Correlation between IGF-1 serum levels and hemoglobin concentration in children with idiopathic growth hormone deficiency (IGHD)


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Abstract
Objective: A functional role for the growth hormone and insulin like growth factor axis (GH/IGF-1) in erythropoiesis has been recognized for a long time. Several reports suggest as erythropoietic precursors are able to express GH and IGF-1 receptors.

Methods: We studied 279 children (196 boys and 83 girls) with isolated idiopathic growth hormone deficiency (IGHD). Results: Forty-eight patients had NC/NC anemia before the starting of the substitution therapy. These patients showed IGF-1 SDS average value (-1.70 SDS) lower than the average values of non anemic patients (-1.24 SDS). Conclusions: IGF-1 lower value is correlated to NC/NC anemia development. These data support the concept that the GH/IGF-1 axis promotes erythropoiesis in vivo.

Keywords: growth hormone deficiency, insulin like growth factor-1, hematopoiesis, normocytic normochromic anemia

Introduction
A vast series of data demonstrates that GH and IGF-1 stimulate the growth of erythroid precursor cells in vitro and in vivo. Studies conducted in murine models indicate that insulin and IGF-1 promote the proliferation of early erythroid colonies: CFU-E and BFU-E stimulate the commitment of bone marrow progenitor cells. All these cells have been shown to express receptors specific pool for these somatotropic peptides (1-3). Studies conducted in murine models indicate that erythropoietin (EPO), a glycoprotein hormone responsible for the differentiation of red blood cells and for proliferation of their progenitor cells, is a prime regulator of red cell production (4). The relationship between the endocrine system and the regulation of the erythropoietin secretion has been highlighted. Some reports have suggested that IGF-1 alone would not be able to act as a single hormone for the erythropoiesis, but that it might synergize with other molecules.

Results
Forty-eight patients had NC/NC anemia. Ten of these patients were anemic according to baseline Hb SDS value (< -2.00 SDS), 20 of these 58 had age- and gender specific means, together with standard deviation, as reported elsewhere. Anemia was defined as hemoglobin levels below 2 SD from the mean normative values for the given age group (20). Similarly, as IGF-1 blood levels change during the development, IGF-1 values were expressed as SDS based on the age and gender normative values from the West Virginia University School of Medicine (21).

Statistical Analysis
We used ANOVA (Friedmann and Wilcoxon), a non-parametric test that was used for the statistical analysis to evaluate the differences in the patients Hb and IGF-1 levels at baseline. We used the Spearman Rank Order correlation test to evaluate the correlations between Hb and IGF-1 levels. P value of less than <0.05 was considered to be statistically significant.We used the STATISTICA 6.0 software package (StatSoft) for statistical analysis.

Results
The median age of the 279 enrolled patients was 10.52 years (range: 3.08–17.5 years) and the mean Hb-SDS and IGF-1-SDS were respectively -0.93 and -1.32. At T0 we intercepted two groups of IGHD patients, (Fig.1) according to baseline Hb SDS value based on the age and gender normative values as show in table 1. Fifty-eight (48 boys and 12 girls) were found to be anemic (Hb < -2SDS). Ten of these 58 anemic patients were excluded from the analysis because they had low-for-age mean corpuscular hemoglobin due to a thalassemia trait or to iron deficiency anemia. Of the remaining 48 children, 41 boys and 7 girls (17.8%), the anemia was normocytic-normochromic. According to patient’s clinical and hematological parameters, we excluded other leading causes of anemia; consequently, their anemia was considered a secondary manifestation of the GH defect. Into two groups the difference of Hb SDS mean values

erythropoietin production; so there is a moderate recovery of NC/NC anemia during the growth hormone replacement therapy (18-19).
was statistically significant (Fig. 2). In anemic patients we have observed a mean value of IGF-1SDS: -1.70 which was statistically lower than value observed in non anemic patients. (Fig. 3)

### Tab. 1 Baseline values from 279 IGHD children

<table>
<thead>
<tr>
<th>Groups</th>
<th>Median Age</th>
<th>%</th>
<th>Hb-SDS</th>
<th>IGF-1-SDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>NC/NC Anemic patients</td>
<td>10.14</td>
<td>17.8</td>
<td>&lt;= -2.50 SDS</td>
<td>&lt;= -1.70 SDS</td>
</tr>
<tr>
<td>NC/NC No Anemic patients</td>
<td>10.12</td>
<td>33.5</td>
<td>&gt; -0.17 SDS</td>
<td>&gt; -1.24 SDS</td>
</tr>
</tbody>
</table>

**Fig. 1** IGHD children distribution: percentage values

**Fig. 2** SDS Hb at T0: mean value in NC/NC anemic and in NO anemic children

**Fig. 3** SDS IGF-1 at T0 mean value NC/NC anemic and in NO anemic children

### Discussion

A considerable amount of evidence deriving from in vivo and in vitro studies suggests that both GH and IGF-1 are able to exert stimulatory effects on erythropoiesis. Significant accumulated data have clearly demonstrated a relationship between the GH axis and the regulation of blood cell production (22-27). Several reports suggest that adults with GH deficiency may have normochromic-normocytic anemia (15-19). Insulin growth factors IGF-1 and IGF-2 contribute to the growth and function of almost every organ. The biological action of IGFs is mediated by specific receptors (4). Insulin receptors and IGF-1 are structurally homologous and they interact with various intracellular mediators (28, 31). In addition, insulin and the activation of IGF-1 receptors evoke similar initial responses within the cell. IGFs and their receptors are involved in normal processes of erythropoiesis, granulopoiesis, and lymphopoiesis, as well as in neoplastic hematopoietic processes. The GH/IGF-1 axis appears to have parallel functions: at normal erythropoietin levels, almost 40% of erythropoiesis depends on erythropoietin, another 30% or less depends on the additive effect of IGF-1 and the remaining 30% or more depends on other serum factors. Normally, hemoglobin concentration increases from the age of 2-3 months (mean value about 11.5g%) to puberty (mean values about 13.5g% in girls and 15.5g% in boys). During growth, the GH/IGF-1 axis plays a critical role in these physiological phenomena. It does so because it promotes the increase of the erythroid mass that induces the erythroid system to produce red cells in correlation to the increase in body mass. Growth hormone treatment results in increased IGF-1 and IGF binding protein concentration. Infusion of IGF-1 in patients with Laron syndrome (primary IGF-1 deficiency) caused a significant rise in red blood cell parameters thus confirming the strong stimulatory effect and the role played by this molecule in the regulation of human erythropoiesis (38). Kotzman et al. (19) reported that adults with GH deficiency did not have anemia but instead they had hematopoietic precursor cells in lower than normal range; GH therapy had a marked effect on erythroid precursors but only a negligible effect on hemoglobin levels. However, Ten Aven et al. (15) found that GH administration corrected hemoglobin levels in adults with GH deficiency and anemia. Barak et al. (39) demonstrated an enhancement of erythroid colony growth in pediatric patients with GH deficiency after they were treated with rhGH. Few studies have been performed in IGHD children to understand the role of GHIGF-1 axis on haematopoiesis. Valerio et al. (40) reported that 6 of 19 children with panhypopituitarism or isolated GH deficiency had normocytic normochromic anemia. GH treatment produced a significant increase in Hb levels in all six patients. Vihervuori and colleagues (41) showed that rhGH treatment increased Hb levels in 36 patients with short stature, but only 6/36 had isolated GH deficiency. Eugster et al. (42) found that 12% of 100 children with GH deficiency were anemic. The frequency of anemia did not differ from that of the general population. Unfortunately, the specific
types of anemia observed were not reported. Antilla et al. (37) reported a correlation between IGF-1 and Hb levels in boys with normal prepubertal height and early puberty. Sivan et al. (43) confirmed the role of IGF-1 in the development of anemia in patients with Laron syndrome; indeed, IGF-1 treatment reversed the anemic conditions of their patients. In the present report, we show that a significant percent of children with isolated GH deficiency have a moderate normochromic-normocytic anemia. Furthermore, we observed that these patients had a lower IGF-1 values compared to not anemic IGHD patients. These results confirm a relationship between Hb and IGF-1 levels; we conclude that in IGHD children serum IGF-1 level (34-46) independently from plasma EPO, can be recognized as a significant independent determinant of Hb concentrations.

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Conflicts of interests
The authors declare no conflicts of interests.

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