

GROWTH HORMONE TREATMENT IN CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

Aleksandra Janchevska, Marina Krstevska-Konstantinova, Velibor Tasic, Zoran Gucev

University Children's Hospital, Medical Faculty Skopje, Republic of Macedonia

Corresponding author: Aleksandra Janchevska, University Children's Hospital Skopje, Macedonia, Medical Faculty Skopje, Republic of Macedonia, Mother Teresa 17, 1000 Skopje, Macedonia, Email: dr.sasha1969@yahoo.com

ABSTRACT

Introduction: Growth failure is a common consequence in small for gestational age (SGA) children.

Patients and Methods: The growth patterns and serum insulin like growth factor 1 (IGF1) concentrations before and after the 1st year under growth hormone treatment of 32 short stature SGA born children have been evaluated. In addition, we investigated the insulin like growth factor 1 receptor (IGF1R) exon 2 as a hotspot for IGF1R genetic alterations. It is of note that no dysmorphic features were observed in this group of children.

Results: The tests for pituitary reserve were within normal ranges for all 32 patients. Growth hormone (GH) treatment (0.037 mg/kg/day) was initiated at the mean age of 9.32±3.19 years. Growth velocity increased yearly from -1.80 SDS after the first year to -0.03 SDS in the sixth year of treatment. Their IGF1 serum concentrations before treatment were age and sex appropriate, while during treatment a significant increase was observed fitting in the upper third of the normal range: before the treatment IGF1 SDS was 0.84±1.78 after 1st year the concentrations increased to IGF1 SDS 0.94±2.23. No genetic alterations were found in the IGF1R exon 2 by PCR analysis.

Conclusions: Herein we present 32 short stature SGA children with no dysmorphic features treated with GH. They all had increased growth velocity and entered the normal growth range on their growth charts. No side-effects were observed. GH treatment in children with no genetic alterations on the IGF1R exon 2 is safe and efficient in treating SGA children with short stature.

Keywords: small for gestational age, short stature, IGF1, insulin like growth factor 1 receptor, growth hormone treatment

INTRODUCTION

Children born SGA are those with birth weight and/or length ≤ 2 SD below the mean for the gestational age (GA). [1, 2, 3, 4]

The prevalence of SGA was estimated to vary between 2.3% to 10% worldwide. In the USA, about 2.3% of all newborns were SGA [5;

2004]. A Japanese study on children born between 2006 and 2008 found the SGA prevalence to be 3.5%. [6] The increasing prevalence of term newborns less than 2400gr was noticed in Korea, from 3.0% in 1995 to 4.6% in 2007. [7] A Swedish study reported 5.4% SGA, [8] while the highest

observed prevalence was observed in South Asia and in Saharan countries of Africa. [9]

SGA born children have health consequences throughout their whole life. The most frequent SGA consequence is stunted growth. Although the majority of SGA born children grow fast during the first year of life, about 5-10 percent of them do not achieve catch-up growth and remain short. In premature SGA children the catch-up growth is slower and takes longer, till the 4th year of age. [7, 10] Potential risk of short stature in adulthood has been estimated to be 5-7 times higher in children born SGA than in their peers born appropriate for their gestational age, AGA. [11]

PATIENTS

We evaluated the growth patterns in the group of 32 short SGA children who underwent growth hormone (GH) treatment.

METHODS

Clinical data included children's birth weight (BW) in kilograms, birth length (BL) in centimeters, BW standard deviation score (SDS), BL SDS and gestation weeks (GW).

Growth parameters were: height, weight, body mass index (BMI), BMI z-score, occipitofrontal circumference (OFC) and target height. The baseline was the start of the study, and in short SGA patients who were treated with GH measurements that were done every year during the follow up period. The Harpenden stadiometer, a wall mounted digital rod, was used for height measurement of the children and their parents. Weight was measured with a precision scale used exclusively for children. Patient's weight and height percentile values were assessed by plotting the measured values in WHO growth curves for the gender. The target height (TH) for boys was calculated using the formula: $(\text{paternal height} + \text{maternal height})/2 + 6\text{cm}$ and the target height for girls as follows: $(\text{paternal height} + \text{maternal height})/2 - 6\text{cm}$. Body mass index (BMI) was evaluated by the standard formula: kg/m^2 adequate for the patient's age and sex. The BMI stratification was: underweight <18.5 ; normal weight = $18.5-24.9$; overweight = $25-29.9$ and obese if BMI is 30 or

greater. [12] In addition, we also used the BMI-z score as a more precise tool in children.

Bone age was determined according to the Greulich and Pyle standards as a standard hand and wrist radiograph. Bone maturation was expressed as the ratio between the bone age and the chronological age for a given visit. The bone age delay was calculated as chronological age minus bone age.

The serum concentrations of GH, IGF1, T4, and TSH were determined by chemiluminescence immune assay method on IMMULITE 2000 Siemens, Immunoassay System apparatus. The blood samples for IGF1 were obtained at the baseline, before the initiation of treatment, and again a year after initiation of the therapy. The insulin-like growth factor 1 binding protein 3 (IGF1 BP3) was not available.

The molecular analysis of the IGF-1R gene was performed on a "Biometra" - T3 Thermo-cycler PCR apparatus. DNA was isolated from leukocytes with a highly concentrated 5M NaCl solution. The exon 2 was amplified with the following primers: 5'TCGACATCCGCAACGACTATC3' as the forward primer and 5'CGAAGATGACCAGGGCGTAG3' as the reverse primer. PCR products were digested with Dde I (Sigma Aldrich), and the resulting fragments were run on a 1% agarose gel and stained with ethidium bromide.

Statistical analysis

The Kolmogorov-Smirnov test (KS test) is used to check whether the values have the expected normal (Gaussian) distribution. A confidence interval (CI) is calculated for the mean of each of the quantities. For the comparison of the IGF1 and IGF1SDS values, Fisher's test is used to check the equivalence of the variances. As the values had a size greater than 30 they were considered to be sufficiently large and a z-test was used, otherwise the standard t-test was applied. All tests had a 99% significance, or $\alpha=0.01$.

RESULTS

Thirty-two SGA born children (M:F=17:15) had mean BW $2254.00 \text{ gr} \pm 392.27$ SDS and BW SDS -2.78 ± 0.90 SDS, BL $46.87 \text{ cm} \pm 2.19$ SDS and BL SDS -1.37 ± 0.86 SDS and were born within 39.06 ± 1.04 SDS GW. Their birth parameters are summarized in Table 1. Those children did not achieve catch-up growth after the 2nd year of age and remained short after the 4th year and had H

SDS -2.77 ± 0.72 SDS, and W SDS (-1.84 ± 0.83 SDS), BMI $15.44 \text{ kg/m}^2 \pm 2.01$ SDS, BMI z-score (-0.97 ± 2.03 SDS), OFC SDS (-0.86 ± 1.27 SDS) and TH SDS (1.16 ± 0.76 SDS). Their auxologic values are summarized in Table 2.

Table 1. Birth parameters: Birth weight (BW), BW SDS, birth length (BL), BL SDS and Gestation Week (GW) in a group of 32 short SGA born children.

GROUP		short SGA children
PARAMETERS		mean
BW	gr	2254.00 ± 392.27 SDS
BW SDS	-	-2.78 ± 0.90 SDS
BL	cm	46.87 ± 2.19 SDS
BL SDS	-	-1.37 ± 0.86 SDS
GW	w	39.06 ± 1.04 SDS
Patients	M	n= 17
	F	n= 15

Table 2. Auxologic parameters: height SDS (H SDS), weight SDS (W SDS), BMI and BMI z-score, OFC SDS, target height (TH) SDS in a group of 32 short SGA born children..

GROUP		short SGA children
PARAMETERS		mean
H SDS	-	-2.77 ± 0.72 SDS
W SDS	-	-1.84 ± 0.83 SDS
BMI	kg/m^2	15.44 ± 2.01 SDS
BMI z-score	-	-0.97 ± 2.03 SDS
OFC SDS	-	-0.86 ± 1.27 SDS
TH SDS	-	-1.16 ± 0.76 SDS

The mean bone age delay was 2.77 ± 0.47 SDS years.

The tests for pituitary reserve for the evaluation of GH reserve were done with L-Dopa and/or Clonidine. T4 and TSH serum concentrations were within normal ranges. The IGF1 serum concentrations and IGF1 SDS values in the whole group have increased significantly ($p=0.00016$) and ($p=0.00036$) after one year of treatment: IGF1 SDS were 0.94 ± 2.23 .

GH treatment was initiated in all subjects with a 0.037 mg/daily dose [13] and at an average age of 9.32 ± 3.19 years for 1-6.5 years at the time of the study. The height velocity significantly increased in all subjects (Fig. 1). At the start of the GH treatment their mean height SDS was -2.77 SDS, and after the first year of treatment height velocity was increased to 8.65 cm , lowering the mean height SDS to -1.80 SDS. The trend continued in the 2nd year with HV of 7.45 cm (mean height SDS -1.50), and in every year consecutively. The 3rd year HV was 6.11 cm (mean height SDS -1.20 SDS), the 4th year HV was 6.73 cm (mean height SDS -0.47 SDS), the 5th year HV was 7.16 cm (mean height SDS -0.35 SDS) and after the 6th year HV was 7.42 cm (mean height SDS -0.03 SDS).

The PCR amplification of the exon 2 of the IGF1R gene did not show any genetic alterations.

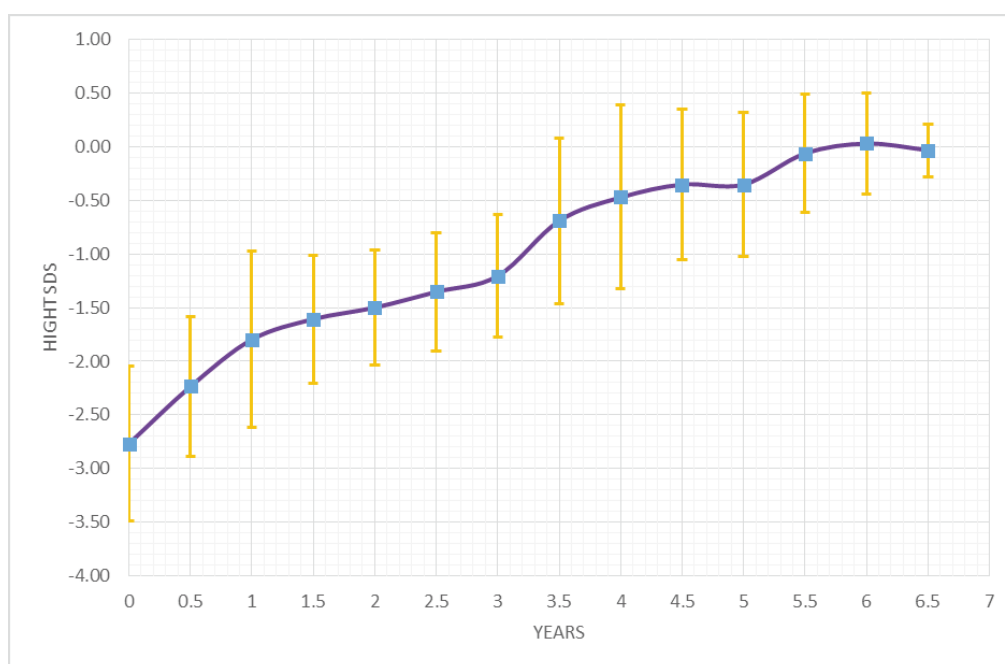


Figure 1. Growth assesment in GH treated SGA born children - height SDS

DISCUSSION

Approximately 8% of all SGA born children have had at least minus two SDS in the final height. Most of children born SGA are not growth hormone (GH) deficient. [14, 15] Nevertheless, GH treatment for SGA children has been approved in USA and EU, starting at the age of 2 years (FDA) or four years (EMEA). [13]

By treating 32 SGA children, we also demonstrated a strongly increased growth velocity in all subjects. Moreover, they got to the point of less than two SDS of their height, and attained normal height

Schwarz et al 2014 [16] have shown gain in the mean height SDS from -3.39 SDS at start to -2.57 SDS and 8.99cm height velocity after 1 year of treatment. Lee et al. [17] in their comparative study have shown 1.03 SDS increment in height in pre-pubertal SGA born children after 2 years of GH treatment which was greater than in children with idiopathic short stature (+0.84 SDS) and children with isolated growth hormone deficiency (+0.97 SDS). The evaluation study performed by Takeda et al. [18] has shown 4 cm higher adult height and significant improvement in height SDS in SGA born children who underwent GH treatment when compared to the untreated SGA born peers.

Time of onset of the GH treatment before puberty is a very important predictor for the height achievement. In fact, a start of treatment even 1 year before puberty is beneficial, but greater effect has been achieved if treatment was initiated two years before puberty. [19] If children have been treated during puberty the estimated height gain was only 0.6 SDS and less than half of them achieved favorable final adult height. [19] Favorable effects on height, height velocity and BMI was also reported by Aurenzanz Clemente et al. 2017. [20]

There is a trend in treating SGA children at a younger age. Although a prevalent criteria for growth hormone treatment is age less than two years and short stature (<-2.0 SD) and a growth velocity < 25th percentile for their age [21], the discussions on the appropriate age of onset of treatment abound.

In 2007, [2] Clayton et al. in their consensus statement proposed an early initiation with GH treatment in SGA children with severe growth retardation (<-2.5 SDS) aged between

2 and 4 years. In the very young SGA children (19-29 months) treated with GH there was a significant increment in height velocity, when compared with their untreated peers. [22] However, not all report a favourable outcome after GH treatment in SGA children. Tauber [23] found a mean adult height that is higher than -2 SDS in 60% of patients and 70% reached an adult height in their target height.

Having in mind the important role of growth hormone and IGF1 on brain development and linear growth, Laron et al. [24] proposed GH commencement before 2 year of age. On the other hand, the safeness and effectiveness of GH treatment in SGA children was also proven by decreasing the frequency metabolic complications further in adolescence and adulthood. [25] Therefore, a multidisciplinary approach (perinatologist, nutritionist and pediatric endocrinologist) is needed in the treatment and follow up of SGA born children. [21]

In our group of 32 SGA children the serum concentrations of IGF1 were within age and sex appropriate values. However, under treatment with GH, those values increased as a group, providing a useful tool for monitoring the adequacy of GH doses. It has been demonstrated that serum IGF1 concentrations is a very important predicting parameter for the safety and effectiveness of growth hormone treatment in children. [26, 27] SGA born children had 90% increment of IGF1 serum concentrations after the first year and 123% after the second year of GH treatment. [28]

A number of SGA children have been found to have genetic alterations in the IGF1R gene. The exon 2 in IGF1R gene was described as a hot spot for possible alterations in SGA born children since 2003 by Abuzzahab et al. [29] Interestingly, some of those children had microcephaly and dysmorphic features. In a child with deletion on 15q26.2 intrauterine growth retardation, postnatal growth failure, and recurrent hypoglycemia were reported and a FISH study using IGF1R probes showed only a single IGF1R gene. [30] The R59X mutation was reported in two half-brothers with primary microcephaly, mild mental retardation, and intrauterine as well as postnatal growth deficits. [31] In addition, among 50 children with short stature with elevated circulating IGF1 concentrations, a R59X mutation was reported. [29] SGA, microcephaly, persistent postnatal growth retardation, and elevated IGF1 levels were reported in a 15-year-old girl with heterozygous deletion

of 15q26.2-qter, including the IGF1R gene. [32] Microcephaly, pre- and postnatal growth retardation were found in patients with heterozygous missense mutations in three unrelated patients, de novo p.Arg1256Ser, de novo p.Asn359Tyr and p.Tyr865Cys. [33]

We checked the exon 2 of the IGF1R gene for possible genetic alterations and found no alterations.

CONCLUSIONS

We described 32 short stature SGA children with no dysmorphic features treated with GH. They all had increased growth velocity and entered the normal growth range on their growth charts. The IGF1 serum concentrations were within normal age and sex range and increased significantly during the GH treatment. No side-effects were observed. GH treatment in children with no genetic alterations on the IGF1R exon 2 is safe and efficient in treating SGA children with short stature.

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Резиме

ТРЕТМАН СО ХОРМОН ЗА РАСТ КАЈ ДЕЦАТА РОДЕНИ МАЛИ ЗА ВОЗРАСТА

Александра Јанчевска, Марина Крстевска-Константинова, Велибор Тасиќ, Зоран Гучев

Универзитетска клиника за детски болести, Медицински факултет, Скопје, Република Македонија

Вовед: Нарушувањето на растот е честа последица кај децата родени мали за гестациската возраст (СГА).

Пациенти и методи: Беа евалуирани постигнувањата во растот и серумските концентрации на ИГФ1 кај 32 ниски СГА родени деца лекувани со хормон за раст (ГХ) пред започнувањето и една година по започнувањето со третманот. Дополнително, го истражувавме егзон 2 на генот за ИГФ1 рецепторот како хотспот за можни генетски аберации во тој ген.

Резултати: Тестовите на питуитаната резерва беа во нормални граници кај сите 32 пациенти. Третманот со хормон за раст (ХР) (0,037 mg/kg/day) беше започнат на средна возраст од $9,32 \pm 3,19$ години. Брзината на раст беше годишно евалуирана и беше најдено постепено зголемување на средната вредност на В СДС од $-1,80$ СДС по првата година до $-0,03$ СДС по шестата година од третманот. Измерените ИГФ1 серумски концентрации пред започнувањето со третманот беа соодветни за полот и возраста, додека во текот на третманот тие значајно пораснаа, одговарајќи на горната третина од нормалниот опсег: пред третманот ИГФ1 СДС беше $-0,84 \pm 1,78$, а една година по започнување со третманот пораснаа и ИГФ1 СДС беше $0,94 \pm 2,23$. Со ПСР анализата не беа најдени генетски алтерации во егзон 2 на ИГФР1 генот.

Заклучоци: Прикажани се 32 СГА родени деца со низок раст, без дизморфични карактеристики, кои беа третираны со ХР. Сите тие ја зголемија брзината на растењето и влегоа во нормалниот опсег на раст на своите табели за раст. Не се забележани несакани ефекти. Лекување со ХР кај децата со СГА без генетски промени на IGF1R во егзонот 2 е ефикасен и безбеден во лекувањето на СГА деца со низок раст.

Клучни зборови: мали за гестациската возраст, низок раст, ИГФ1, ИГФ1 рецептор, третман со хормон за раст

