Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients

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Abstract

Objective: We studied the clinical and hormonal profiles of patients with central hypothyroidism (CH), the adequacy of levothyroxine (L-T4) treatment and the influence of other pituitary hormone replacement therapies.

Methods: We reviewed medical records of 108 adult patients with child-onset (CO; n = 26) or adult-onset (AO; n = 82) CH.

Results: At diagnosis, the most frequently reported symptoms were fatigue and headaches in AO patients, and growth retardation in CO patients. Serum TSH was normal in a majority of CH patients, low in 8% and elevated in 8%. Serum free thyroxine (fT4) was usually reduced, but remained within the low normal range in 28% of the study population (mostly CO patients). Similarly, serum total T4 (tT4), total triiodothyronine (tT3) and free T3 (fT3) were found to be within the normal range in significant subsets of patients. Interestingly, the clinical and biochemical characteristics of CH patients with normal f/t T4 levels were not different from those of the patients with low fT4 values. The thyroid hormonal profile was not influenced by gender, etiology or by the number of hormone deficiencies. At last evaluation, the mean dose of L-T4 was 1.6 ± 0.5 μg/kg/day and was negatively correlated to current age (P < 0.001) but positively correlated to the number of hormone deficiencies (P < 0.05). Treatment suppressed TSH in 75% of the patients, induced normal fT4 in 94%, but normal fT3 in only 49% of them. Male GH-treated patients and estrogen-treated females needed a higher L-T4 dose compared with non-treated patients.

Conclusions: fT4 is clearly the best indicator of CH, but remains in the low normal range in a significant subset of patients, especially in those with CO disease. Adequacy of therapy is mostly reflected by the combination of upper normal fT4 and low normal fT3 levels. Pituitary hormone replacement therapy may require an adjustment of T4 treatment, as female patients under estrogen treatment and male patients under GH treatment will need a higher T4 dose in order to remain in the euthyroid range.

Introduction

Central hypothyroidism (CH) is a state of thyroid hormone insufficiency due to alterations in the pituitary, the hypothalamus or the hypothalamic portal circulation. The disease occurs in either rare genetic forms, where abnormalities of various genes (TSHβ, TRH receptor, Pit-1, Prop-1) have been identified (1–4), or more commonly in a sporadic, acquired form. It is almost always associated with deficient secretions of other pituitary hormones and idiopathic isolated CH remains extremely rare (5).

Although often suspected, CH is sometimes difficult to ascertain, as its clinical manifestations, similar to those of primary hypothyroidism, may be masked by symptoms of other pituitary hormone deficiencies. Additionally, in contrast to its value in the primary disease, serum thyroid-stimulating hormone (TSH) cannot be used as a diagnostic marker, as it has been reported to be in the low, normal or even elevated range (6). TSH dynamics (i.e. the nocturnal TSH surge and the TSH response to thyrotropin-releasing hormone (TRH)) are cumbersome to determine and not always available. Furthermore, they probably do not have sufficient cost-benefit to be recommended as diagnostic tests. Similarly, concerning levothyroxine (L-T4) therapy, absolute laboratory criteria regarding dose adequacy have not yet been established, and the influence of other pituitary hormone replacement therapies has not been extensively investigated.
The aim of this retrospective study was to evaluate
clinical and hormonal profiles at diagnosis of CH and
during follow-up, to examine possible differences
according to gender, etiology and coexisting pituitary
deficits, and to review criteria for diagnosis and
follow-up. We also tried to assess the impact of other
hormonal therapies on the adequacy of L-T4 treatment.

Patients and methods

Patients

We retrospectively reviewed the medical charts of
108 adult (age ≥18 yr) patients (44 females and
64 males, aged 48.9 ±16.8 yr, means±s.d.), followed
in our Department of Endocrinology for a pituitary
disease and in whom CH had been previously diagnosed
and treated. As selection criteria, all these patients
had multiple pituitary hormone deficiencies (≥3 in
96%), caused by a severe hypothalamic–pituitary
disorder (listed in Table 1) and/or its treatment. Data
at diagnosis were only available for 85 patients. In most
of these patients (n = 70), diagnosis of CH had
been made on the basis of a low total (t) or free (f)
thyroxine (T4) concentration. In the remaining cases
(n = 15), diagnosis of CH was established even
though their tT4 and fT4 levels were in the lowest
quarter of the normal range (4.5–6.5 µg/dl and
0.8–1.1 ng/dl respectively). This diagnosis was based
on the clinical context, on observation of a time-related
20% or more decrease in T4 concentrations after diag-
nosis of the pituitary disease in seven patients, and on
the evidence for complete panhypopituitarism due to
total hypophysectomy, pituitary stalk lesion or congeni-
tal hypopituitarism in the other eight patients. A 20% 
decrease in thyroid hormone levels was chosen based
on the recent observation of variation within an
individual over time of about 10% in the normal
population (7). Patients were divided into two groups
according to the age at diagnosis of CH: childhood-
onset (CO) CH patients (n = 26) and adulthood-onset
(AO) CH patients (n = 82). We also analyzed data
from the 108 patients at the last available check-up,
after more than 6 months of T4 treatment. The general
characteristics of these 108 patients at the time of last
evaluation are shown in Table 1. CO patients were
younger, had a longer duration of TSH deficiency and
a lower body mass index (BMI) than AO patients.
Most patients were receiving other hormonal replace-
ment treatments. More specifically, 81/102 (79%) 
were treated with physiological doses of cortisone aceto-
ate/hydrocortisone (10–30 mg/day), 27/102 (27%)
were receiving daily s.c. injections of recombinant
growth hormone (GH). 24/39 women (62%) had estro-
gens either orally (n = 18) or transdermally (n = 6),
while 54/63 men (86%) were treated with i.m. injec-
tions of 250 mg testosterone esters every 2 to 4 weeks.

Methods

Serum TSH was measured by a RIA method (Corning
Medical, Medfield, MA, USA) before 1989 (detection
limit: 0.5 mU/l) and by an IRMA method introduced in
January 1989 (Riabead II, Abbott Diagnostics, Chi-
icago, IL, USA) with a detection limit at 0.05 mU/l. fT4
and free triiodothyronine (fT3) were determined using
the gammacoat Free-T4, two-step method (Diaisorin,
Stillwater, MN, USA) and magic FT3 (Corning Medical),
respectively. Total T4 (tT4) and tT3 levels were assayed
using conventional RIA methods obtained from
Abbott Diagnostics. All other biochemical parameters
were analyzed according to standard laboratory
methods. Height and weight data in CO patients are
expressed as standard deviation scores (SDS) using the
Tanner references (8).

Statistical analysis

Comparisons of proportions were made with the Pear-
son Chi-square test, and comparisons of the continuous
variables between groups were made with the non-
parametric Wilcoxon test as all the variables analyzed
did not show a normal distribution. Independent effects
of parameters on hormone profile at diagnosis and of
other replacement therapies on hormone profile and
on the L-T4 dose at follow-up were tested by a multiple
logistic stepwise regression analysis. Differences were
considered statistically significant if P < 0.05.

Results

Baseline evaluation

The most frequently reported symptoms and signs in
adult patients were fatigue (52%), headaches (39%)
and sexual/gonadal dysfunction (28%), whereas in

Table 1: General characteristics of the study population at the
time of last evaluation.

<table>
<thead>
<tr>
<th></th>
<th>Childhood-onset</th>
<th>Adulthood-onset</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CH (n = 26)</td>
<td>CH (n = 82)</td>
</tr>
<tr>
<td>Sex ratio (F/M)</td>
<td>11/15</td>
<td>33/49</td>
</tr>
<tr>
<td>Age (years)§</td>
<td>30.8 ±11.8</td>
<td>54.7 ±13.9***</td>
</tr>
<tr>
<td>BMI (kg/m2)*§</td>
<td>24.1 ±5.1</td>
<td>28.8 ±6.1**</td>
</tr>
<tr>
<td>Etiology (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pituitary tumor</td>
<td>7</td>
<td>61</td>
</tr>
<tr>
<td>craniohypophygeoma</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>other CNS tumors</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>idiopathic</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>vascular</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>other</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>No. of other pituitary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>deficits (1/2/3/4)</td>
<td>1/1/19/5</td>
<td>3/17/47/15</td>
</tr>
<tr>
<td>Duration of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH (years)§</td>
<td>24.4 ±13.1</td>
<td>6.3 ±6.3***</td>
</tr>
</tbody>
</table>

§Values were determined at last evaluation and are shown as means±
s.d.; ***P < 0.001 vs childhood onset.
children, growth retardation was the main clinical problem (60%) followed by fatigue (31%) and gonadal and cognitive dysfunctions (19%). Table 2 shows the clinical and biological characteristics of the patients at the time of diagnosis, according to the time of disease onset. In CO patients, mean body weight was below the adjusted mean for age by more than one S.D., whereas AO patients had a mean BMI score exceeding 25 kg/m². Furthermore, 26% were obese, as defined by a BMI $\geq 30$ kg/m². Total serum cholesterol was elevated (5.5 mmol/l) in 58% of AO patients and in 71% of CO patients. Creatine phosphokinase (CPK) levels, measured in only 22 patients, were found to be normal in all but 3 patients.

In patients in whom diagnosis of CH was made before 1989, TSH values (determined by RIA) were within the normal range in all but one patient who had a high TSH value (Fig. 1A). When CH was diagnosed after January 1989, TSH (measured by sensitive IRMA) was found to be normal in 84%, elevated (>3.5 μU/ml) in 8% and low (<0.2 μU/ml) in only 8% of CH patients (Fig. 1B). The TRH stimulation test was performed in 39 patients. An impaired TSH response (net TSH increment $<4$ μU/ml) was found in only 36% of the patients and a delayed TSH peak ($\geq 60$ min after TRH) was observed in 60%.

Regarding circulating thyroid hormone levels at diagnosis, a significant subset of patients had one or more values within the normal range, and differences were observed between the AO and CO groups (Fig. 2). tT₄ (Fig. 2A) was in the normal range at diagnosis in 44% of the AO patients and in 20% of the CO patients, while fT₄ (Fig. 2B) was normal in 18% of the AO and in 65% of the CO patients. Both tT₃ (Fig. 2C) and fT₃ concentrations (Fig. 2D) were normal at diagnosis in about 30% of AO patients and in 85% of CO patients. When compared with AO patients, CO subjects had significantly higher levels of fT₄ ($P < 0.01$), tT₃ ($P < 0.001$) and fT₃ ($P < 0.01$) but significantly lower tT₄ concentrations ($P < 0.01$). Interestingly enough, clinical and biological parameters observed at diagnosis in the subgroup of CH patients with tT₄ and fT₄ in the lowest quartile of the normal range were otherwise similar to those found in the patients with tT₄ or fT₄ below the normal range (Table 3).

No gender difference in this hormonal profile was evidenced (data not shown). There was also no clinically relevant difference related to the etiology of pituitary disease. Furthermore, the number of other hormone deficits did not influence baseline hormonal parameters of the hypothalamic–pituitary–thyroid axis (data not shown). In multiple linear regression analysis, using a model including the number of additional hormone deficits, tumor etiology, gender and age at diagnosis of CH (CO vs AO), the only significant effects were independent influences of age at diagnosis on T₄ ($P < 0.01$), T₃ ($P < 0.001$) and fT₃ concentrations ($P < 0.001$).

![Figure 1](https://example.com/figure1.png) SERUM CONCENTRATIONS OF TSH AT THE TIME OF DIAGNOSIS OF CH BEFORE 1989 (PANEL A) OR AFTER JANUARY 1989 (PANEL B) IN CO AND AO PATIENTS. DATA ARE REPRESENTED AS THE MEDIAN, THE INTERQUARTILE RANGE [P25, P75] AND EXTREME VALUES (BOX-AND-WISKER PLOTS). THE SHADED AREA REPRESENTS THE NORMAL RANGE WHICH IS DIFFERENT BETWEEN PANEL A (RIA BEFORE 1989, DETECTION LIMIT: 0.5 mU/l) AND PANEL B (IRMA INTRODUCED IN JANUARY 1989, DETECTION LIMIT: 0.05 mU/l). NOTE THAT SERUM TSH LEVELS CAN BE LOW, NORMAL OR HIGH IN CH.

Table 2. Clinical and biological parameters at diagnosis according to the time of disease onset.

<table>
<thead>
<tr>
<th></th>
<th>Childhood onset (n = 26)</th>
<th>Adulthood onset (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>11.6±5.9</td>
<td>48.4±13.9</td>
</tr>
<tr>
<td>Weight (SDS/kg)</td>
<td>−1.28±2.00</td>
<td>81.8±23.7</td>
</tr>
<tr>
<td>Height (SDS/m)</td>
<td>−2.15±2.06</td>
<td>1.68±0.05</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>NE</td>
<td>28.2±5.7</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>101±16</td>
<td>141±22</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>69±11</td>
<td>86±11</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>75±11</td>
<td>72±10</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.7±1.2</td>
<td>6.3±1.8</td>
</tr>
</tbody>
</table>

Values are shown as means±S.D.; SDS, standard deviation score; BP, blood pressure; NE, not evaluated.
The differences between CO and AO patients are indicated. The shaded area represents the normal range. Significant quartile range [P25, P75] and extreme values (box-and-whisker plots). The shaded area represents the normal range. Significant differences between CO and AO patients. Data are represented as the median, the interquartile range 

O Alexopoulou and others

**Last evaluation under T₄ therapy**

Mean TSH value in treated CH patients (0.2 ± 0.5 µU/ml) was at the lower end of the normal range and most of the patients (75%) had a low (<0.2 µU/ml) or undetectable TSH level under L-T₄ therapy. Levels of fT₄ values were usually within normal limits, with a median close to the midpoint of the reference interval in both AO and CO groups (Fig. 3B). Similar results were obtained for tT₃ concentrations (data not shown). In contrast, fT₃ values were often below the normal limits, with medians at the lower end of or below the normal range (Fig. 3C), and this was also true for tT₄ levels (data not shown).

The mean L-T₄ replacement dose in the whole population was 1.60 mg/kg/day. This dose did not differ between female and male patients but was significantly higher in CO compared with AO patients (1.98 ± 0.56 vs 1.48 ± 0.41 mg/kg/day; P < 0.001) (Fig. 3A). The L-T₄ dose was positively correlated to the number of additional hormone deficits (r = 0.24; P < 0.05) (Fig. 4) and negatively to current age (r = −0.34; P < 0.001). As expected, we observed a negative correlation between L-T₄ dose and serum TSH (r = −0.34; P < 0.01) and a positive relationship with serum fT₄ concentrations (r = 0.25; P < 0.05).

To further determine the value of fT₄ as an indicator of adequate replacement therapy, we subdivided our study population in to two subgroups according to the fT₄ concentration at last evaluation (group 1: fT₄ < 1.4 ng/dl, n = 46; group 2: fT₄ ≥ 1.4 ng/dl, n = 55). In group 1, we observed lower fT₃ (2.7 ± 1.1 vs 3.2 ± 0.8; P < 0.05) and higher TSH levels (0.37 ± 0.70 vs 0.10 ± 0.27 µU/ml; P < 0.05) than in group 2. Interestingly, patients with high fT₄ values had lower BMI and cholesterol levels (26.9 kg/m² and 5.5 mmol/l) than patients from group 1 (28.6 kg/m² and 5.9 mmol/l), and they complained less frequently of fatigue (17% vs 29% in group 1), although these differences were not significant.

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**Effects of other pituitary hormone replacement therapies**

The effects of other hormonal treatments on thyroid parameters and on the L-T₄ dose are shown in Table 3. Administration of glucocorticoids was associated with an increase in fT₄ levels, and with a reduction of TSH levels, despite similar doses of L-T₄. The only significant effect of testosterone replacement was a decrease of TSH levels, without changes in thyroid hormones or in the L-T₄ dose. However, in multiple regression analysis, only hydrocortisone replacement therapy had an independent effect on TSH concentrations (P < 0.05). Serum thyroid hormone and TSH concentrations were not different whether patients received or not recombinant GH or estrogens, but the L-T₄ dose was significantly influenced by these treatments. Patients treated with GH had a significantly higher L-T₄ dose when compared with the non-GH-treated group (P < 0.05). However, when they were subdivided according to gender, the GH effect was observed only in males (P < 0.05) and not in females.

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**Table 3** Comparison of clinical and biological parameters at diagnosis between patients with low fT₄ (<0.8 ng/dl) or fT₄ (<4.5 µg/dl) and patients with low normal fT₄ (0.8–1.1 ng/dl) and fT₄ (4.5–6.5 µg/dl).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Low fT₄ group</th>
<th>Normal fT₄ group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>39±20</td>
<td>43±24</td>
</tr>
<tr>
<td>AO</td>
<td>17/53</td>
<td>4/11</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>25.7±6.6</td>
<td>26.5±7.8</td>
</tr>
<tr>
<td>AO</td>
<td>131±26</td>
<td>131±30</td>
</tr>
<tr>
<td><strong>Systolic BP (mm Hg)</strong></td>
<td>82±13</td>
<td>62±13</td>
</tr>
<tr>
<td><strong>Diastolic BP (mm Hg)</strong></td>
<td>72±10</td>
<td>72±11</td>
</tr>
<tr>
<td><strong>Total cholesterol (mmol/l)</strong></td>
<td>6.2±1.7</td>
<td>6.4±1.4</td>
</tr>
<tr>
<td><strong>Free T₄ (ng/dl)</strong></td>
<td>0.6±0.2</td>
<td>1.0±0.1**</td>
</tr>
<tr>
<td><strong>Total T₄ (µg/dl)</strong></td>
<td>4.1±0.9</td>
<td>5.9±0.8**</td>
</tr>
<tr>
<td><strong>Total T₃ (ng/dl)</strong></td>
<td>2.4±0.8</td>
<td>2.5±0.9</td>
</tr>
<tr>
<td><strong>Free T₃ (pg/ml)</strong></td>
<td>26±18</td>
<td>88±23</td>
</tr>
<tr>
<td><strong>TSH (µU/ml)</strong></td>
<td>2.0±2.0</td>
<td>1.0±1.2</td>
</tr>
</tbody>
</table>

Values are shown as means±S.D., **P < 0.01 vs the low T₄ group.
This was confirmed by multiple regression analysis (data not shown). On the other hand, estrogen-treated female patients also needed a higher $T_4$ daily dose than non-treated women ($P < 0.01$). The mode of estrogen administration did not influence the $L-T_4$ dose ($1.86^{+0.47}$ and $1.81^{+0.66}$ mg/kg/day in transdermally and orally estrogen-treated women respectively).

**Discussion**

CH is considered to be a rare disease with a related incidence of 50 cases per million (9). It is however underestimated and today remains a challenge for the clinician to ensure an early diagnosis and to maintain euthyroidism during treatment. As with those selected in our study, most patients with CH suffer from multiple pituitary hormone deficiencies. This may explain the usual lack of the typical signs of hypothyroidism as symptoms of other hormone deficiencies usually predominate and modify the clinical picture. It is of interest to note that this symptomatology was different between patients with AO and CO disease. A majority of CO

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**Figure 3** Dose of $L-T_4$ (panel A), and serum concentrations of $fT_4$ (panel B) and $fT_3$ (panel C) in CO and AO patients at the time of last evaluation. Data are represented as the median, the interquartile range [P25, P75] and extreme values (box-and-whisker plots). The shaded area represents the normal range.

**Figure 4** Relationship between the $L-T_4$ dose and the number of additional hormone deficits at the time of last evaluation. The $L-T_4$ dose was positively and significantly correlated with the number of hormone deficits ($r = 0.24$, $P < 0.05$).

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**Table 4** Thyroid parameters according to other pituitary hormone treatments.

<table>
<thead>
<tr>
<th></th>
<th>GH</th>
<th>Estrogens</th>
<th>Cortisone</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>$T_4$ (mg/dl)</td>
<td>9.1±2.4</td>
<td>8.6±1.4</td>
<td>8.7±1.6</td>
<td>10.4±2.7</td>
</tr>
<tr>
<td>$fT_4$ (ng/dl)</td>
<td>1.4±0.4</td>
<td>1.5±0.2</td>
<td>1.4±0.3</td>
<td>1.5±0.3</td>
</tr>
<tr>
<td>$T_3$ (ng/dl)</td>
<td>92±32</td>
<td>95±15</td>
<td>92±17</td>
<td>100±28</td>
</tr>
<tr>
<td>$fT_3$ (pg/ml)</td>
<td>2.9±1.1</td>
<td>3.2±0.7</td>
<td>2.7±0.5</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>$TSH$ (mU/ml)</td>
<td>0.2±0.5</td>
<td>0.1±0.2</td>
<td>0.3±0.4</td>
<td>0.2±0.3</td>
</tr>
<tr>
<td>$T_4$ dose (mg/kg/day)</td>
<td>1.6±0.5*</td>
<td>1.8±0.5</td>
<td>1.3±0.3**</td>
<td>1.8±0.6</td>
</tr>
</tbody>
</table>

Values are shown as means ± S.D.; *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ vs respective treated group.
patients (60%) were referred due to growth retardation in relation to thyroid hormone insufficiency and/or coexisting GH deficiency. Therefore, early diagnosis is especially crucial in children to avoid a loss in growth potential and, in some cases, dysregulation of TSH secretion might precede the development of GH deficiency (10).

Routine biochemical parameters such as total cholesterol, CPK or sex hormone binding globulin (SHBG), are considered as useful indexes of thyroid hormone action in adult patients with primary thyroid disorders (11). In our study, these parameters were often not measured at the time of diagnosis, except for total cholesterol, which was found to be elevated, especially in AO patients. It should be noted however that in most of these patients, dyslipidemic disorders persisted even after euthyroidism was restored and thus were probably not related only to CH. On the other hand, CPK levels were found normal in most instances. Therefore, in agreement with Ferretti et al. (6) we do not recommend the routine use of these parameters for assessing the diagnosis of CH.

Neither can a low TSH concentration be used as a criterion for diagnosis of CH. Indeed, in most cases of pituitary insufficiency, daytime TSH concentrations remain in the normal range as TSH pulse frequency and amplitude are preserved (12). Moreover, several studies (13–15) have reported a reduced bioactivity of circulating TSH, resulting in normal or even high serum concentrations of immunoreactive TSH. Among 37 patients with CH, Ferretti and colleagues reported low TSH levels in 19%, normal TSH in 70% and slightly increased hormone levels in 11% of the patients (6). Likewise, in our study, TSH values were normal in most patients with CH, elevated in a few and low in only 8% of them. In contrast to normal daytime TSH concentration, the nocturnal TSH surge is frequently blunted or absent in patients with CH, as a result of the loss of normal circadian variation in TRH release (16). However, this represents a rather cumbersome diagnostic tool and was not used in our center. The TSH response to TRH has also been used to identify CH, but has been recently found to be of limited value because many patients with CH have a normal response to TRH, as also found in the present study (17).

Usually, the diagnosis of CH will rely on the concomitant finding of a low fT4 or fT3 level together with a low or normal TSH concentration in the context of a known hypothalamic–pituitary disease. However, we show here that TSH concentration is a less valuable diagnostic marker of CH. This is particularly true in AO patients, 44% of them showing a normal TSH level at the time of diagnosis. In contrast, CO patients more frequently have a low TSH value at diagnosis and this may partly be explained by a decrease of T4 binding protein in CO patients, as reflected by their slightly higher T3 resin uptake values compared with AO patients.

fT4 is considered to be the best indicator of thyroid status (16) and was indeed low in most of our patients. However, a subset (28%) of our patients with obvious TSH deficiency, in particular those with CO disease, still have a fT4 concentration above the lower normal limit. Such fT4 values in the lowest quartile of the normal range, are however compatible with thyroid dysfunction, as also outlined by Rose et al. who made similar observations in 208 pediatric cancer survivors (10). Interestingly enough, patients with CH and low normal T4 concentrations are not different from individuals with frankly reduced T4 levels, regarding pituitary disease, clinical symptoms or other biochemical parameters, including TSH and T3 concentrations. This situation in fact mirrors that observed in primary hypothyroidism, where fT4 concentrations may be either low or normal.

T4 and fT3 remained within the normal range in the majority of CO patients and in a significant percentage of AO patients, making their use as diagnostic markers clearly inappropriate. Ferretti et al. (6) also found normal values of fT3 and of fT4 in a significant subset of their patients with CH, and this observation is also made in primary hypothyroidism where preferential secretion of T4 occurs. We also show in this study that gender, etiology of the pituitary disease or the total number of pituitary hormone deficits had no significant influence on the hormonal profile at diagnosis of CH.

Our patients with CH were treated with a daily dose of L-T4 (1.6 μg/kg BW) similar to that usually used to treat primary hypothyroidism (18–19). We observed that CO patients needed a much higher L-T4 dose to ensure similar levels of peripheral thyroid hormones as compared with AO patients. Because CO patients were younger, this difference might reflect the influence of age on replacement therapy, as highlighted by previous studies in both primary hypothyroidism and CH (6, 18, 20). This age effect is also suggested by the significant negative correlation found in our study between the L-T4 dose and age, and might be related to a reduction in thyroid hormone metabolism with aging.

While gender did not influence the daily replacement dose, patients with more additional hormone deficits needed a higher L-T4 dose and this increase likely reflects the influence of other hormone treatments on the T4 dose as discussed below. The effect of a more severe disease can be reasonably excluded, as the number of pituitary deficiencies did not influence hormonal parameters of the pituitary–thyroid axis at the time of diagnosis.

Adequate T4 replacement therapy should induce low TSH levels, even before the resolution of clinical symptoms (16) and this effect is not indicative of overtreatment as in primary hypothyroidism. Corazza et al. in a study of 135 patients with CH, reported subnormal TSH levels in two-thirds of their treated patients (21).
Likewise, in our series, 75% of the patients had low or undetectable TSH levels and the remaining subjects were probably undertreated. However, given the overall impaired feedback mechanism in CH, TSH concentrations should not be used for adjusting L-T₄ dose. fT₄ is proposed as the best index for monitoring L-T₄ therapy. About 54% of the patients had fT₄ values in the upper half of the reference interval (≥1.4 ng/dl) and the remainder had normal low fT₄ concentrations (0.8–1.39 ng/dl), probably indicating undertreatment as suggested by several previous studies (19, 21). In addition, more than half of our patients had low fT₃ despite normal fT₄ concentrations. This may be explained by the lack of direct thyroidal T₃ production, which accounts for approximately 20% of circulating T₃, and/or a reduced 5’ deiodinase activity in patients with a defective thyrotrope axis. It remains to be determined whether adding small doses of T₃ would be beneficial in CH patients, as has been proposed in primary hypothyroidism (22). Alternatively, targeting higher fT₄ levels would likely lead to normalization of fT₃ concentrations.

All patients had multiple pituitary hormone deficiencies and we examined the possible effects of other replacement treatments on L-T₄ dose and on thyroid parameters. Corticosteroid replacement therapy did not have any influence on the L-T₄ dose, but was associated with reduced TSH. This effect may result from the known inhibitory action of glucocorticoids on the basal release of TSH. Higher fT₄ levels observed in cortisone-treated subjects probably reflect the decreased conversion of T₄ to T₃ in peripheral tissues (23).

Both estrogen-treated female and GH-treated male patients required a higher daily dose of L-T₄ to maintain a thyroid profile similar to that of non-treated patients. The best characterized effect of estrogens is a dose-dependent increase of serum thyroxine-binding globulin (TBG), due to both a decrease in the clearance of heavily sialylated TBG secreted by the liver (24) and an increase in its biosynthesis (25). Recent data indicate that women with primary hypothyroidism need a higher T₄ dose when under estrogen treatment (26). Likewise, in our study, estrogen-treated women with CH also needed higher doses of T₄, independently of other replacement therapies. The underlying mechanism might be the inability of the failing pituitary–thyroid axis to respond to the estrogen-induced increase in serum TBG concentration with a parallel rise in endogenous T₄ and T₃ secretion.

It has been well documented that exogenous GH administration enhances peripheral deiodination of T₄ to T₃ (27–30). Since monitoring of CH is based on serum fT₄ levels, the decline of its levels during GH treatment will usually lead to an increase in the L-T₄ dose (29, 31). This was indeed observed in the present retrospective study, but mainly in male patients. One possible explanation for this gender difference might be that the L-T₄ dose had been already increased in female patients under estrogen treatment, thus concealing a further GH effect. Besides, women are known to be more resistant to GH action (32, 33).

In summary, our study shows that in patients with CH, TSH concentration often remains normal and is not a reliable marker for diagnosis. fT₄ is clearly the best indicator of CH, although it may be in the low normal range in a subset of patients, especially in CO patients in whom fT₄ seems to be a more appropriate marker. Our data also suggest that adequacy of L-T₄ therapy is mostly reflected by the combination of upper normal fT₄ values and low normal fT₃ levels in adult TSH-deficient patients. Replacement therapy of other pituitary hormone deficiencies may require an adjustment of T₄ replacement doses. More specifically, female estrogen-treated patients and male GH-treated patients will need a higher T₄ dose in order to remain in the euthyroid range.

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