Pituitary function in thalassemic patients and the effect of chelation therapy

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Abstract. This study examined anterior pituitary function and the effect of chelation therapy in 31 patients with β-thalassemia/HbE disease. Patients were divided into those receiving chelation therapy by deferoxamine and those receiving no such therapy (control group). Pituitary function studies were repeated in both groups 18 months later. The results showed decreased pituitary responses following stimulation in 22 patients. Among these, gonadotropin and PRL responses were most affected. After 18 months, serum ferritin levels had significantly decreased in the deferoxamine group. PRL and GH responses were improved in 3 patients receiving chelation therapy without changes in other hormone responses. In contrast, no changes in pituitary responses were shown in the control group at the end of follow-up. There were 6 drop-outs (4 in the control and 2 in the deferoxamine group) and 3 deaths (2 in the control and 1 in the deferoxamine group) during 18 months. In conclusion, gonadotropin and PRL deficiencies occur most frequently in thalassemic patients. Chelation therapy for 18 months markedly reduced serum ferritin level and might preserve or improve PRL and GH secretions, but seems to have no beneficial effects on other pituitary hormone reserves.

Thalassemia is one of the most common genetic disorders in the world (1). In Thailand and Southeast Asia, β-thalassemia and HbE alleles occur more frequently than homozygous β-thalassemia in the western populations (2). Previous studies in thalassemic patients have consistently shown multiple endocrine abnormalities, involving also the pituitary gland (3-11). These abnormalities are thought to be caused by chronic anemia or excessive iron deposits in the endocrine glands, most likely from repeated blood transfusions (3-11). The iron-chelating agent, deferoxamine has been used in thalassemic patients in an attempt primarily to reduce the hepatic and cardiac iron burdens (12). Less information is available on the effect of chelation treatment on the endocrine function. To date, there have been insufficient data regarding the chelation effect on endocrine function in patients with β-thalassemia/HbE disease from Southeast Asia. Pituitary insufficiency has been demonstrated in Thai patients with β-thalassemia/HbE disease (9). In addition, postmortem studies in our patients have shown excessive iron overload in multiple endocrine glands despite the fact that these patients had received minimal or modest blood transfusions (13). Thus, we attempt to determine whether chelation therapy could improve or minimize pituitary dysfunction in β-thalassemia/HbE disease. This paper reports the result after a trial period of chelation for 18 months in 12 patients compared with 19 patients who received no such treatment.

Patients and Methods

The study was approved by the institutional committee for research involving human subjects. All study participants gave informed consent. Thirty-one thalassemic adult patients (12 males and 19 females), aged 20-42 years were studied. Using the breast (in female) and genitalia (in male) criteria according to Turner’s puberty staging (14), 8 female and 3 male adult patients were still in prepubertal stages (Stages 1-3). They were selected, owing to their willingness to participate in the follow-up studies of endocrine function tests, from the thalassemia clinic at Siriraj Hospital. Among these 31 patients, 12 agreed to receive deferoxamine treatment, and the remaining 19 served as the control group. All patients had β-thalasse-
mia/HbE disease according to the criteria previously described (15). No patients had received chelating agents or had recent illnesses before the study. Splenectomy was performed in all of them. Body mass index (BMI) was calculated by dividing weight in kilograms by the square of height in meters.

Patients were divided into two groups: the deferoxamine-treated group (N=12) and the control group (N=19). In the deferoxamine group, 2 g of deferoxamine mesylate was given daily by the sc route via a portable infusion pump over 10 to 12 h for six days a week. Compliance with deferoxamine treatment was checked by periodic counts of the numbers of deferoxamine vials used in each week and by close personal contacts with the patients. No attempt was made to give the patients transfusions to maintain their hemoglobin levels at normal. Blood transfusions were given occasionally to the patients whose hemoglobin levels were below 60 g/l. Other medications and treatments were recorded throughout the study.

Pituitary reserve was tested in both groups at baseline and again at 18 months after initiation of the study. After an overnight fast and with the subjects in the supine position throughout, an iv needle was inserted into an arm vein and kept patent with a slow infusion of normal saline solution. Testing of the pituitary-adrenal axis and growth hormone reserve were done by iv injection of soluble insulin, 0.15 IU/kg. Blood samples were taken before and at 30, 60, 90, and 120 min after insulin injection for measurements of glucose, GH, and cortisol concentrations. Serum FSH and LH were determined before 30, 60, and 120 min following an iv bolus dose of 100 μg of GnRH. Serum TSH and PRL were determined before, 20 and 60 min after an iv injection of 200 μg of TRH. All results of pituitary function tests in thalassemic patients were compared with the reference values obtained from the normal Thai adult subjects with comparable distributions of sex and age (20-45 years) previously studied in our laboratory (9,16,17). The normal values are as follows: GH, basal 0.6-20 μg/l and peak (after insulin-induced hypoglycemia) >8 μg/l plus increment >6 μg/l; cortisol, basal 242-447 nmol/l and peak >552 nmol/l or a rise of more than 276 nmol/l after hypoglycemia. Basal FSH and LH levels for normal females in both the follicular and luteal phase are 4.5-20 and 1.5-10 IU/l, respectively. Basal levels of FSH and LH for normal males are 10-20 and 2-10 IU/l, respectively. Normal peak levels in both sexes are greater than an 0.5-fold rise for FSH and a 3-fold rise for LH after GnRH administration. Other normal values in our laboratory were: TSH 0.5-4 mU/l (basal) and increment of more than 5 mU/l (peak); PRL, basal 3.3-20 μg/l and peak >20 μg/l. In the female patients with normal menstrual periods, the results of GnRH test were compared with the responses tested in the female control subjects during the comparable follicular or luteal phase of menstruation (17). In those patients who had amenorrhea, the FSH and LH responses during GnRH test were compared with those obtained from the female controls in the follicular phase (17). Plasma glucose concentration was determined with a glucose oxidase method on Beckman Glucose Analyzer II. Plasma cortisol level was determined by fluorimetric method (18). Serum concentrations of FSH, LH, PRL, T4, TSH, and GH were measured with radioimmunoassay techniques using commercial kits: Diagnostic Products, California (FSH, LH, and PRL); Amersham, UK (TSH); and Dianabot, Tokyo (GH). Serum ferritin concentration was determined before and during the study in both deferoxamine-treated and control patients, using immunoradiometric technique (19). Inter- and intra-assay coefficients of variation for all assays were less than 10%.

All results are reported as mean ± SEM. Statistical analyses were performed using Student's t-test (two-tailed) for paired and unpaired continuous data. Logarithmic transformation of the individual data on serum ferritin concentration was performed before statistical analysis since the distribution of these data showed considerable skewing. Fisher's exact test was used for categorical data.

**Results**

The clinical details of the patients in both the deferoxamine and the control group at baseline, before any initiation of deferoxamine treatment, are given in Table 1. Sixteen of 31 patients had low BMI (<18 kg/m²). None of them had a BMI greater than 25 kg/m². Comparison between these two groups showed no significant differences (p>0.05) in age and sex distributions, heights, weights, BMI, pubertal (Tanner) stages, and history of previous cholecystectomy. Two patients in the deferoxamine group and 2 in the control group had diabetes mellitus. Among the female patients, 6 in the deferoxamine group (N=8) and 4 in the control group (N=11) had secondary amenorrhea. Four in the deferoxamine group and 2 in the control group were married and all of them were fertile. Among the male patients, 2 out of 4 in the deferoxamine group and 4 out of 8 in the control group were sexually impotent. One in the deferoxamine group was married and fertile; in the control group 2 patients were married and one of them was infertile.

During the 18-month study period, all patients in the deferoxamine group showed good compliance to the chelation regimen as judged by their receiving more than five deferoxamine infusions per week. Each infusion lasted for 10-12 h in all patients. None of the patients had any serious adverse reactions to deferoxamine. Six patients (4
from the control group and 2 from the deferoxamine group) were lost to follow-up. One patient in the deferoxamine group and 2 patients in the control group died of congestive heart failure at 6, 7, and 10 months, respectively, after the beginning of this study. Neither amenorrhea nor sexual impotency were improved in the two groups of patients. None of the married female patients were pregnant during the study period. None of the patients started puberty during these 18 months.

### Hematological findings

The baseline hemoglobin level in the deferoxamine group was 74±3 g/l compared with 73±1 g/l in the controls (p>0.05) (Table 1). All patients in the two groups had elevated levels of serum ferritin (normal range in Thai subjects: 16-160 μg/l) (19). The mean serum ferritin level of the deferoxamine group (3196±553 μg/l) was not significantly different (p>0.05) from that of the control group (4682±680 μg/l) (Table 1). Both groups had received similar numbers of blood transfusions before the deferoxamine trial (Table 1).

Hematologic data obtained 18 months after the beginning of therapy were available for 9 patients in the deferoxamine group and 13 in the control group. During chelation treatment, serum ferritin level fell in each patient (N=9) in the deferoxamine group. The mean posttreatment ferritin value (485±98, range 118-964 μg/l) was significantly lower (p<0.05) than the pretreatment value (3288±738, range 1281-7866 μg/l). However, only 2 patients had posttreatment serum ferritin levels (124 and 118 μg/l, respectively) which were lower than the upper normal limit (160 μg/l). In contrast, serum ferritin level remained high in the control group (mean ±SEM after end of study, 7533±1014 μg/l), and was significantly higher (p<0.05) than the baseline value of 4510±912 μg/l.

Over the 18-month period of follow-up, one unit of blood was transfused to one patient in the deferoxamine group, which was not significantly different (p>0.05) from those given to the control group (2.5±0.7 units). The average pretransfusion hemoglobin levels during the trial did not differ between the two groups (68±3 g/l in control group vs 77±3 g/l in the deferoxamine group).

### Hormonal studies at baseline

**GH and cortisol after insulin-induced hypoglycemia.** Following insulin injection, all patients achieved a 50% or greater fall in blood glucose level, to a value below 2.2 mmol/l within 30-45 min. As compared with the reference values, GH responses to hypoglycemia were impaired in 2 out of 19 patients in the control group and in 2 out of 12 patients in the deferoxamine group, respectively. Mean height and BMI were not different between patients with normal and impaired GH responses. Compared with the normal reference value, one of the 19 patients in the control group and one of the 12 patients in the deferoxamine group had impaired peak cortisol response to insulin-induced hypoglycemia. The blood glucose nadirs in these two patients were 1.6 and 0.5 mmol/l, respectively. The mean GH levels in the deferoxamine group were 4.1±1.1, 4.3±0.9, 17.8±3.3, 17.2±3.1, and 11.4±2.4 μg/l at 0, 30, 60, 90 and 120 min following insulin administration, respectively. These GH levels were not significantly different (p>0.05) from the corresponding values in the control group (2.8±0.6, 5.6±1.5, 19.5±5.3, 19.1±5.4 and 12.7±4.5 μg/l, respectively). Serum cortisol levels during insulin-induced hypoglycemia were not significantly different (p>0.05) between the deferoxamine and the control group (basal, 576.8±52.4 vs 540.9±30.3 nmol/l, 540.8±46.9 vs 485.8±22.1 nmol/l at 30 min, 775.6±71.8 vs 723.1±30.3 nmol/l
at 60 min, 819.7±91.1 vs 723.1±38.6 nmol/l at 90 min, and 786.6±88.3 vs 709.3±38.6 nmol/l at 120 min).

**Gonadotropin secretion.** At baseline, the peak responses of LH were impaired in 6 of the 19 control patients and in 5 of the 12 deferoxamine-treated patients, respectively. Regarding the FSH concentration after GnRH stimulation, 9 of 19 patients in the control group and 9 of 12 patients in the deferoxamine group had inadequate peak responses. With respect to stages of puberty, impaired LH release was found in 8 of 11 prepubertal patients in contrast to only 3 of the 20 pubertal patients. However, FSH response appeared to be different from LH response in relation to pubertal stages, since 7 of 11 prepubertal patients as compared with 11 of 20 pubertal patients had impaired FSH release. There was no relationship between abnormal menstrual history or sexual potency and these defective LH or FSH responses. One patient in the control group who was married and was infertile had subnormal responses of both LH and FSH levels. The mean FSH levels before and 30, 60, and 120 min following GnRH administration in the deferoxamine group were 7.2±1.9, 8.3±2.2, 8.9±2.5, and 8.9±2.4 IU/l, respectively. In the control group, the corresponding FSH levels were 9.5±1.3 before, 13.2±1.8 at 30 min, 13.6±1.9 at 60 min, and 14.2±2.2 IU/l at 120 min. No significant differences (p>0.05) were found for these FSH levels at all time points between the two groups. Similarly, LH levels did not differ significantly (p>0.05) between the deferoxamine and the control groups (basal, 7.2±2.6 vs 9.4±1.7; at 30 min, 19.5±6.3 vs 40.5±8.7; at 60 min, 20.9±7.1 vs 36.5±8.1; and at 120 min, 17.1±5.9 vs 34.4±10.9 IU/l, respectively).

**TSH secretion.** At baseline, TSH responses to TRH administration were impaired in 2 of the 19 control patients and in 3 of the 12 deferoxamine-treated patients. The mean basal TSH level (3.1±1.5 mU/l) and mean TSH responses to TRH at 20 min (12.4±2.4 mU/l) and at 60 min (11.2±2.4 mU/l) in the deferoxamine group were not significantly different (p>0.05) from the corresponding values (1.9±0.2 before, 14.4±1.6 at 20 min, and 12.9±1.5 mU/l at 60 min) in the control group. Serum T₄ concentration was normal (reference ranges 38-116 nmol/l in our laboratory) in all patients (83.6±15.4 nmol/l in control group and 75.9±18.8 nmol/l in deferoxamine group).

**PRL response to TRH.** At baseline, inadequate peak response of PRL concentration after TRH administration was found in 6 of 19 control patients and 6 of 12 deferoxamine-treated patients. Body weight and BMI did not differ between patients with normal and those with defective PRL responses. Mean basal PRL levels in the deferoxamine group was 2.7±0.4 against 3.4±0.3 µg/l in the control group (p>0.05). The mean PRL responses did not differ between the deferoxamine and the control group at 20 min (14.6±2.6 vs 29.8±5.9 µg/l; p>0.05) and 60 min (15.3±3.3 vs 27.6±5.2 µg/l; p>0.05) following TRH administration.

**Comparison between patients with normal and abnormal pituitary functions**

Among 31 patients studied, 9 had normal pituitary responses to all stimulation tests. Twenty-two of them had decreased responses of the GH, cortisol, FSH, LH, TSH, and PRL releases following pituitary stimulation tests. However, comparison between patients with normal and abnormal pituitary function revealed no significant differences (p>0.05) as to age and sex distributions, body weight, height, and BMI, baseline pretransfusion hemoglobin level, serum ferritin level, and numbers of previous blood transfusions (Table 2).

**Table 2.** Comparison on characteristics (mean ± SEM) between patients with normal and abnormal pituitary function tests at baseline.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Normal (N=9)</th>
<th>Abnormal¹ (N=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.3±1.5</td>
<td>32.1±1.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Male/female</td>
<td>2/7</td>
<td>10/12</td>
<td>0.2</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>44.7±1.1</td>
<td>44.9±1.5</td>
<td>0.9</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.56±0.02</td>
<td>1.59±0.02</td>
<td>0.3</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>18.4±0.5</td>
<td>17.7±0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Hemoglobin, g/l</td>
<td>71±1</td>
<td>75±1</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum ferritin, µg/l</td>
<td>3814±659</td>
<td>4282±656</td>
<td>0.7</td>
</tr>
<tr>
<td>Transfusion, units</td>
<td>3.5±0.5</td>
<td>7.5±1.9</td>
<td>0.34</td>
</tr>
</tbody>
</table>

¹ Decreased responses in any of the hormone releases (GH, cortisol, FSH, LH, TSH, and PRL) following pituitary stimulation tests.
Table 3.
Basal and peak hormone releases (mean ± SEM) following pituitary stimulation tests in patients receiving deferoxamine treatment (DFO group) and control patients.

<table>
<thead>
<tr>
<th>Hormones</th>
<th>DFO group (N=9)</th>
<th>Control group (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal Before study Peak Before study</td>
<td>Basal Before study Peak Before study</td>
</tr>
<tr>
<td>GH, µg/l</td>
<td>2.7±0.9 1.9±0.5</td>
<td>20.1±4.3 26.8±5.7</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>587.9±69.1 391.9±49.7*</td>
<td>913.6±107.6 850.1±129.7</td>
</tr>
<tr>
<td>FSH, IU/l</td>
<td>5.8±1.6 3.3±1.2</td>
<td>9.8±1.8 6.5±2.0</td>
</tr>
<tr>
<td>LH, IU/l</td>
<td>4.5±2.1 1.3±0.5</td>
<td>9.6±1.8 8.7±3.1</td>
</tr>
<tr>
<td>TSH, mU/l</td>
<td>1.6±0.3 1.4±0.4</td>
<td>1.8±0.3 1.3±0.3</td>
</tr>
<tr>
<td>PRL, µg/l</td>
<td>2.3±0.4 5.6±0.9*</td>
<td>16.2±3.2 18.5±3.3</td>
</tr>
</tbody>
</table>

*: p<0.05 compared with before study.

Comparison of hormonal studies at baseline and at end of study
Among the 9 patients in the deferoxamine group and 13 patients in the control group in whom endocrine studies were repeated, the hormone levels obtained before study were compared with those available from the same individuals 18 months later (after study). After chelation therapy in the deferoxamine group, the basal and the peak levels following stimulation tests of GH, LH and TSH were not different (p>0.05) from those measured before study. The basal cortisol level was significantly lower (p<0.05, Table 3) at the end of the study than before study, but the peak response to hypoglycemia did not differ (p>0.05). The peak PRL level did not differ (p>0.05), whereas the basal PRL response was significantly higher (p<0.05, Table 3) after chelation therapy as compared with the before-study response. Although both basal as well as stimulated LH secretion after deferoxamine treatment was lower than those obtained before study, these differences were not statistically significant (p>0.05, Table 3).

In the control group of 13 patients, the repeated endocrine studies showed no significant differences (p>0.05); before vs after study with respect to the basal and peak levels of GH, FSH, LH, and TSH. Basal and stimulated LH levels were higher after than before study, but the differences were not statistically significant. Similar to the results in the deferoxamine group, the mean basal cortisol level in the control group was significantly lower (p<0.05, Table 3) after study, but the peak response to hypoglycemia was not different (p>0.05) before and after study. In contrast to the deferoxamine group, the control group showed no significant differences (p>0.05) in the basal PRL level before and after study.

As shown in Table 4, in the deferoxamine group, after chelation treatment, the defects in PRL and GH responses were restored to normal in 1 and 2 patients, respectively. In contrast, no changes in PRL and GH responses were observed in any patient among the control group. However, there were no changes in body weight or height or BMI in the responsive patients. There were no changes in cortisol, FSH, LH and TSH responses in both groups of patients at the end of 18 months (Table 4).

Discussion
In agreement with previous studies (6-8,11,20,21), we found that the most common pituitary abnormalities in thalassemic patients were deficient gonadotropin and PRL releases. TSH, GH, and cortisol releases appeared to be less affected in our thalassemic patients. Impairment of gonadotropin release, especially the FSH release, was found in those of our patients who had already reached puberty. However, it is difficult to interpret these results because of the pulsatile nature of gonadotropin secretion and the lack of data on gonadal ste-
Table 4.
Responses of hormones following pituitary stimulation tests in thalassemic patients before and after receiving deferoxamine treatment (DFO group) and in control patients (control group).

<table>
<thead>
<tr>
<th>Hormones</th>
<th>Number of patients</th>
<th>DFO group (N=9)</th>
<th>Control group (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abnormal/Normal(^1)</td>
<td>Before study</td>
<td>End of study</td>
</tr>
<tr>
<td>GH</td>
<td>2/7</td>
<td>0/9</td>
<td>2/11</td>
</tr>
<tr>
<td>Cortisol</td>
<td>1/8</td>
<td>1/8</td>
<td>2/11</td>
</tr>
<tr>
<td>FSH</td>
<td>9/0</td>
<td>9/0</td>
<td>7/6</td>
</tr>
<tr>
<td>LH</td>
<td>4/5</td>
<td>4/5</td>
<td>4/9</td>
</tr>
<tr>
<td>TSH</td>
<td>1/8</td>
<td>1/8</td>
<td>1/12</td>
</tr>
<tr>
<td>PRL</td>
<td>2/7</td>
<td>1/8</td>
<td>3/10</td>
</tr>
</tbody>
</table>

\(^1\) Responses in each patient as compared with reference values. \(^2\) Comparisons were made before and after 18 months of study in each patient.

roid levels. PRL release following TRH administration might be normal \((8,10,22)\) or impaired \((8,11,22)\). Similarly, cortisol response to insulin-induced hypoglycemia was found to be normal \((5,23)\) or impaired \((7)\). The present study confirmed our previous finding \((9)\) of deficient GH release after hypoglycemic stimulation. Most of the previous studies have shown that GH secretion in thalassemic patients was normal \((4,5,24)\). More recently, however, Pintor et al. \((25)\) reported that 13 of their 17 thalassemic patients had blunted GH response after insulin-induced hypoglycemia. Regarding the TSH reserve in thalassemic patients, previous studies have shown variable results with normal \((3,6-8,26,27)\), exaggerated \((3,6-8,10,11,26,28,29)\) or impaired \((6)\) TSH responses to TRH stimulation.

The plausible mechanisms for hypopituitarism in thalassemic patients may be iron overload or chronic anemia. The pituitary cells, especially the gonadotropes might be damaged by the iron \((8,30)\). This may explain why, among the pituitary functions, the gonadotropin reserve is the one most affected in thalassemic patients. However, there were negative correlations between TSH \((10)\), GH \((25)\), and gonadotropin \((31)\) responses and serum ferritin concentration. Pintor et al. have shown significant correlations between plasma ferritin level and basal PRL and gonadotropin concentrations in thalassemic girls \((32)\). In a longitudinal study, Cavallo et al. \((28)\) demonstrated that TSH responses positively correlated with serum ferritin concentrations. Despite minimal or no blood transfusions, all our patients had markedly elevated levels of serum ferritin, suggestive of severe iron overload. Since all of them were splenectomized, the iron excess may be due to increased intestinal iron absorption following splenectomy \((33)\).

We have shown previously that in thalassemic patients, the chronic anemia may be attributable to defective GH release \((9)\). The patients in the present study also had manifest anemia, since their mean baseline pretransfusion hemoglobin levels were moderately low \((74\pm3 \text{ g/l in the deferoxamine group and } 73\pm1 \text{ g/l in the control group})\). It is possible that chronic anemia might affect pituitary hormones other than GH. However, comparison between patients with normal and abnormal pituitary function \((Table 2)\) showed no significant differences on several factors, including hemoglobin and serum ferritin levels. This might be due to the small number of subjects.

The present study has shown that subcutaneous deferoxamine therapy in thalassemic patients retained or improved PRL and GH secretions in 3 patients \((Table 4)\). All these 3 patients had already attained puberty. They also had normal FSH and LH responses to GnRH both before and after 18 months of study. Thus, PRL and GH defects were more likely to be improved by chelation therapy than that of gonadotropin. PRL and GH secreting cells are most susceptible to early pituitary damage in thalassemic adults. Iron chelation may protect the pituitary gland from further impairment in its hormonal releases. With a trial period of 18 months, it may be too early for the present study to demonstrate any beneficial effect of deferoxamine on other pituitary hormone secretions. Since our patients did not receive hypertransfusion, lack of improvement in other pituitary hormone secretions might be due to the continuous effect of chronic anemia. In addition, despite the marked decrease in serum ferritin concentration in all patients and the significant decrease in the mean value in the deferoxamine group after 18 months of chelation treatment, these levels remained higher than normal in 7 out of 9 patients.

There have been few longitudinal studies on pituitary function during chelation therapy. Masala et al. found normal FSH, LH, PRL, and GH secre-
tions in 20 prepubertal homozygous β-thalassemic patients treated with frequent blood transfusions and long-term (2-6 years) chelation therapy (10). In 7 of these 20 patients, there was an increase in TSH responses to TRH administration, indicating primary hypothyroidism rather than pituitary TSH impairment (10). This finding of preservation of the pituitary-thyroid axis after chelation therapy has also been reported in thalassemic children (28). Another study has shown normal cortisol release following insulin-induced hypoglycemia in 8 homozygous β-thalassemic patients after 4-8 years of deferoxamine therapy and multiple blood transfusions (23). However, no endocrine studies had been performed before the initiation of chelation therapy.

In conclusion, our data show that patients with β-thalassemia/HbE disease may develop pituitary insufficiency. The common pituitary abnormalities found in this study are deficits in gonadotropin and PRL reserves. The causes of abnormal pituitary function in these patients are not clear and might be chronic anemia combined with iron overload. The results of our prospective controlled study over 18 months show that chelation therapy may preserve or improve PRL and GH secretions in thalassemic patients. Further studies are needed with a longer period of follow-up.

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