment and GH data of children with NS, TS, CSS, and GHD. Patients with NS and CSS had higher HtSDS and GV compared to children with GHD and TS. Bone age delay did not differ among the four groups. GH response to provocation and serum IGF-1 concentrations were significantly higher in the CSS and TS groups vs those with NS and GHD.

In 3 children with NS and 3 with TS, who had normal GH peak response to provocation, the integrated nocturnal GH secretion and nocturnal GH peak were lower than those for 6 age-matched children with CSS (Table 3).

Table 4 presents the effects of GH therapy on patients with NS, TS and GHD in comparison with the untreated groups. In 4 children with NS, GH therapy markedly increased GV and Ht SDS than before treatment and vs the untreated group. Skeletal maturation did not accelerate during the year of treatment. The improve-

TABLE 1. Auxological and Hormonal Data of Children with NS Before Treatment

Patient	Age yr	BMI kg/m²	HtSDS	GVS-DS	GH-b ug/L	GH-p-Clon ug/L	GH-p-Glu ug/L	IGF-I ng/ml	FT4 pmol/L	TSH mlU/ml	Cortisol nmol.L
1.	4.5	13.25	-1.2	-1.1	1.7	4.5	3.5	61	15.4	2.2	415
2.	11	14.1	-2.6	-1.5	1.7	5.6	6.8	52	16.5	1.3	314
3.	11	14.2	-2.56	-1.43	1.7	3.3	7.2	30	18.8	1.6	354
4.	5	14.2	-1.96	-1.2	1.7	3	7.8	58	15	1.7	332
5.	11.25	13.12	-2.3	-1.05	1.7	3.7	5.5	48	15.8	2.2	410
6.	9.25	14.4	-2	-1.73	1.7	4.7	9.9	81	21.9	1.9	385
7.	7	13.5	-1.5	-0.8	1.7	5.2	8.3	33	15.5	1.1	269
8.	1.25	15.8	-1.45	-1.1	5.6	7.3	6.5	49	13.2	1.4	310
9.	2	14.5	-1.65	-1.5	1.6	5.2	4.7	38	26.3	2.1	420
10.	8	13.5	-2.2	-1.3	1.5	9.8	12.5	101	18.5	2.8	288
11.	10	17.2	-1.65	-1.9	1.5	11.2	14.2	130	17.2	3.9	355
12.	16	22	-2.7	-1.7	1.7	1.7	1.7	120	18.3	1.9	411
Mean	8.02	15	-1.98	1.36	1.98	5.4	7.39	66.8	17.7	2	355
SD	4.1	2.4	0.48	0.3	1.1	2.7	3.4	32.3	3.4	0.72	51

B = basal, P = peak after stimulation, Clon = clonidine, Glu = glucagon, Cortisol = 8-AM

TABLE 2. Growth Data of Children with NS vs Controls

Groups		Age yr	HtSDS1 (–)	Ht-SDS2 (–)	GV1 cm/yr	GV2 cm/yr	GVS-DS1 (–)	GVS-DS2 (–)	BMI kg/m²	B-del1 yr	B-del2 yr	GH-P-Clon ug/L	GH-P-Glu ug/L	IGF-1 ng/ml
NS	Mean	8	1.98	2.05	4.5	4.3	1.3	1.4	15	2.4	2.2	5.4	7.4	67
(n = 12)	SD	4.1	0.48	0.41	0.84	0.75	0.4	0.48	2.4	1.2	1.1	2.7	3.4	32
TS	Mean	7.5	3.3*	3.6*	3.9	4.2	1.7	1.6	15.3	2.1	2.3	13.9*	11.8*	175*
(n = 6)	SD	1.8	1.2	1.4	1.3	1.4	0.6	0.6	1.1	0.9	1.1	3.1	2.8	61
CSS	Mean	7.6	2.5	2.4	4.6	4.8	1.1	1.1	13.8	2	1.8	14.8*	12.8*	165*
(n = 15)	SD	3.7	0.62	0.75	0.5	0.7	0.3	0.25	1.8	0.4	0.6	3.4	2.8	35
GHD	Mean	6.8	2.9*	3.2*	3.6*	3.5*	1.85*	1.97*	14.6	-2.3	-2.6	7.9	8.1	59
(n = 20)	SD	2.1	0.7	0.65	1.1	0.85	0.4	0.44	1.5	1	0.9	1.3	1.5	33

B-del = bone age delay, 1,2 = before and after 1 year of follow-up without treatment.
GH-p-Clon = GH peak after clonidine, Glu = after glucagon.
* $p < 0.05$ among groups

ment of GV and Ht SDS was comparable to those for the treated group with GHD. The circulating IGF-1 concentrations increased significantly in the three groups of patients receiving GH therapy (NS, TS, and GHD), but not in the untreated groups. FT4 and TSH concentrations did not change before vs after one year of GH therapy.

The basal and GnRH-stimulated gonadotropin concentrations and serum estradiol levels in four girls with NS were within the normal range for prepubertal girls[19]. Neither raised basal gonadotropin levels nor exaggerated response to GnRH were detected in any girl with NS (Table 5). Basal and provoked FSH concentrations were significantly higher in girls with TS vs those with NS. In a 16 year-old boy with NS and bilateral cryptorchidism (Tanner 1 sexual development), the basal concentrations of LH and FSH levels (0.8 and 1.2 iu/ml respectively) were not raised and the peak LH and FSH responses to GnRH were not exaggerated (4.9 and 5.7 iu/ml respectively). His serum testosterone concentration increased significantly from 1.7 nmol/L to 28 nmol/L after 3 days of HCG (1000 u/day i.m. for 3 days). In a 28-year-old

TABLE 3. Nocturnal GH Data of Patients and Controls

	Basal GH ug/L	P-GH after stim. ug/L	Integ. noct. GH ug/L	Noct. peak ug/L	IGF-I ug/L
CSS (n = 6)	2.6 (0.37)	13.2 (1.17)	6.7 (2.9)	21.4 (3.2)	157 (25)
NS (n = 3)	1.6 (0.1)	12.1 (1.6)	2.7 (0.7)*	11.6 (2.5)*	104 (20)
TS (n = 3)	2.1 (0.3)	13.2 (4.5)	3.8 (1.4)*	10.4 (3.9)*	175 (61)

P = peak, Clon = clonidine, Integr = integrated, Noct = nocturnal.
* $p < 0.05$ NS and TS vs CSS

TABLE 4. Auxologic and Hormonal Data After 1 Year of GH Therapy

		Age yr	B-del-B yr	B-del-A yr	GV-B cm/yr	GV-A cm/yr	Ht SDS-B (–)	Ht SDS-A (–)	IGF-I-B ng/ml	IGF-I-A ng/ml
NS on GH	Mean	11.5	2.8	2.5	4.1	7.4*#	-2.2	1.45*#	52	89*#
n = 4	SD	1.8	1	0.9	0.3	0.6	0.6	0.3	21	25
NS not on GH	Mean	7.9	2.2	2.4	4.6	4.4	-1.9	2.08	69	62
n = 8	SD	3.8	0.8	1	0.9	0.85	0.4	0.48	28	18
TS on GH	Mean	7.5	1.6	1.8	4.2	7.5	3.5	2.1	175	220*
n = 6	SD	2	0.6	0.8	1.4	1.6	1.4	1.2	61	69
GHD on GH	Mean	7.1	2.1	2.25	3.5	8.4*#	3.05	2.3*#	58.5	92*#
n = 9	SD	1.9	0.8	0.8	1.1	1.4	0.8	0.45	24	30

B = before, A = after one year of follow-up, *$p < 0.05$ before vs after therapy, # $p < 0.05$ on treatment vs without treatment
B-del = bone age delay in years

male with NS (Ht = 146 cm, Tanner V sexual development), the LH and FSH basal (14.4 and 11.9 iu/ml respectively) and GnRH provoked (32.8 and 14.8 iu/ml respectively) concentrations and basal serum testosterone (21 nmol/L) were normal. His peak GH secretion after provocation with clonidine (2.7 ug/L) and glucagon (3.5 ug/L) were deficient.

DISCUSSION

In our patients with NS, the short stature (Ht SDS and GV), with delayed skeletal maturation resembled that of children with CSS[20]. Their linear growth was faster than those with GHD and TS. Defective GH release after 2 provocation tests was documented in 75% of children with NS in this study. The integrated nocturnal GH secretion of those who had normal GH response to provocation, was significantly lower vs that for children with CSS. Circulating IGF-I concentrations were significantly lower in children with NS vs those with CSS, and TS. These results indicate that abnormal GH secretion is a major factor in the etiology of short stature in children with NS. The effectiveness of treatment with human GH and the significant increase of serum IGF-I concentrations supported this concept and suggested normal GH receptors. However, recent data in children with CSS showed that these children who have normal GH secretion and low growth hormone binding protein concentration might have a variety of mutations in the extracellular GH receptor domain[21]. These patients have significant increase in linear growth after GH therapy. These findings necessitate further studies of the GH receptors in patients with Noonans syndrome. At the time of normal puberty short stature becomes relatively more pronounced due to a delay of the adolescent growth spurt in these patients. Ranke *et al*[22] have shown that in children with TS, endogenous GH levels are below normal af-

TABLE 5. Basal and GnRH-stimulated Gonadotrophin Secretion

Patient	Sex	Age years	P-stage	LH-b U/L	LH-p U/L	FSH-b U/L	FSH-p U/L	Estradiol Pmol/L
11	F	10	1	0.5	3.4	1.4	25	59
6	F	9.5	1	0.5	3.2	0.8	12.1	108
3	F	12	1	1.2	4.2	3.5	7.8	140
2	F	12	1	1.3	5.2	5.2	9.5	64
12	M	16	1	0.5	4.9	0.5	4.8	ND
N.S.	Mean	11.9	1	0.8	4.2	2.3	11.9	93
n = 5	SD	2.3		0.36	0.8	1.8	7	33
T.S.	Mean	12.2	1	33.2	66.2*	58.4*	89.5*	64
n = 6	SD	3.2		13.7	24.5	36.5	55.4	24
Normal	Mean		1	3.7	8.7	2.2	14.4	#
	SD			4.2	7.7	1.2	5	

Estradiol normal range for follicular phase = (84 to 532) # 18
* $P < 0.05$ NS vs TS.

ter the age of 8 years. IGF-1 levels also fall below the normal range. In our study, the integrated nocturnal GH secretion of children with NS, with normal GH response to provocation, were not different than those for age-matched patients with TS, and their serum IGF-1 levels were lower compared to children with TS. These findings suggested the presence of GH neurosecretory dysfunction in some patients with NS.

Sexual development was absent in two girls and a boy with NS at the age of 13, 13.5 and 16 years respectively. Despite the delay in puberty, the 4 prepubertal girls with NS and the two males studied had normal basal and GnRH-stimulated LH and FSH levels, appropriate for their pubertal stage. In addition, the androgen secretion in the adult male with NS and testosterone response to hCG in the prepubertal patient were normal. These results ruled out the occurrence of primary gonadal failure (hypergonadotrophic hypogonadism) in these patients. In support of our findings, Van Metter and Lee reported normal LH and FSH responses to LHRH in a male and female patient with NS[23].

CONCLUSION

In summary, delayed growth and puberty are features of NS. Defective GH secretion and subsequently low IGF-1 **synthesis** plays an important role in this **growth** delay. Short-tem treatment with human GH significantly increases linear growth and IGF-1 synthesis. However, these claims should be contested until final height data is available. Despite delayed onset of puberty, there is no evidence of primary gonadal dysfunction in these children.

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PRIME MINISTER EXPRESSES CONCERN AT HIGH NEWBORN MORTALITY

The Hon'ble Prime Minister Shri Atal Bihari Vajpayee expressed concern about the high neonatal mortality in the country. He said, "Infant mortality rate has come down, but a high newborn mortality is posing a formidable challenge". He added, "Severe malnutrition is on the decline, but stunting and low birth weight remain difficult conditions to grapple with". He further underlined the importance of essential newborn care, saying "The Reproductive and Child Health Programme launched last year combines population control activities with a holistic approach to maternal and child health. It lays emphasis on emergency obstetric care, essential newborn care and management of reproductive tract infections. Let us all put our energies together to make this programme a visible success".

Excerpt from the address Prime Minister of India on the occassion of the 28th Convocation of the All India Institute of Medical Sciences, New Delhi on 24th July 1998.