


# Severe Prolonged Hypothyroidism: Clinical, Anatomical, Physiological, and Metabolic Features

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## Abstract

**Background.** Hashimoto's thyroiditis usually presents with nonspecific systemic symptoms. The purpose of our study was to characterize the various properties of severe ongoing hypothyroidism and the rate of normalization following treatment. **Methods.** An adolescent girl with severe primary hypothyroidism was studied. Clinical evaluation, laboratory testing, brain magnetic resonance imaging, resting metabolic rate (RMR) testing, electroencephalogram, and visual field examination were performed at baseline and following treatment with levothyroxine. **Results.** At baseline, a significant psychomotor retardation was observed, serum thyroid-stimulating hormone concentration was 1088.4 mIU/mL. Magnetic resonance imaging showed a large intrasellar mass. Electroencephalogram was abnormal, and RMR was significantly reduced. Restoration of neurocognitive function and normalization of RMR, electroencephalogram, and laboratory tests occurred rapidly, alongside vanishing of the pituitary mass within 4 weeks of treatment. **Conclusions.** The various signs and symptoms of severe prolonged hypothyroidism may resolve rapidly with treatment, including the disappearance of a large pituitary mass.

## Keywords

endocrinology, general pediatrics, adolescent medicine, neurology, radiology

## Introduction

Hashimoto's thyroiditis is the most common endocrinopathy in children. It occurs as a result of autoimmunity and development of anti-thyroid antibodies. The clinical presentation is usually benign and includes nonspecific systemic symptoms such as weight gain, constipation, difficulty to concentrate, stunting of growth, cold intolerance, and low energy. Rarely may it be complicated by pituitary hyperplasia leading to a variety of manifestations such as hyperprolactinemia, hypogonadotropic hypogonadism, growth hormone deficiency, and menorrhagia.<sup>1–6</sup>

Pituitary enlargement may be due to a primary secreting tumor (macroadenoma) or to secondary hyperplasia.<sup>1</sup> The latter may be due to primary hypothyroidism and the lack of inhibitory feedback by free thyroxine (fT4). Several cases of pituitary hyperplasia in the presence of primary hypothyroidism have been previously described.<sup>3–6</sup> Despite the presence of a large brain lesion in some of the cases, most patients, particularly children, lack symptoms that may be attributed to the lesion (eg, headaches, vomiting, or neurological

symptoms). Usually, complaints are related to the hypothyroid state, unless pressure on the optic chiasm is present. Hence, pituitary enlargement might progress unnoticed in the pediatric age group.

Given the importance of timely identification of such pituitary masses in children, and their treatment options, more information is needed. The purpose of this study was to thoroughly characterize the clinical, anatomical, and biochemical properties of severe ongoing hypothyroidism with a large pituitary mass and the rate of normalization of the different parameters following treatment.

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## Methods

An adolescent girl who was admitted for evaluation of a large pituitary mass, diagnosed with severe primary hypothyroidism, and treated with levothyroxine, was comprehensively studied.

### Laboratory Measurements

Thyroid function tests were performed using a 2-site immunoenzymatic ("sandwich") assay. Prolactin, insulin-like growth factor-1 (IGF-1), anti-thyroglobulin, and anti-thyroid peroxidase (anti-TPO) antibody levels were measured using chemiluminescence immunoassay.

### Imaging Studies

Brain anatomy was determined using a T1, T2 FLAIR, diffusion-weighted imaging series magnetic resonance imaging (MRI) with and without gadolinium contrast. The MRI was performed at baseline and 4 weeks following the start of levothyroxine. Neck ultrasound was used to determine thyroid anatomy, echogenicity, and the presence of nodules.

### Metabolic Studies

Resting metabolic rate (RMR) was measured at baseline and 2 and 4 weeks following start of treatment with levothyroxine, using a face mask connected to a metabolic cart (ZAN ErgoSpiro 680, nSpire Health, Inc, Longmont, CO) for breath-by-breath respiratory gas exchange measurements. Measurements were performed after an overnight fast, while lying recumbent, for 20 minutes; the mean RMR of the final 10 minutes was used.<sup>7</sup> RMR was expressed as both absolute values, in kcal/day, and as percentage of predicted values by age, sex, and anthropometric data by several relevant prediction formulas for sex, age, and body size.<sup>8</sup>

### Electrophysiologic Studies

Electroencephalogram (EEG) at baseline and following 4 weeks of treatment was performed. Visual fields were assessed at baseline and following 4 weeks of treatment.

## Results

### Clinical Presentation

The patient studied was a 13-year-old girl referred for evaluation of an intrasellar mass. The patient was known

to have a minor developmental delay with an unknown etiology, which had significantly worsened over the previous 2 years. She had stopped talking except for single words, and she developed generalized tremor and instability with the need for assistance while walking. A head computed tomography scan was performed in an ambulatory setting and revealed a pituitary mass, after which she was referred to our institution for evaluation. On presentation, the patient denied any thyroid-related symptoms, including fatigue, cold intolerance, and constipation. There was no family history of thyroid dysfunction, autoimmunity, or brain tumors. On physical examination she was in general good condition. Her height was 142.5 cm (−2.3 standard deviation [SD]), her weight was 30 kg (−2.8 SD), and her body mass index was 14.8 kg/m<sup>2</sup> (−2.1 SD). Her blood pressure was 108/75 mm Hg, and she was bradycardic with 50 beats per minute at rest. She was in early puberty, Tanner stage 2 for breast development and Tanner 1 for pubic hair. Her skin was dry. Thyroid gland examination revealed a nontender gland of normal size with no nodules. Neurological examination showed nonspecific findings of slurred speech, a general psychomotor retardation, instability when walking, and pendular reflexes. Visual fields examination was normal in both eyes, but examination was consistent with general suppression.

### Biochemical Evaluation

Thyroid function tests were consistent with severe hypothyroidism (Table 1): serum thyroid-stimulating hormone (TSH) concentration was 1088.4 mIU/mL (normal range = 0.4–4 mIU/mL), with serum fT4 concentration <3.2 mIU/mL (7–16 mIU/mL). Prolactin levels were elevated to 142 µg/L (0–20 µg/L). IGF-1 levels were low at 17.3 nmol/L (24–126 nmol/L). Cortisol level was normal (440 nmol/L; range = 138–690 nmol/L). Luteinizing hormone (LH) concentration was 1.6 IU/L, and follicle-stimulating hormone (FSH) concentration was 6.5 IU/L, consistent with early puberty. Anti-TPO titer was elevated to 430 U/mL (0–35 U/mL). Anti-thyroglobulin antibodies were not elevated, <20 U/mL (0–40 U/mL).

### Imaging Evaluation

Thyroid ultrasound examination showed a nonenlarged thyroid gland with an inhomogeneous echogenicity and increased blood flow, suggestive of Hashimoto thyroiditis. A cranial MRI revealed a large, 18 mm × 21 mm, intrasellar pituitary mass with signs of pressure on the chiasm (Figure 1). Appearance was consistent with macroadenoma or hyperplasia. Optic nerve ultrasound was normal.

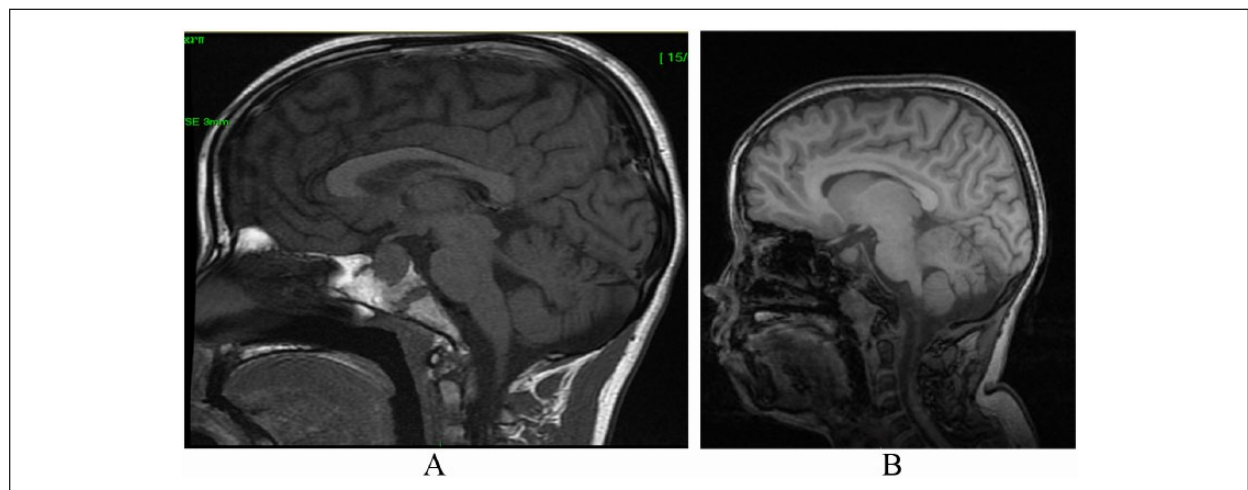
**Table 1.** Clinical and Laboratory Data at Baseline and Following Treatment.

	At Diagnosis	2 Weeks	4 Weeks <sup>a</sup>	6 Weeks	6 Months
Height (cm)	142.5	144	NA	145	147.1
Height SD	-2.3	NA	NA	-2	-1.9
Weight (kg)	30	33	NA	33.4	32.5
Weight SD	-2.8	NA	NA	-2.1	-2.6
BMI	14.8	NA	NA	15.9	15
BMI SD	-2.1	NA	NA	-1.4	-2.1
Fat mass (kg)	6.7			7.4	
Fat-free mass (kg)	24			26.1	
TSH, mIU/L (0.4-4) <sup>b</sup>	1088	455	19.4	9.8	1.49
Free T4, pmol/L (7-16) <sup>b</sup>	<3.2	6.9	12.9	12.2	13.5
Prolactin, µg/L (0-20) <sup>b</sup>	142	168	38	16.6	NA
IGF-I, nmol/L (24-126) <sup>b</sup>	4.8	13	13	17.3	NA
RMR (kcal/day)	706	842	NA	1093	NA

Abbreviations: BMI, body mass index; SD, standard deviation; TSH, thyroid-stimulating hormone; IGF-I, insulin-like growth factor-I; RMR, resting metabolic rate.

<sup>a</sup>Laboratory studies performed by the patient's primary care clinic.

<sup>b</sup>Values in parentheses are normal ranges.

**Figure 1.** Large 18 × 21 mm pituitary mass (A) at diagnosis and vanishing of the mass following 4 weeks of treatment (B).

### Physiologic Evaluation

EEG at baseline showed general brain wave deceleration. RMR results are presented in Table 1. The predicted values according to sex, age, height, and weight alone ranged from 1125 to 1136 kcal/day, according to 3 relevant available prediction formulas. When formulas that include body composition were used, the predicted values ranged from 873 to 991 kcal/day. Therefore, baseline RMR values were decreased from expected values by 37% when formulas using only height and weight were used and by 19% to 29% if body composition was taken into account.<sup>8</sup>

### Treatment Phase

Treatment with increasing doses of levothyroxine up to a final dose of 100 µg per day was started. The normalization of thyroid function tests, prolactin, and IGF-1 was rapid (Table 1). Clinically, 4 weeks after her initial diagnosis and treatment initiation, a significant improvement was seen in her physical findings. A general psychomotor improvement was noted: her gait became steady, and she started talking and completed sentences, which she was unable to do for over 2 years. A significant improvement in height SD occurred with treatment (Table 1). Laboratory tests showed a

significant drop of TSH levels and normalization of prolactin levels (Table 1).

A follow-up EEG test was performed at 4 weeks, with restoration of normal brain wave activity. Repeated RMR testing was carried out following 2 and 6 weeks of treatment, showing significant gradual improvement (Table 1). The final RMR value was 93% to 95% from expected RMR values by formulas using only height and weight and 104% to 121% of expected values when body composition was taken into account.

Finally, a follow-up MRI was performed, showing a pituitary gland and stalk of normal size and shape, with complete regression of the large intrasellar mass seen 4 weeks earlier (Figure 1).

## Discussion

Severe long-standing hypothyroidism is not uncommon, but little is known on the physiological, neurological, and anatomical findings at presentation and on the rate of response to treatment. In this single-patient study, we detailed the clinical presentation of this severe disorder that was undiagnosed for a prolonged period of time and the rate of response to treatment. The prolonged nature of this child's condition and its severity made it possible to appreciate the devastating neurological effects of severe long-standing hypothyroidism in a child and the rapid rate of normalization with treatment. This rapid response within 4 weeks, both in gross motor and speech, has not been previously reported to the best of our knowledge.

The initial size of the pituitary, in combination with extremely high levels of TSH and elevation of prolactin, could have been mistaken for a primary pituitary macroadenoma. The low circulating fT4 concentrations and positive anti-TPO antibodies made this diagnosis unlikely. Despite the extremely high TSH concentrations the thyroid gland was not enlarged, a finding probably attributed to the prolonged nature of the condition in our patient, leading to "burnout" of the gland eventually. The abnormal prolactin level was secondary to stalk compression and therefore normalized with shrinking of the pituitary. Surprisingly, despite all the aforementioned clinical findings in our patient at presentation, puberty, which is frequently delayed in children with hypothyroidism, had spontaneously started.<sup>9</sup>

We were able to show that not only the thyroid function and pituitary size normalized very rapidly in response to treatment, but neurological function, EEG findings, and RMR also normalized within the first month of treatment—despite the long duration of hypothyroid state. We attribute the increase in RMR to both the improvement in thyroid state and body composition. Minor variations in thyroid state had been previously associated with significant changes in RMR,<sup>10</sup> whereas

the relationship between lean body mass and RMR is well known, albeit still incompletely understood.<sup>11</sup>

We identified previous reports that described pituitary hyperplasia secondary to hypothyroidism, which was treated with levothyroxine, with repeat MRI tests showing normalization of pituitary size within 3 to 10 months following treatment initiation.<sup>3-6</sup> In our patient, we were able to show normalization of pituitary gland size within a much shorter period of 4 weeks. Moreover, the initial TSH level at diagnosis in previous reports ranged from 150 to 500 mIU/L. Our patient had much higher TSH levels of 1088 mIU/L, suggesting a very long course of undiagnosed disease.

## Conclusion

In this study, we demonstrated the various clinical, anatomical, physiological, and biochemical properties of severe prolonged hypothyroidism and the rapid change of these properties in response to treatment. Despite the severe and prolonged clinical picture at presentation, resolution was very rapid with restoration of all functions. This study offers insight into the pathophysiology of severe pediatric hypothyroidism and the need to defer surgical intervention in similar cases, even in the face of a large pituitary mass, until conservative measures have been exhausted.

## Author Contributions

YY took part in study design, data acquisition and interpretation and writing of the manuscript. SF took part in data acquisition and writing of the manuscript. RS took part in study design, data interpretation and reviewing of the manuscript. GD-R took part in study design, data acquisition and interpretation and writing of the manuscript.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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