UNIVERSITI SAINS MALAYSIA
PROJEK PENYELIDIKAN JANGKA PENDEK
LAPORAN AKHIR

KEDUDUKAN HORMON TUMBESARAN DI KALANGAN PESAKIT TALASEMIA

PENYELIDIK

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USM J/P-06

BAHAGIAN PENYELIDIKAN & PEMBANGUNAN

CANSELORI

UNIVERSITI SAINS MALAYSIA

Laporan Akhir Projek Penyelidikan Jangka Pendik

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Boleh diterima. pp.

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2) **Pusat Pengajian/Pusat/Unit** : Pusat Pengajian Sains Perubatan

3) **Tajuk Projek:** Kedudukan Hormon Tumbesaran Di Kalangan Pesakit Talasemia

4) (a) **Penemuan Projek/Abstrak**

*(Perlu disediakan makluman di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan Bahasa Inggeris**. Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).*

Berbagai disfungsi organ endokrin diketahui berlaku pada kanak-kanak talasemia yang memerlukan transfusi darah. Keabnormalan ini mungkin disebabkan oleh pengambilan melampau zat besi atau hipoksia yang disebabkan oleh anemia kronik. Kajian-kajian rembesan hormon tumbesaran selepas rangsangan telah memberi keputusan yang berbeza-beza. Kebanyakan kajian ini dilakukan ke atas kanak-kanak yang menghidapi penyakit talasemia major dan tidak banyak kajian dilakukan ke atas kanak-kanak yang menghidap penyakit β-thalassemia/Hb E yang lebih biasa didapati di rantau ini.

Tujuan: Tujuan kajian ini adalah untuk membandingkan corak rembesan hormon tumbesaran dan IGF-1 serum di antara kanak-kanak yang menghidapi penyakit talasemia dan kanak-kanak normal.

Kaedah: Pesakit talasemia berumur 6-12 tahun yang memerlukan transfusi darah secara regular di Hospital USM dari Oktober 1993 hingga Oktober 1995 dipilih secara rawak untuk kajian ini. Semua pesakit ini tidak ada riwayat keluarga malnutrisi, diabetes mellitus, kekerdilan atau penyakit endokrin lain. Kanak-kanak normal yang sihat dipilih daripada anak kakitangan USM.

Ketinggian, umur tulang, feritin serum dan IGF-1 serum disukat pada semua kanak-kanak. Hormon tumbesaran serum disukat selepas dirangsang dengan senaman dan glukagon intravena. Kedua-dua hormon tumbesaran serum dan IGF-1 serum disukat secara radioimunoasai.

Keputusan: Sejumlah 22 pesakit talasemia (4 β-talasemia major and 18 HbE/β-talasemia) dan 10 kanak-kanak normal telah dikaji. Tidak ada perbezaan jantina, min umur kronologikal dan min umur tulang di antara pesakit talasemia dan kanak-kanak normal. "Z-scores" and feritin serum didapati lebih tinggi pada pesakit talasemia jika dibandingkan dengan kanak-kanak normal. Aras tiroksin serum dan hormon perangsang tiroid didapati normal dalam kedua-dua kumpulan.

Min aras puncak hormon tumbesaran serum selepas senaman dan glukagon intravena ialah 4.2 ug/L and 3.8 ug/L dalam pesakit talasemia dan 3.6 ug/L and 4.8 ug/L dalam kanak-kanak normal. Perbezaan hormon tumbesaran serum di antara kedua-dua kumpulan ini tidak signifikan. Tetapi aras min IGF-1 serum adalah lebih tinggi ($p = 0.001$) pada kanak-kanak normal (25.5 ng/L) jika dibandingkan dengan pesakit talasemia (12.3 ng/L). Dalam pesakit talasemia tidak ada korelasi di antara feritin serum dan umur kronologi ($r = - 0.04$). Tetapi terdapat korelasi rendah di antara aras feritin serum dan min aras puncak hormon tumbesaran serum selepas senaman($r = - 0.30$) dan rangsangan glukagon ($r = - 0.29$).

Kesimpulan: Kajian ini menunjukkan bahawa pada kanak-kanak talasemia, rembesan hormon tumbesaran (seperti yang dinilai dengan gerakbelas terhadap rangsangan senaman dan glukagon) tidak terjejas sementara penjanaan IGF-1 serum pula berkurangan. Gangguan hormon tumbesaran mungkin berlaku lebih lewat jika dibandingkan dengan gangguan IGF-1 serum. Kekurangan IGF-1 serum ini merupakan satu daripada beberapa faktor yang menyebabkan kekerdilan pada penghidap talasemia, dan mungkin disebabkan oleh pemendapan zat besi dalam hati. Keabnormalan endokrin ini dapat dielakkan sekiranya aras hemoglobin dapat dikawal dan terapi pengkelatan besi digunakan oleh semua pesakit talasemia.

4) (a) **Penemuan Projek/Abstrak**

*(Perlu disediakan makluman di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan Bahasa Inggeris**. Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).*

Various endocrine organ dysfunctions are known to be affected in children with transfusion dependent thalassemia. These abnormalities may be due to iron overload or chronic hypoxia as a result of chronic anaemia. Studies of growth hormone secretion following provocation tests have shown conflicting results. While most of these studies were done in children with β-thalassemia major, few studies were done in patients with β-thalassemia/Hb E disease which is more prevalent in this region.

Aim: The aim of this study is to compare the pattern of growth hormone secretion and serum IGF-1 in children with transfusion dependent thalassemia and normal children.

Method: Children aged 6-12 years with transfusion dependent thalassemia were randomly selected from children with thalassemia admitted to University of Science Malaysia Hospital from October 1993 to October 1995. None of the patients gave a family history of malnutrition, diabetes mellitus, dwarfism or other endocrine diseases. Normal children volunteers were mainly healthy children of staff members in the hospital.

The heights, bone age, serum ferritin and serum IGF-1 were measured in all the children. Serum growth hormone was measured following stimulation with exercise and intravenous glucagon. Both serum growth hormone and serum IGF-1 were estimated by radioimmunoassay using a double antibody.

Results: A total of 22 thalassemic children (4 β-thalassemia major and 18 HbE/β-thalassemia) and 10 normal children were studied. There was no difference in sex, mean chronological age and mean bone age between thalassemic and normal children. The Z-scores and serum ferritin were significantly more in thalassemic than normal children. The serum thyroxine and thyroid stimulating hormone were normal in both groups.

The mean peak serum growth hormone following exercise and intravenous glucagon was 4.2 ug/L and 3.8 ug/L in thalassemic children and 3.6 ug/L and 4.8 ug/L in normal children respectively. There were not statistically significant. The mean serum IGF-1 levels was significantly higher ($p = 0.001$) in the normal (25.5 ng/L) than the thalassemia children (12.3 ng/L). In thalassemia children there was no correlation between serum ferritin and age ($r = - 0.04$) and between serum ferritin level and serum IGF-1 levels ($r = 0.01$). There was only a weak negative correlation between serum ferritin and peak growth hormone levels after exercise ($r = - 0.30$) and glucagon stimulation ($r = - 0.29$).

Conclusion: GH secretion, as evaluated by the responses to exercise and glucagon stimulation, is not impaired, while the generation of serum IGF-1 is reduced in this group of thalassemic children. Comparison of these data with those of other published reports indicate that impairment of GH secretion may occur later in the course of the disease. A reduction in IGF-1 production probably secondary to excessive iron deposition in the liver is manifested earlier. The presence of impaired IGF-1 production may be a cause of short stature in these children. The achievement of relatively constant haemoglobin levels and reduction of tissue iron stores with long term iron chelation therapy is needed to prevent these endocrine abnormalities.

(b) Senaraikan Kata Kunci yang digunakan di dalam abstrak:

Bahasa Malaysia	**Bahasa Inggeris**
talasemia	thalassemia
hormon tumbesaran	growth hormone
IGF-1	IGF-1

5) Output Dan Faedah Projek

(a) Penerbitan *(termasuk laporan/kertas seminar)*
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbitkan/dibentangkan)

Belum

(b) **Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftran Paten.**
(Jika ada dan jika perlu, sila gunakan kertas berasingan)

Tiada

(c) **Latihan Gunatenaga Manusia**

i) ***Pelajar Siswazah:*** Mazidah Abdul Rasid

ii) ***Pelajar Prasiswazah:*** Tiada

iii) ***Lain-lain:***
Pegawai Sains: Noor Salwah

6. Peralatan Yang Telah Dibeli:

a. Glucagon
b. Growth hormone double antibody radioimmunoassay kit
c. IGF-1 double antibody radioimmunoassay kit
d. Ferritin assay kit
e. Blood sugar assay
f. X-ray films

UNTUK KEGUNAAN JAWATANKUASA PENYELIDIKAN UNIVERSITI

GROWTH HORMONE SECRETION IN CHILDREN WITH THALASSEMIA

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ABSTRACT

Various endocrine organ dysfunctions are known to be affected in children with transfusion dependent thalassemia. These abnormalities may be due to iron overload or chronic hypoxia as a result of chronic anaemia. Studies of growth hormone secretion following provocation tests have shown conflicting results. Most published studies were done in children with β-thalassemia major and there are few studies done in patients with β-thalassemia/Hb E disease which is more prevalent in this region.

Aim: The aim of this study is to compare the pattern of growth hormone secretion following provocation tests and serum IGF-1 in children with transfusion dependent thalassemia and normal children.

Method: Children aged 6-12 years with transfusion dependent thalassemia were randomly selected from children with thalassemia admitted to University of Science Malaysia Hospital from October 1993 to October 1995. None of the patients gave a family history of malnutrition, diabetes mellitus, dwarfism or other endocrine diseases. Normal children volunteers were mainly healthy children of staff members in the hospital and patients who were well.

The heights, bone age, serum ferritin and serum IGF-1 were measured in all the children. Serum growth hormone was measured following stimulation with exercise and intravenous glucagon. Both serum growth hormone and serum IGF-1 were estimated by radioimmunoassay using a double antibody.

Results: A total of 22 thalassemic children (4 β-thalassemia major and 18 HbE/β-thalassemia) and 10 normal children were studied. There were no difference in sex, mean chronological age and mean bone age between thalassemic and normal children. The Z-scores and serum ferritin were significantly more in thalassemic than normal children. The serum thyroxin and thyroid stimulating hormone were normal in both groups.

The mean peak serum growth hormone following exercise and intravenous glucagon was 4.2 ug/L and 3.8 ug/L in thalassemic children and 3.6 ug/L and 4.8 ug/L in normal children respectively. There were not statistically significant. The mean serum IGF-1 levels were significantly higher ($p = 0.001$) in normal (25.5 ng/L) than in thalassemia children (12.3 ng/L). In thalassemia children there was no correlation between serum ferritin and chronological age ($r = - 0.04$) and between serum ferritin and serum IGF-1 levels ($r = 0.01$). There was only a weak negative correlation between serum ferritin and peak growth hormone levels after exercise ($r = - 0.30$) and glucagon stimulation ($r = - 0.29$).

Conclusion: GH secretion, as evaluated by the responses to exercise and glucagon stimulation, is not impaired, while the generation of serum IGF-1 is reduced in this group of thalassemic children. Comparisons of these data with those of other published reports indicate that impairment of GH secretion may occur later in the course of the disease. A reduction in IGF-1 production probably secondary to excessive iron deposition in the liver is manifested earlier. The presence of impaired IGF-1 production may be a cause of short stature in these children. The achievement of relatively constant haemoglobin levels and reduction of tissue iron stores with long term iron chelation therapy is needed to prevent these endocrine abnormalities.

INTRODUCTION

Children with β-thalassemia, a severe hereditary disorder of haemoglobin synthesis, frequently require regular blood transfusion. Many of these children also have short stature that may be secondary to endocrine dysfunction [1,2,3]

Various endocrine organs have been reported to be affected in children with transfusion dependent thalassemia and this is thought to be due to the consequence of iron overload [4,5,6]. It is known that subjects with the disease accumulate large quantities of iron (as ferritin) in many organs secondary to blood transfusion and increased intestinal iron absorption [7]. Besides iron overload, chronic hypoxia secondary to chronic anaemia has also been postulated to cause abnormalities in endocrine function. Iron deposition in the pituitary or hypothalamus[8] may be responsible for impaired secretion of growth hormone reported in many patients with transfusion dependent thalassemia major.

Endocrine studies in these children have frequently but not always revealed the presence of normal growth hormone response to provocative stimuli [5,6,9,10]. Several studies investigating the pattern of growth hormone have been published. While many studies have shown that the secretions of growth hormone to provocative tests were normal, many other studies have demonstrated suppressed secretion of growth hormone following provocative tests. The presence of short stature and normal pattern of growth secretion in thalassemic children have lead others to investigate the levels of somatomedins and neurosecretary function in these children. A marked reduction of somatomedin activity [11,12] and abnormal neurosecretary functions [10]

have both been demonstrated and it is thought to be the underlying cause of short stature in these children.

Most reported studies were done in children with β-thalassemia major and there were few studies done in patients with β-thalassemia/Hb E disease which is more prevalent in this region. This study aims to study the pattern of growth hormone (GH) secretion and serum IGF-1 in children with transfusion dependent thalassemia.

METHODS

The pattern of GH secretion and IGF-1 were analysed and compared in two groups of children; a group of children with thalassemia and a group of normal children.

Children with thalassemia were randomly selected from children with thalassemia admitted to University of Science Malaysia Hospital for blood transfusion from October 1993 to October 1995. All the children require regular blood transfusion to maintain their haemoglobin between 10-12 gm/L and none of the children were on chelation therapy with desferroxamine. Splenectomy was already performed in 10 thalassemic children at a mean age of 6.8 years. Criteria for the diagnosis of thalassemia were as previously reported [13]. None of the patients gave a family history of malnutrition, diabetes mellitus, dwarfism or other endocrine diseases.

Children in the normal group were selected from healthy children of staff members and patients who were well. All the children studied were between 6-12 years old.

The heights of all children were measured to the nearest 0.1 cm using a wall mounted stadiometer. Bone age was determined from a radiograph of the left wrist using the Greulich and Pyle atlas. The severity of iron overload was estimated by measuring the serum ferritin.

Growth Hormone Stimulation Tests

i) Exercise Test

On the day of admission an exercise-induced GH stimulation test was performed by asking all children to climb stairs vigorously for a duration of 15-20 minutes. Blood was collected before the exercise, immediately postexercise and 30 minutes after rest. The exercise test was not done in two children. One child died before the exercise test could be done and another child refused to perform the test.

ii) Glucagon Stimulation Test

Studies were done in the morning at 0830 hr in fasting, recumbent subjects. A 23-gauge cannula was inserted into a peripheral vein in the forearm or cubital fossa. at least 30 minutes before the study. Patency was maintained with heparin in saline (1 in 1000 dilution). After collection of one baseline sample, all subjects received a slow bolus of intravenous glucagon in a dosage of 0.15 mg/kg. Blood was collected from the intravenous cannula 30, 60, 90 and 120 minutes after intravenous glucagon for the estimation of serum GH and random blood sugar. Blood collected before glucagon administration was also estimated for serum insulin growth factor-1 (IGF-1), thyroxin (T4) and thyroid stimulating hormone (TSH). During the whole procedure the pulse and blood pressure were monitored.

All blood specimen for growth hormone and IGF-1 estimation were collected in a glass tube. After clotting at 4°C the blood was centrifuged and serum stored at -20 °C until the radioimmunoassay was done.

Estimation of serum growth hormone and IGF-1

Serum GH was estimated by radioimmunoassay using a double antibody human growth hormone kit from Diagnostic Products Corporation and serum IGF-1 was estimated radioimmunoassay using a double antibody kit from Incstar. The intra and inter assay coefficients of variation were 5% and 7% respectively.

Blood glucose was measured with glucose PAP using a glucose oxidase method. The serum ferritin was estimated using a "two-site" immunoradiometric assay. Serum thyroid stimulating hormone and thyroxin was also determined by radiometric assay.

Informed consent was obtained from the parents of these children. Approval for the study was obtained from the ethical committee of the university.

RESULTS

A total of 32 children was studied. There were 22 children in the thalassemia group with 4 β-thalassemia major and 18 HbE/β-thalassemia patients. Ten normal children were studied as controls. In the control group there were 5 normal volunteers, 1 child with a closed ventricular defect, 1 child with typhoid one month after recovery, 1 child with acute gastroenteritis one month after recovery and 1 child who was admitted for a mild hornet sting.

The clinical characteristics of all the children were as shown in Table 1. The mean chronological age of thalassemia patients (8.6 years) was not significantly ($p = 0.22$) different from the mean chronological age of normal children (9.5 years). The mean bone age in thalassemic patients (7.3 years) was also not significantly ($p = 0.24$) different from the mean bone age of normal children (8.5 years). The mean difference between chronological and bone age in thalassemia patients (1.2 years) was not significantly ($p = 0.77$) different from that in normal children (0.9 years). There were no significantly differences in the sex between the thalassemia and normal group ($p = 0.45$). All the children studied were Malays except for 3 Chinese and 1 Thai in the thalassemia group.

Table 2 shows the Z-scores for height of thalassemia and normal children. The mean Z-score of normal children (-1.1) was significantly ($p = 0.04$) less than that of thalassemia children (0.9). This suggests that children in the thalassemia group were not short as compared to children in the normal group.

The serum ferritin levels (Table 3) as expected was significantly higher ($p = <0.0001$) in thalassemic children than the normal children as all the thalassemia children has received regular blood transfusions. Table 4 shows the serum T4 and serum TSH in these children. The mean serum T4 level in thalassemia group (96.9 umol/L) was not significantly ($p = 0.42$) different from that in the normal group (91.3 umol/L). The serum TSH however was significantly ($p = 0.009$) higher in thalassemia children (2.9 iu/L) as compared to the normal group (1.7 iu/L). The range of serum TSH in patients with thalassemia however was only 0.9 - 6.2 iu/L.

Results of GH release after exercise and glucagon stimulation were as shown in Table 5 and Table 6. There was no significant difference ($p = 0.37$) in the mean peak GH levels after exercise in thalassemic children (4.2 ug/L) and in normal children (3.6 ug/L). There was also no significant difference ($p = 0.5$) in the peak serum GH levels following glucagon provocation in thalassemia (3.8 ug/L) and normal children (4.8 ug/L). The mean serum IGF-1 levels (Table 7) however was significantly higher ($p = 0.001$) in the normal (25.5 ng/L) than the thalassemia children (12.3 ng/L).

There was no correlation between chronological age and serum ferritin in thalassemia children ($r = - 0.04$). There was only a weak negative correlation between serum ferritin and peak growth hormone levels after exercise ($r = - 0.30$) and glucagon stimulation ($r = - 0.29$) . There was also no correlation between serum ferritin and serum IGF-1 levels ($r = 0.01$).

DISCUSSION

The present study was performed on a homogenous group of prepubertal patients receiving regular transfusion but no chelation therapy with desferroxamine. Unlike most previous studies which were done in patients with β-thalassemia major, 18 (81.8%) of our patients have HbE/β-thalassemia and only 4 (18.2%) were children with β-thalassemia major. The only difference between the thalassemia group and normal children was a significantly lower serum level of IGF-1 in children with thalassemia. There was no difference in the secretion of GH between the two groups either following exercise or glucagon provocation.

The poor secretion of growth hormone even in children in the normal group could not be easily explained. Although there were only 5 normal volunteers the medical conditions in the other children in the normal group is unlikely to have affected the pattern of growth hormone secretion. The exercise test was not objective as children were asked to run up and down stairs for 15-20 minutes. Difficulty in getting children to cooperate in the exercise test may result in a low level of stress achieved following exercise. The degree of stress following exercise also could not be assessed objectively.

The dosage of glucagon used in this study (0.15 mg/kg) was higher than the dosage recommended [14]. Previous studies have shown that doses glucagon as low as 15 ug/kg is sufficient to stimulate growth hormone secretion in children [15]. Unlike the insulin tolerance test where a clearly described standardised stimulus is applied and a quantifiable hypoglycaemia stimulus is produced, the glucagon test do not have a measurable standard of stress. However,

Most children in this study did have side-effects of glucagon administration such as vomiting and headaches suggesting that the stress from glucagon was sufficient.

The thyroid status in these children should not have blunted the growth hormone response as the serum thyroxin was normal. Even though the thyroid stimulating hormone (TSH) was significantly higher in patients with thalassemia the level the highest level of TSH was only 6.2 units/L, which is not pathologically raised.

Previous studies of GH response to provocative tests in children with thalassemia have shown conflicting results. Although growth retardation is common in patients with thalassemia, provocative testing of growth hormone response was normal in many studies [5,6,9,10]. On the other hand there are other studies showing impaired GH response in children with thalassemia [15,16,17].

A major difference between children in this and other studies that show a normal GH response is the younger age of the children compared to those studies which reported abnormal GH responses. It is conceivable that the encountered difference reflects chronic effects of tissue iron deposition that has not occurred in our patients. The height of children in the thalassemic group in this study was significantly lower than that of children in the normal group suggesting that children with thalassemia were not short. The bone age was also not significantly more delayed as compared to the normal group. In older children where chronic tissue iron deposition has cause more damage the GH release following stimulation has been shown to be abnormal leading to short stature [15, 16].

The aetiology of growth hormone deficiency was unclear. In a cohort of patients with thalassemia there was an inverse relationship between serum ferritin and peak growth hormone concentration [15]. Although the duration of iron overload is predominantly related to age, there is no clear relation between age and growth hormone deficiency in our patients with thalassemia. An abnormal GH response was not only related to iron overload, as thalassemic children who had never received blood transfusion also demonstrated an abnormal HG response suggesting that chronic anaemia and chronic hypoxia per se may cause abnormal GH secretion [17].

Normal GH response to provocative stimuli in the presence of short stature in many studies has lead others to investigate IGF-1 levels, and neurosecretary function in thalassemic patients. Shehadeh et al showed that in a group of thalassemic patients with growth retardation, GH responses to provocation test was normal but spontaneous GH secretion over a period of 24 hours was abnormal suggesting the presence GH neurosecretary dysfunction [10]. Reduced serum levels of IGF-1 in the presence of normal GH response in thalassemic children has also been shown in many other studies [1,2,3,4,5,12].

The aetiology of low serum somatomedins of IGF-1 is less clear. Among the possible causes postulated are 1) the presence of inhibitors of somatomedin of IGF-1 in thalassemic sera 2) an abnormal GH-receptor interaction resulting from an abnormal GH molecule, an abnormal GH receptor or perhaps, the presence of a nonreceptor GH-binding protein in thalassemic sera, 3) impaired somatomedin or IGF-1 synthesis (or release) due to hepatic iron deposition or tissue hypoxia, and 4) a disturbance of carrier protein synthesis or availability.

Herington et al [11] showed that low levels of nonsuppressible insulin-like activity in thalassemia major is not due to the presence of inhibitors or to impairment of GH binding to its receptor, either as a result of iron or ferritin effects or as a result of an abnormal GH molecule. They suggest that the most likely, but as yet untested causes are the presence of either an abnormal GH receptor or a metabolic defect in the liver cells that decreases their ability to synthesise and/or secrete nonsuppressible insulin like activity and/or its binding proteins. A possible defect at the receptor or post-receptor level was suggested when Werther et al [18] showed no rise of serum nonsuppressible insulin-like activity following administration of exogenous growth hormone in children with thalassemia. No relationship however was found between the severity of growth retardation and the human GH binding to liver membranes in liver tissue specimens, suggesting that a defect in GH-receptor interaction in liver membranes is not the main cause of growth failure [19]. It is possible that the defect responsible for reduced IGF-1 generation is in the postreceptor region.

The major site of somatomedin generation is the liver [20,21] It is known that patients with thalassemia major accumulate large quantities of iron (as ferritin) in their liver, as well as other organs, secondary to the repeated blood transfusions and increased intestinal absorption [22] Iron is known to interfere with membrane and other cellular functions [23] and may therefore impair receptor or post receptor processes. Besides hepatic iron deposition due to repeated transfusions, tissue hypoxia due to chronic anaemia, could also interfere with IGF-1 production by the liver in these children.

CONCLUSION

In summary, this examination of a group of prepubertal thalassemic patients most of whom are HbE/β-thalassemia has shown that GH secretion, as evaluated by the responses to exercise and glucagon stimulation, is not impaired, while the generation of serum IGF-1 is reduced. Comparison of these data with those of other published reports indicate that impairment of GH secretion may occur later in the course of the disease. Liver damage secondary to excessive iron deposition causing a reduction in IGF-1 production precedes the impairment of GH release and may also lead to short stature. The achievement of relatively constant haemoglobin levels and reduction of tissue iron stores with long term iron chelation therapy is needed to prevent these endocrine abnormalities.

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ILLUSTRATIONS

TABLE 1

Clinical data of 22 thalassemic and 10 normal children

		Thalassemia Group n = 22	Control Group n = 10
Chronological Age (Years)	Mean	8.6*	9.5
	Median	8.0	9.7
	Range	5.6 - 13	5.8 - 12.4
Bone Age (Years)	Mean	7.3**	8.5
	Median	7.4	8.7
	Range	3.0 - 11.5	6.0 - 10.0
Difference between chronological and bone age (Years)	Mean	1.2	1.0
	Median	1.3	1.1
	Range	-0.1 to 3.3	-0.2 to 1.9
Sex	Male ***	9	6
	Female	13	4
Race	Malay	18	10
	Chinese	3	0
	Thai	1	0

*p = 0.22 **p = 0.24 *** p = 0.45

Table 2

Z-Scores of Thalassemia and Control Group

Z-Scores	Thalassemia Group n = 22	Control Group n = 10
Mean	- 0.9	- 1.1
Median	- 2.3	- 1.3
Std Dev	4.6	1.0
Range	- 4.9 to 10	- 2.4 to 0.8

p = 0.04

Table 3

Serum Ferritin Levels in Thalassemia and Control Group

Serum Ferritin (ug/L)	Thalassemia Group n = 22	Control Group n = 10
Mean	2256	58
Median	1954	52
Std Dev	1684	25
Range	520 - 7000	28 - 107

p = < 0.0001

Table 4

Serum thyroxin (T4) and thyroid stimulating hormone (TSH) in thalassemia group and control group

		Thalassemia Group n = 22	Control Gorup n = 10
Serum T4 Levels (umol/L)	Mean	96.9*	91.3*
	Median	100	87.5
	Std Dev	16.8	17.7
	Range	68 - 136	67 - 118
Serum TSH Level (iu/L)	Mean	2.9**	1.7
	Median	2.7	1.8
	Std Dev	1.3	0.7
	Range	0.9 - 6.2	0.7 - 2.7

* p = 0.43
**P = 0.009

Table 5

Serum Growth Hormone Levels After Exercise Test

Serum Growth Hormone (ug/L)	Thalassemia Group n = 20	Control Group n = 10
Mean	4.2	3.6
Median	3.3	2.3
Std Dev	3.6	3.5
Range	0.9 - 14.5	0.9 - 10.4

p = 0.37

Table 6

Peak Serum Growth Hormone Levels After

Glucagon Stimulation Test

Serum Growth Hormone (ug/L)	Thalassemia Group n = 22	Control Group n = 10
Mean	3.8	4.8
Median	3.0	3.5
Std Dev	2.6	4.0
Range	0.9 - 10.4	0.9 - 13.0

p = 0.5

Table 7

Serum IGF-1 in children with Thalassemia and Controls

Serum IGF-1 (ng/L)	Thalassemia Group n = 22	Control Group n = 10
Mean	12.3	25.5
Median	11.3	23.7
Std Dev	6.6	11.4
Range	4.0 - 32.6	10.4 - 49.8

p = 0.001