Growth hormone therapy for short stature in adolescents – the experience in the University Medical Unit, National Hospital of Sri Lanka

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Abstract

Introduction: Use of growth hormone therapy (GHT) in adolescents is not common in Sri Lanka. In this study we aimed to assess the response to GHT in adolescents in our setting presenting with short stature.

Materials and methods: This was an observational study carried out at the University Medical Clinic, National Hospital of Sri Lanka. GHT was used for those with growth hormone deficiency (n=15), Turner syndrome (n=5) and Prader Willi syndrome (n=1). All were monitored with anthropometric measurements, IGF-1 and observed for side effects.

Results: Among the 21 adolescents, 15 were males (71.4%). Mean age, height, weight at presentation were 15.0 (10.4-19.1) years, 138.6 (± 7.6) cm and 38.4 (±13.0) kg respectively. Low IGF-1 was found in 16 (76.1%). IGF1 was normal in Turner patients. Impaired response for ITT was seen in 13 (81.3%; n=16). In one patient it was discontinued due to lack of patient cooperation.

Follow up period and mean growth velocity were 2.7 – 35.6 months and 7.1 (+3.7) cm/year respectively. In the group with isolated GHD (n=13) significant negative correlation between initial bone age and growth velocity was found but that of initial chronological age and height was not significant.

Girls with Turner syndrome showed a mean height velocity of 5.9cm/year with therapy.

Side effects were detected in 3 (14.9%) patients which were diabetes mellitus (n=2) and carpal tunnel syndrome (n=1).

Conclusion: Growth hormone replacement therapy is useful in achieving satisfactory height gain in adolescents with short stature due to GHD, Turner syndrome and Prader Willi syndrome and is usually a safe treatment.

Key words: growth hormone, short stature, adolescents

Introduction

Short stature is a distressing problem for the affected children or adolescents or their families. It is defined as height more than 2 standard deviations below the mean or below the 3rd percentile for age, sex and ethnicity (1). Genetic and familial factors, intrauterine factors affecting the intrauterine growth, environmental factors such as malnutrition, chronic illnesses and endocrine disorders have an important place among the many determinants of growth. However only 20% will have an identifiable pathological cause while almost 80% accounts for constitutional delay (1).

Prevalence of growth hormone deficiency (GHD) is estimated to be ranging from 1:4000 to 1:10,000 worldwide (2), but data on the prevalence of short stature or growth hormone deficiency in Sri Lanka is limited. The first report on short stature in Sri Lanka was by de Mel et al in 1987 which reported a prevalence of 5.3% among Sri Lankan children (3). A study carried out in 1991 in Sri Lanka showed that out of 16,001 children screened for short stature 172 were identified as short out of which 12 children were diagnosed to have growth hormone deficiency by provocative testing (4).

Growth hormone deficiency commonly occurs due

to idiopathic isolated GHD and less frequently due to other pathological causes (5). Anthropometric measurements, provocative testing, measurement of IGF1 and IGF binding protein-3, radiographic assessment of bone age and cranial MRI (6) are helpful in the diagnosis of growth hormone deficiency in a child with persistently subnormal growth with no other identifiable cause (6,7).

The recommendations for recombinant growth hormone therapy are growth hormone deficiency, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, children with intrauterine growth restriction who have not reached a normal height range by the age of 2 years, children with severe idiopathic short stature (height >2.25 SD below the mean height) who are unlikely to catch up in height and short stature due to homeobox-containing gene (SHOX) deficiency (5, 7). In addition to these, growth hormone therapy is indicated in adults with growth hormone deficiency and adults with wasting. Treatment should be monitored by a specialist endocrinologist for both children and adults (7).

In this report we present data on 21 adolescents attending our endocrine clinic who were treated with growth hormone therapy for short stature.

Materials and methods

Study population and study setting

21 adolescents who were treated with recombinant growth hormone therapy for short stature attending the Endocrine Clinic of the University Medical Unit of National Hospital of Sri Lanka were studied.

Study period

Study was carried out between February 2010 and June 2013.

Procedure

Informed written consent was provided by the patients or guardians.

Patients were selected for growth hormone treatment by a consultant endocrinologist. Anthropometric measurements (height and weight) were recorded and clinical and biochemical investigations (renal function tests, liver function tests, fasting blood glucose, haemoglobin levels) were carried out to exclude chronic illnesses. All patients underwent serum cortisol, serum TSH, free T4 and when appropriate serum FSH, LH and testosterone measurements to assess co-existing endocrinopathies.

All patients were investigated with IGF-1 levels and those with low IGF underwent ITT. Priming with sex steroids were carried out prior to provocative testing in adolescents with pubertal delay (girls aged 11.5-12 years and boys aged 13-13.5 years with no evidence of puberty or only initial signs). ITT was carried out in patients with Turner syndrome only if there was evidence of pituitary insufficiency.

Bone age was assessed using skeletal x-rays of left wrist and hand. MRI was carried out in all patients with growth hormone deficiency or suspected intracranial abnormality.

Patients with growth hormone deficiency were treated with human recombinant growth hormone 0.3 mg/kg/week subcutaneously and dose adjustments were made according to the response. Dose for Turner syndrome was 0.375 mg/kg/week (8) and for children with Prader Willi syndrome initial dose of 0.5mg/m^2 was given and dose gradually increased to 1mg/m^2 with time (9).

Serial anthropometric measurements were monitored during each clinic visit. IGF-1 levels, bone age and other relevant investigations were periodically performed. Serum TSH was measured intermittently as growth hormone therapy may unmask hypothyroidism (7, 10). Adverse effects of growth hormone therapy were noted. Further treatment with growth hormone was discontinued if there was no increase in growth rate or static serum IGF concentration was detected within the first 6 to 12 months in a compliant patient receiving an appropriate dose of GH (7).

Results

Sociodemographic variables

Among the 21 adolescents who were observed, 15 were males (71.4%). Mean age at presentation of all patients was 15.1 (±2.0) years and that of bone age was 11.1 (±2.2) years. There was no significant difference in the age of presentation between males and females (p=0.08). Mean height and weight at presentation were 138.6 (± 7.6) cm and 38.4 (±12.9) kg. Follow up period was 2.7- 35.6 months (mean=17.6 months). Characteristics are summarized in Table 1.

Aetiology

Aetiology of short stature in the patients was identified to be as mentioned in Table 2.

Biochemical findings

IGF1 levels were low when compared with age appropriate ranges in 16 (76.1%) patients. All Turner patients had normal IGF-1 levels. In the 16 patients with low IGF-1, ITT was carried out and a failed response was found in 13 (81.3%) and 2 (12.5%) showed normal growth hormone response to stimulation. ITT was discontinued in one patient due to lack of patient cooperation.

Table1. Sociodemographic variables of different groups of adolescents with short stature in the cohort

	All		*Isolated growth hormone deficiency*		*Turner syndrome*	*Prader Willi syndrome*	*Panhypopiturism*	*Growth hormone deficiency and hypothyroidism*
	Male (n=15)	(n=6)	Female (n=10)	(n=1)	Male (n=5)	Female (n=1)	(n=3)	Male (n=1)
Height (cm)								
Mean	139.6	136.3	137.8	146	134.3	146	143.3	140
SD*	8.2	6.1	7.7		4.3		12.1	
Weight (kg)								
Mean	38.8	37.3	32.8	46	35.6	80	40.7	52
SD*	15.0	6.8	9.0		5.9		9.1	
BMI (kgm^2)								
Mean	19.6	20.1	17.1	21.6	19.8	37.5	19.8	26.5
SD*	6.5	3.4	3.8		3.7		3.7	
Age of presentation (years)								
Mean	14.6	16.3	14.5	15.6	16.4	10.4	17.0	12.8
SD*	2.1	0.9	1.5		0.9		1.8	

*Sample standard deviation

Table 2. Aetiology of short stature of adolescents who were initiated on growth hormone therapy

Cause	*Number of patients diagnosed*
Genetic	
Turner syndrome without other endocrinopathy	3 (14.3%)
Turner syndrome and hypothyroidism	2 (9.5%)
Prader Willi syndrome	1 (4.8%)
Endocrine	
Isolated growth hormone deficiency	11 (52.4%)
Hypothyroidism and growth hormone deficiency	1 (4.8%)
Panhypopituitarism	3 (14.3%)
Total	**21 (100%)**

Imaging

All patients confirmed with GHD were investigated with MRI scan of the pituitary. MRI was abnormal in 3 patients. One patient was diagnosed as pituitary hypoplasia with probable empty sella syndrome while the others were diagnosed with pituitary microadenoma. In those with abnormal MRI there was no significant difference between the initial height (143.3 (±12.1) cm vs. 137.3 (±7.2) cm; p=0.26), age at presentation (17.0 (±1.8) years vs. 14.7 (±2.0) years; p=0.10) and growth velocity achieved (5.9 (±3.7) cm/year vs. 8.03 (±4.1) cm/year; and p=0.43) when compared with those with normal MRI.

Growth velocities

In the entire sample, the mean growth velocity among males (n=15) was 8.3 (± 4.0) cm and among females (n=6) was 5.5 (±1.9) cm.

In Turner patients (n=5) mean growth velocity achieved was 5.8 (±1.9) cm/year. In those with isolated growth hormone deficiency there was no significant correlation between growth velocity and age at initiation of therapy (r = -0.28, p=0.392), height at initiation of therapy (r=-0.45, p=0.162) and mid parental height, which indicates the genetic growth potential of the patient (r = 0.171; p=0.614). But bone age at presentation had a significant negative correlation with growth velocity (r = -0.641; p = 0.046) in the same group.

Along with growth hormone, testosterone therapy was initiated in 2 male patients out of the 15 males. They were able to achieve a mean growth velocity of 2.3 cm/ year which was significantly low compared to the rest without testosterone therapy (p=0.006).

Prader Willi syndrome

The patient with Prader Willi syndrome showed impaired ITT and low IGF-1 levels at the initial assessment.

The child with Prader Willi syndrome lost 11 kg during initial 3 months of growth hormone therapy, following which he was diagnosed to have diabetes mellitus. He was initiated on insulin therapy and optimal glycaemic control was achieved. His weight was stable there onwards. His height increased 4 cm over the 9 months of observation.

Panhypopituitarism

The adolescents with panhypopituitarism showed a mean height velocity of 5.9cm/year (±3.7)

Final height

The table below depicts the percentiles and standard deviation of the patients' initial and final height.

Table 3. Percentile and standard deviation of patients' initial and final height

Patient no	*Age (years)*	*Initial height (cm)*	*Centile*	*SD*	*Duration of therapy (months)*	*Final height (cm)*	*Centile*	*SD*
1	14.67	132.00	0.1	-4.1	17.53	151.00	0.3	-2.8
2	14.91	137.50	0.1	-3.6	20.60	150.00	0.1	-3.1
3	14.49	142.00	0.2	-2.9	28.70	159.00	1.8	-2.1
4	12.84	140.00	2.4	-2.0	20.82	157.30	11.9	-1.2
5	15.64	148.50	0.2	-2.9	25.50	151.00	0.1	-3.3
6	14.85	120.00	0.1	-5.2	35.78	146.50	0.1	-3.9
7	15.64	146.00	0.6	-2.5	16.53	151.00	3.3	-1.8
8	16.77	142.00	0.1	-4.2	16.99	155.00	0.2	-2.9
9	16.13	139.00	0.1	-4.2	35.64	150.00	0.1	-3.7
10	16.92	140.00	0.1	-3.5	8.50	145.50	0.3	-2.7
11	16.14	133.00	0.1	-4.6	10.82	138.50	0.1	-3.8
12	12.08	138.00	6.1	-1.6	26.32	155.00	11.7	-1.2
13	15.41	137.00	0.1	-3.9	13.03	143.00	0.1	-3.1
14	15.73	129.00	0.1	-5.2	21.60	137.00	0.1	-4.0
15	15.78	137.00	0.1	-4.2	12.38	147.00	0.1	-3.5
16	12.72	143.00	7.8	-1.4	9.74	154.00	23.9	-0.7
17	13.15	138.00	0.8	-2.4	33.57	157.00	2.5	-2.0
18	15.77	157.00	2.3	-2.0	3.85	160.00	4.1	-1.7
19	19.12	134.00	0.1	-5.8	3.82	135.00	0.1	-5.7
20	17.73	132.50	0.1	-4.7	5.74	134.00	0.1	-4.5
21	10.42	146.00	77.3	0.8	2.74	146.50	75.8	0.7

Side effects

During growth hormone therapy 3 (14.9%) patients developed side effects. One patient was diagnosed with carpal tunnel syndrome 23 months after commencement of therapy. Two patients were diagnosed with diabetes mellitus after 5 months and 3 months of commencement of therapy and one of them was the patient with Prader Willi syndrome.

Discussion

Growth hormone was initially extracted from pituitary of cadavers in the 1950's but the safety was an issue due to diagnosis of Creutzfeldt-Jakob disease (11). Recombinant growth hormone came in to use in early 1980's which was safer, and provided large amounts of growth hormone according to the demand (11).

In our patients mean age of presentation of growth hormone deficiency was 14.9 years. Severe growth hormone deficiency due to complete absence of growth hormone presents at a younger age, usually before 3 years (13). Those with late onset growth hormone deficiency or those with milder forms present at an older age (13). But delay in presentation in our context could also be attributed to lack of parents' knowledge in reaching medical advice, attributing short stature in their children as a normal phenomenon and poor growth monitoring at child welfare clinics and school health programmes.

Same dose of growth hormone is found to be less effective in accelerating the growth velocity after 6-12 months of therapy. Catch up growth can be obtained with increasing the replacing doses of growth hormone (12). Therefore we altered the dose, titrating it with the IGF values in the upper normal range and our patients were able to achieve a satisfactory increase in height.

There were 2 children who had low IGF-1 levels but normal ITT response. This kind of a picture is seen in growth hormone resistance but these adolescents did not show severe growth retardation which is seen in some forms of growth hormone resistance. These two adolescents were given a trial of growth hormone therapy to which they showed a good response with a growth velocity of 9.12cm/year. Moreover there is growing debate on the need of ITT in diagnosing growth hormone deficiency as stimulation tests are found to be highly variable, inaccurate and non-physiological (14-16). Therefore, serum IGF-1 levels along with the probable clinical features are considered to be a better marker (14-16).

At the end of mean follow up period of 1.3 (±0.8) years our patients with isolated growth hormone deficiency were able to achieve a growth velocity of 8.6 cm/year (±3.0 cm/year). Studies carried out in other countries have shown mean growth rates of 8.4-9.5 cm/year in the first year of treatment [17]. Genetic potential of the Caucasians would have contributed to the differences.

Several studies have reported a significant negative relationship between the linear growth response following GH therapy and chronological age, height, bone age. But in our adolescents we were able to establish a significant negative correlation between growth velocity and the bone age only.

Our patients did not show significant difference in age and height at presentation and growth velocity between those with normal and abnormal MRI scans. But according to Coutant et al (18) patients with growth hormone deficiency and MRI abnormalities are found to have severe short stature at diagnosis, younger age at diagnosis and significantly high catch up growth in response to treatment when compared with those with normal MRI scans. Despite this, when growing in to adulthood, studies show that > 63% of those with normal MRI scans have normalized their growth hormone secretary status while those with abnormal MRIs tend to have persistent growth hormone deficiency.

Turner syndrome is found to be a common cause for short stature among girls. Normal IGF1 levels were found in 4 of the 5 girls with Turner syndrome in our adolescents. Lebl J et al (19) states that the pathogenesis of growth failure in Turner syndrome could be due to reduced sensitivity to IGF1 or its reduced activity. In that study, IGF-1 levels done in 78 untreated Turner patients revealed low normal IGF-1 levels and treatment with growth hormone had lead to supraphysiological levels of IGF-1. In the same study, there had not been additional increase in IGF1 with addition of oestradiol to the growth hormone regimen. In our patients the IGF1 levels increased and maintained at an upper normal range in response to growth hormone therapy and were able to achieve a mean height velocity of 5.8cm/ year. Several studies have shown that at the end of treatment patients are able to achieve an increase in height of 5-10 cm but the growth improvement tends to decrease with time (20). Duration of treatment in Turners, though those who are treated are taller than untreated females, is still controversial because of the high cost and the final height is found to be below normal range (20).

We had one patient with Prader Willi syndrome who had biochemical evidence of growth hormone deficiency. It was found that more than half of Prader Willi children will have biochemical evidence of GHD (21,22). Obesity, poor growth, and hypotonia in these children are associated with abnormal body composition resembling a GH-deficient state (23). Recommended dosage for these children differs from the others. Continuation of growth hormone therapy is necessary until risks outweigh the benefits. Severe obesity was considered as exclusion criteria in children with Prader Willi syndrome for growth

hormone therapy. Though our child was obese (BMI= 37.53kgm^2) he did not fit in to 'severely' obese criteria. According to the consensus guidelines severe obesity is defined if a child is with a BMI of >95th centile and manifests complications of obesity such as sleep apnoea, non-alcoholic fatty liver disease or abnormal carbohydrate metabolism (9). Evaluation for diabetes risk should be carried out in children more than 12 years of age or in those with a family history of diabetes (9). Since our child did not fit into the above criteria prior screening was not done. But within 3 months of therapy he developed hyperglycaemic symptoms and we started insulin regimen and continued with growth hormone therapy.

Continuation of growth hormone into adulthood is still controversial. Most children outgrow from growth hormone deficiency when they reach adulthood. Transition period from adolescence to adulthood involves achieving the adult height, peak bone mass, adult body composition and reproductive maturity so continuation therapy in deficient individuals is important (23). Thus discontinuation of treatment in deficient individuals may lead to deleterious effects. Persistent growth hormone deficiency can be best predicted (PPV 100%) in those with organic hypothalamic pituitary disorder or ≥2 additional pituitary hormone deficiencies. In those with idiopathic growth hormone deficiency IGF-1 levels below -5.3 SD measured ≥ 6 weeks after completion of growth hormone treatment (PPV 100%) is also a good predictor (24). Therefore, in patients with pathologic disease a stimulation test to confirm growth hormone deficiency is required in the transition period. The appropriate dose of growth hormone during this period is controversial as secretion of the hormone is lower than during puberty but higher than during adulthood (23). Still our patients were not assessed for changes occurring during the transition period.

Since growth hormone is given as once a day subcutaneous injection, it is difficult to produce the normal pulsatile pattern of secretion. Despite this, the growth hormone therapy in deficient individuals leads to improved generalized wellbeing, improved body composition with increased lean body mass and reduced fat deposition. It improves bone mineral density, and lipid profile. In order to assess effects of therapy on the cardiovascular disease, bone fracture and the quality of life, it will require many years of growth hormone replacement (23).

Conclusions

In this study we were able to demonstrate an increase in growth velocity and IGF-1 levels in patients with growth hormone deficiency by growth hormone replacement. However lack of growth charts appropriate for Sri Lankan population is a main disadvantage as growth monitoring is difficult in growth charts for Caucasians. Also focusing the attention on early initiation of growth hormone therapy in Turner syndrome is important for clinicians. As a whole, growth hormone therapy is usually safe and is useful in gaining satisfactory height gain in adolescents.

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