GH response to provocation and circulating IGF-I and IGF-binding protein-3 concentrations, the IGF-I generation test and clinical response to GH therapy in children with β-thalassaemia

Ashraf T Soliman, Nagwa El Banna and B M Ansari

Department of Paediatrics, University of Alexandria School of Medicine, Alexandria, Egypt, and 1Department of Paediatrics, University of Glamorgan School of Medicine and East-Glamorgan General Hospital and School of Applied Sciences, University of Glamorgan, Pontypridd, Wales, UK

(Correspondence should be addressed to A T Soliman, Alexandria University Children’s Hospital, El-Chatby, Alexandria, Egypt)

Abstract

The causes of growth retardation of children with thalassaemia major are multifactorial. We studied the GH response to provocation by clonidine and glucagon, measured the circulating concentrations of insulin, IGF-I, IGF-binding protein-3 (IGFBP-3) and ferritin, and evaluated IGF-I generation after a single dose of GH (0.1 mg/kg per dose) in 15 prepubertal patients with thalassaemia, 15 age-matched children with constitutional short stature (CSS) (height standard deviation score less than −2, with normal GH response to provocation) and 11 children with isolated GH deficiency (GHD). Children with thalassaemia had significantly lower peak GH response to provocation by clonidine and glucagon (6.2 ± 2.3 and 6.8 ± 2.1 μg/l respectively) than the CSS group (18.6 ± 2.7 and 16.7 ± 3.7 μg/l respectively). They had significantly decreased circulating concentrations of IGF-I and IGFBP-3 (47.5 ± 19 ng/ml and 1.2 ± 0.27 mg/l respectively) compared with those with CSS (153 ± 42 ng/ml and 2.06 ± 0.37 mg/l respectively), but the IGF-I and IGFBP-3 concentrations were not different from those with GHD (56 ± 25 ng/ml and 1.1 ± 0.32 mg/l respectively). These data demonstrate that the GH–IGF-I–IGFBP-3 axis in thalassaemic children is defective. Serum ferritin concentration correlated significantly with GH peak response to provocation (r = −0.36, P < 0.05) and circulating IGF-I (r = −0.47, P < 0.01) and IGFBP-3 (r = −0.42, P < 0.01) concentrations. In the IGF-I generation test, after GH injection, the thalassaemic children had significantly lower IGF-I and IGFBP-3 levels (86.7 ± 11.2 ng/ml and 2.05 ± 0.51 mg/l respectively) than those in the CSS group (226 ± 45.4 ng/ml and 2.8 ± 0.43 mg/l respectively). The IGF-I response was significantly higher in children with GHD (158 ± 50 ng/ml) than in thalassaemic children. Six short (height standard deviation score less than −2) thalassaemic children who had defective GH response to provocation (<10 μg/l), all the children with GHD and eight short normal children (CSS) were treated for 1 year with human GH (18 units/m² per week divided into daily s.c. doses). After 1 year of GH therapy there was a marked acceleration of growth velocity in both thalassaemic children (from 3.8 ± 0.6 cm/year to 7.2 ± 0.8 cm/year) and controls. However, the linear acceleration of growth velocity on GH therapy was significantly slower in thalassaemic children (3.3 ± 0.3 cm/year increment) compared with those with CSS (5.3 ± 0.4 cm/year increment) and GHD (6.9 ± 1.2 cm/year increment) (P < 0.05). Their circulating IGF-I concentration (105 ± 36 ng/ml) was significantly lower than those for CSS (246 ± 58 ng/ml) and GHD (189 ± 52 ng/ml) after 1 year of GH therapy. These data prove that some children with β-thalassaemia major have a defective GH–IGF-I–IGFBP-3 axis and suggest the presence of partial resistance to GH.

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Introduction

Growth and maturational delay are striking features of β-thalassaemia major. After the age of 4 years, significant growth retardation involves stature, sitting height, weight and skeletal maturation (1–3). Delayed or complete lack of pubescent changes are common in both girls and boys (4, 5). Haemosiderosis-induced damage of the endocrine glands is implicated as one of the main causes for the growth failure (6). Basal circulating concentrations of various hormones have been studied by different authors with no consensus defining the different endocrine abnormalities of the growth hormone (GH)–insulin-like growth factor-I (IGF-I)–IGF-binding protein-3 (IGFBP-3) axis. Both normal (7, 8) and subnormal GH response (9, 10) to
provocative stimulation tests have been reported. Some of those with normal GH response to provocation have neurosecretory dysfunction of GH secretion (9, 11, 12).

IGF-I is a GH-dependent polypeptide that has a 3-fold function as a mediator of the growth-promoting action of GH, as a potent mitogenic factor, and as a metabolic regulator with insulin-like activity (13, 14). Alterations in IGF-I regulation may provide an attractive explanation for thalassaemia-associated growth impairment. The predominant IGFBP in blood is IGFBP-3, which forms a large 150 kDa ternary complex. The serum level of this complex determines the total concentration of circulating IGF-I and regulates its growth-promoting potential (15, 16). Current opinion favours GH as the major regulator of IGF-I and IGFBP-3 levels in humans. In addition, serum IGF-I and IGFBP-3 are positively related to nutritional status (17) and affected by other hormones such as insulin (18). Estimation of circulating concentrations of IGF-I and IGFBP-3 markedly improves the interpretation of GH data in response to provocation and allows better evaluation of the hypothalamic–pituitary growth axis.

This study was conducted to (i) investigate the GH–IGF-I–IGFBP-3 axis in prepubertal children with β-thalassaemia major, (ii) test the hypothesis that these patients might have GH resistance, and (iii) study the effect of GH therapy for 1 year on their growth parameters.

Patients and methods

Fifteen prepubertal children, between the age of 7.5 and 14 years, with β-thalassaemia major were randomly recruited for the study from the thalassaemia clinic of the Alexandria University Children’s Hospital, Alexandria, Egypt. All had been treated with a chronic low-transfusion regimen (to keep haemoglobin concentration above 8 g/dl), with i.m. administered chelation treatment (3 times per week; suboptimal chelation for economic reasons) and were taking 5 mg folic acid per day. Fifteen prepubertal age-matched children with constitutional short stature (CSS), age range 7–13 years (with height standard deviation scores (HtSDS) at or below −2 and normal GH response to provocation) and 11 children with isolated GH deficiency (GHD), age range 6.5–10.5 years (GH peak response <5 µg/l in two or more provocative tests) served as controls. Informed consent was obtained from the parents of all the patients and, when appropriate, from the children before including them in the study. The ethical committee of Alexandria University approved the protocol of the study. None of the children had intrauterine growth retardation, severe malnutrition, diabetes, dysmorphic traits, exposure to irradiation, or any other systemic illness. All were prepubertal, with pubarche Tanner 2 or less, gonadarche stage in the boys of 1 and larche stage in the girls of 1, and all were euthyroid.

Anthropometric measurements included weight (obtained to the nearest 100 g using a digital scale (Seca model 770)), height (using the Harpenden scale), mid-arm circumference (using a metal tape) and triceps skinfold thickness (using the Holtain calliper). Growth velocity (cm/year) was measured over a whole year for all the patients before the start of any GH therapy. HtSDS and body mass index (BMI) were calculated. Normal population data were those reported by Tanner & Whitehouse (19). Nutritional assessment included evaluation of dietary intake using the recall method for the preceding 3 days. These data were recorded every clinic visit for the whole year (minimum of three visits a year).

After an overnight fast, a venous sample was withdrawn for measurement of free thyroxine (FT4), thyrotropin, IGF-I, IGFBP-3 and 0800 h cortisol concentrations. Serum ferritin, albumin, globulin, bilirubin, alanine aminotransferase, creatinine, calcium, phosphate and alkaline phosphatase were measured. Cortisol concentration was measured 1 h after i.v. injection of adrenocorticotropic hormone (ACTH; 0.5 mg Synacthen, Ciba Geigy, Basel, Switzerland), Two GH provocative testings with clonidine (0.15 mg/m2 orally) and glucagon (0.1 mg/kg i.m.) were performed on two occasions. After 3 days of adequate carbohydrate intake, a standard oral glucose tolerance test (1.75 g/kg glucose) was carried out in thalassaemic children. The IGF-I generation test (20) was performed in all the patients. The test entails measurement of morning basal circulating IGF-I concentration, followed by injection of human GH (0.1 mg/kg per dose, s.c.) and remeasuring IGF-I concentration next morning.

Six patients with β-thalassaemia major with growth retardation (HtSDS and growth velocity standard deviation score at or below −2 for their chronological age and for their respective bone age, determined by the method of Greulich and Pyle (45)) and defective GH release in two provocative tests were treated with human GH (18 units/m2 per week divided into daily s.c. doses) for 1 year. Growth parameters were followed-up every 3 months for the whole year, and IGF-I concentrations remeasured at the end of the year. Children with GHD (n = 11) and those with CSS (n = 8) treated with GH (18 units/m2 per week divided into daily doses) for the same period were used as controls. The oral glucose tolerance test was performed every 6 months in the GH treatment groups.

Human GH and IGF-I were measured by radioimmunometric assay, employing reagents purchased from Nichols Institute (San Juan Capistrano, CA, USA). Intra-assay coefficients of variation (CVs) averaged 5.8 and 6.6% respectively, and interassay CVs averaged 7.6 and 8.4% respectively in the range of GH and IGF-I values detected. IGFBP-3 was measured by RIA by via free access.
Data are presented as mean ± S.D. Statistical analyses were performed using the ANOVA test to compare analyte concentrations among groups. The paired t-test was used to compare data before and after therapy in the same group. Wilcoxon test was used when the data were not normally distributed. Correlations between variables of interest were examined by linear regression analysis and, when appropriate, multiple regression analysis.

Results

Table 1 summarises the auxologic data of prepubertal children with thalassaemia, GHD and CSS. The HI-SDS was significantly lower in children with GHD vs children with CSS and thalassaemia. Linear growth velocity and BMI did not differ significantly among the three groups studied. The bone age was significantly delayed in the GHD group. The upper/lower segment ratio was significantly lower in thalassaemic children than in the other two groups denoting slower growth of the spine compared with the limbs in this group of patients.

The biochemical and hormonal data (Table 2) show that thalassaemic children had significantly higher concentrations of serum ferritin and bilirubin and alanine aminotransferase activity, and lower haemoglobin and haematocrit values than those with CSS. All the children had normal serum creatinine and albumin concentrations. Two children with thalassaemia had impaired tolerance to oral glucose (1.75 g/kg) and were excluded from the GH treatment group. Serum calcium and phosphorus concentrations and alkaline phosphatase activity were comparable with those for controls, ruling out the diagnosis of hypoparathyroidism in any of the patients. After ACTH stimulation, circulating cortisol concentrations were significantly lower in thalassaemic children than controls. In three thalassaemic children, cortisol concentrations did not rise to 400 nmol/l. However, none of them had symptoms or signs of cortisol deficiency. Thyroid function was normal in 14 of 15 children with thalassaemia. One patient had mild hypothyroidism. His FT4 was 9 pmol/l (normal 10–25 pmol/l) and he had elevated thyroid-stimulating hormone of 8 μU/ml (normal 0.5–5 μU/ml). GH testing was performed after T4 replacement for 1 month in this boy. Fasting serum insulin concentrations did not differ between thalassaemic children (12 ± 7.8 μg/l) and controls (14.5 ± 5.8 μg/l).

GH/IGF-I/IGFBP-3 data are presented in Table 3. Thalassaemic children had significantly lower peak GH response to provocation by clonidine and glucagon than the children with CSS. Their circulating IGF-I and IGFBP-3 concentrations were significantly lower than those for the controls with CSS. The IGF-I and IGFBP-3 responses to GH injection were significantly lower in thalassaemic patients than controls, suggesting partial resistance to GH in these children. Their serum IGF-I concentrations after stimulation with GH were still lower than the basal circulating levels for the controls.

Table 3 shows the GH, IGF-I and IGFBP-3 data of all the patients. The peak GH response to provocation and circulating IGF-I concentrations was significantly lower in thalassaemic children than in those with CSS (P < 0.005). The IGF-I response to GH administration (IGF-I D in Table 3) (equal to the 24 h IGF-I value minus the basal value) was significantly lower in children with thalassaemia than in those with CSS or GHD (P < 0.01).

Table 4 compares growth and IGF-I data of six thalassaemic children with those for eight children with CSS and 11 children with GHD. After 1 year of GH therapy (18 units/m2 per week divided into daily s.c. doses) the growth velocity of patients with thalassaemia (7.2 ± 0.8 cm/year) was slower than that for children with CSS (9.9 ± 1.2 cm/year). The increments of growth velocity per year of thalassaemic patients was significantly lower than for the other two groups. Despite slower growth in thalassaemic children, their growth velocity doubled (from 3.8 ± 0.6 cm/year to 7.2 ± 0.8 cm/year). After GH therapy for 1 year the circulating IGF-I concentrations were significantly lower in thalassaemic patients than controls. None of the children developed impaired glucose tolerance or hypertension during treatment.

Correlations between circulating hormonal and ferritin concentrations for all the children are presented in Table 5. Serum ferritin concentration correlated significantly (negatively) with GH peak response, IGF-I, IGFBP-3 and insulin concentration. Peak GH response correlated significantly with IGF-I and IGFBP-3, supporting the view that GH is the major regulator of both IGF-I and IGFBP-3 synthesis.

Table 1 Auxologic data of patients and controls. Values are means ± S.D.

<table>
<thead>
<tr>
<th></th>
<th>No</th>
<th>Sex (M/F)</th>
<th>Age (years)</th>
<th>Bone age delay (years)</th>
<th>HI-SDS-1</th>
<th>HI-SDS-2</th>
<th>Upper/lower segment</th>
<th>Growth velocity (cm/year)</th>
<th>BMI (kg/m2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassaemia</td>
<td>15</td>
<td>9/6</td>
<td>7.9 ± 1.8</td>
<td>1.7 ± 0.4</td>
<td>1.9 ± 0.55</td>
<td>2.04 ± 0.5</td>
<td>0.85 ± 0.05</td>
<td>4 ± 1.3</td>
<td>14.8 ± 1.1</td>
</tr>
<tr>
<td>CSS</td>
<td>15</td>
<td>8/7</td>
<td>8.1 ± 0.8</td>
<td>2.5 ± 0.8</td>
<td>2.3 ± 0.3</td>
<td>2.2 ± 0.5</td>
<td>1.1 ± 0.07</td>
<td>4.6 ± 0.6</td>
<td>13.8 ± 0.6</td>
</tr>
<tr>
<td>GHD</td>
<td>11</td>
<td>6/5</td>
<td>7.3 ± 1.8</td>
<td>2.8 ± 0.4</td>
<td>3.1 ± 0.58*</td>
<td>3.4 ± 0.5*</td>
<td>1.18 ± 0.08</td>
<td>3.7 ± 0.6</td>
<td>15.5 ± 1.2</td>
</tr>
</tbody>
</table>

HI-SDS-1 and -2 means before and after 1 year of GH therapy. * P < 0.05 among groups.
Discussion

The growth-promoting activity of IGF-I is determined not only by the concentration of IGF-I but also by the amounts of various IGFBPs (21, 22). Of these, IGFBP-3 is the major binding protein (23). It has been observed to potentiate the effects of IGF-I in bone (24–26). In addition, recent data clearly indicate that IGFBP-3 prolongs the half-life of circulating IGF-I levels and changes the clearance pattern of plasma IGF-I (27). Current opinion favours GH as the major regulator of IGF-I and IGFBP-3 in humans. In this study, the GH response to provocation with clonidine and glucagon was impaired in short prepubertal children with \( \beta \)-thalassaemia major compared with that in short normal children. Ten of the 15 children with thalassaemia did not mount an appropriate GH response (>10 \( \mu \)g/l) in both provocation tests. These findings support previous reports indicating impairment of function along the hypothalamic–pituitary growth axis (9–12, 28). In malnourished children with decreased IGF-I synthesis, the basal and stimulated GH levels are significantly higher than normal (29), indicating stimulation of their hypothalamic–pituitary axis by the low circulating concentrations of IGF-I. In thalassaemic children, the presence of normal basal GH levels despite low circulating IGF-I levels suggests a defective hypothalamic–pituitary feedback mechanism. This might be secondary to defective GH secretion. Histopathological changes with significant siderosis of the pituitary gland and secondary atrophy of the somatotrophs can explain the dysfunction of this axis (6) and the increased incidence of defective GH secretion in our children, with defective chelation therapy, compared with other studies with properly chelated patients. Impaired GH secretion can explain in part the significantly lower IGF-I and IGFBP-3 synthesis with subsequent growth impairment in children with thalassaemia major. However, haemosiderosis of the liver in these patients with disturbed hepatic function may also decrease IGF-I synthesis. In our study serum ferritin concentration correlated significantly with IGF-I concentration \( (r = -0.47, P < 0.01) \), IGFBP-3 \( (r = -0.42, P < 0.01) \) and peak GH response to provocation \( (r = -0.36, P < 0.05) \), which supports the view that iron overload may affect GH/IGF-I/IGFBP-3 secretion adversely. The deficiency of IGFBP-3 in thalassaemic patients may contribute to their growth impairment by decreasing the growth-promoting effects of IGF-I. We (30) and others (31) reported progressive impairment of insulin secretion in children with thalassaemia because of haemosiderosis of the pancreas. Other investigators stressed as well the importance of insulin resistance in these patients (31, 32). The progressive loss of the anabolic functions of insulin may contribute to the delayed growth of these children either directly and/or through inhibition of IGF-I synthesis and function (18, 33). In our study basal (fasting) serum concentrations

### Table 2

<table>
<thead>
<tr>
<th>Test</th>
<th>Thalassaemia</th>
<th>CSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortisol (nmol)</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Ferritin (g/dl)</td>
<td>411</td>
<td>54</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>78±13*</td>
<td>76±38*</td>
</tr>
<tr>
<td>ALT (U/l)</td>
<td>24±6</td>
<td>24±38*</td>
</tr>
<tr>
<td>Bilirubin (( \mu )mol/l)</td>
<td>41±54</td>
<td>21±45</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>39±6.2</td>
<td>22±0.03</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.1±0.02</td>
<td>1.4±0.03</td>
</tr>
<tr>
<td>Phosphate (mmol/l)</td>
<td>2.1±0.02</td>
<td>1.4±0.03</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>137±172</td>
<td>128±172</td>
</tr>
<tr>
<td>Thyrotroph (ng/ml)</td>
<td>157±34</td>
<td>157±34</td>
</tr>
<tr>
<td>FT(4) (pmol/ml)</td>
<td>15±2.9</td>
<td>15±2.9</td>
</tr>
<tr>
<td>Thalassaemia</td>
<td>138±6.8</td>
<td>138±6.8</td>
</tr>
</tbody>
</table>

*P < 0.05 compared with values for CSS group.

1, 2 mean cortisol concentration before and after ACTH administration.
despite regular transfusion and desferroxamine therapy, malnutrition in our children with thalassaemia.

Quantitative and qualitative dietary intake. These intake, by using the recall method, showed normal and skinfold thickness, and normal serum albumin and synthesis and insulin release (29). However, our group through inhibition of IGF-I (29) and IGFBP-3 (17) thalassaemic children. Malnutrition can inhibit growth (39), is another correctable cause of growth delay in appropriately when provided with nutritional support intake, as indicated by the capacity to gain weight vertebral changes observed in our thalassaemic group. Relatively short upper segment, in addition to the mild of thalassaemic children (38). This may explain the relatively short upper segment, in addition to the mild vertebral changes observed in our thalassaemic group.

Malnutrition, primarily caused by inadequate nutrient intake, as indicated by the capacity to gain weight appropriately when provided with nutritional support (39), is another correctable cause of growth delay in thalassaemic children. Malnutrition can inhibit growth through inhibition of IGF-I (29) and IGFBP-3 (17) synthesis and insulin release (29). However, our group of patients had normal BMI, mid-arm circumference and skinfold thickness, and normal serum albumin and basal GH concentrations. Analysis of their dietary intake, by using the recall method, showed normal quantitative and qualitative dietary intake. These factors collectively exclude any major role played by malnutrition in our children with thalassaemia.

Impaired linear growth in thalassaemic children, who are regular transfusion and desferroxamine therapy, who have normal GH secretion suggests the possibility of GH resistance. In this study the IGF-I generation test showed that these patients do not secrete adequate IGF-I after GH stimulation when compared with normal short children or those with GHD. After 1 year of GH therapy, despite the same dose/m² being given to all the children, their circulating IGF-I concentrations were significantly lower than those for the short normal control group and those with GHD. These data are in concert with those of Werther et al. (40), who reported lack of response of non-suppressible insulin-like activity to short-term administration of human GH in their thalassaemic patients. In our six thalassaemic children treated with GH, the growth velocity increased significantly from 3.8 ± 0.6 cm/year to 7.2 ± 0.8 cm/year (doubling). However, the increment in the rate of growth was significantly smaller than that of the control groups. Collectively these findings may suggest the presence of significant GH resistance in these patients, which could attenuate the growth-promoting effects of GH therapy. Low et al. (41) showed that, with higher (supraphysiological) (30 units/m² per week divided into daily s.c. doses) doses of exogenous GH, there was a progressive increase in IGF-I production in their thalassaemic patients. It is known that higher GH doses during treatment possibly elicit a higher IGF-I and growth velocity response; however, this high dose may be necessary in thalassaemic children to overcome the possible GH resistance. However, supraphysiological doses of GH may increase the risk of inducing diabetes (30–32) and hypertension (42) in these high-risk patients. Human IGF-I therapy, alone or in combination

| Table 3 Responses of IGF-I and IGFBP-3 to GH. Values are means ± S.D. |
|----------------|----------------|----------------|
|                | Thalassaemia   | CSS            | GHD            |
|                | (n = 15)       | (n = 15)       | (n = 11)       |
| IGF-I (ng/ml) before GH | 47.5 ± 19       | 153 ± 42#      | 56 ± 25        |
| IGF-I (ng/ml) after GH  | 86.7 ± 11.2     | 226 ± 45.4**   | 158 ± 50*      |
| IGFBP-3 (mg/l) before GH| 38.2 ± 11.8     | 73 ± 11.7#     | 95 ± 24*       |
| IGFBP-3 (mg/l) after GH | 1.2 ± 0.27      | 2.06 ± 0.37#   | 1.1 ± 0.32     |
| Peak GH response to clonidine (µg/l) | 2.05 ± 0.51     | 2.8 ± 0.43#    | ND             |
| Peak GH response to glucagon (µg/l) | 0.8 ± 0.36      | 0.71 ± 0.35    | ND             |
| D means the response of IGF-I or IGFBP-3 above basal levels after GH injection. ND, not determined. |
| *P < 0.05, #P < 0.01 and **P < 0.005, compared with values for thalassaemic children. |

of insulin correlated significantly with concentrations of IGF-I (r = 0.541, P < 0.01) and IGFBP-3 (r = 0.42, P < 0.05). Delayed or arrested puberty is common in patients with thalassaemia (4, 5) because of disturbed gonadotrophin-releasing hormone secretion (5, 34) with consequent deficiency of sex steroids. Sex steroids can influence growth through the modulation of IGF-I-induced cellular response (35–37), and their deficiency adds significantly to the growth delay and osteoporosis of thalassaemic children (38). This may explain the relatively short upper segment, in addition to the mild vertebral changes observed in our thalassaemic group.

Malnutrition, primarily caused by inadequate nutrient intake, as indicated by the capacity to gain weight appropriately when provided with nutritional support (39), is another correctable cause of growth delay in thalassaemic children. Malnutrition can inhibit growth through inhibition of IGF-I (29) and IGFBP-3 (17) synthesis and insulin release (29). However, our group of patients had normal BMI, mid-arm circumference and skinfold thickness, and normal serum albumin and basal GH concentrations. Analysis of their dietary intake, by using the recall method, showed normal quantitative and qualitative dietary intake. These factors collectively exclude any major role played by malnutrition in our children with thalassaemia.

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with GH and/or IGFBP-3 appears to be an attractive alternative to be used to overcome the GH resistance and avoid the high risk of developing diabetes. In human (43, 44) and animal (26, 27) experiments this combination of growth factors appears to be useful.

In summary, children with β-thalassaemia and short stature have a defective GH–IGF-I–IGFBP-3 axis that might be secondary to haemosiderosis of the pituitary gland, liver and pancreas. In addition to regular blood transfusion and proper chelation therapy, these patients need early management of their endocrinopathy. Treatment of their hypothyroidism, hypogonadotropic hypogonadism, diabetes mellitus and defective GH–IGF-I–IGFBP-3 axis can markedly improve their growth. In addition, these patients may have partial GH resistance which requires supraphysiological doses of GH and/or human IGF-I therapy.

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