Determinants of Pubertal Growth Spurt in Constitutional Delay of Growth and Puberty in Boys Treated With Testosterone

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ABSTRACT

BACKGROUND: Constitutional delay of growth and puberty (CDGP) is the most common cause of short stature and delayed puberty in children. Little is known about the changes in sex steroid and insulin like growth factor-1 (IGF-1) concentrations, body mass index (BMI), and growth velocity (GV) after testosterone therapy for CDGP.

CASE PRESENTATION: Retrospective chart review of 16 boys with CDGP treated with six monthly doses of testosterone cypionate 50 mg was carried out. Data on weight, BMI, height, GV, IGF-1, testosterone level and bone age radiographs were collected prior to testosterone treatment, six months and one year after the last testosterone injection. At six months and one year from last dose of testosterone, the mean height, weight, GV, mean IGF-1 and testosterone levels improved from baseline. There was a positive correlation between testosterone and GV (r= 0.74, p-value= 0.008) six months after the last testosterone injection.

CONCLUSION: At six months and one year after the last testosterone injection, the weight, BMI, growth velocity, IGF-1 concentrations and testosterone levels were higher than at baseline, and puberty progressed when compared to baseline. Testosterone levels six months after completion of testosterone cypionate were positively correlated with growth velocity confirming the effect of sex steroids in pubertal growth.

KEYWORDS: Constitutional delay of growth and puberty; boys; growth velocity; testosterone injection

INTRODUCTION

Constitutional delay of growth and puberty (CDGP) is the most common cause of short stature and delayed puberty in children.[1] The characteristic features of CDGP are short stature, delayed puberty, and delayed epiphyseal maturation. It is a physiological variant of normal and does not represent a pathology. The cause of CDGP is unknown. In some families, an autosomal dominant pattern of inheritance is noted.[2]

Testosterone and its metabolites are important for sexual maturation, the development of normal muscle and connective tissue growth and bone density and pubertal growth spurt. Though CDGP is considered a normal variant of growth, marked growth retardation accompanied by delayed puberty may result in sense of incompetence and vulnerability, low self-esteem, social isolation and poor academic performance in male adolescents. Testosterone therapy has been used in the treatment of such patients to initiate and accelerate puberty and stimulate pubertal growth spurt.[3,4] Treatment to accelerate pubertal onset includes a short course of intramuscular (IM) testosterone with different protocols, such as 50 mg IM monthly for six months or 100–150 mg IM every three-four weeks for four months.[5–9] Current data do not recommend growth hormone therapy to improve final adult height in these patients.[4] Current evidence also do not suggest that initial testosterone therapy diminishes future fertility.[4]

Some boys with CDGP will achieve their genetic height potential, while others reach an adult height within two standard deviations (SD) below their mid-parental target height, regardless of whether they received testosterone therapy or not.[6,7,9,10] Predictive factors that may affect adult height after treatment with low dose testosterone are a short upper body segment due to delayed puberty, lower height SDS at initiation of testosterone treatment, and family history of short stature.[7,11,12] Little is known about the impact of a short course of low dose IM on testosterone and IGF-1 concentrations, change in body mass index (BMI), and on growth velocity (GV). We evaluated the magnitude of pubertal growth rate and its relation to IGF-1, testosterone, weight, and BMI at six months and one year after completing a course of testosterone for CDGP in 16 boys.

METHODS

This was a retrospective chart review of male patients ≥14 years who were diagnosed with CDGP at the Pediatric Endocrinology Clinic, Hasbro Children's Brown University Health between January 2007 and January 2017. Criteria for inclusion in the study were: 1) height >2 SD below the mean, 2) delayed bone age (BA) by one to three years compared to chronologic age (CA), 3) birth size within two SD of the mean for gestational age, 4) parental heights within two SD of the mean, 5) normal endocrine function with no clinical and laboratory evidence of growth hormone, thyroid or sex steroid deficiency, 6) no evidence of underlying chronic

disease or skeletal dysplasia, and 7) pubertal staging of testicular volume at Tanner 2 (4–6 mL testicular volume) or below at initial assessment.

Data extracted from the electronic medical record include height (cm), height z score, weight (kg), weight z score, BMI (kg/m²), BMI z score, GV, Tanner staging of puberty,[13] mid- parental height, bone age (BA), IGF-1 level, IGF-1 z score, and testosterone level at the initial pediatric endocrinology appointment, the appointment prior to treatment, then six months and one year after completion of testosterone therapy. Predicted adult height (PAH) was calculated by the Bayley-Pinneau method.[14] Mid-parental height (MPH) was calculated by adding the average parent's height with 6.5 cm.[15] Z score is calculated using the WHO formula, (X- m)/SD where X is the observed value (height, weight or BMI), m, mean and SD standard deviation of the distribution corresponding the reference population.[16] Labcorp IGF-1 calculator was used for IGF-1 z score calculation.[17]

Testosterone levels were measured using high-pressure liquid chromatography/tandem mass spectrometry (HPLC/MS-MS) at Esoterix Laboratories (Calabasas, California,). IGF-1 levels were measured by blocking radioimmunoassay (RIA) after acid: alcohol extraction by Esoterix Laboratories (Calabasas, California).

Statistical Analysis

The clinical characteristics of the patients are summarized by mean, standard deviation for continuous variables, such as age, BA, chronological age, height, height SDS, weight, weight SDS, BMI, BMI SDS, GV, IGF-1, IGF-1 SDS, IGFBP-3, testicular volume (left and right), and mid-parental height. Wilcoxon-signed rank tests were implemented to compare continuous variables among treatment groups. Correlation coefficients were computed to analyze associations between continuous variables as appropriate. Observations greater than three standard deviations away from the mean were considered outliers and were excluded for analyses. Statistical significance was accepted when p-value <0.05. All statistical analyses were performed using statistical programming software R version 3.6.

RESULTS

A total of 337 charts were reviewed with ICD-9 and ICD-10 codes for the diagnoses of short stature and delayed puberty. Out of the 337 patients, 113 patients fulfilled the criteria for diagnosis of CDGP, 63 of whom were treated with low dose testosterone cypionate 50 mg IM injection for six months. Out of the 63 patients, 16 were included in the final study and 47 were excluded due to missing data. Family history of delayed puberty was present in 11/16 patients (68%), six of which were mothers and five were fathers.

The patient characteristics prior to initiation and six months and one year after the completion of testosterone therapy are given in **Table 1**. Participants had higher mean height (157.1 ± 6.3 cm vs. 149.5 cm ± 5.9, p <0.05) and weight (50.3 ± 10.3 kg vs. 44.2 ± 10.2 kg, p <0.05) at six months after completion of testosterone therapy compared to pretreatment measures [**Table 1**, **Figure 1**]. GV velocity six months after testosterone treatment was 7.66 ± 1.7 cm/year vs 4.61 ±- 2.21 cm/year in the pretreatment period (p <0.05) [**Table 1**, **Figure 1**]. The mean testicular volume increased from 6.5 ± 2.2 mL before treatment to 12.0 ± 4.0 mL at six months after testosterone injection [**Table 1**].

At one year after completion of testosterone therapy, height and weight improved compared to pre-treatment measurements [**Figure 1**]. The mean GV improved when compared to the pre-treatment values (7.9 ± 2.2 cm /year vs. 4.6 ± 2.2 cm/year vs, P <0.003 [**Figure 1**], with mean BA increasing to 15.0 ± 0.7 years from pre-treatment mean BA of 13.1 ± 0.4 years [**Table 1**].

We assessed weight, BMI and IGF 1 and testosterone levels in relation to growth velocity [**Figure 2**]. We found a positive correlation between testosterone and GV (r= 0.74, p-value= 0.008) at six months after last testosterone injection. There was no positive correlation between the other variables at six months and one year after last dose of testosterone injection [**Figure 2**].

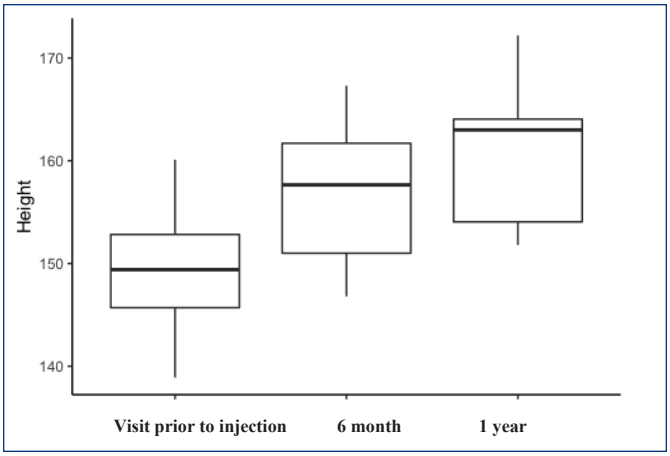
Table 1. Auxological and anthropometric data before and six months and one year after completion of treatment

Variables	Visit prior to injection (n=16)	N	Six months post-completion of treatment	N	One year post-completion of treatment
Age (years)	14.4 ± 0.5	16	15.0 ± 0.7	16	15.5 ± 0.9*
BA (years)	13.1 ± 0.4	11	13.7 ± 0.4	5	15.0 ± 0.7
Height (cm)	149.5 ± 5.9	16	157.1 ± 6.3*	16	160.6 ± 6.2*
Height SDS	–2.20 ± 0.6	16	–1.86 ± 0.7*	16	–1.64 ± 0.7*
Weight (kg)	44.2 ± 10.2	16	50.3 ± 10.3*	16	52.1 ± 10.9*
Weight SDS	–1.54 ± 1.7	16	–1.24 ± 1.5	16	–1.31 ± 1.5
BMI (kg/m²)	19.6 ± 3.8	16	20.2 ± 3.5	16	20.2 ± 3.4
BMI SDS	–0.49 ± 1.9	16	–0.35 ± 1.5	16	–0.59 ± 1.5
IGF-1 (ng/ml)	170.5 ± 83.5	5	321.60 ± 73.6	2	366.0 ± 2.83
IGF-1 SDS	–2.07 ± 0.9	5	–0.44 ± 1.0	2	–0.54 ± 0.03
Testosterone (ng/dl)	57.5 ± 28.5	11	316 ± 155.2	4	403.5 ± 283.5
Left testis (mL)	6.5 ± 2.2	16	11.7 ± 3.4*	16	15.9 ± 4.7*
Right testis (mL)	6.5 ± 2.3	16	12.0 ± 4.0*	16	15.4 ± 4.0*
MPH (cm)	174.1 ± 5.5	16	174.1 ± 5.5	16	174.1 ± 5.5
PAH (cm)	170.8 ± 7.8	11	171.2 ± 4.5	5	168.1 ± 2.9
GV (cm/year)	4.61 ± 2.2	16	7.66 ± 1.7*	16	7.97 ± 2.2*

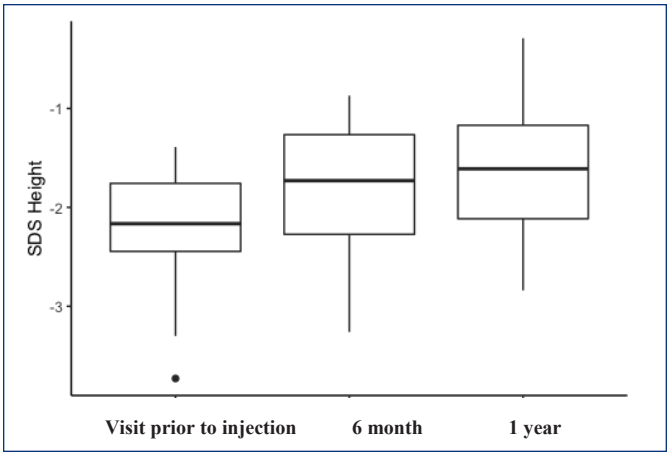
Values are expressed as the mean ± SD
BA-bone age, BMI-body mass index, IGF-1-insulin like growth factor 1, GV-growth velocity, MPH-mid-parental height, PAH-predicted adult height. * P < 0.05.

Figure 1A–C. Height, Height z score and GV of the treatment group

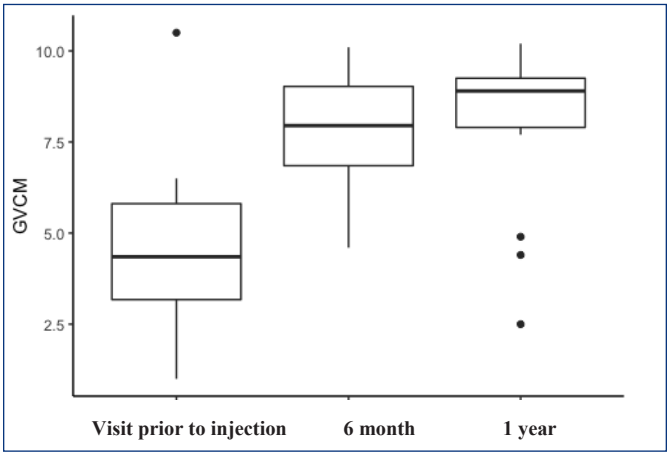
[**A**] Height (cm) measures for the treatment group prior to treatment, at six months and one year from last dose of testosterone injection



[**B**] Height SDS measures for the treatment group prior to treatment, at six months and one year from last dose of testosterone injection



[**C**] GV (cm/year) measures for the treatment group prior to treatment, at six months and one year from last dose of testosterone injection



DISCUSSION

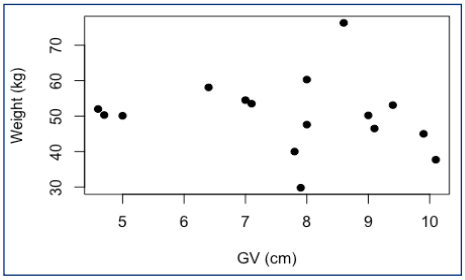
Our study found a positive correlation between GV and serum testosterone concentration at six months from the last testosterone injection, confirming the effect of sex steroid in pubertal growth. In contrast, the weight, height, BMI, and IGF-1 concentration did not have a positive correlation with GV. Study participants had significant weight gain at six months and one year post completion of testosterone treatment.

Pubertal growth represents approximately 15–20% of adult height and precedes the fusion of growth plates.[18] Factors affecting the pubertal growth spurt in males include variations in pubertal timing, interaction between the different endocrine hormones (thyroid hormones, testosterone, growth hormone and IGF-1 level) and nutritional status.[19,20] Our study observed a positive correlation between testosterone level at six months after the last dose testosterone injection and GV, but no correlation was observed between the testosterone level and GV at one year after completion of testosterone treatment. This could be partly explained by the missing data since only 4/16 participants had repeat testosterone levels during follow-up. Stronger association between testosterone level and growth spurt during early puberty compared to late puberty was reported by another study.[21] A cross-sectional study on 26 healthy boys ages 8.7–15.4 years that assessed serum testosterone levels in relation to pubertal growth spurt observed correlation between serum testosterone and growth velocity in boys with testicular volumes between 3 and 6 ml ($r=0.87$, $p<0.001$) and the association was weaker in boys with testicular volume >6 ml ($r=0.56$, $p<0.05$)[21]. Sex hormones, androgens and estrogens, play a major role in the pubertal growth spurt through their direct effect on bone growth plates and indirect effect on GH – IGF1 axis, explaining the correlation between testosterone level and GV.[22]

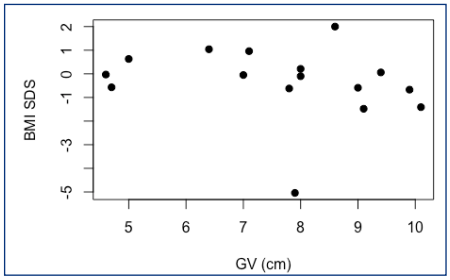
Our subject's GV six months after the completion of testosterone injections 50 mg monthly for six months was 7.6 cm/year, which was less than that was reported by Soliman et al (11.5 cm/year)[23] and Giri et al (8.4 cm/year)[24] and Kaplowitz (11.2 cm/year).[25] This may be due to differences in testosterone regimens used by different groups. Soliman et al used six doses of monthly testosterone 100 mg, which was double the testosterone dose used in our study.[23] Giri et al treated boys with CDGP with testosterone enanthate 125 mg every six weeks for a total of three doses.[24] Kaplowitz used four doses of testosterone enanthate 100 mg monthly in 23 patients with CDGP and reported a GV of 11.2 cm and 8.3 cm respectively at one month and four months after the last testosterone injection.[25] Higher doses of testosterone may lead to a robust GV, and randomized study exploring different testosterone doses on growth velocity is needed. However, it is known that some adolescents with CDGP may have blunted pubertal growth spurt that can lead to a shorter adult height compared to genetic height potential.[9]

Figure 2A–G. Correlation coefficients between analyzed variables and GV six months post-testosterone treatment

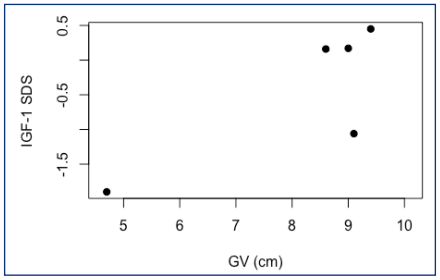
[**A**] r=-0.157, p-value=0.5747



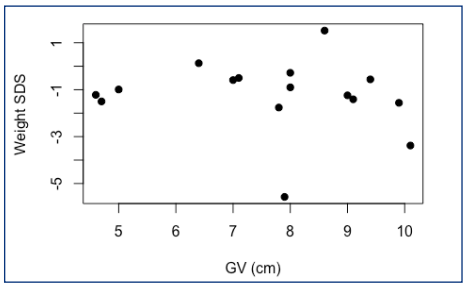
[**D**] r= 0.21, p-value= 0.4193



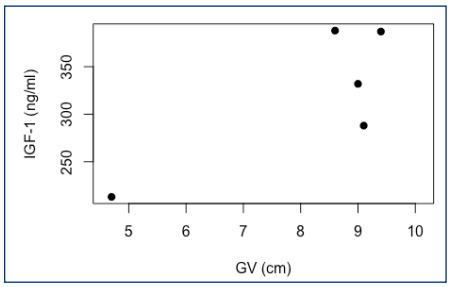
[**F**] r= 0.03, p-value= 0.909



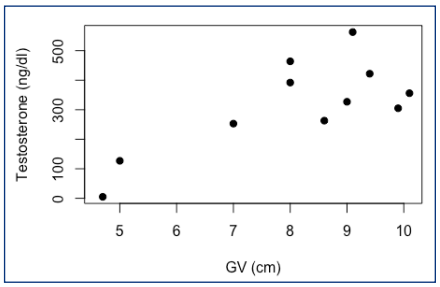
[**B**] r= 0.137, p- value= 0.6126



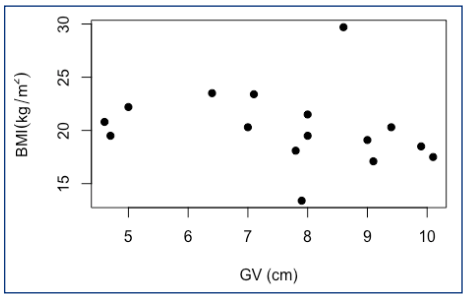
[**E**] r= 0.80, p- value = 0.1012



[**G**] r= 0.74, p-value= 0.008



[**C**] r=-0.227, p-value=0.4154



In our study, the mean weight gain was 6 kg after testosterone therapy. This finding was similar to what was reported by prior studies.[21,23] Soliman et al observed a weight gain of 4.8 kg after testosterone therapy in patients with CDGP.[21] Kaplowitz reported a four-fold increase in weight velocity (11.2 Kg/year) at the initial follow-up at one month after the last testosterone injection with an average weight gain of 4.2 Kg.[23] Significant increase in weight occurs during puberty with a gain of about 50% of adult body weight occurring during this time. In boys, peak weight velocity happens at about the same time as peak height velocity, around 14 years and averages 9 kg/year.[17]

Adverse effects of testosterone therapy are rare in the short-term therapy of three to six months, usually indicated in patients with CDGP. Common side effects of testosterone therapy include erythrocytosis, acne and oily skin. Mild elevation in liver enzymes can also occur.[26,27] None of our patients experienced any significant side effects.

The effect of sex steroids for patients with delayed puberty on adult outcomes including fracture risk, metabolic and cardiovascular outcomes remain unclear.[28]

Limitations of our study include the lack of control group, retrospective design and small sample size. Growth hormone markers and testosterone levels were not available for all the patients. Growth hormone provocative stimulation testing to rule out growth hormone deficiency was not done in our cohort. However, we observed a two- three-fold increase in IGF-1 levels after treatment, arguing against undiagnosed GH deficiency in the patients included in this study.

CONCLUSION

Six months and one year after the last testosterone injection, the weight, BMI, GV, IGF-1, and testosterone concentrations were significantly higher in adolescent boys with CDGP compared to baseline. The testosterone concentration was positively correlated with the GV at six months after the last dose of testosterone. A short course of six months of testosterone injection is safe and effective in accelerating growth velocity and pubertal progression in boys with short stature and delayed puberty and who are psychologically distressed by their short stature and slow pubertal progression. Future studies should examine the effect of different doses of a short course of testosterone treatment in pubertal growth among adolescent boys with CDGP.

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