Isolated Central Hypothyroidism in Short Stature

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ABSTRACT

Mild hypothyroidism can be difficult to diagnose, particularly when it is caused by deficiency of TSH or TSH-releasing hormone (TRH). Such central hypothyroidism occurs most often in association with growth hormone deficiency (GHD). Isolated central hypothyroidism has been considered rare. The TSH surge test is the most sensitive test currently available for confirming the diagnosis. Results are abnormal in many cases where response to TRH is normal. Short children referred between 1986 and 1994 for evaluation ($n = 235$, 74 girls; height 2 or more SD below mean for age; no history of radiation therapy) were selected for study. TSH samples were obtained hourly for study of TSH surge (1400–1800 h and 2200–0400 h). Growth hormone (GH) samples were obtained every 20 min (2000–0800 h). GH stimulation tests included arginine, insulin, and L-dopa. Thirty-nine children were found to have GHD (peak GH ≤ 7 $\mu\text{g/L}$) and 15 had mild primary hypothyroidism (TSH 5–15 mU/L). Of the remaining 181 children with apparent idiopathic short stature (ISS), 30 had a blunted TSH surge. All 30 had free thyroxine (FT_4) in the lowest third of the normal range, consis-

tent with values seen in documented central hypothyroidism. They were 13% of the total group, 16% of the ISS children, and 32% of the ISS children with FT_4 in the lowest third of normal. (In comparison, diagnosis of GHD was made in 16% of the total group.) In conclusion, use of a direct FT_4 assay to screen short children for possible subtle hypothyroidism (along with other appropriate testing) identifies a subgroup with a one in three possibility of an easily treated cause—isolated central hypothyroidism. (*Pediatr Res* 38: 967–973, 1995)

Abbreviations

TRH, TSH-releasing hormone
 T_4 , thyroxine
 FT_4 , free T_4
TSH-D, central hypothyroidism
GH, growth hormone
GHD, GH deficiency
ISS, idiopathic short stature group

The etiology of short stature in slowly growing children who are not GH deficient continues to be diagnostically challenging (1–4). Some clinicians have proposed that such children must have insufficient GH secretion (5–7) despite normal results on standard tests of stimulated or spontaneous GH (8–10) (Rose SR, unpublished data). Others have sought subtle hormonal or medical abnormalities as the cause of the short stature.

Mild hypothyroidism can cause slowed growth. In mild primary hypothyroidism, slightly elevated TSH concentrations serve to alert the clinician to the disorder. However, in mild TSH-D, caused by loss of normal hypothalamic-pituitary regulation of the circadian pattern of TSH secretion, morning TSH concentrations are most often normal. As a result, the diagnosis can be very difficult to confirm even when suspected. Most commonly, TSH-D is suspected in patients with an already identified hypothalamic-pituitary disorder (11–13). Iodothyronine levels in TSH-D are commonly only slightly below the

normal range, and TSH concentrations are commonly within the normal range. Some patients with iodothyronine levels in the lower part of the normal range and with normal TSH concentrations may also have TSH-D due to dysfunction of TSH secretion. Such values may be interpreted as normal. These patients may remain clinically puzzling and thus are often not treated with thyroid replacement medication. Failure to recognize and treat TSH-D can result in poor growth and less than optimal state of health (13, 14).

In normal infants, children, and adults, the circadian pattern of serum TSH concentration is characterized by declining values throughout the morning, nadir values in the afternoon, and an approximate doubling or surge in the evening with peak values in the early morning (15–20). In normal children and adults, nocturnal TSH concentrations typically rise 50–300% above the nadir value after early evening. In the TSH surge test, the circadian pattern of TSH secretion is sampled as a probe of the intactness of the hypothalamic-pituitary-thyroid axis (11, 16). The author has previously shown that in TSH-D the nocturnal TSH surge is blunted or absent, the nocturnal TSH surge is a sensitive (and specific) test for identification of TSH-D, whereas use of a TRH test is less sensitive than the TSH surge in children with multiple hormone deficiencies (11).

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It was hypothesized that some slowly growing children with no other identifiable cause of their short stature might have isolated TSH-D. This report describes the incidence of isolated TSH-D identified using the nocturnal TSH surge in children otherwise diagnosed with ISS.

METHODS

The study was approved by the Human Research Committee at each of the following institutions: the National Institute of Child Health and Human Development of the National Institutes of Health (National Institutes of Health), the University of New Mexico (UNM), and the University of Tennessee, Memphis (UT). The population from which children were identified for this study included all sequential admissions by the author between 1986 and 1994 for evaluation of height two or more SD below the mean for age. Two-thirds of the children were male ($n = 235$, ages 1–17 y, 74 girls), consistent with frequently found referral patterns in the United States. Causes for exclusion included intercurrent acute or chronic illness, glucocorticoid requirement, depression or other psychiatric diagnosis, rapid growth, history of radiation therapy for oncologic processes, Turner syndrome, and skeletal dysplasias. The subjects were admitted to the National Institutes of Health Clinical Center, the UNM General Clinical Research Center, or the UT General Clinical Research Center.

Procedures. Signed informed consent was obtained from one parent and assent from each child. Morning height was measured by stadiometer. Radiograph of the left hand and wrist was interpreted for bone maturation according to the standards of Greulich and Pyle. A standard pediatric diet was provided, and sleep period was monitored by nursing observation.

An i.v. catheter for blood drawing access was maintained with 0.5–1.0 mL of heparin (100 U/mL) after each blood draw. Blood samples were drawn hourly from 1400 until 1800 h (time of TSH nadir) and from 2200 until 0400 h (time of TSH peak) for TSH assay (Fig. 1). Simultaneous study of overnight GH concentrations (2000 until 0800 h, every 20 min of sampling for GH assay) was performed in 162 of the children. Subsequently, standard GH stimulation tests (arginine, insulin, and L-dopa; or arginine and L-dopa) were performed in all children after pretreatment with estradiol in peripubertal children (older than age 8 but not yet stage 3 of puberty) (8, 10). TRH test (protirelin 7 $\mu\text{g/kg}$ i.v., maximum dose, 500 μg) was performed in 145 of the children (11).

To evaluate the clinical utility of the TSH surge in predicting growth response to therapy with thyroid hormone, a pilot study was performed. Ten of the ISS children with FT_4 in the lowest third of the normal range, 22 of the ISS children with FT_4 in the upper two-thirds of the normal range, and 6 of the children with FT_4 in the lowest third of the normal range and blunted TSH surge participated in a treatment trial during 18 mo, with evaluation of basal growth velocity during the first and third 6-mo intervals. During the second 6-mo interval, patients took levothyroxine (Synthroid) daily in doses that achieved an increase in serum FT_4 concentration of 6.0 ± 1.0 pmol/L (mean $\pm$ SD), resulting in FT_4 concentrations during treatment that remained in the normal range. The Synthroid dose required

Figure 1. Assessment of the nocturnal TSH surge. The closed circles indicate the mean serum TSH and the shaded region represents ± 2 SE in 96 normal children. Arrows signify sampling times. The nadir TSH was the mean of the three consecutive lowest TSH values in the afternoon. The peak TSH was the mean of the three consecutive highest TSH values in the night. TSH surge (%) = $100 \times (\text{peak} - \text{nadir})/\text{nadir}$. [Adapted from Rose and Nisula (16).]

in these children to achieve treatment concentrations was 2.8 ± 0.4 $\mu\text{g/kg/d}$. Growth velocity data were used in analysis only from those children who remained prepubertal throughout the 18-mo period.

Assays. The specific methodology available for TSH assay was different at each study location; however, each assay was ultrasensitive and involved antibodies to three sites on the TSH molecule (Table 1). Because each patient's peak TSH value was analyzed relative to his or her own nadir TSH value, minor differences between assays were compensated for in interpre-

Table 1. FT_4 and TSH assay available at the study locations: National Institutes of Health (NIH), University of New Mexico (UNM), and University of Tennessee Memphis (UT)

Assay	Normal range	Method	Cut-off used to identify lower third of normal range
FT_4 (pmol/L) ^a			
NIH	13–26	Baxter-Travelol	≤ 17
UNM	10–32	Ciba-Corning	≤ 17
UT	9–24	Abbott	≤ 14
TSH (mU/L) ^b			
NIH	0.5–4.6	Ciba-Serono	
		Maiacalone TSH, IRMA	
UNM	0.6–4.6	Nichols Allegro	
		HS-TSH RIA	
UT	0.32–5.0	Abbott IMX US TSH	
		MEIA	

^a To convert FT_4 to SI units, $\text{ng/dL} \times 12.87 = \text{pmol/L}$.

^b To convert TSH to SI units, $\text{mcU/mL} \times 1.0 = \text{mU/L}$.

tation of results. FT₄ assay at each study site involved direct RIA of FT₄ rather than calculated or derived values (Table 1).

Serum GH was assayed by polyclonal RIA: National Institutes of Health and UNM samples at Hazleton Washington (Vienna, VA), and UT samples at Endocrine Sciences (Cala-basas Hills, CA). Samples for all spontaneous GH studies were assayed at Hazleton Washington.

Analysis. The short children were divided into four groups (Table 2): ISS included children with entirely normal GH and thyroid studies; the GHD group (peak stimulated GH of 7 µg/L or less); the high TSH group included children with mild primary hypothyroidism (TSH 5–15 mU/L); and the TSH-D group (blunted TSH surge).

Peak GH referred to the highest GH value observed during any stimulation test. Mean night GH referred to the mean of all 37 GH values obtained during the overnight GH study (21).

The nocturnal TSH surge was calculated by subtracting the TSH nadir (three sequential values in the afternoon yielding the lowest mean TSH) from the TSH peak (three sequential values at night yielding the highest mean TSH) and dividing the difference by the TSH nadir, expressing the result as percent rise over nadir (Fig. 1). Results were compared with 95% confidence limits of values observed in 96 normal children previously reported by the author (16). TSH surge results between 50 and 300% were considered normal.

The TRH test was evaluated according to magnitude of TSH peak (amount of rise above baseline TSH level), time of TSH peak (minutes after TRH was given), and response curve decline (percent of magnitude of TSH peak remaining at 60 min after time of TSH peak). Results were compared with 95% confidence limits of values observed by the author in 76 normal children (11).

Analysis of variance with the Bonferroni adjustment for multiple comparisons was used to evaluate possible statistical differences among groups. Repeated measures analysis of variance was used in evaluating changes in growth velocity in the treatment trial.

RESULTS

During the 9-y period of study, the author diagnosed in this population 39 children with GHD (GH peak ≤ 7 ng/dL) and 15 children with mild primary hypothyroidism (TSH at 0900 h,

5–15 mU/L) not previously apparent as an outpatient. The remaining 181 children met generally accepted criteria for the diagnosis of ISS.

However, 30 of the 181 children (four girls, 13%) were found to have a low TSH surge, whereas 151 children (51 girls, 33%) had a normal TSH surge (Table 3). All 30 children with a blunted TSH surge had FT₄ in the lower third of the normal range. Thus, use of a FT₄ cutoff value dividing the lower third from the rest of the normal range (to identify a subgroup of short children in whom the TSH surge should be performed) would have identified 100% of these children with isolated TSH-D (Fig. 2).

The children with TSH-D were 13% of the total group of referred short children but were 32% of the 92 children with apparent ISS who had FT₄ in the lowest third of the normal range. By comparison, GHD was concurrently diagnosed in 16% of the total group of referred short children. Of 39 children diagnosed with GHD, 7 (18%) were identified as also having TSH-D, a commonly associated deficiency. The incidence of children with TSH-D was similar at each of the study locations, suggesting no regional differences in distribution of diagnoses. Bone age was significantly delayed in GHD (2.1 y) and 1.9 y delayed in TSH-D, whereas delay was less in the other groups (1.2 y in high TSH, 1.5 y in ISS) (Table 2).

TSH response to TRH did not differ significantly among groups, with the exception of high TSH in which an exaggerated magnitude of TSH peak response to TRH was seen (Table 3). In TSH-D, only 2 of the 22 patients who had the TRH test performed had delayed time of TSH peak and also delayed response curve decline. No patient had a subnormal magnitude of TSH peak (Fig. 3). Thus, TRH testing would have failed to confirm the diagnosis in 91% of the TSH-D patients.

The peak stimulated GH and mean night GH results in GHD were significantly lower than in ISS (both $p < 0.01$). However, GH results in TSH-D or high TSH were not different from GH results in ISS (Table 2). Both hypothyroid groups had mean FT₄ values which were significantly lower than mean FT₄ in the ISS group, but which remained within the low part of the normal range. These observations suggest that mild hypothyroidism of the degree observed in these two groups does not in itself significantly alter the clinician's ability to accurately and simultaneously assess GH status (Fig. 4).

Table 2. Clinical characteristics of the 235 children with short stature: ISS, GHD, mild primary hypothyroidism (high TSH), and isolated TSH-D

Group	n	Female gender n (% of group)	CA (y)	BA (y)	T ₄ (nmol/L)	FT ₄ (pmol/L)	TSH (mU/L)	Stim GH (µg/L)	mNGH (µg/L)
ISS	151	51 (34)	11.0 ± 3.1	9.5 ± 3.2	102 ± 19	18 ± 4	2.5 ± 1.1	19.4 ± 4.8	4.1 ± 2.7
GHD	39	11 (28)	9.1 ± 4.0	7.0 ± 3.7*	103 ± 23	18 ± 4	2.8 ± 1.4	4.8 ± 1.9*	2.2 ± 1.8*
High TSH	15	8 (53)	12.0 ± 4.1	10.8 ± 3.7	95 ± 23	15 ± 3*	7.3 ± 2.9*	17.2 ± 6.1	3.1 ± 2.2
TSH-D	30	4 (13)	9.1 ± 4.5	7.2 ± 4.1	84 ± 22*	15 ± 3*	2.4 ± 1.2	18.3 ± 12.6	4.3 ± 3.2
Normal subjects	96†		11.4 ± 2.0		100 ± 30 (64–154)	18 ± 5 (13–26)	2.4 ± 1.5 (1.0–4.8)		4.0 ± 3.0 (ref. 21)

CA, chronologic age; BA, bone age; Stim GH, highest GH concentration after GH stimulation test; mNGH, mean of all GH values during 12-h overnight sampling every 20 min. Values are mean ± SD.

* $p < 0.01$ compared to result in ISS group.

† Data from Rose and Nisula (16).

‡ Data from Marin *et al.* (10).

Table 3. TSH surge and TRH test results in ISS, GHD, mild primary hypothyroidism (high TSH), and TSH-D

Group	TSH surge		Magnitude of TSH Peak after TRH	
	%	n	TSH (mU/L)	n
ISS	144 ± 76	151	18.8 ± 7.5	91
GHD	106 ± 68	39	18.9 ± 7.9	21
High TSH	124 ± 47	15	40.3 ± 8.9*	11
TSH-D	33 ± 15*	30	19.3 ± 10.6	22
Normal subjects	144 ± 70 (50–300)†	96	16.0 ± 11 (9–42)‡	76

Values are mean ± SD (95% confidence limits of normal values).

* $p < 0.01$ compared to result in ISS group.

† Data from Rose and Nisula (16).

‡ Data from Rose *et al.* (11).

Figure 2. Nocturnal TSH surge in two groups of children with apparent ISS: those with FT₄ in the upper two-thirds of the normal range, and those with FT₄ in the lowest third of the normal range. Each dot represents the TSH surge result in one child. The two vertical lines at 50% and 300% define the upper and lower 95% confidence limits of normal children reported previously (16).

Levothyroxine treatment during 6 mo resulted in no significant change in growth velocity in either group of ISS children. However, a significant increase in growth velocity was observed in TSH-D during levothyroxine therapy compared with both baseline growth velocity and follow-up growth velocity ($p = 0.03$ and 0.01 , respectively) (Fig. 5). Increase in growth velocity in TSH-D was comparable to that observed in children with primary hypothyroidism when treated. Change in bone age during 6 mo of levothyroxine treatment was not significantly different between groups (0.7 ± 0.2 -y change in TSH-D versus 0.6 ± 0.1 y in ISS, mean ± SEM).

DISCUSSION

In this study of children referred for evaluation of height shorter than 2 SD below the mean for age, a significant incidence of isolated TSH-D was found (13%). This was four-fifths of the incidence of classic GHD identified by the author during the same time period. This surprisingly high incidence was a product of using a new diagnostic test, the TSH surge, which has been shown to have increased sensitivity compared with the TRH test in the diagnosis of TSH-D (11). It was possible to use FT₄ as a screening test to identify those children most at risk for this disorder. Isolated TSH-D was

Figure 3. Magnitude of TSH peak response to TRH in normal children (11), ISS children, children with mild primary hypothyroidism (*High TSH*), and children with isolated TSH-D. Bars show mean ± SE. The asterisk (*) signifies $p < 0.01$ compared with ISS. **Figure 4.** Peak stimulated GH in relation to FT₄ in three groups of children: ISS children, children with mild primary hypothyroidism (*High TSH*), and children with isolated TSH-D.

identified in 32% of those short children with FT₄ in the lowest third of the normal range.

In contrast, only 9% of the children with isolated TSH-D would have been identified using a TRH test. This observation

Figure 5. Growth velocity shown in SD units from the mean for age (SD) at baseline, during a 6-mo period of therapy with levothyroxine, and during a subsequent 6-mo period of follow-up while receiving no therapy, in three groups of children: ISS with FT₄ in the upper two-thirds of the normal range (ISS, Higher FT₄), ISS with FT₄ in the lowest third of the normal range (ISS, Lower FT₄), and isolated TSH-D. Bars show mean $\pm$ SE. The asterisk (*) signifies $p < 0.05$ compared with baseline growth velocity.

is consistent with the finding by the author and others that, although i.v. TRH has been the most frequent test used to confirm TSH-D, 50–85% of patients with TSH-D have demonstrated a TSH response to TRH which was normal in both amplitude and timing (11, 13, 22). Thus, there is a significant overlap between the normal pattern of TSH response to TRH and that seen in hypothalamic disorders of TSH release. In a patient with TSH-D, the TSH response to TRH may be abnormal and confirm the disorder or may resemble the response to TRH seen in primary hypothyroidism, but is even more likely to be normal and miss the diagnosis (11, 13, 22, 54).

Children with TSH-D given levothyroxine therapy for 6 mo had a significant increase in growth velocity, whereas ISS children given similar doses for 6 mo did not significantly increase their growth velocity. Growth velocity in hypothyroidism has been described to be sensitive to small changes in thyroid hormone concentration in the absence of other symptoms of hypothyroidism (23). The results of the pilot treatment study suggest that short children with blunted TSH surge and slow growth velocity will probably benefit from thyroid hormone therapy.

The mild degree of hypothyroidism observed in these children with either TSH-D or mild primary hypothyroidism did not result in "low" GH responses to stimulation tests or in low overnight GH measures. This suggests that GH evaluation can be accurately performed simultaneously with TSH evaluation in children with FT₄ in the lower third of the normal range.

At a practical level it is difficult to cause a false positive blunting of the TSH surge. Artifactual blunting of the TSH surge can occur after fasting (24) (Rose SR, unpublished observation); however, this was not the cause in the current study where the testing conditions included a standard age-appropriate diet with monitored intake. Delayed time of falling asleep or altered quality of sleep in the hospital will not cause

a blunted TSH surge. In fact, poor sleep or delayed sleep latency result in augmentation of the rise in TSH at night (25). For these reasons, blunting of the TSH surge is rare in the test setting and commonly correlates with true clinical abnormality rather than artifact.

Transient or permanent alteration of the TSH surge has been described in hypercortisolemia (26), critical illness (27–30), postoperative recovery (31), hyperglycemia (32), chronic renal failure (33, 34), depression (35–38), and aging (39). None of these was present in the children studied in this project. Mild primary hypothyroidism does not significantly alter the TSH surge (11, 40).

TSH-D can be observed in association with any etiology of hypothalamic-pituitary disorder (11, 13, 17, 41). It is present as a second deficiency in approximately 10–25% of children with idiopathic GHD and in 25–50% of children with organic causes of hypopituitarism (11–14). However, isolated TSH-D is thought to be rare and reportable. The case reports in the literature tend to be of patients with low serum TSH and no response to TRH. Congenital hypothyroidism with low TSH concentrations due to abnormality of the β subunit of the TSH molecule has been described in several Japanese and Greek families (42–45). A dozen other individuals with isolated TSH deficiency (low TSH levels and failure to respond to TRH) have been reported (46–51). There are only two case reports of isolated TRH deficiency, one after meningitis, and one proposed to be secondary to hypophysitis (52, 53). In contrast, the abnormalities in circadian pattern of TSH concentrations reported in the current study are less easily recognized without specialized testing such as the TSH surge. However, testing of the TSH surge has only recently been used in diagnosis. It is probable that, to date, testing methods have been inadequately sensitive to identify this condition without the presence of strong clinical suspicion.

The mechanism by which isolated TSH-D occurs could include limitation of hypothalamic TRH secretion, alteration of neuroendocrine signals mediating the circadian clock, or alteration of the structure of the TSH molecule (13, 14, 51). The abnormality could be congenital or could result from subtle birth injury, infection, mild head injury, or other acquired cause.

Subtle or subclinical primary hypothyroidism ("low-normal" thyroid function tests with an elevated TSH) is a commonly recognized clinical condition. In the setting of TSH-D (low-normal thyroid function tests with TSH in the normal range), the diagnosis is usually not made because the patient is unable to elevate TSH concentrations. Thus, TSH-D is a subtle abnormality which is often missed in clinical and laboratory diagnosis of the etiology of short stature. Loss of the nocturnal serum TSH rise represents impairment of TSH secretion which is not revealed by baseline morning measures of TSH or evaluation of the TSH response to TRH. The absence of rise in TSH secretion at night (approximately 30% of the total daily TSH secretion) is associated with a proportionate decrease both in stimulation of the thyroid gland and in total iodothyronine production. This decrease, although subtle, may be enough to account for slowed growth in some children otherwise thought to have ISS. Subtle hypothyroidism can also

result in delay of maturation, perhaps contributing in an occasional child to a clinical picture similar to that seen in constitutional delay of puberty.

In short children where the cause of slow growth may otherwise be obscure, FT_4 can be used to screen for those short children most likely to have this abnormality. The fact that FT_4 can be used as a screening test for those at risk permits important cost-efficacy. TSH surge testing is indicated only in those short children (2 or more SD below the mean for age) whose growth velocity is slow and whose FT_4 value is in the lowest third of the normal range. Thus, use of this test can be targeted or reserved using FT_4 as a screening test.

In children with short stature (-2 SD), slow growth velocity with or without evidence of pubertal delay, and a FT_4 in the lower third of normal, the next diagnostic step should be a TSH surge study with GH stimulation tests. Such children have a one in three chance of subtle TSH-D. This is a significant incidence of a diagnosable and treatable cause of short stature.

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