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CLINICAL STUDY

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 (fT_4) was usually reduced, but remained within the low normal range in 28% of the study population (mostly CO patients). Similarly, serum total T_4 (tT_4), total triiodothyronine (tT_3) and free T_3 (fT_3) 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 T_4 levels were not different from those of the patients with low fT_4 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-T_4 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 fT_4 in 94%, but normal fT_3 in only 49% of them. Male GH-treated patients and estrogen-treated females needed a higher L-T_4 dose compared with non-treated patients.

Conclusions: fT_4 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 fT_4 and low normal fT_3 levels. Pituitary hormone replacement therapy may require an adjustment of T_4 treatment, as female patients under estrogen treatment and male patients under GH treatment will need a higher T_4 dose in order to remain in the euthyroid range.

European Journal of Endocrinology **150** 1–8

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 thyrotrophin-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-T_4) 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-T_4 treatment.

Patients and methods

Patients

We retrospectively reviewed the medical charts of 108 adult (age $\geq$ 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 ($\geq$3 in 96%), caused by a severe hypothalamic–pituitary disorder (listed in Table 1) and/or its treatment. Data at diagnosis were only available for 85 patients. In most of these patients ($n = 70$), diagnosis of CH had been made on the basis of a low total (t) or free (f) thyroxine (T_4) concentration. In the remaining cases ($n = 15$), diagnosis of CH was established even though their tT_4 and fT_4 levels were in the lowest quartile of the normal range (4.5–6.5 μg/dl and 0.8–1.1 ng/dl respectively). This diagnosis was based on the clinical context, on observation of a time-related 20% or more decrease in T_4 concentrations after diagnosis of the pituitary disease in seven patients, and on the evidence for complete panhypopituitarism due to total hypophysectomy, pituitary stalk lesion or congenital hypopituitarism in the other eight patients. A 20% decrease in thyroid hormone levels was chosen based on the recent observation of variation within an individual over time of about 10% in the normal population (7). Patients were divided into two groups according to the age at diagnosis of CH: childhood-onset (CO) CH patients ($n = 26$) and adulthood-onset (AO) CH patients ($n = 82$). We also analyzed data from the 108 patients at the last available check-up, after more than 6 months of T_4 treatment. The general characteristics of these 108 patients at the time of last evaluation are shown in Table 1. CO patients were younger, had a longer duration of TSH deficiency and a lower body mass index (BMI) than AO patients. Most patients were receiving other hormonal replacement treatments. More specifically, 81/102 (79%) were treated with physiological doses of cortisone acetate/hydrocortisone (10–30 mg/day), 27/102 (27%) were receiving daily s.c. injections of recombinant growth hormone (GH). 24/39 women (62%) had estrogens either orally ($n = 18$) or transdermally ($n = 6$), while 54/63 men (86%) were treated with i.m. injections of 250 mg testosterone esters every 2 to 4 weeks.

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

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

§ Values were determined at last evaluation and are shown as means± S.D.; ***$P < 0.001$ vs childhood onset.

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, Chicago, IL, USA) with a detection limit at 0.05 mU/l. fT_4 and free triiodothyronine (fT_3) were determined using the gammacoat Free-T4, two-step method (Diasorin, Stillwater, MN, USA) and magic FT3 (Corning Medical), respectively. Total T_4 (tT_4) and tT_3 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 Pearson 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-T_4 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 2 Clinical and biological parameters at diagnosis according to the time of disease onset.

	Childhood onset ($n = 26$)	Adulthood onset ($n = 82$)
Age (years)	11.6±5.9	48.4±13.9
Weight (SDS/kg)	−1.28±2.00	81.8±23.7
Height (SDS/m)	−2.15±2.06	1.68±0.05
BMI (kg/m^2)	NE	28.2±5.7
Systolic BP (mm Hg)	101±16	141±22
Diastolic BP (mm Hg)	69±11	86±11
Heart rate (beats/min)	75±11	72±10
Total cholesterol (mmol/l)	5.7±1.2	6.3±1.8

Values are shown as means±S.D.; SDS, standard deviation score; BP, blood pressure; NE, not evaluated.

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/m^2. Furthermore, 26% were obese, as defined by a BMI ≥ 30 kg/m^2. 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 (≥ 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). tT_4 (Fig. 2A) was in the normal range at diagnosis in 44% of the AO patients and in 20% of the CO patients, while fT_4 (Fig. 2B) was normal in 18% of the AO and in 65% of the CO patients. Both tT_3 (Fig. 2C) and fT_3 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 fT_4 ($P < 0.01$), tT_3 ($P < 0.001$) and fT_3 ($P < 0.01$) but significantly lower tT_4 concentrations ($P < 0.01$). Interestingly enough, clinical and biological parameters observed at diagnosis in the subgroup of CH patients with tT_4 and fT_4 in the lowest quartile of the normal range were otherwise similar to those found in the patients with tT_4 or fT_4 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 T_4 ($P < 0.01$), T_3 ($P < 0.001$) and fT_3 concentrations ($P < 0.001$).

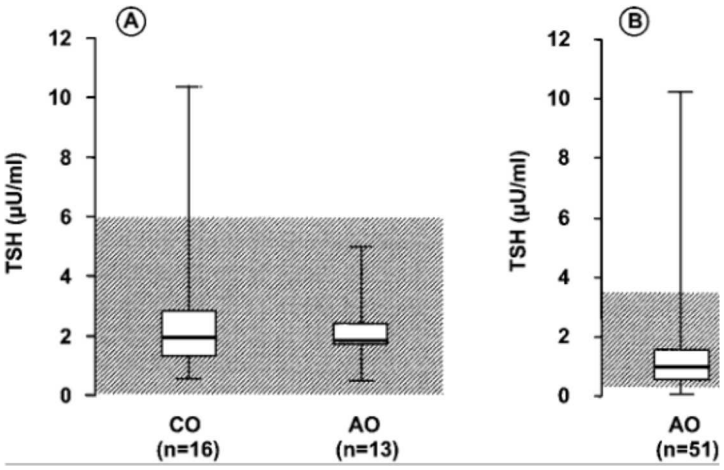

Figure 1 Serum concentrations of TSH at the time of diagnosis of CH before 1989 (panel A) or after January 1989 (panel B) in CO and AO patients. Data are represented as the median, the interquartile range [P25, P75] and extreme values (box-and-whisker plots). The shaded area represents the normal range 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.

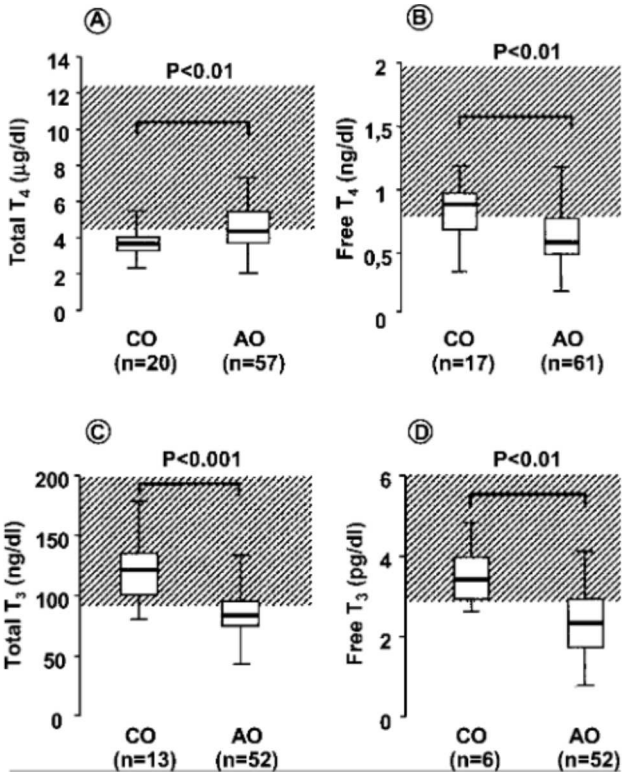

Figure 2 Serum concentrations of tT_4 (panel A), fT_4 (panel B), tT_3 (panel C) and fT_3 (panel D) at the time of diagnosis of CH in CO and AO patients. Data are represented as the median, the interquartile range [P25, P75] and extreme values (box-and-whisker plots). The shaded area represents the normal range. Significant differences between CO and AO patients are indicated.

Last evaluation under T_4 therapy

Mean TSH value in treated CH patients ($0.2\pm0.5\,\mu U/ml$) was at the lower end of the normal range and most of the patients (75%) had a low ($<0.2\,\mu U/ml$) or undetectable TSH level under L-T_4 therapy. Levels of fT_4 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 tT_4 concentrations (data not shown). In contrast, fT_3 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 tT_3 levels (data not shown).

The mean L-T_4 replacement dose in the whole population was $1.60\,\mu g/kg/day$. 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 $1.48\pm0.41\,\mu g/kg/day$; $P<0.001$) (Fig. 3A). The L-T_4 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-T_4 dose and serum TSH ($r=-0.34$; $P<0.01$) and a positive relationship with serum fT_4 concentrations ($r=0.25$; $P<0.05$).

Table 3 Comparison of clinical and biological parameters at diagnosis between patients with low fT_4 ($<0.8\,ng/dl$) or tT_4 ($<4.5\,\mu g/dl$) and patients with low normal fT_4 (0.8–1.1 ng/dl) and tT_4 (4.5–6.5 µg/dl).

	Low T_4 group ($n=70$)	Normal T_4 group ($n=15$)
Age (years)	39±20	43±24
Onset (CO/AO)	17/53	4/11
BMI (kg/m^2)	25.7±6.8	26.5±7.8
Systolic BP (mm Hg)	131±26	131±30
Diastolic BP (mm Hg)	82±13	80±13
Heart rate (beats/min)	72±10	72±11
Total cholesterol (mmol/l)	6.2±1.7	6.4±1.4
Free T_4 (ng/dl)	0.6±0.2	1.0±0.1**
Total T_4 (µg/dl)	4.1±0.9	5.9±0.8**
Free T_3 (pg/ml)	2.4±0.8	2.5±0.9
Total T_3 (ng/dl)	91±26	88±23
TSH (µU/ml)	2.0±2.0	1.0±1.2

Values are shown as means±S.D., **$P<0.01$ vs the low T_4 group.

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 fT_4 concentration at last evaluation (group 1: $fT_4<1.4\,ng/dl$, $n=46$; group 2: $fT_4\geq1.4\,ng/dl$, $n=55$). In group 1, we observed lower fT_3 (2.7 ± 1.1 vs 3.2 ± 0.8; $P<0.05$) and higher TSH levels (0.37 ± 0.70 vs $0.10\pm0.27\,\mu U/ml$; $P<0.05$) than in group 2. Interestingly, patients with high fT_4 values had lower BMI and cholesterol levels ($26.9\,kg/m^2$ and $5.5\,mmol/l$) than patients from group 1 ($28.6\,kg/m^2$ and $5.9\,mmol/l$), and they complained less frequently of fatigue (17% vs 29% in group 1), although these differences were not significant.

Effects of other pituitary hormone replacement therapies

The effects of other hormonal treatments on thyroid parameters and on the L-T_4 dose are shown in Table 4. Administration of glucocorticoids was associated with an increase in tT_4 levels, and with a reduction of TSH levels, despite similar doses of L-T_4. The only significant effect of testosterone replacement was a decrease of TSH levels, without changes in thyroid hormones or in the L-T_4 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-T_4 dose was significantly influenced by these treatments. Patients treated with GH had a significantly higher L-T_4 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.

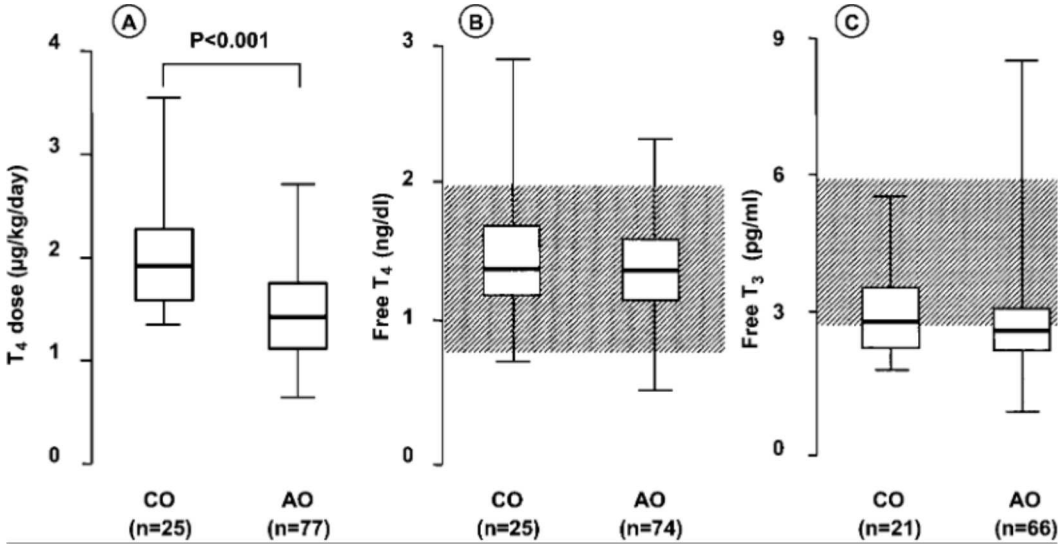

Figure 3 Dose of L-T_4 (panel A), and serum concentrations of fT_4 (panel B) and fT_3 (panel C) in CO and AO patients at the time of last evaluation. Data are represented as the median, the interquartile range [P25, P75] and extreme values (box-and-whisker plots). The shaded area represents the normal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

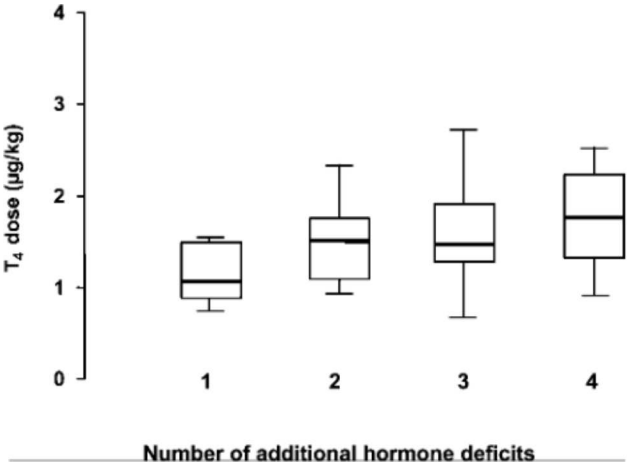

Figure 4 Relationship between the L-T_4 dose and the number of additional hormone deficits at the time of last evaluation. The L-T_4 dose was positively and significantly correlated with the number of hormone deficits ($r = 0.24$, $P < 0.05$).

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 µg/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

Table 4 Thyroid parameters according other pituitary hormone treatments.

	GH		Estrogens		Cortisone		Testosterone	
	no	yes	no	yes	no	yes	no	yes
T_4 (µg/dl)	9.1±2.4	8.6±1.4	8.7±1.6	10.4±2.7	7.9±2.0*	9.1±2.1	7.6±2.1	8.5±1.8
fT_4 (ng/dl)	1.4±0.4	1.5±0.2	1.4±0.3	1.5±0.3	1.3±0.3	1.4±0.3	1.3±0.4	1.4±0.2
T_3 (ng/dl)	92±32	95±15	82±17	100±28	99±40	89±21	82±12	92±31
fT_3 (pg/ml)	2.9±1.1	3.2±0.7	2.7±0.5	3.1±0.9	3.3±1.4	3.0±0.8	2.7±0.5	3.2±1.1
TSH (µU/ml)	0.2±0.5	0.1±0.2	0.3±0.4	0.2±0.3	0.5±0.8*	0.1±0.3	0.5±0.5***	0.2±0.5
T_4 dose (µg/kg/day)	1.6±0.5*	1.8±0.5	1.3±0.3**	1.8±0.6	1.5±0.5	1.6±0.5	1.4±0.4	1.6±0.5

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 tT_4 or fT_4 level together with a low or normal TSH concentration in the context of a known hypothalamic–pituitary disease. However, we show here that tT_4 concentration is a less valuable diagnostic marker of CH. This is particularly true in AO patients, 44% of them showing a normal tT_4 level at the time of diagnosis. In contrast, CO patients more frequently have a low tT_4 value at diagnosis and this may partly be explained by a decrease of T_4 binding protein in CO patients, as reflected by their slightly higher T_3 resin uptake values compared with AO patients.

fT_4 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 fT_4 concentration above the lower normal limit. Such fT_4 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 T_4 concentrations are not different from individuals with frankly reduced T_4 levels, regarding pituitary disease, clinical symptoms or other biochemical parameters, including TSH and T_3 concentrations. This situation in fact mirrors that observed in primary hypothyroidism, where fT_4 concentrations may be either low or normal.

tT_3 and fT_3 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 fT_3 and of tT_3 in a significant subset of their patients with CH, and this observation is also made in primary hypothyroidism where preferential secretion of T_3 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-T_4 (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-T_4 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-T_4 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-T_4 dose and this increase likely reflects the influence of other hormone treatments on the T_4 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 T_4 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-T_4 dose.

fT_4 is proposed as the best index for monitoring L-T_4 therapy. About 54% of the patients had fT_4 values in the upper half of the reference interval (≥ 1.4 ng/dl) and the remainder had normal low fT_4 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 fT_3 despite normal fT_4 concentrations. This may be explained by the lack of direct thyroidal T_3 production, which accounts for approximately 20% of circulating T_3, and/or a reduced 5′ deiodinase activity in patients with a defective thyreotrope axis. It remains to be determined whether adding small doses of T_3 would be beneficial in CH patients, as has been proposed in primary hypothyroidism (22). Alternatively, targeting higher fT_4 levels would likely lead to normalisation of fT_3 concentrations.

All patients had multiple pituitary hormone deficiencies and we examined the possible effects of other replacement treatments on L-T_4 dose and on thyroid parameters. Corticosteroid replacement therapy did not have any influence on the L-T_4 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 tT_4 levels observed in cortisone-treated subjects probably reflect the decreased conversion of T_4 to T_3 in peripheral tissues (23).

Both estrogen-treated female and GH-treated male patients required a higher daily dose of L-T_4 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 sialyated TBG secreted by the liver (24) and an increase in its biosynthesis (25). Recent data indicate that women with primary hypothyroidism need a higher T_4 dose when under estrogen treatment (26). Likewise, in our study, estrogen-treated women with CH also needed higher doses of T_4, 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 T_4 and T_3 secretion.

It has been well documented that exogenous GH administration enhances peripheral deiodination of T_4 to T_3 (27–30). Since monitoring of CH is based on serum fT_4 levels, the decline of its levels during GH treatment will usually lead to an increase in the L-T_4 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-T_4 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. fT_4 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 tT_4 seems to be a more appropriate marker. Our data also suggest that adequacy of L-T_4 therapy is mostly reflected by the combination of upper normal fT_4 values and low normal fT_3 levels in adult TSH-deficient patients. Replacement therapy of other pituitary hormone deficiencies may require an adjustment of T_4 replacement doses. More specifically, female estrogen-treated patients and male GH-treated patients will need a higher T_4 dose in order to remain in the euthyroid range.

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