

# HASHITOXICOSIS IN CHILDREN: CLINICAL FEATURES AND NATURAL HISTORY

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**Objective** To determine the incidence, natural history, and clinical characteristics of Hashitoxicosis (Htx) in pediatric patients with autoimmune thyroiditis.

**Study design** Medical records of children diagnosed with Hashimoto thyroiditis between 1993 and 2002 were reviewed. The clinical course of patients presenting with hyperthyroidism was determined. Variables including sex, age, family history, thyroid hormone levels, anti-thyroid antibody titers,  $^{123}\text{I}$  thyroid scan results, and presenting features were investigated as possible predisposing factors for the development of Htx.

**Results** Out of 69 patients with autoimmune thyroiditis, 8 were diagnosed with Htx. The duration of hyperthyroidism ranged from 31 to 168 days. Three patients became hypothyroid after an average of  $46.3 \pm 13.2$  days, and 5 patients became euthyroid after an average of  $112.8 \pm 59.8$  days. Additional findings included an elevated thyroid stimulating immunoglobulin (TSI) titer in 3 of the 8 patients with Htx, and increased uptake on  $^{123}\text{I}$  scan in 2 patients.

**Conclusion** Htx is an uncommon yet important cause of hyperthyroidism in children that has a variable clinical course. The diagnosis may be complicated, as presenting features sometimes exhibit significant overlap with Graves' disease. No factors predisposing to the development of Htx were identified. (*J Pediatr* 2005;146:533-6)

**H**ashimoto thyroiditis, also called chronic lymphocytic thyroiditis, is the most common cause of acquired hypothyroidism in children and adolescents.<sup>1,2</sup> Hypothyroidism is diagnosed by the presence of an elevated thyrotropin level in association with an elevated anti-thyroglobulin antibody titer, anti-microsomal antibody titer, or both. No specific mode of inheritance for Hashimoto thyroiditis has been identified, although there is strong evidence for genetic susceptibility to autoimmune thyroiditis. This includes associations with specific human leukocyte antigen alleles and certain alleles of the gene for cytotoxic T lymphocyte-associated protein 4.<sup>3-8</sup> Children with Hashimoto thyroiditis may present with a euthyroid goiter, subclinical hypothyroidism, profound hypothyroidism with growth retardation and delayed bone age, and, rarely, hyperthyroidism.<sup>9</sup>

Hashitoxicosis (Htx) refers to the presence of biochemical hyperthyroidism in patients with autoimmune thyroiditis.<sup>10</sup> It is believed to result from unregulated release of stored thyroid hormone during inflammatory-mediated destruction of the thyroid gland.<sup>10</sup> The incidence and typical clinical course of Htx in pediatric patients has not been well characterized. In addition, it is unknown whether features of the disease differ in patients with thyroiditis who develop hyperthyroidism compared with those who do not, which could be of predictive value. This study investigated Htx in a large cohort of children with Hashimoto thyroiditis.

## METHODS

Following institutional review board approval, medical records of patients followed for Hashimoto thyroiditis in the pediatric endocrine clinic at Riley Hospital for Children between July 1993 and August 2002 were reviewed. Hashimoto thyroiditis was diagnosed by a pediatric endocrinologist on the basis of anti-thyroid antibodies. Patients with Hashimoto thyroiditis who presented with biochemical hyperthyroidism that subsequently spontaneously resolved were considered to have had Htx. Hyperthyroidism was defined as a suppressed thyrotropin level in association with elevated or normal thyroid hormone levels. Variables examined included sex, age, family history, anti-thyroid antibody titers, thyroid scan results, and presenting features. The clinical course in patients diagnosed with Htx was determined through follow-up visits and serial measurements of thyroid hormone levels.

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Htx	Hashitoxicosis	TSI	Thyroid stimulating immunoglobulin
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**Table I. Summary of patient characteristics**

<b>Age (y)</b>	10.9 ± 3.1
<b>Gender</b>	Girls: 63 (91%); boys: 6 (9%)
<b>Family history</b>	Positive: 40 (58%); negative: 29 (42%)
<b>Goiter</b>	Present: 51 (74%); absent: 18 (26%)
<b>Anti-thyroid antibodies</b>	AMA: 559.3 ± 1019 (range, 1-5650); ATA: 142.6 ± 379 (range, 0-2174)
<b>Thyroid function</b>	Hypothyroidism: 49 (71%); euthyroidism: 12 (17.4%); hyperthyroidism: 8 (11.5%)

Normal ranges: Anti-thyroglobulin antibody (ATA): <2 U/mL;  
anti-microsomal antibody (AMA): <2 U/mL.

### Statistical Analysis

Statistics were done using Microsoft Excel 2000 (Microsoft Corp., Redmond, Wash) (for descriptive statistics) and Statistical Package of the Social Sciences, version 11.5 (SPSS Inc., Chicago, Ill) (for other analyses). Data are expressed as means ± standard deviations. Fisher's exact test (for categorical variables) and *t* tests (for continuous variables) were used for comparisons between groups when the data were normally distributed. The Mann-Whitney *U* test was used for data that were not normally distributed.

## RESULTS

Of 104 patients identified, 69 were included (6 boys; 63 girls). Of the 35 patients excluded, 25 had other forms of acquired hypothyroidism and 10 had congenital hypothyroidism. The patients included in the study had an average age of 10.9 ± 3.1 years (range, 1.3-17.3 years). A goiter was noted in 51 patients (74%). Forty subjects (58%) had a known family history of thyroid disease. All patients had an elevated anti-thyroglobulin antibody titer, anti-microsomal antibody titer, or both. The average anti-thyroglobulin antibody titer was 142.6 ± 379 U/mL (normal, <2 U/mL; range, 0-2174), and the average anti-microsomal antibody titer was 559.3 U/mL ± 1019 (normal, <2 U/mL; range, 1-5650 U/mL). Of the 69 patients, 49 (71%) had hypothyroidism at presentation and were started on levothyroxine. Twelve children (17.4%) were euthyroid at presentation, 10 of whom subsequently became hypothyroid. Eight patients (11.6%) were initially hyperthyroid, and were eventually diagnosed with Htx. These results are summarized in Table I.

Details of the patients with Htx are provided in Table II. No difference was seen in the average anti-thyroid antibody titers in patients with Htx compared with those who were hypothyroid or euthyroid at presentation. Similarly, no statistically significant correlations were identified between patient characteristics and the presence of hyperthyroidism. Thyroid stimulating immunoglobulin (TSI) titer was measured in 7 patients with Htx, and it was found to be elevated in 3. One had a TSI of 137% (normal, <130%) in association with an elevated thyrotropin of 7.5 uIU/mL, whereas another had a TSI titer of 137% in association with a suppressed thyrotropin of <0.01 uIU/mL but a low uptake on <sup>123</sup>I scan

(1%). This patient later became hypothyroid 54 days after the diagnosis of Htx. The third patient had a TSI of 187% concurrent with normalization of his thyropropin of 0.915 uIU/mL. <sup>123</sup>I thyroid uptake scan was obtained in 4 patients. Of these, 2 patients had increased uptakes of 61% and 53% (normal, 10%-35%), respectively, although thyroid function tests performed on the same day as the scans were entirely normal. In the other 2 patients, low uptakes of 1% in one patient while hyperthyroid and 12% in the other patient while euthyroid were noted. No patient had both an elevated TSI titer and increased uptake on <sup>123</sup>I scan. Three patients had classic symptoms of hyperthyroidism including tremor, tongue fasciculations, and palpitations.

Two children required pharmacological treatment for hyperthyroidism. One patient received beta blocker therapy and 1 month later became hypothyroid, whereas another was treated with methimazole for 3 months, after which the decision was made to stop the medicine. This patient became euthyroid 1 month after stopping methimazole, and has remained so after 28 months. One subject was referred to Ophthalmology for possible proptosis, which was ruled out by exophthalmometry. Because of persistence of eye pain magnetic resonance imaging was ordered to evaluate the ocular muscles. The findings were normal.

The duration of hyperthyroidism in subjects with Htx ranged from 31 to 168 days after diagnosis. Three patients became hypothyroid after an average of 46 ± 13 days, and 5 patients became euthyroid after an average of 112.8 ± 59 days. These 5 subjects have subsequently remained euthyroid with a follow-up of 3 to 32.5 months, as shown in the Figure.

## DISCUSSION

Graves' disease is the most common cause of hyperthyroidism in children, adolescents, and adults.<sup>11-13</sup> In addition to Graves' disease, the differential diagnosis of hyperthyroidism during childhood includes Htx, toxic adenoma, multinodular goiter, exogenous ingestion of thyroid hormone, McCune-Albright syndrome, struma ovarii, and subacute thyroiditis.<sup>11</sup> It is essential that the correct cause be identified because the prognosis and appropriate therapy depend upon the underlying mechanism of hyperthyroidism.

Htx is a rare complication of autoimmune thyroiditis.<sup>10</sup> Although it has long been recognized that some features may be shared between different types of autoimmune thyroid disease (such as positive anti-thyroid antibodies),<sup>14-15</sup> differentiating between Graves' disease and Hashimoto thyroiditis is usually straightforward. The finding of an elevated TSI titer is typically considered supportive evidence of Graves' disease, as it is increased in the vast majority of children with this disorder.<sup>16</sup> An additional test used to differentiate Htx from Graves' is the <sup>123</sup>I uptake scan, with a low to normal uptake suggesting Htx and a high uptake favoring Graves' disease.<sup>11,17</sup>

In our study, 8 of 69 patients with Hashimoto thyroiditis (11.5%) initially presented with hyperthyroidism. Although a presumptive diagnosis of Htx was made, this was confirmed by spontaneous resolution of the hyperthyroidism

**Table II. Characteristics of patients with Htx**

Patient No.	Sex	Age at dx of Htx (y)	Total T4	Free T4	Thyrotropin	Total T3	<sup>123</sup> I scan	TSI titer (% activity)	Treatment for hyperthyroidism
1	F	14	11.7	2.14	0.06	167	24hr-61%*	127	None
2	F	10	15	ND	<0.1	312	ND	110	Methimazole
3	F	9	15.7	ND	0.03	ND	24hr-53%*	80	None
4	F	10	ND	1.2	<0.01	ND	ND	ND	None
5	F	14	ND	1.78	0.13	ND	ND	100	None
6	F	15	ND	1.28	<0.01	ND	ND	137	None
7	F	11	23.8	6.3	<0.03	ND	24hr-1%	137	Beta blocker
8	M	12	8.6	1.85	0.11	ND	24hr-12%	187	None
Average/ Total	7F IM	12.24 (SD 2.32)	14.96 (SD 5.69)	2.42 (SD 1.93)	0.06 (SD 0.044)	239.5 (SD 102.5)		125.4 (SD 34.18)	

M, Male; F, Female; dx, diagnosis; T4, thyroxine; T3, triiodothyronine; ND, not done.

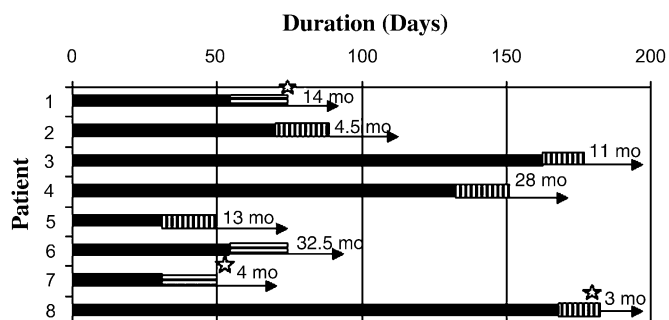
Normal ranges: Thyroid stimulating immunoglobulin, TSI <130% activity; Thyrotropin = 0.2 to 6.2 uIU; total T4 = 5 to 12 ug/dL; free T4 = 0.8 to 2.3 ng/dL; total T3 = 82 to 179 ng/dL. Normal <sup>123</sup>I uptake scan: 24 hr (15%–35%).

Thyroid function tests (TFTs) reported in the table are the initial TFTs obtained on presentation.

\*TFTs at the time of the scan were normal.

with subsequent development of hypothyroidism or euthyroidism. Remarkably, 5 of the 8 patients had features that made the diagnosis confusing. In 3 patients, a positive TSI titer was found. In these 3 subjects, the TSI titer was not checked initially but was measured later in the clinical course when additional test results were inconsistent with hyperthyroidism. No obvious explanation exists for the elevated TSI titer. Theoretically, this could represent concurrent intermittent Graves' disease with simultaneous Htx.<sup>18</sup> However, such a phenomenon would not be consistent with the natural history of Htx in our patients, and would be difficult to prove. Alternatively, this could represent some degree of non-specificity of the immune dysregulation characteristic of autoimmune thyroid disease. In the two cases in which an elevated <sup>123</sup>I scan was observed in conjunction with a normal TSI titer, the possibility of TSI-negative Graves' disease was entertained. However, these 2 patients subsequently developed euthyroidism without treatment. Some reports involving adults suggest that the thyroid scan in Hashimoto thyroiditis can mimic a wide range of thyroid disorders, including Graves' disease.<sup>10,19-21</sup> It is possible that some aspects of the dynamic evolution in thyroid function from hyperthyroidism to euthyroidism is responsible for this phenomenon.

In summary, this report characterized the frequency and natural history of Htx in children with autoimmune thyroiditis. One flaw of our study is that it consists solely of a clinic-referred sample. Therefore, the actual incidence of Htx may well be higher, especially because the majority of our patients were asymptomatic. Our results demonstrate the extreme clinical variability and potential diagnostic pitfalls that are sometimes encountered. Although transient, the hyperthyroid phase is of variable duration and may be followed by extended periods of euthyroidism in some cases. Factors predisposing to the development of Htx in patients with Hashimoto thyroiditis were not identified. These findings expand the clinical and biochemical spectrum of autoimmune



**Figure.** The duration of biochemical hyperthyroidism in days is demonstrated for each of the 8 patients with HTx, with 0 representing the time of diagnosis. The black bars refer to the period during which the patients were hyperthyroid. The bars with vertical lines signify the development of euthyroidism, whereas the bars with horizontal lines indicate the development of hypothyroidism. The star represents patients who had an elevated TSI titer. The arrow at the end of each bar refers to the duration of follow-up after resolution of the hyperthyroid phase.

thyroid disease in the pediatric population and provide valuable prognostic information for clinicians taking care of children with hyperthyroidism.

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## 50 Years Ago in *The Journal of Pediatrics*

### INFANT SPEECH DEVELOPMENT: A REPORT OF THE STUDY OF ONE CHILD BY MAGNETIC TAPE RECORDINGS

Parmelee, AH Jr. *J Pediatr* 1955;46:447-50

Using magnetic tape recordings—a new technology for that period 50 years ago—and a captive subject in his own home, Parmelee recorded his daughter's utterances and the sequences of speech development at monthly intervals during the first 2 years of her life. However, being the quintessential developmental pediatrician, Parmelee did not rely on the novel technological instrument alone. He also simultaneously recorded the social responsiveness, reciprocity, motor milestones, and feeding behaviors, all of which are intricately related in the development of speech. Through a correlation table, Parmelee illustrates that as his daughter's oro-motor mechanisms became more versatile with acceptance of a greater variety of food textures and emerging control over her mouth and jaw, her vocalizations became increasingly more complex. With the acquisition of progressive motor skills, such as mobility, her vocal-social development enlarged concomitantly within the wider world around her. Parmelee also noted changes in the tone and inflection of her speech, which became more interactive and sophisticated with age. Ultimately, despite technology, the human ear is called on to discern these nuances.

In short, Parmelee single-handedly integrated the complex utterances, behaviors, and motor activity of his daughter, which can now be recorded simultaneously and with considerably less effort, by the video-digital cameras of today.

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