Prevalence of IGF1 deficiency in prepubertal children with isolated short stature

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Abstract

Background/aims: ‘Primary IGF1 deficiency (IGFD)’ is defined by low levels of IGF1 without a concomitant impairment in GH secretion in the absence of secondary cause. The aims of this study were to evaluate the prevalence of non-GH deficient IGFD in prepubertal children with isolated short stature (SS) and to describe this population.

Methods: This retrospective study included all children with isolated SS seen in our Pediatric Endocrinology Unit from January 2005 to December 2007. Children were included based on the following criteria: i) SS with current height SDS \( \leq -2.5 \), ii) age \( \geq 2 \) years, and iii) prepubertal status. Exclusion criteria were: i) identified cause of SS and ii) current or past therapy with rhGH. IGFD-deficient children were defined as children without GH deficiency and with IGF1 levels below or equal to \(-2\) SDS.

Results: Among 65 children with isolated SS, 13 (20%) had low IGF1 levels, consistent with a diagnosis of primary IGFD, four of which were born small for gestational age and nine were born appropriate for gestational age. When compared with non-IGFD children, IGFD children had higher birth weight (0.7 vs \(-1\) SDS, \( P = 0.02 \)) and birth height (1.7 vs \(-2\) SDS, \( P = 0.04 \)) and more delayed bone age (2.6 vs 1.7 years, \( P = 0.03 \)).

Conclusion: The prevalence of primary IGFD was 20% in children with isolated SS. Concerning the pathophysiology, our study emphasizes that IGFD in some children may be secondary to nutritional deficiency or to maturational delay.

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Introduction

The GH–insulin-like growth factor 1 (IGF1) system could be viewed like other endocrine systems, with a central tropic hormone, GH, and a peripherally active hormone, IGF1.

Clinical trials have demonstrated the long-term efficacy of recombinant human (rh) GH treatment in children with GH deficiency (GHD) and also non-GH-deficient short stature (SS; Turner syndrome, idiopathic SS (ISS), small for gestational age (SGA), Prader–Willi syndrome) (1–5).

The first children treated with rhIGF-I were those with SS resulting from defects in GH action due to GH-receptor (GHR) abnormalities or GH inactivating antibodies following rhGH treatment of GHD from GH-gene deletion. Clinical trial studies have established the long-term efficacy and safety of rhIGF-I treatment in these patients (7). A recent publication showed that rhIGF-I stimulates linear growth in children with severe IGFD due to GH insensitivity whether or not there was an evidence of GHR abnormalities (8). Based on these studies, rhIGF-I was approved by the US Food and Drug Administration as therapy for severe primary IGFD defined by a height SDS \( \leq -3 \) and a basal IGF1 SDS \( \leq -3 \) and normal or elevated GH levels. More recently, rhIGF-I therapy was approved by the European Medicines Agency (EMEA) in children with primary IGFD defined by height SDS \( < -3 \) and a basal IGF1 percentile \( < 2.5 \) (equivalent of \(-2\) SDS) and normal or elevated GH. In these two indications, severe primary
IGFD included patients with mutations in the GHR, defects in post-GHR signaling pathway, and IGF1 gene mutations. Moreover, secondary forms of IGFD are excluded, such as malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

To date, the prevalence data of IGFD has been not evaluated thoroughly in Europe. The aims of this retrospective study were to assess the prevalence of primary IGFD in children with isolated SS, to describe this population, to discuss pathophysiology, and treatment.

Subjects and methods

Subjects

The study group comprised all short children admitted to our Endocrinology Unit in 2005, 2006, and 2007. Children were included according to the following criteria: i) SS with current height SDS below or equal to $-2.5$, ii) age between 2 and 13 years in girls and 14 years in boys, and iii) prepubertal status, defined as Tanner-breast stage I for girls and testicular volume $<4$ ml for boys. Exclusion criteria were: i) identified cause of SS (identified syndromes or chromosomal defects, skeletal dysplasia, severe neurological impairment, severe chronic illness, chronic corticosteroid treatment), and ii) patients presently on rhGH therapy or having received either therapy. None of our patients had received rhIGF-I during this period.

Methods

For each child, the family history and parental heights were recorded, with calculation of the target height as absolute value and SDS. Birth weight and height were expressed as SDS with reference to gestational age according to the Usher & McLean tables (9). SGA was defined as birth height and/or birth weight $\leq -2$ SDS according to the Usher & McLean tables. Weight, height, and head circumference were expressed as absolute values and SDS, with reference to chronological age according to the French standards (10). Body mass index (BMI) was calculated as the ratio of weight in kilograms divided by the square of height in meters. BMI was expressed as $Z$-score ($Z_s$) with reference to chronological age according to the French curves (11). Pubertal stage was assessed by Tanner’s score (12). The onset of puberty was defined clinically by the appearance of breast development in girls and a testicular length of 30 mm or more in boys. Bone age was assessed using the atlas of Greulich & Pyle (13).

Assays

Two assay kits were used to measure serum GH concentrations; one immunoradiometric (hGH, RIACT, CisBio, Gif sur Yvette, France) and the Nichols Automate Advantage (Nichols Institut Diagnostic, San Clemente, CA, USA). Both the assay standards and controls have been calibrated against the same international standard, the second World Health Organization International Reference Reagent for GH WHO second IS 98/574. IGF1 analysis was performed by means of IRMA kits either from DSL (Webster, TX, USA) or from Nichols (Nichols Institut Diagnostic), depending on the date of the test. All standards and controls have been calibrated against the WHO International Reference Reagent for IGF1 code 87/518. The coefficient of variation (CV) of the methods was $<8\%$ for the DSL and the Nichols tests. In order to define SDS for IGF1, we have established the reference values from 100 normal children aged 2–18 years with the DSL kit. We further established accurate correlation values between the values given by DSL and Nichols kits (Nichols = 0.882 $\times$ DSL $- 19.84$, $R^2 = 0.8819$). We used this correlation in order to define the SDS values in patients tested further with the Nichols kit. IGFD children were defined as children without GHD, which was defined as at least one GH peak above 7 $\mu$g/l under stimulation test, and with IGF1 levels below or equal to $-2$ SDS. GHD was defined as two GH peaks $<7$ $\mu$g/l under stimulation test.

Serum IGF binding protein-3 (IGFBP-3) levels were measured by an IRMA kit from Immunotech (Marseille, France), with inter-assay CV being 9.5%. IGF generation test involved daily s.c. injections of rhGH (0.033 mg/kg) at bedtime for five consecutive days as standardized by Blum et al. (14). Fasting blood samples were drawn in the morning before the first injection and on day 6 for IGF1 and IGFBP-3 measurement.

The GH binding protein (GHBP) assay was performed with an ELISA kit from DSL with inter-assay CV being 8.3%.

Analysis of coding exons of the GHR

Genomic DNA of the patient and a healthy control were extracted from peripheral blood leukocytes. The coding region of the GHR gene was PCR amplified from exon 2–10 in 12 fragments. The nucleotide sequences of the primers and conditions of PCR amplification are available on request. All coding exons were purified from an agarose gel with the QIAquick PCR purification kit (Qiagen GmbH) and then directly sequenced by the dideoxy method using the DNA sequencing kit Big Dye Terminator Cycle Sequencing (PE Applied Biosystem, Foster City, CA, USA), at conditions recommended by the manufacturer. Sequencing reaction products were analyzed using the Applied Biosystem Model 3100 sequencer (PE Applied Biosystem).
**Statistical methods**

The results are expressed as median values and ranges. For continuous variables, groups were compared using the non-parametric Mann–Whitney U-test. The χ²-test was used to compare percentages. Correlations were analyzed with Spearman’s test. A value of \( P < 0.05 \) was considered statistically significant.

**Results**

**Screening and frequency of IGFD**

We aimed to make precise the diagnostic process of patients with IGFD among patients referred for SS (height ≤ −2 SDS). Children older than 2 years and prepubertal, with present height SDS below or equal to −2.5 and without identified cause of SS, were included.

Patients screening process is shown in Fig. 1. Our final cohort comprised 65 prepubertal children with isolated SS below or equal to −2.5 SDS, all older than 2 years. In this cohort, 19 (29%) children presented with GHD and 46 (71%) children presented with non-GH-deficient SS. 22 born appropriate for gestational age (AGA), and 24 born SGA. Among the non-GH-deficient, 13 children, nine born AGA and four born SGA, had low IGF1 levels, consistent with a diagnosis of IGFD (Fig. 2). The prevalence of IGFD represents 20% of the entire original cohort of short children comprising 65 children.

The number of patients undergoing a GH stimulation test (normal peak GH > 7 μg/l) and an IGF1 measurement (normal > −2 SDS) falling into each diagnostic category is shown in Table 1.

**Auxological and hormonal characteristics of the 13 children with IGFD**

Auxological and hormonal characteristics, expressed as median value and ranges, of IGFD patients are shown in Table 2 and are compared with characteristics of non-IGFD and GHD patients.

All children with IGFD except one had a BMI above −2 Zs. Among IGFD children, when children born AGA were compared with children born SGA, the only significant difference, besides birth weight and height, was BMI (respectively, −0.6 vs 1.2 Zs, \( P = 0.03 \)). Three IGFD children (23%) had a height below −3 SDS. When IGFD children were separated according to height (i.e. height between > −3 SDS and ≤ −2.5, and height ≤ −3 SDS), no difference in the auxological or hormonal data was found between these two groups. IGF1 levels were correlated with bone age (\( P = 0.03, r^2 = 0.44 \)), there was no correlation between IGF1 levels and the other data particularly BMI and GH peak.

When compared with non-IGFD children, IGFD children had higher birth weight (−0.7 vs −1 SDS, \( P = 0.02 \)) and birth height (−1.7 vs −2 SDS, \( P = 0.04 \)) and more delayed bone age (2.6 vs 1.7 years, \( P = 0.03 \)).
Between these two groups, there were no differences concerning the parental, auxological or hormonal data.

When compared with GHD children, IGFD children had higher target height (−1 vs −2 SDS, \( P=0.003 \)) and height (−2.8 vs −3.3 SDS, \( P=0.05 \)).

Precise auxological and hormonal characteristics and complementary analysis performed in IGFD children are shown in Table 3. IGFBP-3 levels were low in all but one patient. CV of IGF1 and IGFBP-3 expressed in percentage of baseline levels were obtained in four patients and abnormal in one. GHBP had been measured in only six patients and tended to be in the low-range values. Molecular studies of GHR were undertaken in three patients (patients' number 2, 6, and 8) and were normal in all cases.

When non-IGFD children were compared with GHD children, the only significant differences were target height (respectively −1.1 vs −2 SDS, \( P=0.0023 \)), GH peak (respectively 10.5 vs 4.5 \( \mu \)g/l, \( P<0.0001 \)), and IGF1 levels (respectively −1.4 vs −1.7 SDS, \( P=0.0002 \)).

### Table 1

<table>
<thead>
<tr>
<th>Peak GH level (( \mu )g/l)</th>
<th>IGF1 status (SDS)</th>
<th>Patients % (n)</th>
<th>AGA % (n)</th>
<th>SGA % (n)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, &gt; 7</td>
<td>Normal, &gt; −2</td>
<td>51 (33)</td>
<td>20 (13)</td>
<td>31 (20)</td>
<td>Normal GH–IGF1 axis</td>
</tr>
<tr>
<td>Normal, &gt; 7</td>
<td>Low, ≤ −2</td>
<td>20 (13)</td>
<td>14 (9)</td>
<td>6 (4)</td>
<td>IGFD</td>
</tr>
<tr>
<td>Low, ≤ 7</td>
<td>Normal, &gt; −2</td>
<td>15 (10)</td>
<td>8 (5)</td>
<td>5 (1)</td>
<td>GHD</td>
</tr>
<tr>
<td>Low, ≤ 7</td>
<td>Low, ≤ −2</td>
<td>14 (9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AGA, appropriate for gestational age; SGA, small for gestational age; SDS, SDS; GHD, GH deficiency; IGFD, IGF1 deficiency.

### Discussion

The aim of this retrospective study was to evaluate the prevalence of IGFD in prepubertal children with isolated SS below or equal to −2.5 SDS. IGF1-deficient children were defined as children without GHD, i.e. having had at least one GH peak above 7 \( \mu \)g/l under stimulation test, and with IGF1 levels below or equal to −2 SDS. In our entire cohort including 65 children, 20% of the children presented with IGFD, 14% were born AGA and 6% were born SGA. In the Genentech National Cooperative Growth Study, IGFD represents 25% of a cohort of 4663 short children (15), which is similar to that of Clayton’s study in 190 short children (16). In these two studies, SS was defined by height below or equal to −2 SDS and IGFD by IGF1 levels below or equal to −2 SDS.

Children with SGA were not excluded from our study because persistent SS after SGA is a condition that may overlap from what is called ISS in that some etiologies

### Table 2

<table>
<thead>
<tr>
<th></th>
<th>Non-IGFD (n=33)</th>
<th>( P )-value IGF1 deficiency (IGFD) compared to non-IGFD</th>
<th>IGFD (n=13)</th>
<th>( P )-value IGF1 deficiency (IGFD) compared to GHD (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (boys/girls)</td>
<td>18/15</td>
<td>8/5</td>
<td>11/8</td>
<td>10/12</td>
</tr>
<tr>
<td>Father height (SDS)</td>
<td>−0.7 (−2.4, 1.7)</td>
<td>0.420</td>
<td>−0.8 (−1.9, 0.3)</td>
<td>0.095</td>
</tr>
<tr>
<td>Father height ≤ −2 SDS (%)</td>
<td>9</td>
<td>0.618</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mother height (SDS)</td>
<td>−1.5 (−3.1, 2.7)</td>
<td>0.588</td>
<td>−1.6 (−3.1, 0.3)</td>
<td>0.686</td>
</tr>
<tr>
<td>Mother height ≤ −2 SDS (%)</td>
<td>25</td>
<td>0.863</td>
<td>33</td>
<td>0.800</td>
</tr>
<tr>
<td>Target height (SDS)</td>
<td>−1.1 (−3.2, 2)</td>
<td>0.958</td>
<td>−1.1 (−1.9, −0.7)</td>
<td>0.037</td>
</tr>
<tr>
<td>Target height &lt; −2 SDS (%)</td>
<td>19</td>
<td>0.2623</td>
<td>0</td>
<td>0.988</td>
</tr>
<tr>
<td>Height-target height (SDS)</td>
<td>−1.6 (−5, 0.8)</td>
<td>0.916</td>
<td>−1.7 (−2.1, −1)</td>
<td>0.565</td>
</tr>
<tr>
<td>Height-target height &lt; −2 SDS (%)</td>
<td>37</td>
<td>0.100</td>
<td>7</td>
<td>0.1013</td>
</tr>
<tr>
<td>Birth weight (SDS)</td>
<td>−1 (−3.6, 1.9)</td>
<td>0.012*</td>
<td>−0.7 (−1.5, 0.8)</td>
<td>0.377</td>
</tr>
<tr>
<td>Birth height (SDS)</td>
<td>−2 (−6.2, 0.2)</td>
<td>0.040*</td>
<td>−1.7 (−3.1, 0.0)</td>
<td>0.659</td>
</tr>
<tr>
<td>Birth head circumference (SDS)</td>
<td>−0.6 (−3.4, 2)</td>
<td>0.086</td>
<td>−0.1 (−1.1, 1.8)</td>
<td>0.052</td>
</tr>
<tr>
<td>Chronological age (years)</td>
<td>7.1 (2.143)</td>
<td>0.121</td>
<td>11 (3.7, 14)</td>
<td>0.095</td>
</tr>
<tr>
<td>Height (SDS)</td>
<td>−2.7 (−5.1, −2.5)</td>
<td>0.613</td>
<td>−2.6 (−3.4, −2.5)</td>
<td>0.055</td>
</tr>
<tr>
<td>Weight (SDS)</td>
<td>−2.2 (−3.7, −1.2)</td>
<td>0.633</td>
<td>−2.1 (−3.1, −0.9)</td>
<td>0.282</td>
</tr>
<tr>
<td>BMI (Z-score)</td>
<td>−0.3 (−3.4, 3)</td>
<td>0.583</td>
<td>0.6 (−2.7, 1.6)</td>
<td>0.161</td>
</tr>
<tr>
<td>Bone age delay (years)</td>
<td>1.7 (−0.5, 4.5)</td>
<td>0.030*</td>
<td>2.6 (1.3)</td>
<td>0.260</td>
</tr>
<tr>
<td>GH peak (( \mu )g/l)</td>
<td>10.5 (7.4, 24.3)</td>
<td>0.583</td>
<td>11.8 (7.1, 25.2)</td>
<td>&lt;0.0001^‡</td>
</tr>
<tr>
<td>IGF1 (SDS)</td>
<td>−1.4 (−1.7, 0.4)</td>
<td>&lt;0.0001^‡</td>
<td>−2 (−2.5, −2)</td>
<td>0.013*</td>
</tr>
</tbody>
</table>

All data are expressed as median values and ranges unless indicated otherwise. For continuous variables, groups were compared using the non-parametric Mann-Whitney \( U \)-test. The \( \chi^2 \) test was used to compare percentages. \(^* P<0.05\), \(^{1} P<0.01\), \(^{2} P<0.001\). GH, GH; GHD, GH deficiency; IGFD, IGF1 deficiency; IGF1, Insulin-like growth factor-I; IGFD, IGF1 deficiency; BMI, body mass index.
might cause both the two conditions. Moreover, the distinction between idopathic SGA and ISS may be arbitrary in that the Gaussian distribution of birth weight and birth length in ISS is shifted to the left by 1 SDS. So children with a birth weight or length below −2 SDS can be considered as the left tail of the distribution for children with ISS (17).

In our entire cohort, 71% of the children presented with isolated non-GH-deficient SS, of which 52% were born SGA. Of the children referred to specialized growth centers because of SS, the percentage with no organic causes for their impaired growth was about 70%, with 76% (212 out of 278 children) and 60% (119 out of 198) in the studies of Grimberg et al. and Green et al. respectively (18, 19). In these reports, the percentage of short children born SGA was not clear. In our study, 40% (9 out of 22) of the ISS children and 16% (4 out of 24) of the children born SGA presented IGFD.

In our study, it was unexpected that children with IGFD presented with higher birth weight (−0.7 vs −1 SDS, P = 0.02) and birth height (−1.7 vs −2 SDS, P = 0.04) than children without IGFD. Indeed, IGFD plays a major role in the prenatal growth and patients with deletion in the IGF1 gene or mutations in the IGF1 receptor presented with marked SGA (20, 21). These unexpected results may be partly explained by the greater number of SGA patients among non-IGFD patients compared to IGFD patients (60 vs 30%) in our study. Moreover, it should be noted that children with IGFD presented with lower birth weight and height compared to the normal population.

IGF1 is regulated by GH, but also by nutritional intake and by age. Therefore, IGFD could be secondary not only to GHD but also to nutritional deficiency or to maturational delay.

There is evidence that nutritional deficiency contributes to ISS (22) and is also associated with lower IGF1 levels. In our study, children with IGFD presented normal BMI; however, BMI is significantly lower in ISS children compared with children born SGA (respectively, −0.6 vs 1.2 Zs, P = 0.03). When ISS subpopulation was studied, despite no statistical difference, the BMI was lower for the IGFD children compared with non-IGFD children (respectively, −0.6 vs 0.3 Zs); this finding could reflect that some of the IGFD may be partly explained by nutritional deficiency. In the ISS population, no significant correlation between BMI and IGF1 was found as suggested by some previous studies (23).

Many children with SS have some degree of maturational delay, including delayed bone age, dental age, and puberty (24, 25); this condition is often called constitutional delay in growth and maturation. Because serum IGF1 levels are correlated with skeletal maturation (26, 27) and increase with age, even before puberty, a maturational delay might include a delayed rise in IGF1. In our study, when compared with non-IGFD children, IGFD children had significantly more delayed bone age (2.7 vs 1.7 years, P = 0.03), in addition IGF1 levels were correlated with bone age (P = 0.03, r² = 0.44). These data confirm the relationship between maturational delay and IGFD.

Finally, IGFD could be secondary to GH insensitivity (GHI). As impaired IGF production leads to an increase in GH secretion, decreased IGF1 is associated with elevated GH in complete GHI.

As previously reported, the children with ISS tended to have serum IGF1 concentrations in the lower portion of the normal range or below the lower limits of normal. Moreover, these subjects also failed to raise their serum IGF1 concentrations in response to GH (28). Several studies suggested that a subset of children with ISS has some degree of GHI (29, 30). Concerning neonates born SGA, they show increased levels of GH and reduced
IGF1 and IGFBP-3 concentrations, suggesting that these newborns present GH insensitivity (31–33). This alteration in the GH–IGF axis is transient, however, and normalization of GH, IGF1, and IGFBP-3 secretion occurs in early postnatal life (34). In short children born SGA, hormonal status is variable. Some of them show normal GH responses to stimulation testing and normal serum levels of IGF1 and IGFBP-3 (35). However, several studies have reported altered patterns of spontaneous GH release associated with a reduced concentration of IGF1, suggesting GH insufficiency (36–38). A case-control study of older children who were born SGA did not show any significant differences in IGF1 and IGFBP-3 levels between short and normal SGA (39), and no relationship was found between the IGF-related variables at birth and during postnatal growth (31). The large variation in hormone sensitivity patterns in patients with SGA explains the inability to classify SGA patients according to the relative GH and IGF1 concentrations (40).

Children with IGFD should be further analyzed in terms of GHI syndrome. In our IGFD patients, low serum levels of IGF1 were associated with low serum levels of IGFBP-3 suggestive of GHI. In patients with IGFD, the IGF1 generation test could be helpful in differentiating between low serum levels of IGF1 that are responsive, or partially responsive to rhGH, from low serum levels of IGF1 that do not respond to rhGH administration with an increase in IGF1 levels and would not be expected to respond to rhGH treatment with an improvement in linear growth and adult height. However, because of controversies regarding the optimal protocol, diagnostic interpretation, lack of assay standardization, and nearly no correlation of test results with the clinical response to rhGH, there is a need for more studies in this area (41). In our study, four IGF1 generation tests were performed and only one (patient 6) showed no increment in IGF1 and IGFBP-3 levels; in this child, the molecular study of the GHR was normal. The GHBP levels performed in six children were low in all cases. Serum GHBP level generally correlates positively with GHR and GH activity. In addition to complete GHI secondary to mutation in the GHR gene, several clinical GH-resistant conditions, such as liver cirrhosis, renal insufficiency, insulin-dependent diabetes mellitus, hypothyroidism, malnutrition and critical illness, are associated with reduced GHBP levels (42).

Many studies have now demonstrated the efficacy of rhIGF-I in increasing growth in conditions of low serum IGF1 in which rhGH administration is not effective, including GHR mutations, post-receptor signal transduction defects, GH gene deletions with inhibitory GH antibodies after GH treatment and IGF1 gene deletion. These conditions are approved indications for rhIGF-I treatment. In our study, only three patients fulfilled the EMEA criteria for IGF1 treatment recommendations. These patients presented with height SDS below -3 and IGF1 SDS below -2, and secondary forms of IGFD were excluded, such as malnutrition, hypothyroidism or chronic treatment with pharmacologic doses of anti-inflammatory steroids. However, no particular etiology was found in these patients. The role of rhIGF-I administration in ISS patients is presently unclear. Carefully controlled prospective studies are necessary to determine the benefits of rhIGF-I treatment compared with rhGH treatment. Moreover, considerations of economic, social or psychological costs are in addition to the therapeutic concerns of safety and efficacy and the risk to benefit ratio. Although presently, many growth disorders are still diagnosed and treated on empirical bases, it might soon be possible to stratify patients predominantly by genetic defect, with treatment based on our molecular understanding of the role of the affected gene in the disease (43).

In conclusion, the prevalence of primary IGFD was 20% in the children of our study with isolated SS. Concerning the pathophysiology, our study emphasize that IGFD in some children may be secondary to nutritional deficiency or to maturational delay.

Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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