CHILDREN BORN SMALL FOR GESTATIONAL AGE (SGA)

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Abstract: SGA (small for gestational age) is a child born with birth weight and/or length (BW/BL) under two standard deviations (2 SDS) for the gestational age and sex of the population. ~5% of all newborn children are SGA. A broad spectrum of factors are found to be causative: maternal, placental, foetal, metabolic, and genetic. In the newborn period the SGA children are at greater risk of life-threatening conditions: hypoglycaemia, hypercoagulability, necrotic enterocolitis, direct hyperbilirubinemia, hypotension, etc. Approximately 10 percent of SGA children do not achieve catch-up growth and remain short (≤ -2 SDS) into adulthood. SGA people have an increased incidence of metabolic syndrome, coronary artery disease, stroke, low bone density and osteoporosis. SGA children aged more than 4 years with no evidence of spontaneous catch-up and with a height ≥ 2.5 SD are considered for growth hormone (GH) treatment.

Key words: Small for gestational age, etiology, consequences, GH treatment.

SGA (small for gestational age) is a child born with a birth weight and/or length (BW/BL) under two standard deviations (2 SDS) for the gestational age and sex of the population. [1]. Determining the gestational age is oftentimes difficult, the most precise is with ultra-sound, while assessing the GA from the time of the last period can be deceitful. The rump-heel measurement in the first trimester is considered to be correct [2, 3].

The SGA born can have their birth weight (SGAweight) affected, their birth length (SGAlength) or both (SGAweight/length). These subgroups have different outcomes in final height achievement. SGAweight born children are mostly likely to achieve catch-up growth after the second year of life, while SGA weight/length children more frequently remain short in adulthood [4].
IUGR (Intrauterine growth retardation) is a growth failure during the intrauterine development. If intrauterine growth retardation has been detected, both mother and foetus should undergo adequate monitoring by foetal biometry and Doppler ultrasonography of uterine and foetal blood vessels [1].

**Incidence**

3–10% of all newborns are born SGA [5–7]. In Sweden (1973–75) among 3650 healthy newborn children 5.4% were SGA, 1.5% of them were born with a low birth weight and low birth length (SGA_{wl}), 2.4% were born only with low birth length (SGA_{l}) and 1.6% were low birth weight (SGA_{w}) [8]. About 95000 children (2.3%) of all healthy newborns (4,115,590) in USA were born SGA [9].

**Etiology**

There are several groups of causative factors for SGA:

1. **Maternal** – insufficient substrate supply to the foetus during development is a major maternal factor in SGA occurrence. Various causes have been found: reduced maternal food intake, maternal diseases (e.g. hypertension), abnormal utero-placental blood supply or disruption of the placental transfer, abruption, infarction or mal-development of the placenta. Most of these factors influence growth during the last trimester of pregnancy and result predominantly in IUGR [10–11]. Other maternal contributing factors to low foetal size are: parity, ethnicity, delivery at age less than 16 and more than 35 yrs and previous history of SGA born children. Paternal height is less influential on the baby's birth weight.

2. **Exposure of the foetus to toxins** – smoking, alcohol or drug abuse increases the risk of SGA/IUGR births. Smoking during pregnancy is thought to have the most significant influence with a relative risk of 3.24 [11, 12].

3. **Foetal:**

   3.1. **Chromosomal anomalies:** gonadal disgenesy (trisomy 13), Edward Syndrome (trisomy 18), Turner Syndrome (45 × 0), Down Syndrome (trisomy 21), Prader-Willi Syndrome;

   3.2. "Thrifty phenotype" – Several mechanisms are proposed to explain growth retardation of the foetus and the infant. The growth is assumed to be
quantitatively and qualitatively altered by a poor nutritional environment. Metabolic disturbances depend on the period of gestation in which a famine affected the children, as a Dutch SGA study showed in examining the population who suffered from famine during the Second WW [13]. If foetal exposure is during early pregnancy it will affect lipid metabolism, but if famine exposure is during later pregnancy, it will affect the glucose metabolism [13]. An inadequate development of pancreatic beta cell mass and their function are supposed to be the link between poor foetal nutrition and type 2 DM later on in life. Foetal malnutrition is also supposed to lead to insulin resistance. A thrifty descendant ("thrifty phenotype") created thus is adapted to survive in poor nutritional circumstances. Later in adulthood, abundant food intake and decreased energy expenditure lead towards obesity, glucose intolerance and hypertension [14–15].

3.3. GH-IGF-axis – Genetic causes for isolated GHD, multiple pituitary deficiencies, genetic alterations in acid-labile-subunit (ALS) and the GH receptor have been described [reviewed in 16–19]. Few IGF mutations have been described [as reviewed in 20–24].

3.4. IGF-1R gene alterations – IGF-1R is a heterotetrameric (α2β2) transmembrane glycoprotein with intrinsic kinase moiety. The human IGF-1R (OMIM *147370) gene maps to chromosome band 15q26.3. Abbott et al. 1991 [25] reported that the IGF-1R gene contains 21 exons and spans about 115 kb.

Recent studies have found convincing evidence that IGF-1R alterations are causally linked to the etiology of SGA [as reviewed in 24, 26–31; Table 1]. It was hypothesised that at least 2.5% of SGA born children may have IGF-1R gene defects [29]. Several point to mutations and partial deletions in the IGF-I and insulin-like growth factor 1 receptor (IGF-1R) genes have been demonstrated and each patient exhibits a different phenotype [31]. Mutations that affect IGF-1R biosynthesis, signal reception and receptor kinase activity have been identified. All reported IGF 1R mutations are heterozygous, homozygous mutations or other gene alterations that have not been described so far [32].

Abuzzahab et al. 2003 [33] described a girl and a boy with mutations in the IGF-1R, among 42 investigated IUGR children. The girl was compound heterozygous for two missense mutations in exon 2, that altered the amino acid sequence to Arg108Gl in one allele and Lys115Asn in the other, resulting in reduced ligand binding and decreased receptor phosphorylation on IGF-I stimulation. The boy had a nonsense mutation in exon 2, resulting in reduced expression of IGF-1R. Both children had severe intrauterine growth retardation and postnatal growth failure [33]. Kawashima et al. 2005 reported a heterozygous mutation in the cleavage site of the proreceptor of IGF-1R in a 6-yr-old Japanese girl and her mother, presenting with mild intrauterine growth retardation and postnatal short stature [34]. Walenkamp et al. 2006 described a
mother and her daughter with the first missense mutation in the intracellular kinase domain of the IGF-1R [35]. In a family with several members with short stature Inakagi et al. 2007 reported a novel mutation demonstrated as substitution of arginine for glutamine at amino acid 481 (R481Q) in the IGF-IR

Table 1

Summary of reported IGF-1R alterations

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<th>IGF-1R gene alteration</th>
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<tr>
<td>4.</td>
<td>Walenkamp et al. 2006, JCEM (35)</td>
<td>E1050K (Gly1050Lys) (heterozygous)</td>
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<td>5.</td>
<td>Inagaki 2007, JCEM (36)</td>
<td>R481Q (Arg481Gln) (heterozygous)</td>
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<td>7.</td>
<td>Wallborn 2010, JCEM (38)</td>
<td>V599E (Val599Glu) (heterozygous)</td>
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<td>8.</td>
<td>Gucev et al. 2011, ESPE Meeting (39)</td>
<td>(c.3453C &gt; T) and (c.3234_3236delCAT) (heterozygous)</td>
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gene at SGA born 13.6-yr-old girl and her 45-yr-old aunt [36]. Kruis et al. 2010 reported a new heterozygous glycine 1125 alanine IGF-1R mutation within a highly conserved motif of the kinase domain. It was identified in a Greek-Caucasian girl and six maternal relatives with varying degrees of intrauterine and postnatal growth failure [37]. Direct sequencing of the IGF-1R [38] revealed a novel mutation in a 9-yr-old IUGR born girl with short stature (-2.10 SDS) and her mother who was also born SGA (-3.30 SDS). It was a heterozygous mutation in position 1886, resulting in an amino acid exchange from valine 599 to glutamic acid (V599E). We reported two novel gene alterations of the IGF-1R gene in 2 short SGA children [39]. Choi JH et al. 2011 described two children with unexplained IUGR and persistent short stature (< -2.0 SD score), and their father possessed a novel c.420del (p.A110fs × 20) mutation in exon 2 of the IGF-1R gene [40]. Kawashima et al. 2012 [41] reported a higher frequency of heterozygous IGF-1R mutations or haploinsufficiency of IGF-1R gene in

families with several members with short stature, born with low birth weight/length, with normal or increased IGF-I level and normal or increased GH response to the GH stimulation test, and/or less response to GH treatment than other SGA short-stature patients.

Several reported heterozygous mutations of the IGF-1R gene lead to IUGR and post-natal retardation of growth, moderate mental retardation but without hearing loss or microcephaly [33]. A severe clinical expression is found in patients with IGF-1 deficiency due to homozygous mutations or deletions of the IGF-1R gene.

3.5 Genes responsible for retardation of growth – Studies performed in mice show that IRS-1, PDK1, AKT1, and S6K1 as a group of genes for signalling proteins might play an important role in growth retardation and are involved in glucose homeostasis and in fat metabolism too. Some of them – IGF-1R, PDK1, AKT1 – are oncogenes (41–47). Mutations in the sonic hedgehog (SHH) and the transcription factors LHX4, GLI2 and SOX3 have been described in patients with postnatal growth failure (reviewed in 22, 23 and 42).

Nevertheless, most patients born SGA have not been etiologically clarified.

SGA consequences:

Newborn period

SGA newborns have more hypoglycaemic and hypothermic episodes in the perinatal period than AGA (appropriate for gestational age) children. They also have an increased risk of hypercoagulability, necrotic enterocolitis, direct hyperbilirubinaemia, hypotension, chronic lung disease [48].

A neonatal death is ~20 times more frequent in SGA than in AGA newborns [49]. SGA neonates also have a higher risk of a lower Apgar score (less than 3 at 5th min), umbilical artery acidosis and probability of intubation at delivery [50].

Infancy

As many as 90–95% of children born SGA have catch-up growth during the first 2 years of life [51]. The majority (> 80%) of SGA infants achieve catch-up growth during the first 6 months of life [52].

The catch-up growth in short SGA born children correlates with birth length, weight and parental (target) height. The birth length and target height are predictive in the first 2 years of life, but later in childhood the influence of target height is dominant [53].
Childhood

About 10% of children born SGA do not achieve catch-up growth after the second year of life and remain short (≤ -2 SDS) during childhood, adolescence and adulthood [51, 54]. The risk of short final adult height was found to be five times higher for children with low birth weight and seven times higher for those with low birth length compared with children with normal birth size [54].

Children born SGA have a greater risk of being psychosocially disadvantaged compared with their AGA-born peers. They have less social competence and more behavioural difficulties and learning deficits due to low scores of alertness, mood and stability, deficit in attention and lower levels of attainment [55–57].

In addition, puberty starts early and is rapid, while the amplitude of the pubertal spurt is small in SGA children. The menarche is advanced by 5–10 months in girls born SGA. Hypospadias and cryptorchidism are more frequent in SGA boys [51].

Adulthood

Several studies in adults born SGA show an increased risk of metabolic syndrome (obesity, hypertension, disturbed glucose homeostasis, diabetes type 2), coronary artery disease, stroke, low bone density and osteoporosis [11, 51].

Some studies have found insulin resistance with hyperinsulinaemia, reduced insulin sensitivity and higher beta-cell activity during mid- and late-adulthood in SGA [58]. Others have not confirmed those results [59].

SGA and GH therapy

FDA (Food and Drug Administration, USA, July 2001) approved recombinant human growth hormone (rhGH) for the treatment of SGA children who did not have catch-up growth by 2 years of age resulting in a height below -2SDS. Two years later the EMEA (European Agency for the Evaluation of Medicinal products) approved rhGH for treatment of SGA children. The SGA children aged 2 to 4 who show no evidence of spontaneous catch-up with a height -2.5 or less SD should be eligible for GH treatment. Treatment should be considered in children older than 4 years who show no catch-up at a height of -2.0 SD or less [60–62].

The decisive factors that determine the growth response to GH treatment are: age of the children at initiation of treatment, GH dose and parental-adjusted individual height deficit.
Endogenous preferences in the somatotrophic axis (lower overnight peak of GH, lower baseline levels of IGF-1 and IGF-BP3) predict response to growth hormone in SGA children [63–64]. The responsiveness to GH treatment in patients with IGF-1R mutations differs with the type of mutation. SGA children with detected partial deletions have better growth improvement with rhGH therapy than those with point IGF-1R mutations [24].

Conclusions

An adequate assessment of measured body parameters at birth (weight, length and head circumference) and gestational age is crucial for determining whether a newborn is SGA, AGA or IUGR. A long-term follow up of SGA born children is recommended for various reasons: about 10% have not sufficient growth achievement after the 2nd year of life (≤ 2 SD) compared with their peers and remain short; endocrine, metabolic and neurodevelopmental disturbances are expected during childhood, but are not frequent; an increased possibility of metabolic-syndrome-related conditions, coronary artery diseases, stroke and osteoporosis are noticed among adults born SGA [62]. SGA born children without spontaneous catch-up growth and with short stature (≤ 2.5 SD or less) after the 2nd and (≤ 2 SD) after the 4th year of life need GH treatment. The growth improvement in SGA born children on GH therapy depends on: age at the start of treatment, reference to midparental height and GH dose. SGA born children treated with GH are also recommended for long-term follow up.

REFERENCES


Резиме

ДЕЦА РОДЕНИ МАЛИ ЗА ГЕСТАЦИСКАТА ВОЗРАСТ (МГВ)

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Приближно 5% од сите новородени се родени мали за гестациската возраст (МГВ). Широк спектар на причинитeli се одговорни за нивната родилна тежина/должина. За време на неонаталниот период МГВ децата имаат голем ризик од животно-загрозувачки состојби: хипогликемија, хиперкоагулабилност,
некротичен ентероколит и др. Околу 10 проценти од МГВ родените деца не го постигнуваат растот на дофат по втората година од животот. Тие остануваат ниски (-2 СДС) во текот на детството, адолесценцијата и врзгвото доба. МГВ родените деца постари од 4 години, а коеј кон нема постигнато раст на дофат и имаат висина ≥ 2.5 СД се земаат во предвид за третман со ХР. Децата родени мали за возраста имаат зголемена инциденца на метаболен синдром, болест на срцевите артерии, мозочен удар, намалена коскена густина и остеопороза.

Ключни зборови: мали за гестациската возраст, етиологија, последици, третман со ХР (хормон за раст).

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