Exploring the use of recombinant human TSH in the diagnosis of central hypothyroidism

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Abstract

Context: The diagnosis of central hypothyroidism (CH) is often difficult to establish as serum TSH levels may be low, normal, or slightly increased.

Objective: To explore the use of recombinant human TSH (rhTSH) in the diagnosis of CH.

Design: Randomized single-blind clinical trial.

Setting: Outpatient clinic of a tertiary care referral center.

Intervention: A single intramuscular injection of 0.1 and 0.9 mg rhTSH in random order with 1-week interval.

Participants: Eighteen adult patients with pituitary insufficiency and six healthy age-, sex-, and body mass index-matched controls. Six patients had untreated CH (newCH), six had treated CH (CH), and six patients were TSH sufficient (nonCH). Five weeks before TSH stimulation, levothyroxine was replaced with tri-iodothyronine (T3) for 4 weeks. One week before stimulation, treatment was withdrawn.

Main outcome measures: Thyroid hormones and thyroglobulin (Tg) before and 2, 3, 7, 24, 48, and 72 h after each injection.

Results: In the newCH group, basal free thyroxine (FT4) levels were lower than in controls (P < 0.05). After 0.9 mg rhTSH, the increases in FT4 and reverse T3 (rT3) were less marked in the newCH group than in controls (FT4 ± S.E.M. 9.2 ± 0.5 to 19.7 ± 1.2 vs 11.3 ± 0.5 to 27.8 ± 2.4 pmol/l, P < 0.05). The CH group exhibited reduced basal and stimulated FT4 compared with the TSH-sufficient groups. Tg increased similarly among all study groups after rhTSH injection.

Conclusion: In this pilot study, patients with untreated CH had lower response to 0.9 mg rhTSH in FT4 and rT3 than controls. An rhTSH test may be useful in the diagnosis of CH, but further studies are required.

Introduction

Central hypothyroidism (CH) occurs due to insufficient synthesis and secretion of biologically active thyroid-stimulating hormone (TSH). It may present as part of a general hypopituitarism or as consequence of a limited pituitary damage. The diagnosis of CH may often be difficult as serum TSH levels can be both low, normal, or slightly increased (1). The bioactivity of TSH (2) is also reduced because of an inadequate hypothalamic stimulation that causes the pituitary to secrete an abnormally glycosylated TSH. TSH in this form has a longer half-life than normal TSH (3), which explains the normal and sometimes slightly elevated levels of TSH seen in CH. In addition, thyroid hormone levels in mild hypothyroidism may be within the lower normal range (4–7). Because of this uncertainty of using basal thyroid hormone levels in the evaluation of CH, other tests have been developed. Patients with CH have a blunted nocturnal surge (8, 9) in the TSH circadian secretion (10–12). This may, however, be found in non-thyroidal illness (13), in postoperative patients (14, 15), during starvation (16), and in severe primary hypothyroidism (17). The thyrotropin-releasing hormone stimulation test has been used in the diagnosis of CH (18, 19), but its value has been questioned (20). However, authors of a recent study of children with congenital CH claim the value of the thyrotropin-releasing hormone test to differentiate between isolated CH and CH combined with multiple hormonal insufficiencies (21). Hence, the diagnosis of CH may be difficult and an additional test to clarify the diagnosis is warranted.

In some early studies, bovine TSH (bTSH) stimulation was explored for the diagnosis of CH (22). In 1949, an increased iodine uptake in the thyroid was detected in normal subjects after bTSH administration that was sustained if the subjects were treated with thyroid hormone during the stimulation (23). It was later established that an inactive gland in CH can be stimulated to resume thyroid hormone synthesis after numerous bTSH injections (22). However, bTSH usage was terminated due to commonly occurring allergic
reactions (24) and the appearance of neutralizing and hemagglutinating antibodies (24, 25).

Through its receptor, TSH regulates the expression of all gene products required for thyroid hormone synthesis (26–28). TSH receptor knockout mice are, however, able to produce and store thyroglobulin (Tg) that has a low iodine and hormone content (29). In addition, animal studies demonstrate that Tg synthesis and secretion into the follicular lumen continues in the absence of TSH (29, 30). Moreover, subsequent to the elimination of endogenous TSH, the acute endocytic response to TSH is gradually diminished due to the reduction of membrane material available for the formation of endocytic vesicles (31). Therefore, a different response to TSH in a TSH-depleted thyroid gland than under normal conditions could be expected, which is in analogy with the short adrenocorticotropic (ACTH) stimulation test that is proven to be valid in the diagnosis of ACTH deficiency (32).

The primary aim of the present pilot study was to investigate whether the stimulation of the thyroid gland with recombinant human TSH (rhTSH) could distinguish between patients with CH and those who are TSH sufficient. The second aim was to investigate the physiology of a TSH-depleted thyroid gland.

**Subjects and methods**

**Subjects**

Eighteen Caucasian patients with well-defined pituitary disease and pituitary insufficiency were recruited from our endocrine clinic. These patients comprised of three groups: the CH group (n = 6) was treated with levothyroxine (Levaxin, Nycomed AB, Stockholm, Sweden), the newCH group (n = 6) had a newly diagnosed CH not yet replaced, and the nonCH group (n = 6) had hypopituitarism but unaffected TSH secretion, which was reflected by normal pre-study free thyroxine (FT₄) levels (range 11–14 pmol/l). The consecutively recruited newCH patients had an established pituitary disease, a FT₄ below the normal range (pre-study mean ± s.e.m.; range, FT₄: 7.8 ± 0.9 pmol/l (6.6–8.9); TSH, 0.74 ± 0.62 mU/l (0.02–1.9)), and additional pituitary insufficiencies. Six healthy Caucasian controls were also included. As one control was subnormal in FT₄, he was replaced with another individual. The groups were matched for age, sex, and body mass index (Table 1). The exclusion criteria were: current thyroid disease, presence of thyroperoxidase antibodies, cardiac disease and treatment with antiepileptic, antipsychotic, or anticoagulation drugs.

**Ethics**

Subjects received oral and written information about the study and were included after giving written informed consent. The study protocol was approved by the Ethics Committee at Göteborg University and the Swedish Medical Products Agency, Uppsala, Sweden. The study was performed according to the Declaration of Helsinki.

**Study design**

This was a prospective, randomized single-blinded trial using two doses of rhTSH. Before the start of the study, all subjects underwent a routine clinical investigation, including an electrocardiographic registration. In the

<table>
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<th>Subjects</th>
<th>NewCH (n=6)</th>
<th>CH (n=6)</th>
<th>NonCH (n=6)</th>
<th>Controls (n=6)</th>
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<td>55.7 (40–61)</td>
<td>51.8 (37–62)</td>
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<td>26.6 (21.7–30.8)</td>
<td>26.0 (20.1–30.0)</td>
<td>25.4 (21.8–27.8)</td>
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<td>5ᵇ</td>
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N=number.
ᵃTwo males with unreplaced hypogonadism, two postmenopausal-aged women without estrogens.
ᵇOne postmenopausal woman on estrogens.
ᶜOne postmenopausal woman without estrogens.
CH group, the levothyroxine substitution was changed to 20 μg tri-iodothyronine (T₃; Liothyronin, Nycomed AB, Stockholm, Sweden) thrice daily 5 weeks before study start because of its shorter half-life. If symptoms indicating over replacement appeared, the dose was reduced by half. T₃ substitution was discontinued 1 week before commencement of the study and levothyroxine substitution was re-instituted after study completion.

All participants received an i.m. glutal injection at 0900 h of 0.1 and 0.9 mg rhTSH (Thyrogen, Genzyme, Boston, MA, USA) given in random order with 1 week in-between. Subjects were randomized in blocks by the hospital pharmacy. Before each injection, blood samples were taken for the assessment of hemoglobin, serum sodium, potassium, calcium, creatinine, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase. Samples were collected at −45 min, immediately before and 2, 3/1/2, 7, 24, 48, and 72 h after each injection, and a mean was calculated of the two baseline measurements. Side effects were recorded simultaneously. The newCH patients and the replaced control were recruited after the completion of the other study groups. Based on previous experience, less frequent blood sampling was performed in the newCH group: before and 24, 48, and 72 h after each injection.

After study termination, samples were analyzed for TSH, FT₄, total T₃ (TT₃), free T₃ (FT₃), total T₄ (TT₄), reverse T₃ (rT₃), Tg, and Tg antibodies. In addition, IGF-I and insulin levels were measured before any rhTSH injection.

**Hormonal assays**

Immunochemoluminometric methods (Architect, Abbott) were used for the analyses of TSH (interindividual coefficient of variation (CV) 3%, reference range (refr) 0.20–4.0 mIU/l), FT₄ (CV 6% at low level and 5% at high level, refr 10–22 pmol/l), TT₄ (CV 5%, refr 56–147 nmol/l), FT₃ (CV 9% at low level and 4% at high level, refr 2.6–5.7 pmol/l), and TT₃ (CV 7% at low level and 3% at high level, refr 0.9–2.4 nmol/l). rT₃ was determined by a radioimmunometric assay (Wallac Adaltis, Bologna, Italy, CV 5%, refr 0.14–0.54 nmol/l). Tg was analyzed by an immunoaurimetric method (Delphia, Wallac Sweden AB, Turku, Finland, CV 3% at low level, 8% at medium level, and 4% at high level, refr 2–20 μg/l). Tg antibodies (Lumitest, Brahms, Henningsdorf, Germany, CV 9%, refr <60 U/ml) and TPO antibodies (Berilux 400, Perkin–Elmer BRAHMS Diagnostica, Berlin, Germany, CV 11%, refr <60 kU/l) were measured by immunoluminescence technique. IGF-I was determined with a RIA after acid ethanolic extraction (Nicols Institute Diagnostics, San Juan Capistrano CA, USA, CV 6.3% at low level, 6.5% at medium level, and 7.7% at high level) and insulin by a chemoluminometric method (Advia Centaur, Bayer Corporation, Tarrytown, NY, USA, CV 5% at low level and 6% at medium and high level). Specimens were analyzed in the same batch, except for the newCH specimens and the exchanged control specimens that were analyzed separately but with the same immunoassays, except, in the control, for IGF-I that was determined by Immulite 2500, DPC, Siemens, Los Angeles, CA, USA.

**Statistical methods**

Descriptive data are presented as mean ± S.E.M. The effect before and after rhTSH administration was analyzed with paired t-test and comparisons of hormone levels between groups were performed with unpaired t-test. Statistical significance was considered if P<0.05.

**Results**

All subjects completed the study, however, one control was unable to leave specimens twice. One patient on T₃ substitution experienced headache and nausea, and one tiredness; their dose was reduced by half according to the study protocol. Symptoms after the rhTSH administrations were mild and transient. Marked symptoms of hypothyroidism (n = 1) and a brief period of chest pain not related to ischemic heart disease (n = 1), occurred in the CH group. Tiredness was, otherwise, the most frequent symptom (newCH n = 1, CH n = 5, and nonCH n = 1) followed by sensation of warmth (newCH n = 1 and controls n = 2), nocturnal perspiration (controls n = 2), slight discomfort (controls n = 2), palpitation (controls n = 1), pain in the calves (controls n = 1), dizziness (nonCH n = 1), and less nocturia (nonCH n = 1).

In subjects randomized to receive 0.9 mg as first dose, the hormonal levels had not completely returned to baseline before the next injection. Baseline was, therefore, characterized as the values before any rhTSH administration and compared with peak levels after each injection. Moreover, the response in thyroid hormones from 0.1 mg rhTSH was less pronounced compared with the 0.9 mg dose response and did not discriminate newCH patients from controls. The emphasis in the results section is therefore on the 0.9 mg rhTSH dose.

**TSH**

Basal levels of TSH did not differ between groups. After rhTSH injection, serum TSH increased similarly in the four groups to a peak of 16.1 ± 6.0 mIU/l after 0.1 mg and >100 mIU/l after 0.9 mg within the first 24 h, results of groups combined (Table 2).

**Thyroglobulin**

Basal Tg levels were similar in all groups. In CH subjects, basal Tg levels were increased before the second injection, regardless of given dose (data not shown). RhTSH stimulation resulted in a distinct and comparable increase in Tg in all groups, with similar peak
levels 48 h after the 0.9 mg dose (Fig. 1A and Table 2). In the CH group, an extreme outlier (max Tg 600 μg/l) occurred and after the exclusion of this subject, the Tg analyses did not differ between groups (Fig. 1A).

**FT4 and TT4**

The nonCH and control groups had similar baseline FT4 levels (range 8.6–14.5 and 10–13.0 pmol/l respectively), whereas FT4 levels in the CH group were low (Table 2). The lowest FT4 in the nonCH group was a mean of FT4 9.8 and 7.3 pmol/l. FT4 in the newCH group (range: 7.8–11.0 pmol/l) was lower than in control subjects but higher than in CH patients. After the administration of 0.9 mg rhTSH, the increase in the newCH group was less pronounced than in controls (Figs 1B, 2A and 3A). A small overlap in the peak FT4 level occurred between the two groups, range: newCH 15–23 pmol/l and controls 20–36 pmol/l. Overlapping values were seen in 67 and 50% of newCH patients and controls after 0.9 and 0.1 mg rhTSH respectively. However, the lowest FT4 level in the controls after 0.9 mg rhTSH was from one subject unable to leave specimens on two out of three occasions where FT4 used to peak. If this patient was excluded from the overlap analysis, no overlap existed between the newCH and the control group after 0.9 mg rhTSH. The mean increase of FT4 after the high-dose stimulation was in the newCH group 10.5 pmol/l (range 7–13.2) and in controls 16.5 pmol/l (range 10.0–23.5, P < 0.05). The FT4 concentration peaked after 48 or 72 h (n = 10, n = 2 respectively). A much smaller increase in FT4 was observed in the CH group and no overlap was detected with the TSH-sufficient subjects (Figs 2A and 3A). In the CH group, however, basal levels of FT4 were higher before the second than before the first injection of rhTSH, regardless of the dose administrated (data not shown). Serum TT4 concentrations displayed a similar pattern as FT4.

**FT3 and TT3**

Baseline serum levels of FT3 and TT3 were similar in the nonCH patients and controls, whereas reduced levels were observed in the CH group (Table 2). In the newCH group, FT3 levels were lower than in controls, but higher than in the CH group. After 0.9 mg rhTSH, a marked increase in FT3 and TT3 was seen in newCH patients, nonCH patients, and controls (Figs 2B and 3B). However, there was a considerable overlap comparing the rhTSH response of the newCH group and the TSH-sufficient patients.

**RT3**

NewCH groups, nonCH groups, and controls did not differ in baseline rT3 (Table 2). The CH group had decreased levels compared with the other groups. After
the high-dose rhTSH stimulation, a less pronounced increase was observed in the newCH patients than in controls. The CH group had a lower response than newCH (Figs 2C and 3C). Stimulated rT₃ levels did not differ between TSH-sufficient groups. A small overlap was detected in the increase and the maximum rT₃ levels after high-dose stimulation: mean ΔrT₃ in newCH patients 0.17 nmol/l (range 0.02–0.40) and in controls 0.34 nmol/l (range 0.26–0.46), P<0.05 and peak range in newCH group 0.32–0.56 nmol/l and in controls 0.56–0.81 nmol/l. The peak occurred after 48 or 72 h in the majority of cases.

### IGF-I and insulin

The serum IGF-I level from the replaced control was not included in analysis as methods differed (Table 2). Serum IGF-I levels were decreased in the newCH group compared with controls and the GH replaced patients in the CH group. Fasting serum insulin levels did not differ among the groups.

### Discussion

This pilot study has explored the response of the thyroid gland to rhTSH in adults with and without TSH deficiency. Patients with newly diagnosed CH and no previous levothyroxine treatment exhibited a less pronounced increase of thyroid hormone levels after administration of 0.9 mg rhTSH than controls. An rhTSH test may, therefore, become useful in the diagnosis of CH. Notably, patients with and without TSH deficiency displayed a similar increase in serum Tg levels in response to rhTSH.

In multiple pituitary hormone deficiency, the determination of peripheral thyroid hormones is usually enough in the diagnosis of CH. Nevertheless, some of the newCH subjects exhibited baseline FT₄ values within the normal range. This is probably best explained by 'regression to the mean' as their low thyroid hormone level was used for selection into the study. This is also illustrated by the nonCH patient with a baseline FT₄ of 8.6, which was a mean of two analyses: FT₄ 9.8 and 7.3 pmol/l. In addition, the six controls had mean FT₄ concentrations in the lower part of the normal range by chance. The newCH group had significantly lower baseline FT₄ levels than controls, although there was some overlap.

By including well-characterized hypopituitary patients with sufficient TSH production, we explored the possibility of subjects having partial CH. The results in baseline and stimulated thyroid hormone levels in the nonCH group were, however, consistent with controls; hence, no evidence of partial CH existed. Nonetheless, in clinical work, newly diagnosed CH patients may exhibit FT₄ levels in the low normal or subnormal range (7). This is explained by the small intra-individual variation, commonly ±25%, of thyroid hormone levels (4). Subsequently, a CH patient may have considerably reduced circulating thyroid hormone levels, but still exhibit FT₄ levels within the lower normal reference interval (5, 6).

The aims of this study were to investigate whether the rhTSH test was sufficient as a diagnostic device and to...
evaluate the response of the thyroid gland to rhTSH in CH patients. The decreased thyroid hormone response to rhTSH was most pronounced in the CH group. These results are, however, difficult to interpret because of previous levothyroxine replacement. Therefore, it is more appropriate to investigate newly diagnosed untreated CH patients. Although the response to 0.9 mg rhTSH in FT₄ and rT₃ was reduced in newCH patients, the test did not entirely discriminate patients with CH from controls. However, this shall be interpreted with caution as two peak data were missing on one control. The discriminative value may therefore be better than that observed in this study. In addition, under the circumstances of unreplaced growth hormone deficiency (GHD) FT₄ may be higher than under GH treatment because of a decreased peripheral deiodination of T₄ to T₃. NewCH patients with untreated GHD may therefore have higher FT₄ levels than they would have if GH treated. Therefore, the CH of the newCH patients may be more severe than what is illustrated from FT₄ levels. Nonetheless, the rhTSH test may identify patients with CH if rT₃ < 0.56 nmol/l or FT₄ < 20 pmol/l 48–72 h after 0.9 mg of rhTSH (exact figures assay specific). Moreover, no newCH patient had an increment of FT₄ > 14 pmol/l. Consequently, in patients with suspected CH, the rhTSH test may be used as an adjuvant diagnostic tool.

The low-dose rhTSH (0.1 mg) was not as sensitive as the 0.9 mg dose to detect CH, still, the experience from the ACTH stimulation test indicates that a low dose may be more useful in ACTH deficiency than in primary adrenal failure (33, 34). However, rhTSH stimulations in patients with nodular goiter demonstrated that a dose of 0.3 mg is as potent as 0.9 mg to increase the iodine uptake (35). Therefore, 0.3 mg rhTSH may be an option in CH to minimize the risk of cardiac side effects, even though the 0.9 mg dose was well tolerated in this study.

Before the availability of rhTSH, an increase in ¹³¹I thyroid uptake was observed after multiple repeated bTSH injections in patients with CH (22), demonstrating that a dormant gland could be activated. However, these studies were performed before the introduction of sensitive immunomethods to determine thyroid hormones and, therefore, no radioiodine uptake was performed in this study. However, patients with severe CH (CH group) produced higher thyroid hormones level after the second rhTSH injection, regardless of dose. This is most likely due to the activation of the thyroidal cellular system by TSH increasing the iodine content of the thyroid gland and thereby making it more responsive to the next stimuli (22).

Figure 2

Peak levels after 0.9 mg rhTSH in six patients with central hypothyroidism (CH), six patients with newly diagnosed CH (newCH), six patients with hypopituitarism but regarded TSH-sufficient (nonCH) and six healthy controls for FT₄ (A), FT₃ (B) and rT₃ (C). The broken line represents the normal range. a = P < 0.05, b = P < 0.01, c = P < 0.001 non-CH-, newCH- or CH-group vs controls. d = P < 0.01 CH- vs nonCH-group, e = P < 0.05 newCH- vs nonCH-group. f = P < 0.05 CH- vs newCH-group.
The rhTSH-induced Tg response in CH patients indicates that the diminished response in thyroid hormones was not due to unresponsiveness of the TSH receptor of thyroid follicular cells. As endocytosis and, consequently, the removal of Tg from the lumen are diminished, the net result is a gradual accumulation of poorly iodinated Tg (29). This low-iodinated Tg has a low hormone content; hence, a smaller amount of hormones are released from the thyroid after TSH stimulation. This is probably the main reason for the blunted thyroid hormone response to rhTSH found in the two patient groups with CH. Individuals within the CH group probably had a less iodinated Tg compared with newCH individuals, most of whom apparently had a partial stimulation of the thyroid with low, but detectable levels of thyroid hormones. Therefore, the sensitivity of this suggested diagnostic tool may be lower in mild cases of CH.

The normal Tg levels in CH contradicts, however, a reduction in the endocytosis of Tg. As the amount of Tg increases in the absence of TSH, the high concentration in the lumen may allow a large amount of Tg to be taken into the cell by endocytosis, in spite of the reduction in the volume of the endocytotic compartment. Moreover, although the major regulator of Tg synthesis is TSH (27, 28), insulin and IGF-I are able to stimulate Tg synthesis in the absence of TSH (30, 36). Insulin levels did not differ between groups and normal serum IGF-I levels were found in all groups except for the newCH group, where IGF-I levels were low, reflecting untreated GH deficiency. A reduction of basal Tg levels could, therefore, be suspected in the newCH group. Hence, in addition to accumulation of Tg in the lumen, some other factor, yet unknown, may contribute to the normal Tg production in TSH insufficiency.

In conclusion, patients with CH have an attenuated increase in serum FT4 and rT3 in response to 0.9 mg rhTSH compared with healthy controls. This observation may be useful in the diagnostic procedure of patients with suspected CH. However, further studies are needed to establish optimal dose and cut-off levels before implementation of the rhTSH test can occur in clinical practice.

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