Review (KSPE-JSPE Plenary Lecture)

Long-term care, from neonatal period to adulthood, of children born small for gestational age

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Abstract. Children born small for gestational age (SGA) face an increased risk of health problems in later life, particularly persistent short stature, neurocognitive dysfunction, impaired renal and pulmonary function, decreased bone density, sensorineural hearing loss, premature adrenarche, and metabolic syndrome. Insulin resistance appears to be a key component underlying these metabolic complications. Long-term, continuous, GH treatments in short children born SGA lead to a normalization of height through childhood to adulthood. Recombinant human GH has been proven to be relatively safe. We recommend early surveillance in a growth clinic for children born SGA without catch-up growth. Obesity, insulin resistance, and the risk of metabolic syndrome increase with catch-up growth, but short stature and cognitive dysfunction increase without catch-up growth in children born SGA. A solution to this catch-up dilemma is breast feeding for a minimum of 6 to 12 mo. Because the overall prevalence of metabolic risk factors is very low, routine evaluation of metabolic parameters is not recommended for all children born SGA, but it may be useful to consider metabolic evaluations in overweight or obese children born SGA. Since children born SGA have many risk factors, long-term management from neonate to adulthood is very important.

Key words: small for gestational age, cognition, growth, metabolic syndrome

Introduction

In Korea, 715,826 children were born in 1993, and the number of births dropped to 438,531 in 2005, similar to levels in 2013 to 2015, with only 438,420 babies born in 2015.

The percentage of children with a birth weight of < 2,400 g was 2.6% in 1993 and 5.7% in 2015. According to these data from Korea’s National Statistical Office, the number of children with low birth weight has clearly been increasing (1). The classification of small for gestational age (SGA) has been variably defined as being at the 3rd or 10th percentile or at less than –2 standard deviation (SD) from the mean in relation to gestational age for the same sex (2). Infants born SGA are at an increased risk of persistent short stature, neurocognitive dysfunction, impaired renal and pulmonary function, decreased bone density, sensorineural hearing loss, premature adrenarche, and metabolic syndrome in later life (3) (Table 1).
In this report, we reviewed mainly issues concerning neurocognitive dysfunctions, short statures, and metabolic syndromes.

**Neurocognitive Dysfunction**

Crude neurological handicaps, such as cerebral palsy, are extremely rare in children born SGA at term. Some studies have shown that term SGA infants are at an increased risk for mild cognitive deficits, learning difficulties, and poorer performance in childhood and adolescence (4–6). Studies have also demonstrated that these children have problems related to behavior and mood control in addition to psychological problems such as attention deficit hyperactive disorder (ADHD) (6). Hwang et al. reported marked behavioral problems such as delinquency, aggressiveness, anxiety, and depression as well as lower verbal Intelligence Quotient in the SGA group than in the appropriate for gestational age (AGA) group (7).

Currently, neonatologists recommend nutrient-enriched formula for preterm as well as SGA babies. However, nutrient-enriched formula has been shown to improve head growth, but not neurodevelopment in SGA infants (8), and increases the risk of rapid weight gain and eventually obesity. There is much ongoing discussion related to the issue of undernutrition vs. overnutrition. De Curtis and Rigo have discussed this problem and the various potential harmful effects in SGA children. There is controversy between the risks of rapid weight gain and reduced neurodevelopment due to undernutrition (9). In SGA babies, the quality of the food during months 6 to 12 of life appears to be very important, with breast feeding showing the best results compared to high-energy formula.

**Short Stature**

Accelerated growth begins between 2 wk to 3 mo after birth. Average weight and length increase from the 10th to the 25th percentile at 6 mo. Most children born premature and SGA have a slower and more prolonged catch-up growth period than term SGA children, and it can take 4 or more yr for premature children to fully catch up (10).

Birth length is the most important predictor for catch-up growth, but is not associated with gestational age, multiple births, or sex (11–13). Approximately 80 to 85% of children born SGA experience a rapid catch-up growth period during the first 12 months of life, while 10 to 15% do not undergo this period of catch-up growth (11, 12, 14). The mechanisms that lead to the persistence of short stature in children born SGA are not yet well understood.

Among children who are born SGA without attaining the catch-up growth by 2 yr of age, the relative risk of short stature at 18 yr of age is 5.2% for those born lighter than normal range and 7.1% for those born shorter than normal range (15).

Short children born SGA usually do not have a classic GH deficiency, but have been found to exhibit either low GH secretion or reduced sensitivity to GH (16). Approximately 50 to 60% of short children born SGA have either 24-h GH profile abnormalities or subnormal responses to arginine provocation with reduced plasma insulin-like growth factor (IGF)-I and IGF-II levels, which indicate GH insufficiency (16–19).

A wide ranges of IGF-I generation and resistance indicate that the SGA group is heterogeneous. GH stimulation testing is not required to identify candidates for GH therapy.
among children born SGA who fail to achieve catch-up growth (20), and GH stimulation test results do not accurately predict response to GH therapies (21). GH stimulation testing is recommended when GH deficiency (GHD) is suspected in a child born SGA. Children born SGA have abnormal bone maturation rhythms throughout childhood. In untreated, short children born SGA, bone age is typically delayed compared to chronological age. In short, prepubertal children born SGA, a spontaneous acceleration in bone maturation and a decrease in height SDS for bone age occurs from 6 to 8 yr of age. Predictions of final height based on bone age estimates have been shown to be unreliable in children born SGA who then fail to show catch-up growth (3, 22). For these reasons, bone age is not a consideration when initiating GH treatment in SGA children.

**GH Treatment**

Objectives of GH therapy are initiated to induce catch-up growth, to normalize height during childhood, and to achieve an adult height within the normal target range.

GH was approved by the Food and Drug Administration (FDA) in 2001, by the European Agency for the Evaluation of Medicinal Products (EMEA) in 2003, by Japan in 2008, and by Korea in 2014. The approved minimum age for treatment is 2 yr according to the FDA, 4 yr according to the EMEA, 3 yr according to Japan, and 4 yr according to Korea. While the FDA approved the GH dosage at 70 μg/kg/d, others have approved dosages of 33–35 μg/kg/d (Table 2).

The average height gain after 3 yr of GH treatment ranges from 1.2 to 2.0 SD for dosages of 35–70 μg/kg/d. The growth rate decreases over time in GH therapy (3). The annual height velocity was significantly greater among children receiving GH than among untreated children during the first and second years of treatment.

Untreated SGA children did not experience an increase in height velocity SDS (23). A multicenter, phase III clinical study in Korea reported that height velocity significantly increased from 5.36 ± 1.59 cm/yr at baseline to 10.66 ± 2.03 cm/yr at 6 mo in the treated group (24).

Van Pareren et al. (25) reported that 98% of children born SGA reached an adult height within the target height range after long-term GH treatment, and a low dose proved to be as effective as a high dose for the final height. A high dose of 100 μg/kg/d produced a dramatic and rapid increase in height SDS over 2 yr of treatment, but after discontinuation of GH treatment, height velocity decreased significantly, with a subsequent decrease in height SDS. In contrast, height SDS showed a sustained improvement in patients treated continuously with a GH dosage of 33 μg/kg/d over 6 yr (26).

Factors associated with GH responses over the first 2 to 3 yr of therapy included age and height SDS at the start of therapy, mid-parental heights, and GH dosage (21).

Ranke et al. (27) reported that the GH dose was the most important response predictor

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Table 2. GH use in small for gestational age (SGA) children without catch-up growth

| FDA (2001) | EMEA (2003) | JAPAN (2008) | KOREA (2014) |
|------------|-------------|--------------|--------------|
| Age at start (yr) | 2 | 4 | ≥ 3 | 4 |
| Height SDS at start | Not stated | < – 2.5 SD | < – 2.5 SD | ≤ 3 percentile |
| Growth velocity before treatment | Not catch-up | < 0 SD for age | < 0 SD for age | Not catch-up |
| Reference to MPH | Not stated | Height SDS > 1 SD below MPH SDS | Not stated | Not stated |
| Dose (μg/kg/d) | 70 | 35 | 33–67 | 35–70 |

FDA: Food and Drug Administration, EMEA: European Agency for the Evaluation of Medicinal Products, MPH: mid-parental height, SDS: standard deviation score, SD: standard deviation.
accounting for 35% of the growth response variability. Other predictors of growth response during the first year of treatment were the age at the start of treatment, weight SDS, and mid-parental height SDS.

According to the North European Small-for-Gestational-Age Study (NESGAS), IGF-I titration of GH doses in SGA children proved less effective than current dosing strategies. During the 3 yr of GH treatment, IGF-I titration resulted in physiologic IGF-I levels correlating with a wide range of GH doses and poorer GH responses. These results indicated the role of IGF-I resistance and highlighted the heterogeneity in short SGA children (28). The optimal GH dose in short children born SGA is currently under debate. To maximize the effects of GH treatments, individual GH dose adjustments are needed in short children born SGA.

GH treatments in short SGA children also had a positive effect on blood pressure and lipid metabolism in 79 SGA patients (29). Pre-treatment systolic blood pressure SDS was significantly higher and diastolic blood pressure was significantly lower in children born SGA than in healthy age-matched children. During GH therapy, both systolic and diastolic blood pressure SDS decreased significantly. After 6 yr of GH therapy, systolic blood pressure in the SGA children did not differ from that in the controls and diastolic blood pressure was even lower than that in the controls. After 4 yr of GH therapy, there were significant decreases in total cholesterol, low-density lipoprotein cholesterol, and the atherogenic index, although high-density lipoprotein cholesterol remained unchanged.

Sas et al. (30) also reported a positive effect of GH therapy on body proportions in 79 SGA children. Height, sitting height, and hand, feet, bi-acromial, and bi-iliac diameters were measured before and during GH therapy. At the start of GH therapy, mean SDS values for all measurements were significantly lower than zero, but during 6 yr of GH therapy, the mean SDS for all measurements increased significantly from baseline and closer to zero. There were significant improvements from baseline in the proportions of the hands, feet, and bi-iliac diameters in relation to height, but the bi-acromial diameters in relation to height did not change. None of the changes in body proportions differed significantly between the dosage groups.

GH treatment also had long-term beneficial effects on muscle and adipose tissue in short children born SGA. Leger et al. (31), studied long-term effects on muscle and adipose tissue in 14 short children born SGA during 3 yr of GH therapy and observed an increase in muscle tissue mass. Adipose tissue mass decreased significantly during the first year of therapy, but increased during the second and third years of therapy.

Fasting serum HbA1c or glucose levels should be monitored during GH treatment. This is especially important in children who are overweight or have a family history of type 2 diabetes (31).

IGF-I levels should not exceed 2 SDS above the mean for age and gender during treatments. If IGF-I levels are excessive (> 2 or even 3 SD), it seems reasonable to adjust the GH dose downwards until IGF-I levels are in the upper-normal range.

Recombinant human GH has been proven to be relatively safe. Treatment interruption or withdrawal as a result of adverse events is uncommon. The effect of GH on glucose metabolism in short children born SGA was generally mild and transient (32). Since insulin resistance had been reported in SGA children, fasting insulin and glycosylated hemoglobin or glucose concentrations should be monitored during and after GH treatments in these patients, particularly those with risk factors for obesity or a family history of type 2 diabetes. The French study, Sante Adulte GH Enfant, reported increased mortality rates among adults treated with recombinant GH as children, particularly in those who had received the highest dose (above 50 μg/kg/d). Specific effects in terms of death
Long-term care of children born small for gestational age were detected because of bone tumors or cerebral hemorrhages, but not for all cancers (33).

**Metabolic Syndrome**

Metabolic syndrome comprises central obesity, dyslipidemia, hypertension, glucose intolerance, and insulin resistance. Insulin resistance appears to be a key component underlying these metabolic complications. Insulin resistance has been observed in babies born SGA who achieved catch-up growth at 1 yr of age (34) and until the age of 2 (35). Insulin resistance is sharply amplified by obesity and in prepubertal children, which is more evident in those with catch-up growth and rapid weight gain and BMI >17 kg/m² (36). At 50 yr of age, the risk of insulin resistance syndrome was 10-fold higher in subjects with birth weight < 2,500 g than in subjects with birth weight ≥ 4,500 kg (37). At 22 yr of age, 2.3% of individuals born SGA were affected by metabolic syndrome compared with only 0.3% in the AGA group (33). However, Cho et al. reported that birth weight is related to current height and weight SDS in Korean adolescents, but is not related to individual components of metabolic syndrome (38). Meta-regression showed a U-shaped relationship between birth weight and later risk of type 2 diabetes (39). Birth weight and risk of coronary heart disease and stroke are inversely associated in adult women (40). Because the overall prevalence of metabolic risk factors is very low, routine evaluation of metabolic parameters is not justified in all children born SGA. This may be useful to consider, however, in overweight or obese SGA children.

In conclusion, SGA neonates require long-term management because short statures, neurocognitive dysfunctions, and metabolic syndromes persist until adulthood. Breastfeeding is recommended in SGA neonates for 6–12 mo after birth. It is important that short children born SGA who may benefit from GH treatments be referred to a pediatric endocrinologist as early as possible. To maximize the effects of GH, individual GH dose adjustments are necessary in short SGA children.

Understanding SGA heterogeneity may be the next step in further improving GH treatments.

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