Growth in small-for-gestational-age for term-born children

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Abstract
Children born small for gestational age (SGA) has been associated to increased childhood mortality and morbidity and poorer quality of life. Several gestational factors can impair fetal growth, being intrauterine growth restriction is the most commonly seen. After term, SGA are prone to develop debilitating and high costly chronic diseases in adult life. There are more SGA patients that reaching adult age, making highly relevant the need for adequate early diagnosis an appropriate intervention at childhood and adolescence. This case-report presents a 6-years follow-up of SGA 9-15 years-old patient that received growth hormone (GH) to stimulate growth and showed improved outcomes.

Introduction
Children born small for gestational age (SGA) is decreased birthweight and length at term twice standard-deviation (Z-score) [1,2]. It has been associated to increased childhood mortality and morbidity and poorer quality of life [3]. According to the United Nations Children’s Fund State of the World’s Children Report, SGA affects approximately 14% of term deliveries in developing countries, though many cases remain unreported [4].

Fetal human growth results from the combination of genetics, fetal and mother health and nutritional availability [5]. The unbalance of any of these aspects can impair fetal growth. Intrauterine growth restriction is the most commonly seen gestational complications that impairs fetal growth [5].

After term, SGA are prone to develop cardiorespiratory diseases, musculoskeletal growth impairment, obesity, immunologic deficits and cognitive impairment [6]. Nowadays, there are more SGA patients that reaching adult age, making highly relevant the need for adequate clinical follow-up for this group of patients [7]. This case-report presents a 6-years follow-up of SGA 9-15 years-old patient that received growth hormone (GH) to stimulate growth and showed improved outcomes.

Case presentation
Identification: 8-years and 6-months old, male children, pale skin, born and raised in São Paulo-SP, and accompanied by their parents.

Main complaint: Low stature and slow growth.

History of the present disease: Parents report that the child grows less than expected since the first year of life. The patient is smaller than siblings and schoolmates. No pediatric medical following for more than 4 years.

Familial history: Born at term through normal delivery, weighing 2.250 g (Z-score: -2.19) and 45 cm length (Z-score: -1.89). No disabilities and adequate Neuropsychomotor development. Parents deny gestational complications, drug abuse, alcohol and smoking. There no history of continuous medications, surgeries or pre-existent diseases. Familial history revealed normal stature for both parents.


Laboratory assessment: Were assessed venous blood gases, fasting blood glucose, thyroid stimulating hormone (TSH), somatomedin (IGF-1), free thyroxine (free T4), total calcium, phosphorus, alkaline phosphatase, and anti-endomysium.

Magnetic resonance imaging of the pituitary revealed preserved anatomical structures. Growth hormone (GH) stimulation test with clonidine was also performed and the results are described in Table 1.

After data collection it was hypothesized that slow growth rate due SGA. Differential diagnosis included hormonal deficiencies and chronic diseases. Cutaneous GH (0.15 U/kg/day) was administered and growth rate follow-up every month.

Evolution: Patient evolved with good response to hormonal treatment, without intercurrences. Discomfort or pain during treatment was not reported. The hormonal treatment provided a good growth rate, ranging from 7 to 9 cm/year (Figure 1). Stature follow-up and laboratory assessment are described in Table 2.

Treatment disruption: Hormonal treatment was disrupted at 14 years old due patient absence.

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Resume hormonal treatment due to the advanced bone age (18 years). At this moment, it was not possible to complaint of slowing growth rate, though presented weight and body obesity, drug or alcohol abuse, smoking and/or chronic diseases [8-13]. Recently, inherited predisposition may influence in fetal growth. SGA is associated to increased risk of chronic diseases, being strongly correlated to metabolic syndrome and cardiovascular disease in adult life. [14,15].

The majority of live SGA newborns are able to recover their weight and height deficits in the first years of life. Though, 10-20% of individuals will present deficient growth and short stature after puberty [16-18].

GH is an indicated treatment for growth recovery in SGA children who did not catch-up in the first years of life. It was recognized and approved in 2001 by the US Food and Drug Administration (FDA) for SGA children whose stature remains two standard deviation (-2 SD) below the mean for age and sex, starting at 2 years of age. In Europe, since 2003 by the Committee for Proprietary Medicinal Products, the treatment of SGA children with growth hormone is indicated from 4 years with a deficit of less than 2.5 SD. It is also indicated when the child has a low growth rate or height below 1 SD of the familiar stature target. In this clinical case the child presented P: 2.250 g (Z-score: -2.19) at birth, being classified as SGA, being other causes of short stature excluded after laboratory exams and magnetic resonance imaging of the pituitary gland. In this case, short stature could have been diagnosed earlier and he could have started treatment with growth hormone between 2 and 4 years, but only started using GH at 8 years old due to late diagnosis.

Height and age at the onset of puberty, as well as the magnitude and duration of pubertal growth are important in determining the final height. Pubertal studies in PIGs are controversial, but most authors seem to agree that puberty is initiated within the normal range, but relatively early for their short stature [17,19-21]. At 8 years and 6 months, this patient had a height of 118 cm. At 9 years and 5 months with a height of 126.5 cm, puberty started. At 10 years and 6 months there was already a testicular increase (G2P2), height of 136.5 and bone age of 10 years. At 14, GH treatment was disrupted, despite guidelines and medical counselling for treatment maintenance until the end of puberty. Though the patient achieved satisfactory stature, he did not achieve estatural target.

Follow-up: Three years after treatment disruption patient complained of slowing growth rate, though presented weight and body mass index adequate for the age. At this moment, it was not possible to resume hormonal treatment due to the advanced bone age (18 years).

Discussion

SGA can occur in both pre-term and term born children, generally due to gestational complications such as maternal health impairment, obesity, drug or alcohol abuse, smoking and/or chronic diseases [8-13]. Recently, inherited predisposition may influence in fetal growth. SGA is associated to increased risk of chronic diseases, being strongly correlated to metabolic syndrome and cardiovascular disease in adult life. [14,15].

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Height and age at the onset of puberty, as well as the magnitude and duration of pubertal growth are important in determining the final height. Pubertal studies in PIGs are controversial, but most authors seem to agree that puberty is initiated within the normal range, but relatively early for their short stature [17,19-21]. At 8 years and 6 months, this patient had a height of 118 cm. At 9 years and 5 months with a height of 126.5 cm, puberty started. At 10 years and 6 months there was already a testicular increase (G2P2), height of 136.5 and bone age of 10 years. At 14, GH treatment was disrupted, despite guidelines and medical counselling for treatment maintenance until the end of puberty. Though the patient achieved satisfactory stature, he did not achieve estatural target.

Precocious puberty is also a concern in SGA [19]. At 10 years the puberal axis and puberty block with GnRH analogue could have been evaluated. In instance, due to poor attendance, the patient returned only after 1 year, at 11 years and 6 months (142.0 cm in height, G3P4, 10:12 years). Within this evolution it was chosen to maintain only the use of GH at the dose of 0.15 U/kg/d. Aromatase inhibitors could be administered to block puberty axis, however, since its use is still off label, this strategy was not undertaken in the present case.

Regarding bone age, at the age of 18 y, the patient had epiphyseal extermities closed, discarding GH administration at this point. If other causes of short stature are excluded, as long as secondary comorbidities and cancer, early age hormonal treatment with close follow-up remains an important preventive strategy for reducing incidence of chronic diseases and to improve quality of life in adulthood [22].

Conclusion

This clinical case shows us the importance of the growth in the SGA patient's puberty to guarantee an adequate final height. Adequate and frequent follow-up should be maintained throughout childhood and adolescence. In this case the final height of the patient was impaired by the abandonment of treatment during puberty.
References


