Limitations of the IGF1 generation test in children with short stature

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Abstract

The IGF1 generation test (IGFGT) is often used during the assessment of suspected GH insensitivity (GHI). We report the results of a survey undertaken in 2010 to determine the use of IGFGT amongst members of the European Society for Paediatric Endocrinology to evaluate suspected GHI. The literature surrounding the usefulness and limitations of IGFGT are reviewed, and recommendations provided for its use. Of 112 paediatric endocrinologists from 30 countries who responded to the survey, 91 (81%) reported that they had used the IGFGT in the previous 2 years; >10 IGFGT protocols were used. The IGFGT impacted treatment decisions for 97% of the respondents and was a prerequisite for recombinant human IGF1 treatment for 45% of respondents. From a literature review, sensitivity of the IGFGT was evaluated as 77–91% in molecularly proven cases of GHI; specificity was ≥97%, depending on the protocol. The positive predictive value of the IGFGT is likely to be low, as the frequency of normality is predictably higher than that of abnormality in GH signalling. Given the limitations of the IGFGT in the most severe cases of GHI syndrome (GHS), the ability of the IGFGT to detect less severe GHIS is doubtful. In a pragmatic approach, the IGFGT may not be useful for the diagnosis of GHIS.
endocrinologists under the auspices of the European Society for Paediatric Endocrinology (ESPE). This survey was primarily designed to get an insight into the practical use of the IGFGT in clinical settings rather than an exhaustive view across European countries.

The aims of this paper are: i) to report the results of this survey; ii) to explore the clinical usefulness and limitations of the IGFGT for diagnosis from data in the published literature; and iii) to examine the role of the IGFGT in the current clinical practice and provide recommendations for its use.

**The use of the IGFGT: a survey**

A total of 91 out of 112 (81%) participants from 30 countries declared having used the IGFGT in the previous 2 years, mostly to diagnose GHI (Table 1). Two participants did not take part in the further survey, but of the remaining 89 participants, 87 (98%) said that they used IGFGT. The main patient criteria for selection were short stature (defined by the physician as $<-2$, $<-2.5$ or $<-3$ SDS), with low IGF1 levels and a normal or high GH response to GH provocation tests. A total of 81 individuals detailed how they used the IGFGT. A range of protocols was described, using standard-, low-, high- and very-high dose GH over 2 days to 1 month. The results of IGFGT were declared to impact treatment decisions by 76 of 78 (97%) respondents and to influence the initiation of rhIGF1 treatment by 63 of 75 (84%) respondents. The IGFGT was compulsory for obtaining access to rhIGF1 for 34 of 75 (45%) participants. Although these results suggested that the survey was biased towards respondents who were very familiar with the IGFGT, the number of protocols used (more than ten) as well as the variety of measured parameters was striking (Table 1).

**Table 1** Results of the survey conducted under the auspices of ESPE between 24 August 2010 and 8 September 2010, regarding the use of the IGFGT: 115 individuals responded from 30 countries.

<table>
<thead>
<tr>
<th>Questions</th>
<th>Respondents</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have you used the IGFGT in the past 2 years?</td>
<td></td>
<td>112</td>
<td>81/19</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For what purpose do you use the IGFGT?a</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnosis of GH insensitivity</td>
<td></td>
<td></td>
<td>94/5</td>
</tr>
<tr>
<td>Prognosis (response to rhGH therapy)</td>
<td></td>
<td></td>
<td>28/15</td>
</tr>
<tr>
<td>Diagnosis of GH deficiency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In which patients do you use the IGFGT?</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All paediatric patients with short stature</td>
<td></td>
<td></td>
<td>2/98</td>
</tr>
<tr>
<td>Selected patients with short stature</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is the IGFGT used in your country a standardised test?</td>
<td>81</td>
<td></td>
<td>37/63</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What dose/duration of rhGH is used (μg/kg per day)?a</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard dose (33 μg/kg per day for 4 days, total 132 μg/kg)</td>
<td></td>
<td></td>
<td>24/1</td>
</tr>
<tr>
<td>Standard dose (33 μg/kg per day for 7 days, total 231 μg/kg)</td>
<td></td>
<td></td>
<td>11/3</td>
</tr>
<tr>
<td>Low dose (25 μg/kg per day for 4 days, total 100 μg/kg)</td>
<td></td>
<td></td>
<td>3/12</td>
</tr>
<tr>
<td>Low dose (25 μg/kg per day for 7 days, total 175 μg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High dose (50 μg/kg per day for 4 days, total 200 μg/kg)</td>
<td></td>
<td></td>
<td>4/14</td>
</tr>
<tr>
<td>High dose (50 μg/kg per day for 7 days, total 350 μg/kg)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very high dose (100 μg/kg per day for 4 days, total 400 μg/kg)</td>
<td></td>
<td></td>
<td>4/10</td>
</tr>
<tr>
<td>Very high dose (100 μg/kg per day for 7 days, total 700 μg/kg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Escalating doses (0.7 mg/m² then 1.4 mg/m², then 2.8 mg/m², each for 7 days)c</td>
<td></td>
<td></td>
<td>9/34</td>
</tr>
<tr>
<td>Other protocols</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What parameters do you measure in the test?a</td>
<td>81</td>
<td></td>
<td>100/73/7</td>
</tr>
<tr>
<td>IGF1/IGFBP3/ALS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>What measurements do you use to assess these parameters?a</td>
<td>81</td>
<td></td>
<td>58/63/51</td>
</tr>
<tr>
<td>Absolute level/incremental level/percent increase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have set cut-off levels for these parameters?</td>
<td>81</td>
<td></td>
<td>43/57</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the results from the IGFGT impact your treatment decisions?</td>
<td>78</td>
<td></td>
<td>43/57</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do the results of the IGFGT affect whether you initiate treatment with rhIGF1?</td>
<td>75</td>
<td></td>
<td>97/3</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is an IGFGT compulsory in your country for getting access to treatment with rhIGF1?</td>
<td>75</td>
<td></td>
<td>84/16</td>
</tr>
<tr>
<td>Yes/no</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ALS, acid-labile subunit; ESPE, European Society for Paediatric Endocrinology; IGF1, insulin-like growth factor 1; IGFBP3, IGF binding protein; IGFGT, IGF generation test; rhGH, recombinant GH; rhIGF1, recombinant IGF.

aPhysicians could respond to more than one answer.
bThis protocol is used in Belgium for getting access to rhIGF1 treatment.
cThis protocol is used in The Netherlands for getting access to rhIGF1 treatment.
A brief historic perspective on the IGFGT: from the investigation of patients with severe GHIS (Laron syndrome) to broader causes of short stature

In studies initiated in the 1990s, the IGFGT was used in patients with severe short stature for the identification of severe GHIS (Laron syndrome), presumed to be of genetic origin (3, 4, 5, 6, 7, 8). The IGFGT has also been evaluated in the characterisation of patients with short stature (9, 10, 11). The rationale for the use of IGFGT in patients with short stature, in particular in those with apparent idiopathic short stature (ISS), is to determine whether reduced GH sensitivity is an explanation for the phenotype (10, 12, 13). Investigators have also used the IGFGT to assess whether GHI contributes to short stature associated with various medical conditions, such as β-thalassaemia (14, 15, 16, 17), HIV infection in children (18), juvenile idiopathic arthritis (19), osteogenesis imperfecta (20), immunodeficiency (21) and Turner syndrome (22, 23).

In addition to its diagnostic use, the IGFGT has also been used to support therapeutic decisions, for example, to predict the response to rhGH or to help determine the optimal dose of rhGH (9, 11, 24, 25). More recently, physiological determinants of GH sensitivity and/or responsiveness have been described following the use of IGFGT in groups of normal individuals or normal individuals with short stature according to height, body mass index, gonadal steroid production and age (from prepuberty to menopause) (16, 26, 27, 28).

Reflection on the use of IGFGT and the different protocols employed

IGFGT in the investigation of genetic GHI (Laron syndrome or severe GHIS): good sensitivity despite lack of standardisation

The IGFGT has been the most widely accepted tool to assist in the diagnosis of severe GHIS. In a child with the clinical and biological features of Laron syndrome, including high basal GH and low basal IGF1 and IGFBP3, the response to the IGFGT has been proposed as a step towards the diagnosis (3, 29).

The IGFGT may be administered using a number of different protocols. One of the most widely used is the ‘standard IGFGT’, which is performed over 5 days and requires four rhGH injections (33 μg/kg per day; total dose of 132 μg/kg) (3, 29, 30). In several studies in the 1990s, the diagnosis of severe GHIS was based presumptively on a scoring system that included the standard IGFGT (Table 2) (3, 29). As the molecular diagnosis of Laron syndrome was not available in most of the patients, it was impossible to draw any firm conclusions about the sensitivity of the test (3, 29). However, from these initial studies, cut-off values were arbitrarily defined as twice the intra-assay coefficient of variation (3), or an absolute IGF1 increment of 15 ng/ml (29). Blum et al. (29) also suggested that measuring IGFBP3 levels may improve the significance of the test, with an arbitrary cut-off of 0.4 mg/l for the absolute IGFBP3 increment. Several other protocols proposed rhGH injections over 4–7 days with either low (25 μg/kg per day; total dose 100–175 μg/kg) or high (50 μg/kg per day; total dose 200–350 μg/kg) doses (31). The first coordinated effort to assess the sensitivity of IGF1 generation testing was performed by Buckway et al. (31, 32), in 22 patients from Ecuador with GHIS who were homozygous for the GHR E180 splice mutation. The study demonstrated that patients with GHIS had a low response to the test; however, 17 of 22 subjects had an absolute increase in IGF1 <15 ng/ml, indicating 77% sensitivity with the use of a 4-day, low-dose protocol (total dose 100 μg/kg) (31, 32). The sensitivity was not improved with the use of a 7-day, low-dose protocol or a 4-day, high-dose protocol (total dose 175 or 200 μg/kg respectively) (32). The best sensitivity was obtained with the use of the higher stimulation (7-day, high-dose protocol, total 350 μg/kg), which provided 91% sensitivity for IGF1 and 100% sensitivity for IGFBP3, with the above-defined cut-offs (32). These results suggested that the use of increasing doses of GH could have helped to build a dose–response curve allowing a better definition of GHI.

There are few additional data on the IGFGT in patients with GHIS and a confirmed genetic defect (GHR, Stat5b or NF-kappaB mutations). Most data are from individual cases or small studies. In reports where the standard protocol was used, the mean IGF1 increment was <15 ng/ml (7, 33, 34, 35, 36). Similarly, in reports where the 7-day, high-dose protocol

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**Table 2** Scoring systems for severe GHIS.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Basal GH</th>
<th>Basal IGF1</th>
<th>IGFGT</th>
<th>Height (SDS)</th>
<th>GHBP (%)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3)</td>
<td>&gt;5 μg/l</td>
<td>&lt;50 μg/l</td>
<td>&lt;2× intra-assay variation (10%)</td>
<td>&lt;−3</td>
<td>&lt;10</td>
<td>1</td>
</tr>
<tr>
<td>(29)</td>
<td>&gt;4 mIU/l</td>
<td>&lt;0.1 centile for age IGFBP3 &lt;0.1 centile for age Δ IGF1 &lt;15 μg/l</td>
<td>Δ IGFBP3 &lt;0.4 mg/l</td>
<td>&lt;−3</td>
<td>&lt;10</td>
<td>1 Max 7</td>
</tr>
</tbody>
</table>

GHB, GH binding protein; GHIS, GH insensitivity syndrome; IGF, insulin-like growth factor; IGFBP3, IGF binding protein 3; IGFGT, IGF generation test.
was used, the mean increment in IGFI was also <15 ng/ml (37, 38, 39). In only one patient with genetically confirmed GHS, in whom a very high rhGH dose was used (100 μg/kg for 7 days, totalling 700 μg/kg), IGFI responses >15 ng/ml were reported (37). It should be noted that in most of these reports, GHS was already apparent on the basis of clinical and biochemical measures, whereas the IGFGT added little to the diagnosis.

Overall, this indicates that in patients with genetically proven GHS, the standard and longer IGFGTs provide good, but not absolute, sensitivity, likely to be between 77 and 91%.

**Lack of normative data for the IGFGT: the unsolved question of specificity**

Lack of normative data is also a concern for interpretation of the IGFGT. Only two small studies of the IGFGT have been reported in children who were growing at a normal rate (40, 41) and both used a different IGFGT protocol. In 26 prepubertal children with normal growth given a single rhGH injection (67 μg/kg), the mean IGFI increment was 104 ng/l with the 5th percentile as low as 5 ng/l (41). As the range largely overlapped responses seen in true GHS patients with longer IGFGT protocols, this suggests that a single dose of rhGH will not be adequate for distinguishing true GHS from normal individuals. In a study of 39 adults and mostly pubertal children, who underwent a 4-day, low-dose protocol, an IGFI increment of 15 ng/ml corresponded to the 3rd percentile, that is 97% specificity, thus indicating an increase in specificity with repeated rhGH administration (31, 32). This was not improved by the use of a 7-day, high-dose protocol, whereas the measurement of IGFBP3 instead of IGFI in the same individuals was associated with a decrease in specificity (31, 32). True specificity would only be established from the determination of cut-off values for the rise in IGFI and/or IGFBP3 rise from infancy to adulthood in a number of normally growing individuals. However, it seems unlikely from the above-mentioned studies that this will improve specificity over 97%. As the prevalence of true severe GHS is expected to be low in comparison with that of ‘normal GH sensitivity’, the 3% false positive rate in normally growing individuals (without GHI) will exceed the 77–91% true positive rate in subjects with proven severe GHS.

**Reproducibility and other caveats about the IGFGT**

Divergent data have been published concerning the IGFGT reproducibility. A study by Jorge et al. (42), in 12 prepubertal children with short stature and normal GH secretion, demonstrated a discordant IGFI response between two standard IGFGTs in five of 12 patients. As with other provocative tests, the authors recommended that two tests should be performed (42). However, in the population studied by Buckway et al., in which two different doses of rhGH were used, highly significant correlations between the first and second tests were observed in all studied groups (patients with GHS, GH deficiency (GHD), ISS and those with normal growth), suggesting good reproducibility (43). Two other studies evaluated the reproducibility of an acute IGFGT using one single rhGH administration in children with short stature and adults (44, 45). An intra-class correlation coefficient of around 0.7 was found, indicating fair reproducibility, although a 30% coefficient of variation suggested low test precision. Similar intra-class correlation coefficients have also been shown with the insulin tolerance test for the diagnosis of patients with GHD (46), suggesting that reproducibility of the IGFGT is roughly similar to that of the GH provocative tests.

The heterogeneity of the IGFI and IGFBP3 assays used in different centres could also influence interpretation of the IGFI levels; cross comparisons of different assays have shown high systematic variation and different performance characteristics when concentrations are either above or below the normal range. The development of standard procedures and reagents that eliminate this degree of variability would be necessary (47).

**IGFGT in the investigation of the GH–IGF1 axis in short stature due to other aetiologies, including ISS, Turner syndrome and GHD**

**Idiopathic short stature** Several studies focused on the detection of less severe GHS in subjects with apparent ISS. In the study by Buckway et al. (31, 32) where the GHR gene was sequenced, baseline and GH-stimulated IGFI and IGFBP3 levels during an IGFGT in 16 patients from Ecuador with ISS (not harbouring GHR mutation) as well as in 65 subjects heterozygous for the E180 GHR mutation were within the age-matched ranges of children with normal stature. Cotterill et al. (9) found no difference in IGFI or IGFBP3 response to a standard IGFGT in 37 patients with short stature divided by peak GH levels (<7, 7–13, >13 ng/ml): the responses during an IGFGT did not clearly identify a group of children with ISS who had GHI. Blair et al. (12) showed that amongst 21 children with ISS, two failed to achieve an IGFI increment above 15 ng/ml during the standard IGFGT. Although no molecular study of the GHR pathway was performed in these short subjects, the authors considered the likelihood of an abnormality to be low. In another study of 14 children with ISS, three (21%) had an IGFI increment to a standard IGFGT of below 15 ng/ml (10). Although none of these children had a GHR mutation, one, who failed to respond to a 21-day IGFGT, had an abnormal activation of tyrosine phosphorylation by GH, suggesting abnormal GH receptor signalling.
Overall, these results demonstrated that between 80 and 97% of children with apparent ISS had an IGF1 increment in a standard IGFGT of >15 ng/ml, with the important caveat that no complete molecular study of the GHR pathway was performed. Nevertheless, these figures were very close to those in normally growing subjects, thus suggesting that the sensitivity and specificity of the IGFGT to detect putative partial GHI in individuals with short stature would be very low. In agreement, in a recent trial of rhIGF1 in short children with low IGF1 levels (height and IGF1 levels below –2 SDS) and normal GH levels (‘suspected partial GHI’), circulating IGF1 increased from 65.5±33.0 to 114.5±58.0 ng/ml following a 7-day high-dose IGFGT (48, 49).

Whether the IGFGT would be able to predict the growth response to rhGH or rhIGF1 in ISS has been poorly studied (11, 48, 49). In the above cited study, the test did not predict the first-year response to rhIGF1 (48). In another study on children with ISS, a high-dose long IGFGT (14 days, dose 67 μg/kg per day) was correlated with the first-year response to rhGH \( (r = 0.55, P < 0.05) \) (11). Further studies are needed to better understand this point.

**Turner syndrome** In a study of girls with Turner syndrome, baseline serum IGF1 and IGFBP3 values were normal and not different from their sibling controls (23). Following an IGFGT (administration of rhGH at 50 μg/kg per day for 4 days), the IGF1 response was positive (>15 ng/ml) in ten of 11 girls with Turner syndrome compared with all 11 controls. IGFBP3 response was positive in four of 11 patients compared with six of 11 controls. These results suggest that the test is not useful for the evaluation of short stature in Turner syndrome.

**GH deficiency** In the study by Buckway et al. (31, 32), patients with GHD had low baseline IGF1 levels, as expected. Of 23 individuals with GHD, the IGF1 increment was <15 ng/ml in one patient. Similar to patients with ISS, several patients with GHD had IGF1 levels in the low to normal range following GH stimulation. Measuring the IGFBP3 increment may be more accurate than measuring IGF1, although both parameters are unable to distinguish definitively GHIS from GHD (31, 32).

**Physiological and molecular determinants of the responsiveness to GH**

Notable factors known to affect GH responsiveness include age, gender, nutritional status, associated diseases, pubertal stage, sex steroid administration and body composition. The IGF1 response to GH is related to body mass index SDS, fat mass and insulin levels in children and adults (27, 41). In a study of 117 healthy children with short stature at different stages of puberty, an increased IGF1 increment in response to GH was found with the onset of puberty in both sexes, whereas a reduction in IGF1 increment to GH after oral oestrogen was found in girls (26). This negative impact of oral oestrogen on GH responsiveness is well known in adults with GHD (28).

One study on patients with ISS evaluated the effect of GH receptor exon 3 polymorphisms on responses to an IGFGT in 45 prepubertal children. The homozygous or heterozygous GH receptor d3 allele was associated with a higher IGF1 SDS increment than the fl/fl genotype, with no difference in IGFBP3 (50). Although interesting, these results did not translate into practical significance. Some studies of patients with GH receptor d3 polymorphism have shown a better growth response to rhGH therapy in those with ISS (51) or Turner syndrome, and in those born small for gestational age (52).

**Recommendations for the diagnosis and management of severe primary IGFD**

In general, investigators have been disappointed in the ability of the IGFGT to identify patients with GHIS in subjects with short stature (9, 10, 29, 31, 32). The positive predictive value is the ability of the IGFGT to detect subjects with molecular defects in the GH receptor signalling pathway. Assuming a sensitivity and specificity of 77–91 and 97% for severe GHIS, respectively, the positive predictive value is likely to be low, as the frequency of ‘normality’ is predictably much higher than the frequency of abnormality in GH signalling. The rate of false positives will, therefore, outnumber the rate of true positives.

Given the limitations of the IGFGT in the most severe cases of GHIS, the ability of the IGFGT to detect less severe GHIS is certainly doubtful. As the IGF1 response to the IGFGT overlaps between patients with ISS, GHD and individuals with normal stature, it is unlikely that the IGFGT will be a sensitive and specific tool for the diagnosis of partial GHIS.

As the diagnostic utility of the IGFGT is limited, its use for influencing treatment decision and initiating IGF1 treatment, as reported by most respondents of the survey, should be questioned.

**Conclusions**

1. The sensitivity and specificity of the IGFGT (either standard, 4-day or 7-day low- or high-dose protocol) are not high enough to appropriately identify severe GHIS in children with short stature.

2. The information afforded by the IGFGT in cases of suspected partial GHIS, as well as in children with ISS, Turner’s syndrome, or GHD, is not useful.
Declaration of interest

R Coutant, H-G Dörr and J Argente have received honoraria from Ipsen, Lilly, Novo Nordisk, Serono and Pfizer for participation in scientific activities and lectures.

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