Research paper

Screening of growth hormone deficiency in short thalassaemic patients and effect of L-carnitine treatment

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Abstract

Introduction: Evaluation of growth hormone (GH) in short thalassaemic patients and effect of L-carnitine therapy in those with hormone deficiency.
Material and methods: The study included 30 β-thalassaemic patients aged 13.8 ±1.7 years and 30 children with constitutional short stature as controls. Anthropometric measurements (basal and after 6 months), thyroid profile, insulin-like growth factor-1 (IGF-1) and GH provocation by 2 tests were carried out. Eight patients with inadequate GH response to both clonidine and ITT were given L-carnitine treatment for 6 months. They were re-evaluated (clinically, anthropometrically and in the laboratory by doing GH stimulation test) after 6 months of therapy.
Results: Twelve (40%) patients had sub-clinical hypothyroidism and 10 (33.3%) had growth hormone deficiency (GHD). Peak GH and growth velocity (cm and standard deviation score [SDS]) were significantly lower while weight (SDS) and weight/height SDS were significantly higher than in patients with constitutional short stature ($p < 0.05$). A significant positive correlation was found between height and target height (cm). Haemoglobin levels, peak GH, IGF-1 and growth velocity (cm & SDS) were significantly higher and the number of blood transfusions was significantly lower in GH deficiency patients after L-carnitine treatment ($p < 0.05$). Delta changes were higher in height (cm & SDS), estimated mature height and sitting height and lower in target height – height (SDS and cm) six months after L-carnitine treatment in β-thalassaemic patients with GHD ($p < 0.05$).
Conclusions: Growth hormone deficiency is an aetiological factor in thalassaemic patients with short stature. L-carnitine can promote GH secretion and growth.

Key words: thalassaemia, growth hormone, L-carnitine treatment.

Introduction

Patients with multi-transfused thalassaemia major may develop severe endocrine complications due to iron overload. The anterior pituitary is particularly sensitive to iron overload, which disrupts hormonal secretion resulting in hypogonadism, short stature, acquired hypothyroidism and hypoparathyroidism. Glucose intolerance and diabetes mellitus are also common [1].

Growth failure has been attributed to growth hormone deficiency (GHD), hypothyroidism, delayed sexual maturation and hypogonadism [2]. The

role of growth hormone (GH) in growth retardation is controversial. Low insulin-like growth factor-1 (IGF-1) level has been suspected as being related to either reduced spontaneous growth hormone secretion, hepatic damage or growth hormone insensitivity. The treatment of stunted thalassaemic patients with physiological GH doses seems to be inefficient, indicating that other factors are responsible for this type of growth retardation [3, 4].

Carnitine is a natural substance synthesized in the liver, brain and kidney from protein bound lysine and methionine. The final synthetic step occurs in the liver [5]. It is present in all tissues and several factors such as sex hormones and glucagon may impact on carnitine distribution and level in tissues. Many authors have reported that failure to thrive and developmental delay are associated with secondary carnitine deficiency [6, 7].

The study was planned to estimate GH and insulin-like growth factor-1 (IGF-1) and their possible relation to growth impairment in thalassaemic patients. In addition, evaluation of the effect of L-carnitine treatment on growth of thalassaemic patients with growth hormone deficiency (GHD) was assessed.

Material and methods

Patients

Thirty β-thalassaemic patients from the haematology clinic of Cairo University Children's Hospital were included in this study. All patients were on a chronic low transfusion regimen (to keep their haemoglobin level above 9 g/dl) and subcutaneous Desferal 5 days/week.

Inclusion criteria included age > 3 years < 18 years and height < –2 standard deviation score (SDS) below the mean. Written consent from the patients or their parents was taken to be included in the study. Exclusion criteria included serious hepatic or cardiac diseases and anaemia from sources other than the main disease.

Thirty children of matching age and sex, with constitutional short stature (height SDS < –2) and normal growth hormone response to provocation were included as controls.

Methods

Thorough history taking and clinical evaluation of growth were done for all subjects. Height, sitting height and weight were measured twice using a Harpenden stadiometer and electronic balance. Other anthropometric data were calculated by the program Growth Vision version 2.

Laboratory investigations were carried out including complete blood count (CBC), kidney and liver functions on a Hitachi 911 autoanalyser (Roche Diagnostics, Mannheim, Germany), and serum ferritin by means of particle-enhanced immunonephelometry [8] using a Behring nephelometer 100 analyser (BN100) (kits supplied by Dade Behring, Marburg, Germany). Thyroid profile (FT3, FT4, TSH) was also done. FT3, FT4 [9] and TSH [10] were estimated on Automated Chemiluminescence System ACS: 180 by a competitive and two site sandwich immunoassay respectively using direct chemiluminometric technology (Bayer Diagnostics, Dublin, Germany).

Stimulation of GH secretion by 2 provocation tests (clonidine and insulin tolerance test [ITT]) separated by one week interval was done. Growth hormone was analysed by immunoradiometric assay (IRMA) as described by Miles *et al*. [11]. The dose of clonidine given before the test was 0.15 mg/m^2 orally while that of insulin was 0.1 IU/kg *i.v*. In the ITT test, the blood glucose should decrease by 50% or more of the basal value or decrease to 40 mg/dl. If no hypoglycaemia occurred another dose of insulin (0.05 IU/kg) was given. With adequate hypoglycaemia, peak GH levels less than 10 ng/ml indicated GHD.

Patients with delayed puberty were primed with sex hormones prior to GH testing. Ethinyl oestradiol was given to girls at a dose of 20 µg three times per day for 3 days and testosterone was given to boys at a single dose of 100 mg *i.m*. 3 days before the test.

Insulin-like growth factor-1 (IGF-1) was determined at diagnosis using solid phase immunoradiometric assay (IRMA) [12] using kits from Diagnostic System Laboratories Inc (DSL) (Texas, USA).

Follow-up study

Anthropometric measurements and pubertal assessment were done for all patients after 6 months. Ten patients were found to have inadequate GH response to both clonidine and ITT; one of them died and another one developed chronic renal failure before starting treatment and was excluded from the follow-up study. The remaining eight patients received L-carnitine treatment at a dose of 50 mg/kg/day divided into three doses (recommended dose of L-carnitine is 50-100 mg/kg/day) for 6 months. They were re-evaluated after 6 months of therapy (clinically, anthropometrically and in the laboratory by doing growth hormone stimulation test).

Statistical analysis

Statistical Package for the Social Sciences (SPSS) software version 9.0 was used for data analysis. All anthropometric data were expressed in standard deviation score (SDS) applying the formula

$$\frac{\text{variable} - \text{mean}}{1\ \text{SD}}$$

by using the software Growth Vision version 2 provided by Novo Nordisk Denmark. Data were presented as mean ± SD. For comparison of two groups Student's *t*-test for dependent and independent variables was used. Linear Pearson's correlation was also done.

Table I. Comparison between anthropometric and hormonal data of patients with and without growth hormone deficiency

Variables	Normal growth hormone (n = 20) Mean ± SD	Growth hormone deficiency (n = 10) Mean ± SD	*P*-value
Weight (SDS)	–2.1 ±0.8	–2.1 ±0.9	0.7
Height (SDS)	–4.2 ±1.2	–4.1 ±1.1	0.8
Target height [cm]	167.6 ±6.1	168.4 ±5.9	0.7
Target height (SDS]	–0.3 ±0.4	–0.2 ±0.4	0.4
Growth velocity [cm]	2.5 ±1.2	2.2 ±1.2	0.5
Growth velocity (SDS)	–2.4 ±2.4	–2.2 ±2.9	0.9
Sitting height (SDS)	–4.4 ±1.7	–3.9 ±1.6	0.4
US/LS (SDS)	0.2 ±1.9	1.2 ±2.6	0.2
BMI (SDS)	–0.7 ±1.3	–0.9 ±1.4	0.7
Free T3 [pg/ml]	2.7 ±0.7	2.6 ±0.9	0.8
Free T4 [ng %]	1.4 ±0.4	1.5 ±0.6	0.8
TSH [MIU/ml]	4 ±1.9	3.3 ±1.9	0.3
Maximum peak GH [ng/ml]	11.8 ±0.7	8.6 ±1.9	0.0001
IGF-1 (SDS)	–0.9 ±0.3	–0.8 ±0.4	0.8

US/LS – upper segment/lower segment, BMI – body mass index

Results

Thirty thalassaemic patients (12 females and 18 males) were included in the study. Their mean age was 13.8 ±1.7 years (10.1-17.1 years), mean duration of the disease was 11.1 ±2.6 years (6-16 years) and mean age of onset of the disease was 2.6 ±1.6 years (0.5-6 years). Twelve patients (40%) had sub-clinical hypothyroidism and none were found to have clinical hypothyroidism. Ten patients (33.3%) had inadequate GH response (peak GH was < 10 ng/ml). No significant difference was found between age of patients, duration of disease, age of onset of Desferal and serum ferritin level in patients with and without growth hormone deficiency ($p > 0.05$). Tables I and II show the comparison between demographic, laboratory and anthropometric data of thalassaemic patients with and without GHD and between thalassaemic patients and patients with constitutional short stature respectively. Follow-up of the studied thalassaemic patients with normal growth hormone for 6 months showed a significant increase in height SDS and estimated mature height (EMHt) ($p < 0.05$). Patients with GHD showed no significant difference in anthropometric measures ($p > 0.05$). A significant positive correlation was found between height and target height (cm) (Figure 1). Haematological data and growth velocity of studied thalassaemic patients with growth hormone deficiency showed improvement after L-carnitine treatment (Table III). Delta changes were higher in height (SDS and cm), EMHt, sitting height and lower in target height – height (SDS and cm) 6 months after L-carnitine treatment in β-thalassaemic patients with growth

Table II. Comparison between demographic, anthropometric and hormonal data in patients with β-thalassaemia and constitutional short stature

Variables	Thalassaemia major (N = 30) Mean ± SD	Constitutional short stature (N = 30) Mean ± SD	*P*-value
Age [years]	13.8 ±1.7	13.1 ±3.1	0.3
Weight (SDS)	–2 ±0.8	–2.7 ±1.1	0.005
Height (SDS)	–4.1 ±1.1	–3.7 ±0.9	0.1
Growth velocity [cm]	2.4 ±1.2	7.9 ±2.5	0.0001
Growth velocity (SDS)	–2.3 ±2.5	4.7 ±5.3	0.0001
US/LS (SDS)	0.5 ±2.2	0.1 ±1.5	0.2
Weight/height (SDS)	1.1 ±1.9	–3.3 ±1.6	0.02
EMHt [cm]	143.3 ±8.8	155.4 ±8.3	0.0001
Target height – height [cm]	33.9 ±8.7	32.6 ±15.1	0.7
Maximum GH [ng/ml]	10.7 ±1.9	18.1 ±6.5	0.0001
IGF-1 (SDS)	–0.9 ±0.3	–1.3 ±1.5	0.1

GH – growth hormone, IGF-1 – insulin-like growth factor-1, US/LS – upper segment/lower segment, EMHt – estimated mature height

hormone deficiency (Table IV). No side effect of L-carnitine was reported from the patients except for occasional diarrhoea at the beginning of treatment.

Discussion

Delayed or complete lack of pubertal changes are common in both sexes of thalassaemic patients. As haemosiderosis leads to damage of their endocrine glands, it is implicated to be one of the main causes of their growth failure [13]. Hypothyroidism and delayed puberty could affect growth secretory dynamics; thus thyroid state should be normalized before testing the GH. Also sex hormones were recommended to be given to patients with delayed puberty as priming [14].

We studied 30 β-thalassaemic patients with short stature (height < –2 SDS); 12 patients (40%) had sub-clinical hypothyroidism diagnosed by normal free thyroxin level and elevated thyroid stimulating hormone (TSH). This agrees with Landau *et al.* [15], who reported sub-clinical hypothyroidism in 43% of thalassaemic patients due to thyroid damage by iron overload. None of our patients had overt primary hypothyroidism, which agrees with other studies that reported a low prevalence, 2.1% [16] and 3.2% [4]. On the other hand higher prevalence of 6% [17] has been reported.

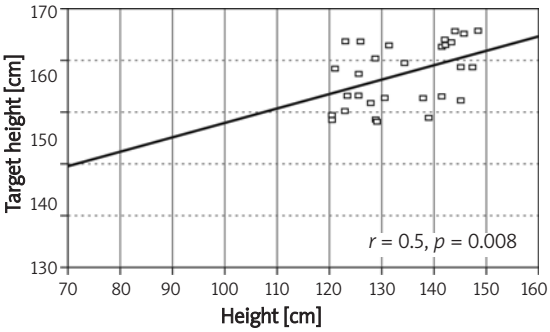

Figure 1. Correlation between height and target height of thalassemic patients

Ten of our thalassaemic patients (33.3%) had GH response to stimulation lower than 10 ng/ml in two GH provocation tests (low responders). This coincides with the results of Vidergor *et al.* [18] and Moayeri and Oloomi [14], who reported that GHD in thalassaemic patients was 25 and 38% respectively. On the other hand, it was higher than that reported by De Sanctis *et al.* [4], who found that the prevalence of GHD was 7.9% in males and 8.8% in females.

Table III. Haematological data and growth velocity of β-thalassaemic patients with growth hormone deficiency before and after L-carnitine treatment

Variables	Before L-carnitine (*N* = 8) Mean ± SD	After L-carnitine (*N* = 8) Mean ± SD	*P*-value
Hb [g/dl]	5.9 ±0.4	6.6 ±0.3	0.01
No. of blood transfusion/month	8 ±2.4	6.8 ±1.8	0.005
Maximum GH [ng/ml]	9.1 ±1.4	16.6 ±2	0.01
IGF-1 (SDS)	–0.8 ±0.4	0.1 ±1.1	0.02
Growth velocity [cm]	2.1 ±1	6.3 ±1	0.01
Growth velocity (SDS)	–2.8 ±2.8	2.5 ±4.6	0.03

Hb – haemoglobin, GH – growth hormone, IGF-1 – insulin-like growth factor-1

Table IV. Delta changes of anthropometric data of growth hormone deficiency in β-thalassaemic patients 6 months before and after L-carnitine treatment

Variables	Six months before L-carnitine (*N* = 8) Mean ± SD	Six months after L-carnitine (*N* = 8) Mean ± SD	*P*-value
Height (SDS)	–0.2 ±0.3	0.3 ±0.5	0.0001
Height [cm]	1.2 ±0.5	5.4 ±0.9	0.002
Target height – height (SDS)	0.2 ±0.3	–0.3 ±0.5	0.01
Target height – height [cm]	–1.2 ±0.5	–5.3 ±0.9	0.01
EMHt [cm]	–2.0 ±4.0	3.0 ±2.9	0.02
Sitting height (SDS)	–0.2 ±0.2	0.4 ±0.4	0.02
US/LS (SDS)	–6.3 ±0.2	0.2 ±0.4	0.1
BMI (SDS)	0.5 ±1.4	–3.8 ±1.2	0.6
Weight /height (SDS)	0.7 ±1.6	0.03 ±1.8	0.6

There was no significant difference in age of patients, age of start of chelation therapy and serum ferritin between patients with and without growth hormone deficiency, which agrees with Moayeri and Oloomi [14], Vidergor *et al.* [18] and Cavallo *et al.* [19].

In our study there was no significant difference in anthropometric data between normal and low GH responder groups. These data probably suggest that GHD is not the only factor contributing to growth retardation in Egyptian thalassaemic patients. Other factors may be involved such as nutrition, haemosiderosis and genetic factors [2].

No significant difference was found between IGF-1 SDS in our patients with and without GHD (–0.9 ±0.3 and –0.8 ±0.4 respectively). DeLuca *et al.* [20] reported that low IGF-1 in thalassaemic patients in general could be attributed to disturbed liver function secondary to iron overload and malnutrition.

Low IGF-1 in normal growth hormone responders has led to the speculation of complete or partial growth hormone insensitivity syndrome (GHIS) rather than GHD as the most likely cause of their growth retardation [3, 18, 21].

Follow-up of the studied thalassaemic patients with normal growth hormone for 6 months showed a significant increase in height SDS and estimated mature height (EMHt) ($p < 0.05$). On the other hand, patients with GHD showed no significant difference in anthropometric measurements ($p > 0.05$). These findings suggest that GH has an important role in growth of thalassaemic patients and its deficiency contributed to their growth impairment.

In the present study, peak GH in thalassaemic patients was significantly lower than constitutional short stature (CSS) ($p < 0.05$). This agrees with the results of Soliman *et al.* [22], who found that peak GH was significantly lower in thalassaemic patients than CSS, and this was explained by impairment of the hypothalamic-pituitary axis in thalassaemic patients secondary to pituitary siderosis and somatotroph atrophy [13].

Although height SDS was insignificantly lower in thalassaemic patients than in CSS, growth velocity (GV) cm and SDS were significantly lower in thalassaemic patients than CSS ($p = 0.0001$) and this agrees with the results of Soliman *et al.* [23].

The estimated mature height (EMHt) of our thalassaemic patients was significantly lower than those of CSS ($p = 0.0001$). Both British and Italian studies have suggested that a marked deceleration in growth occurs between the age of 12-13 years in almost all thalassaemic children. Although many of these patients had "catch up" growth in later years, their final height was always markedly lower than their potential height [24].

A significant positive correlation was found between height (cm) and target height (cm) in our study (Figure 1). This coincides with Saka *et al.* [25], who suggested that height in thalassaemic patients is conditioned by genetic factors.

Eight of our patients with GHD (GH < 10 ng/ml) received L-carnitine for 6 months. There was a significant increase of peak GH and IGF-1 (SDS) in our thalassaemic patients after L-carnitine therapy. Similar results were reported by Di Mazio *et al.* [26]. Increase of G.V. after treatment from 2.1 ±1.0 to 6.3 ±1.0 cm/year was also observed. This coincides with El Beshlawy *et al.* [27], who reported an increase of G.V. from 3.3 ±2.1 to 4.8 ±1.3 cm/year after L-carnitine treatment.

There was a significant increase in delta changes of height (SDS and cm), estimated mature height and sitting height (SDS) 6 months after L-carnitine treatment in GH deficient thalassaemic patients. No statistically significant difference was found in delta changes of upper segment/lower segment (US/LS) (SDS) 6 months after L-carnitine treatment. This coincides with the results of El Beshlawy *et al.* [27], which denotes that there is a proportional increase in upper and lower seg-ments.

There was an insignificant decrease in delta change of body mass index (SDS) and weight/height (SDS) 6 months after L-carnitine treatment in this study. This also coincides with El Beshlawy *et al*. [27], who found a significant decrease of body mass index (BMI) (SDS) and weight/height SDS after L-carnitine treatment, explained by the increase in height more than the increase in weight.

A significant difference was found between mean haemoglobin level and number of blood transfusions per month before and after L-carnitine therapy ($p < 0.05$). This is in agreement with Yesilipek *et al.* [7], and El Beshalwy *et al.* [27, 28], who reported a prolongation in transfusion interval in thalassaemic patients after L-carnitine therapy. L-carnitine is essential for normal oxidation of fats by the mitochondria and energy production as well as stabilizing cell membranes [29].

Susceptibility to oxidative stress is increased in erythrocytes in β-thalassaemia major. L-carnitine may prove beneficial in vivo by protecting the erythrocytes in which peroxidative damage of the cell structure is increased. L-carnitine as a butyric acid analogue might have a stimulatory effect on HbF synthesis. Furthermore, its anti-oxidant effects may show additional benefit in β-thalassaemia patients [7].

In conclusion, GHD is an aetiological factor in β-thalassaemic patients with short stature. L-carnitine can promote GH secretion and growth. So we recommend the use of L-carnitine as routine treatment in short thalassaemic patients with growth hormone deficiency.

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