

RECENT ADVANCES

Should recombinant human growth hormone therapy be used in short small for gestational age children?

L B Johnston, M O Savage

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Short small for gestational age (SGA) children represent 20% of all children with short stature¹ and therefore constitute a significant portion of the caseload in a growth clinic. The recent approval of recombinant human growth hormone (GH) for the treatment of short stature in SGA children by the European Union's Committee on Proprietary Medicinal Products offers a new licensed therapeutic option. This article examines the role of GH therapy in short SGA children with particular reference to selection of patients, effectiveness, safety, and its potential metabolic implications.

acceleration, or catch-up growth, results in approximately 87% SGA children being within the normal population height standards (± 2 SDS) by 2 years of age.¹ The mean final height in the subjects with catch-up growth was -0.7 SDS compared with -1.7 SDS in those who had not caught up by 2 years. At 18 years of age, 7.9% of the subjects born SGA remained short; thus only a small minority (5%) continued to catch up spontaneously during childhood. The best predictors of catch-up growth were longer birth length and taller midparental height.

A significant number of SGA infants are born prematurely; they have a different pattern of postnatal growth where catch-up growth occurs at a later age than term SGA infants^{4,5} (see table 1). In the Dutch study, shown in table 1, there was no significant difference in the proportion of term and preterm SGA children who had caught up at 2 years, but at 6 months and 1 year fewer premature SGA children had catch-up growth. Thus consideration of the gestational age of the SGA child at birth is important during any assessment of their early postnatal growth, to avoid wrongly assigning a premature infant, with delayed catch-up growth, to a non-catch-up group. It is therefore appropriate that the GH therapy licence for short SGA children recommends that treatment should not be commenced before the age of 4 years. In addition it is recommended that the height velocity SDS should be below zero to reduce the possibility of treating any SGA child with spontaneous catch-up growth.

Small for gestational age (SGA) describes an infant's size at birth compared to appropriate population standards and is not synonymous with intrauterine growth retardation (IUGR). IUGR requires antenatal fetal auxology that demonstrates subnormal prenatal growth velocity. Infants born following IUGR may or may not be SGA. The definition of SGA is arbitrary, but in growth clinics SGA is commonly defined as birth weight and/or length two or more standard deviation scores below the mean for gender and gestation (-2 SDS), which is consistent with the definition of childhood short stature (standing height ≤ -2 SDS). As birth length is not always available in the UK and is often not as reliably measured as weight, SGA is most commonly defined by birth weight alone in the UK.

The aetiology of being SGA at birth is complex, involving the interplay of fetal, maternal, and placental environmental and genetic factors.^{2,3} Although some SGA infants are dysmorphic, the majority are not and the cause in the individual patient is not always apparent. Thus SGA children form a heterogeneous group that may include some children with familial SGA. The cause of SGA should always be investigated, preferably shortly after birth, because a positive finding will increase the potential for counselling the parents regarding the likely prognosis and allow any appropriate specific therapies to be instigated. Causes such as preeclampsia, maternal smoking, or drug abuse may be apparent from the history, while other causes such as congenital infection or chromosomal abnormalities will require specific investigation.

NATURAL GROWTH PATTERNS SEEN IN SGA INFANTS

A Swedish cohort study of 3650 term singleton SGA infants showed that postnatal growth

GH:INSULIN-LIKE GROWTH FACTOR I (IGF-I) AXIS STATUS IN SHORT SGA CHILDREN

The pathophysiology of the poor postnatal growth in short SGA children is not fully understood and is likely to vary between individuals given the heterogeneity of the group.

GH levels are higher in the newborn period in SGA infants compared to controls, but by mid-childhood the situation has changed.⁶ Spontaneous GH secretion studies and GH provocation tests have shown that up to half of short SGA children have subnormal peak GH (<20 mU/l) and/or low mean GH secretion rates compared to normal controls.^{7,8}

In the newborn SGA infant, cord IGF-I, IGF-II, and insulin levels are lower than levels in appropriate for gestational age infants which

Abbreviations: GH, growth hormone; IGF, insulin-like growth factor; IUGR, intrauterine growth retardation; SGA, small for gestational age

See end of article for authors' affiliations

Correspondence to:
Dr L B Johnston, Senior Lecturer Honorary Consultant, Paediatric Endocrinology, St Bartholomew's Hospital, London EC1A 7BE, UK; l.b.johnston@qmul.ac.uk

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Table 1 Percentage of premature (n = 423) and term (n = 301) Dutch SGA children with catch-up growth at 6 months, and 1 and 2 years of age⁴

	At 6 months	At 1 year	At 2 years
Premature SGA	40%	65%	82.5%
Term SGA	71%	81%	87.5%

may relate to placental insufficiency but, in the majority, this reverses within the first few days of life.⁶⁻⁹ In childhood, serum IGF-I levels may lie within the normal reference range, but the majority of short SGA children (80% in a Swedish study) have IGF-I levels below the 50th centile, supporting the diagnosis of GH and/or IGF-I insufficiency.¹⁰

Subtle defects in the GH:IGF-I axis may therefore contribute to poor postnatal catch-up growth. This observation led to the first trials of GH therapy, with subsequent observation of growth acceleration, in short SGA children.¹¹ However, the larger more recent trials do not report any significant difference in response between those with and without GH insufficiency.¹² Therefore the evidence suggests that GH provocation or GH profile testing is not necessary before treatment with GH as the status of GH secretion is not going to change the decision to treat or the dose of GH recommended. However, IGF-I and IGFBP-3 should always be measured before the start of treatment (see below).

Recently endocrine studies comparing Italian children born SGA with and without catch-up have been reported. These studies found that the non catch-up SGA children tended to have higher TSH levels and higher cortisol levels.^{13, 14} Thus subtle defects of the thyroid axis or adrenal axis may also influence postnatal growth in SGA children.

THE EFFECT OF GH THERAPY ON LINEAR GROWTH IN SHORT SGA CHILDREN

The impact of GH therapy on linear growth in short SGA children has been the subject of a large number of published trials. Table 2 summarises the findings of some of the principal studies showing doses in comparable units.

Randomised control trials have proven that treated subjects have significant growth acceleration in childhood, maximal in the first year but continuing into the second and third years when compared to untreated or placebo treated short SGA controls.^{12, 15-25} There is some growth deceleration on discontinuing therapy but the majority of the height gain is retained.^{18, 22, 26}

The optimal dose is currently debated in Europe. The initial growth response is dose dependent with those on higher doses showing more rapid catch-up growth.^{12, 15} Proponents of the higher dose (0.067 mg/kg/day) claim the importance of rapid normalisation of height and the importance of dose in the growth prediction models justifies the higher IGF-I levels (30% of cases have IGF-I SDS >2) seen in these subjects (Professor Paul Czernichow, personal communication). However, the commonly used lower dose (0.033 mg/kg/day), which is greater than the replacement dose for growth hormone deficiency (0.025 mg/kg/day), results in significant gains in linear growth, lower IGF-I levels, and a similar gain in final height to the higher dose at lower cost.¹⁶ Therefore the new licence has opted to recommend a dose of 0.035 mg/kg/day.

The gain in final height is greater if the treatment is started at an earlier age. The Dutch SGA study treated children for six years from the mean age of around 7 years and documented a final height gain of 2.2 SDS (controls 0.3 SDS gain) compared to a French high dose treatment

study where adolescent subjects were treated for a mean 2.7 years from a mean age of 12.7 and height gain was 1.1 SDS (controls 0.4 SDS gain).^{16, 23} Two further studies compared growth in GH insufficient short SGA children treated with lower doses of GH, with growth in untreated non GH deficient short SGA children and found no significant gain in final height.^{24, 27} Commencing treatment around the time of puberty results in more modest height gain and higher GH doses may be required. Families should be warned of this.

In order to achieve maximum benefit continuous GH therapy is thus recommended from 4 years of age, which is supported by the recently published response prediction model, generated from 618 GH treated short SGA subjects and validated in 68 independent patients.²⁸ This model shows that 52% of the variability in the first year growth response can be attributed to the dose of GH given, the mid-parental height, and the weight and age at the start of treatment. The first three variables are positively correlated whereas age is negatively correlated. This prediction model could be used in the future to individualise therapy by refining the recommended GH dosage in individual patients.

Several studies have observed a deceleration of growth on stopping GH therapy which is less marked than the previous acceleration—that is, a net benefit may be achieved with short courses of therapy. One small study giving intermittent treatment with high doses of GH has shown treatment (alternating two years on and two years off) resulted in a height gain of 1.7 SDS after six years—that is, four treated and two untreated years.²² The new licence recommends continuous therapy but there may be significant benefits to the family and also potential cost reduction in discontinuous regimens. Such protocols require continuing research before they can be recommended and may only be appropriate in a child starting GH therapy at an early age.

Thus the goals of treatment, which are induction of catch-up growth with normalisation of childhood height and growth, and increased final adult height can be achieved. Few adverse drug reactions have been reported which are related to the GH therapy itself. In addition the improvements in linear growth do not negatively influence body proportions or unduly accelerate skeletal maturation.^{12, 26, 29} However, GH therapy also has some metabolic effects.

EFFECTS OF GH THERAPY ON BODY COMPOSITION IN SHORT SGA CHILDREN

The Dutch SGA study found that body mass index (BMI) in short SGA children was significantly reduced compared to controls (-1.3 SDS).³⁰ However, with GH treatment, BMI normalised over five years.

But what is the effect of GH therapy on body composition? Leger *et al* studied 14 short SGA children during three years of GH therapy and one year off therapy using magnetic resonance imaging of adipose tissue and muscle in the thigh.³¹ They found that during GH therapy short SGA subjects increased muscle and decreased adipose tissue cross sectional area. At the end of three years the SGA children had greater muscle surface area than controls but adipose tissue was similar. One year after stopping GH therapy there was maintenance of the muscle and adipose tissue suggesting these changes in body composition may be long lasting.

WHAT HAPPENS TO IGF-I LEVELS ON GH THERAPY?

IGF-I levels, which are typically in the lower half of the normal range, increase on GH therapy.^{10, 12} In the Swedish SGA study IGF-I levels rose by 55% on day 10, 90% after one year and by 123% at the end of two years GH treatment (0.033 mg/kg/day). The increase was dose dependent, with higher doses stimulating greater increases in serum IGF-I. Increasing the levels of IGF-I is probably the major

Table 2 Principal growth hormone therapy trials in short SGA patients

Definitions SGA/short	GH dose/protocol	At start		Delta height (Ht) SDS							Final Ht		Delta bone age	Ref	
		n	Age	Ht SDS	HV SDS	1y	2y	3y	4y	5y	6y	n			Ht SDS
<-2 SDS	Unreated	12	5.18	-2.91		0.07	-0.03								15
	0.033 mg/kg/d	16	4.4	-3.29		1.09	0.45	0.18							1
	0.067 mg/kg/d	20	4.63	-3.22		1.43	0.7	0.41							1
<-1.88 SDS	Unreated	29	7.8	-2.6											12
	0.033 mg/kg/d	41	7.3	-3						2.2					16
	0.067 mg/kg/d	38	7.2	-3.1						2.6					1.3
<-2 SDS	Placebo 6 months then	18	8.24	-3.16	-1.63										17
	0.02 mg/kg/d for 2.5y	20	8.16	-3.36	-0.64										
	Placebo 6 months then	20	8.16	-3.36	-0.64										
<-2 SDS/>-2.5 SDS	0.06 mg/kg/d for 2.5y	15	8.4	-3.1	0.1		0.66	0.77	-0.3						18
	0.02 mg/kg/d for 3y, 1y off	40	8.1	-3.2	-1		1.25	1.61	-0.22						1.15
	0.06 mg/kg/d for 3y, 1y off	23	7.9	-3.1	-0.7		0.66	0.93	-0.25						1.27
	0.02 for 2y, 0.06 for 3rd y, 1y off	396	8.6	-2.9				0.9							1.13
	Median 0.027 mg/kg/d	593	9.2	-2.8											1.47
<-2 SDS/>-2.5 SDS	Median 0.033 mg/kg/d	13	4.9	-3.4	-0.6		0.2								20
	Unreated	20	5.4	-3.5	-0.9		2.1								21
	0.1 mg/kg/d	19	5.1	-3.7	-0.7		2.5								1.35
	0.077 mg/kg/d for 2y, 2y off, then	5	4.4	-3.5	-1					-1.8					1.33
	0.066 mg/kg/d for 2y														
<-2 SDS/>-2.5 SDS	0.077 mg/kg/d for 2y	13													22
	Unreated	47	12.8	-3.2											
<10th centile not GHD	0.067 mg/kg/d	102	12.7	-3.2											23
	Unreated	20	10.7	-1.97											24
<10th centile HD	0.038 mg/kg/d	29*	10.9	-2.28											29

Information box

Indications for GH therapy in short SGA child

- Birth size < -2 SDS
- Height < -2.5 SDS (≥ 1 SDS below target height)
- Age over 4 years
- Height velocity < 0 SDS

Achievable goals of therapy

- Induce catch-up growth in childhood
- Normalise growth in childhood
- Improve adult height

Potential risks of therapy

- Supraphysiological circulating IGF-I
- Insulin resistance

Important aspects of therapy

- Should be initiated and monitored by a paediatric endocrinologist
- Before starting treatment
 - Check IGF-I, IGF-BP3, fasting lipids, insulin, and glucose
 - Measure BP
- On treatment
 - Regular auxology to monitor linear growth response
 - Monitor serum IGF-I, fasting insulin, and glucose
 - Monitor BP

mechanism of inducing catch-up growth in short SGA subjects and clear correlation between rise in IGF-I and linear growth response has been reported.¹⁰ Indeed IGF-I response predicts 42% of the variance of the one year growth response in the Swedish study.

However, there is no evidence showing what other short or long term effects high IGF-I levels have in childhood. There are theoretical risks of acromegalic symptoms and complications, including cardiomyopathy and bowel pathology.³² It is therefore important not only to monitor growth response on GH therapy but also to monitor IGF-I at least annually and reduce the GH dose if IGF-I levels are more than two standard deviations above the normal reference range.

WHAT ARE THE METABOLIC EFFECTS OF GH THERAPY IN SHORT SGA CHILDREN?

Epidemiological studies have documented, initially in adult life but more recently also in children, that small birth size is associated with an increased risk of insulin resistance, type 2 diabetes, hypertension, hyperlipidaemia, and cardiovascular disease—all features of the metabolic syndrome.^{33–35}

Systolic blood pressure in untreated short children born SGA was raised at baseline (0.7 SDS) but diastolic blood pressure was similar (-0.1 SDS).³⁰ During five years of GH therapy, both the systolic and diastolic blood pressures fell to normal levels compared with control data. In the same group of patients, total cholesterol, LDL cholesterol, and the atherogenic index improved over five years although no change was noted in HDL cholesterol levels. On discontinuation of therapy this improvement in blood pressure and lipid profile was not lost over six months.³⁶

Decreased insulin sensitivity (raised insulin levels following an oral glucose load compared to age matched controls)

can already be documented in childhood and early adulthood in subjects born SGA.^{34, 35} Recently a study comparing SGA children with and without catch-up found higher fasting insulin levels and increased post-load insulin secretion in those who had caught up in terms of weight and linear growth compared to non-catch-up subjects and controls.³⁷ This needs to be confirmed in other populations, but suggests that the short children who have not caught up may be at lower risk of this feature of the metabolic syndrome.

It has been confirmed that fasting glucose, insulin, and proinsulin levels rise and insulin sensitivity falls on GH therapy (44% in 12 short SGA subjects with a mean age of 9.3 years).^{38, 39} However these studies have different findings three months after GH therapy has been discontinued, with one showing significant improvement in insulin sensitivity and the other showing no improvement. Studies six months after stopping GH treatment have found that glucose and insulin levels on an oral glucose tolerance test are similar between controls and SGA children (mean age 16 years).³⁶ Thus the adverse effects on insulin sensitivity would appear to be reversible.

In summary, there is a clearly documented increased risk of hypertension, insulin resistance, hyperlipidaemia, and cardiovascular disease in SGA subjects later in life. These risks appear to be greater in those that show catch-up, particularly where this is rapid or exaggerated.³⁷ Treatment with GH therapy in short SGA subjects would appear to improve blood pressure and lipid profiles but increase insulin resistance in the short term. Fortunately the insulin resistance appears to be reversible on discontinuing treatment. However, the long term effects are not known, so continued monitoring of variables of insulin sensitivity in these subjects is required into adulthood.

OTHER INFLUENCES OF GH THERAPY IN SHORT SGA SUBJECTS

Children born SGA may also have a small head circumference and learning difficulties. These features are predicted by the severity of SGA as opposed to just the presence of SGA.⁴⁰ Short SGA children also have lower self-concept (measured by Self Perception Profile for Children, SPPC) and poorer attention when compared with controls.^{41, 42} Following two years' treatment with GH there was improved attention capacity and improved self-esteem such that with treatment there was no difference between cases and controls in scholastic competence, social acceptance, athletic competence, physical appearance, behavioural conduct, and general self-worth.^{41, 42}

CONCLUSIONS

On the present evidence from studies to final height GH therapy appears to be a safe and effective therapy in appropriate short SGA subjects. Short SGA children should first be investigated in order to identify causes of being born SGA and reasons for poor postnatal growth. Any specific cause found should be treated appropriately. In the child that then remains short or in whom no remediable cause has been identified, GH therapy may have a role to play in normalising height, and the earlier the child is identified the greater the potential response to treatment. The child must have clearly demonstrated that there has been no spontaneous catch-up growth. In other words there must be short stature (height SDS < -2.5), age 4 years or over, and height velocity below average. Determination of the GH status is not necessary but pretreatment IGF-I, IGF-BP3, fasting insulin, glucose, and lipids should be determined and blood pressure measured.

Treatment should be started after clinical assessment by a paediatric endocrinologist and can follow similar shared care guidelines currently used for other GH indications. The dose

recommended in the new licence (0.035 mg/kg/day) appears to be adequate for the younger child but higher doses may give better results in the peri-pubertal patient. The response prediction model may allow refinement of the recommended dose in individual cases in the future. Continuous treatment is recommended and further research is needed to investigate whether intermittent treatment or different dose regimens may also be successful.

Detailed post-licensing surveillance should include long term follow up and careful metabolic monitoring supported by the pharmaceutical industry, as the implications of GH therapy on these subjects, at risk of the metabolic syndrome, will take many years to observe.

Authors' affiliations

L B Johnston, M O Savage, Paediatric Endocrine Section, Department of Endocrinology, William Harvey Research Institute, Barts and the London Queen Mary School of Medicine, London, UK

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