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Growth in small for gestational age children. Growth hormone therapy

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A small for gestational age (SGA) child is defined as a child whose birth weight and/or birth length is less than -2 SD of the mean for their gestational age. There are multiple causes of fetal growth restriction, which may be classified into placental, maternal, and fetal causes. The latter may be due to genetic and epigenetic causes, making up a heterogeneous group with associated dysmorphology and postnatal growth failure.[1]

These children have a greater risk for being short during childhood and end up with an adult height below the average height for their age, sex, genetic target height (GTH), and population of origin. The risk for being short is 5 times higher in children born with a low birth weight and 7 times higher in those born with short stature; approximately 20% of short adults were found to have been SGA.

Once born, 86% of these children show catch-up growth velocities. In most cases, catch-up occurs up to 2 years of age in term infants and up to 3 years of age in preterm infants.[2]

After catch-up, the prepubertal growth observed in these children is similar to that of children born with a weight and length that is adequate for gestational age (AGA). An early onset or rapid progression of puberty, earlier peak height velocity (PHV) of smaller amplitude and duration, earlier pubarche and adrenarche, and earlier fusion of the growth plate have been described during puberty. Such auxological and clinical parameters must be taken into account because of the risk of ending up with a shorter final height.

Treatment with recombinant human growth hormone (rhGH) is indicated in children who have not shown spontaneous catch-up growth.[3] This indication has been approved by the Food and Drug Administration (FDA) as of 2 years of chronological age, by the European Medicines Agency (EMA) as of 4 years of age, and in Argentina as of 5 years of age since 2010 (Resolution 2091/2010, National Ministry).[4] The goal of treatment is to achieve a height within the normal range during childhood and a final height adequate for the population, sex, and GTH.

Although many studies have assessed the effectiveness of rhGH for this condition, few studies have been conducted in a randomized manner with control groups. Maiorana et al.,[5] provided a systematic review describing 4 studies of moderate to high impact that included 391 patients. They reported a final height gain of 1.5 SD (9.5 cm) in children who received treatment versus 0.25 SD (1.6 cm) in untreated children. In

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any case, approximately 15% of children failed to reach an adequate final height. Although it is ideal to start treatment at an early age, Lem et al.,[6] described, in pubertal children with a predicted height of less than -2 SD, the usefulness of combining rhGH treatment with gonadotropin-releasing hormone analogues (GnRHa), the latter for 2 years, to improve their final height. The patients treated with the combined treatment grew 35.5 cm and 24.5 cm, respectively.

During the first years of treatment, a correlation has been established between its effectiveness and a younger age at onset, and a lower SD score for height, rhGH dose, and parental height. In the second year, the strongest correlation was observed with growth velocity in the first year.

SGA children include a heterogeneous group of patients, including preterm infants and those with genetic syndromes. Their diagnosis is essential because they may not respond to rhGH treatment, require other types of medication, or have contraindications to its use (Bloom syndrome or SHORT syndrome, among others). These syndromes also include Silver-Russell syndrome (SRS), which has been recognized as an indication for rhGH use due to its benefits, with improvements in height, body composition, appetite, motor development, and fewer hypoglycemia episodes. Preterm infants respond adequately and similarly to SGA children as of 3 years of age, so rhGH use would be recommended if they have not shown catch-up growth.

Treatment also improves metabolic parameters: increased lean mass, reduced fat mass, improved systolic and diastolic blood pressure, and reduced total cholesterol, and high- and low-density lipoproteins (HDL and LDL) levels during treatment and years after discontinuation.[7] An improvement in the quality of life of these children, with improved self-esteem and body image have been described, but there are controversies regarding cognitive changes.

Treatment with rhGH is well tolerated. However, these children may have a lower insulin sensitivity, and since rhGH may increase blood glucose and insulin levels and result in insulin resistance, these parameters should be monitored. Several studies have shown that these events are reversible. rhGH treatment may also increase the levels of insulin-like growth factor 1 (IGF-1) and IGF-3 transporter protein (IGFBP-3), which should be monitored during treatment. It may also cause headaches and endocranial hypertension.

CONCLUSION

SGA children are a heterogeneous group. Being aware of the different etiologies helps to make the correct diagnosis and consider the different treatment options and expectations about the response to them. Argentina has approved treatment with rhGH as of 5 years of age, so an early detection, diagnosis, and referral is critical to initiate treatment appropriately.

Treatment with rhGH is effective in these children; however, 15% may not respond to it. It is necessary to start rhGH treatment early, ideally far from the onset of puberty, in order to improve final height and body composition; however, if puberty has started, the possibility of associating rhGH with GnRHa to prolong the pre-pubertal period should be considered.

Auxological and laboratory parameters should be monitored during treatment. It is critical to avoid excessive weight gain to reduce the risk for metabolic syndrome and to work as a multidisciplinary team in the management and control of these children. ■

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