CLINICAL VIGNETTE

Hashitoxicosis: An Uncommon Presentation of Autoimmune Thyroid Disease:

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Case Report

The patient is a 10-year-old female with a history of GERD and urinary reflux who was referred by her pediatrician to an endocrinologist because of growth delay. Endocrine work-up was negative with a normal growth hormone stimulation test, IGF binding protein-3, and somatomedin-C (IGF-1). CBC was remarkable for a slight lymphocytosis with normal WBC, hemoglobin, and platelet count. MCV was slightly low at 77.0 fL (79.0 - 95.0 fL) with normal iron indices. TSH was normal at 1.7 mcIU/mL with a normal free T4 of 1.5 ng/dL. 25-hydroxy vitamin D was low at 17 ng/mL (30-80 ng/mL). Chromosomal analysis was performed and found to be normal XX with normal cytogenetics. Bone age was assessed with a left wrist x-ray and was consistent with normal skeletal maturity for chronologic age. The patient was followed over time with nutritional support and on routine follow-up was noted to have an elevated free T3 of 958 pg/dL (249-405 pg/dL) with a normal free T4 of 1.5 ng/dL (0.8-1.6 ng/dL) with a normal TSH of 1.1 mcIU/mL. Two days later, her labs were repeated and her free T3 was dramatically increased to 1358 pg/dL and her free T4 had increased to 1.9 ng/dL. Her TSH had decreased to 0.43 mcIU/mL. Antibody levels were positive for thyroid peroxidase antibodies at >600 (<20 IU/mL), but negative for TSH-receptor antibodies, thyroid stimulating immunoglobulins, and thyroglobulin antibodies. Celiac disease antibodies were negative for gliadin peptide IgG, tissue-transglutaminase IgA, endomysial IgA, and gliadin antibodies IgA and IgG. Total IgA was normal.

Her past medical history is remarkable for GERD, urinary reflux treated with bilateral ureteral reimplantation, and short stature. She was on no medications. She had no drug allergies. Her social history was unremarkable. Her family history was remarkable for Grave's disease, asthma, atopic dermatitis and hypothyroidism.

Her physical examination reveals a blood pressure of 110/58 mm hg., pulse of 78 beats/minute temperature of 36.9 C, Her physical examination was unremarkable other than for short stature for chronologic age. The patient began to notice palpitations and dyspnea with exertion. Based on the clinical picture and laboratory evaluation, the patient was diagnosed as being in the hyperthyroid (inflammatory) phase of Hashimoto's thyroiditis (hashitoxicosis).

General Discussion

Hashimoto's thyroiditis (chronic lymphocytic thyroiditis or chronic autoimmune thyroiditis) is a progressive autoimmune disease involving T-cell cytokine mediated and antibody-mediated infiltration of the thyroid gland[1]. It is the most common cause of acquired hypothyroidism in the United States[2]. The inflammatory autoimmune response can occur as a steady, low grade process or can be episodic resulting in periods of transient hyperthyroidism[3]. Either way, the ultimate outcome of this inflammatory process is that the follicular cells become atrophied and hypothyroidism is the eventual outcome in most patients. Thus, Hashimoto's can present either as overt hypothyroidism, subclinical hypothyroidism, or rarely during the hyperthyroid phase. This period of hyperthyroidism is called hashitoxicosis and is believed to result from uncontrolled release of thyroid hormone during the active inflammatory phase of the disease[4]. Enlargement of the thyroid is common during the Hashitoxicosis phase and results from lymphocytic infiltration of the gland which typically leads to eventual fibrosis[3].

Epidemiology

Hashimoto's thyroiditis was first described by Japanese surgeon Dr. Hakaru Hashimoto in 1912 while he was practicing in Germany. It has become very common in the United States affecting about 5-10% of the population[5]. Hashimoto's thyroiditis is much more common in females occurring about seven times as often as in males[6]. It is most prevalent among patients aged 30-60, but can occur at any age including the very young or very old[7]. Although Hashimoto's can occur at any age, the incidence

increases with age[8]. Although most cases of Hashimoto's present as overt or subclinical hypothyroidism (often associated with growth delay in children), hashitoxicosis is the second most common cause of hyperthyroidism in children after Graves' disease[9].

Diagnosis and Pathogenesis

Hashimoto's is diagnosed by the presence of elevated thyroid peroxidase and/or thyroglobulin antibodies. TSH-receptor antibodies and thyroid stimulating immunoglobulins are generally negative in Hashimoto's. Thyroid function tests can reveal a hypothyroid, euthyroid, or hyperthyroid clinical picture depending on the stage of the disease. Generally, early in the disease most patients are euthyroid while a hypothyroid state is typically found late in the course of the disease[10].

The differential diagnosis typically includes Graves' disease, toxic adenoma, multinodular goiter, other forms of thyroiditis, and exogenous ingestion of thyroid hormone. Because many of the symptoms are nonspecific, many patients are misdiagnosed so the diagnosis may be delayed for months or years. Occasionally an I-131 uptake scan is necessary to clarify the diagnosis with low to normal uptake suggestive of Hashimoto's and high uptake favoring Graves' disease or toxic adenoma[10]. Patients typically have a family history of autoimmune thyroid disease or autoimmune disease in other organs[11]. The genetics of Hashimoto's appears to involve HLA-related genes and/or genes related to CD-152 T-cell proteins[12]. Biochemically, Hashimoto's thyroiditis involves a complex type IV hypersensitivity that involves activation of cytotoxic and helper T-lymphocytes, release of cytokines, and recruitment of of macrophages as part of the Th1 lymphocyte axis lymphocytes[13].

Clinical Features and Outcomes

The most common presenting symptoms for hashitoxicosis are weight loss, fatigue, alteration in behavior and heat intolerance[9]. Other symptoms can include depression, paresthesias, panic attacks, palpitations, changes in bowel habits, migraines, muscle weakness, cramps, memory loss, infertility and hair loss. The most common signs are goiter (usually painless, firm, large, and lobulated) and tremor[9]. The duration of the hyperthyroid phase of Hashimoto's can vary but usually lasts 2-6 months[4].

Etiology

Although there have been many theories for the etiology of Hashimoto's, no definitive causative agent has yet been identified. The disease is believed to result from a complex interplay of genetic susceptibility, environmental exposures, and perhaps other factors[14]. Hashimoto's patients have a higher than normal incidence of other autoimmune diseases such as type-1 diabetes, autoimmune hepatitis, Rheumatoid arthritis, eczema, and Celiac disease[15].

These associations appear to relate to a common genetic predisposition that involves similar HLA genetic makeup[16]. This genetic link has been noted in studies of monozygotic twins[17]. Environmental factors that have been discussed include iodine intake, pollutants, food additives, selenium intake, tobacco smoke, infectious agents, and certain medications[18].

Treatment

The management of hashitoxicosis typically involves observation. Most of these patients will spontaneously revert to and remain in a euthyroid state for an extended period of time. As long as Grave's has been ruled out, the thyrotoxicosis is usually transient in Hashimoto's and pharmacological treatment is rarely needed. In some rare cases, thyroid function does not resolve on it own and/or patients experience significant clinical problems related to the hyperthyroidism. Rarely, hashitoxicosis can progress to muscle failure, CHF, and/or encephalopathy. Intervention may be needed in these select cases and methimazole is usually the treatment of choice to modulate the thyroid levels while beta blockers are the mainstay for treatment of the cardiac symptoms[2]. Unfortunately, most of these patients will eventually progress over time to a hypothyroid state and thyroid replacement is almost always eventually necessary. The best timing for institution of thyroid replacement continues to be debated in the literature with no clear consensus[19]. Consideration should be given to screening Hashimoto's patients for other autoimmune diseases such as Celiac disease, type-1 diabetes, and Rheumatoid arthritis[20]. Family members may also need to be screened. Hashimoto's is rarely associated with lymphoma of the thyroid so this also needs to be kept in mind in these patients.

Clinical Course and Follow-Up

The 10-year old patient was observed clinically over time and her hyperthyroidism was nearly resolved within a few weeks. Her thyroid function was

repeated in one month and her free T3 was decreased to 793 pg/dL (249-405 pg/dL), her free T4 was in the normal range at 1.5 ng/dL, and her TSH was also in the normal range at 0.85 mcIU/mL. Her thyroid peroxidase antibody titer was decreased to 302 IU/mL (<20 IU/mL). Her symptoms of palpitations and dyspnea were resolved. Her laboratory and clinical status will continue to be monitored over time.

REFERENCES

1. **Burek CL, Rose NR**. Autoimmune thyroiditis and ROS. *Autoimmun Rev*. 2008 Jul;7(7):530-7. doi: 10.1016/j.autrev.2008.04.006. Epub 2008 May 9. Review. PubMed PMID: 18625441.
2. **Nabhan ZM, Kreher NC, Eugster EA**. Hashitoxicosis in children: clinical features and natural history. *J Pediatr*. 2005 Apr;146(4):533-6. PubMed PMID:15812459.
3. **Rallison ML, Dobyns BM, Keating FR, Rall JE, Tyler FH**. Occurrence and natural history of chronic lymphocytic thyroiditis in childhood. *J Pediatr*. 1975 May;86(5):675-82. PubMed PMID: 48541.
4. **Wasniewska M, Corrias A, Salerno M, Lombardo F, Aversa T, Mussa A, Capalbo D, De Luca F, Valenzise M**. Outcomes of children with hashitoxicosis. *Horm Res Paediatr*. 2012;77(1):36-40. doi: 10.1159/000334640. Epub 2012 Jan 26. PubMed PMID: 22286076.
5. **Bindra A, Braunstein GD**. Thyroiditis. *Am Fam Physician*. 2006 May 15;73(10):1769-76. PubMed PMID: 16734054.
6. **Dayan CM, Daniels GH**. Chronic autoimmune thyroiditis. *N Engl J Med*. 1996 Jul 11;335(2):99-107. Review. PubMed PMID: 8649497.
7. **Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, Franklyn JA, Hershman JM, Burman KD, Denke MA, Gorman C, Cooper RS, Weissman NJ**. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA*. 2004 Jan 14;291(2):228-38. Review. PubMed PMID: 14722150.
8. **Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F, et al**. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf)*. 1995 Jul;43(1):55-68. PubMed PMID: 7641412.
9. **Williamson S, Greene SA**. Incidence of thyrotoxicosis in childhood: a national population based study in the UK and Ireland. *Clin Endocrinol (Oxf)*. 2010 Mar;72(3):358-63. doi: 10.1111/j.1365-2265.2009.03717.x. Epub 2009 Sep 21. PubMed PMID: 19769613.
10. **Paltiel HJ, Summerville DA, Treves ST**. Iodine-123 scintigraphy in the evaluation of pediatric thyroid disorders: a ten-year experience. *Pediatr Radiol*. 1992;22(4):251-6. PubMed PMID: 1523044.
11. **Tamai H, Uno H, Hirota Y, Matsubayashi S, Kuma K, Matsumoto H, Kumagai LF, Sasazuki T, Nagataki S**. Immunogenetics of Hashimoto's and Graves' diseases. *J Clin Endocrinol Metab*. 1985 Jan;60(1):62-6. PubMed PMID: 3838076.
12. **Kavvoura FK, Akamizu T, Awata T, Ban Y, Chistiakov DA, Frydecka I, Ghaderi A, Gough SC, Hiromatsu Y, Ploski R, Wang PW, Ban Y, Bednarczuk T, Chistiakova EI, Chojm M, Heward JM, Hiratani H, Juo SH, Karabon L, Katayama S, Kurihara S, Liu RT, Miyake I, Omrani GH, Pawlak E, Taniyama M, Tozaki T, Ioannidis JP**. Cytotoxic T-lymphocyte associated antigen 4 gene polymorphisms and autoimmune thyroid disease: a meta-analysis. *J Clin Endocrinol Metab*. 2007 Aug;92(8):3162-70. Epub 2007 May 15. Review. PubMed PMID: 17504905.
13. **Jacobson EM, Tomer Y**. The CD40, CTLA-4, thyroglobulin, TSH receptor, and PTPN22 gene quintet and its contribution to thyroid autoimmunity: back to the future. *J Autoimmun*. 2007 Mar-May;28(2-3):85-98. Epub 2007 Mar 21. Review. PubMed PMID: 17369021; PubMed Central PMCID: PMC2043086.
14. **Tomer Y, Huber A**. The etiology of autoimmune thyroid disease: a story of genes and environment. *J Autoimmun*. 2009 May-Jun;32(3-4):231-9. doi: 10.1016/j.jaut.2009.02.007. PubMed PMID: 19307103.
15. **Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, Manji N, Allahabadia A, Armitage M, Chatterjee KV, Lazarus JH, Pearce SH, Vaidya B, Gough SC, Franklyn JA**. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. *Am J Med*. 2010 Feb;123(2):183.e1-9. doi: 10.1016/j.amjmed.2009.06.030. PubMed PMID: 20103030.
16. **Collin P, Kaukinen K, Välimäki M, Salmi J**. Endocrinological disorders and celiac disease. *Endocr Rev*. 2002 Aug;23(4):464-83. Review. PubMed PMID: 12202461.
17. **Chistiakov DA**. Immunogenetics of Hashimoto's thyroiditis. *J Autoimmune Dis*. 2005 Mar 11;2(1):1. PubMed PMID: 15762980; PubMed Central PMCID: PMC555850.
18. **Saranac L, Zivanovic S, Bjelakovic B, Stamenkovic H, Novak M, Kamenov B**. Why is the thyroid so prone to autoimmune disease? *Horm Res Paediatr*. 2011;75(3):157-65. doi: 10.1159/000324442. Epub 2011 Feb 22. Review. PubMed PMID: 21346360.
19. **Özen S, Berk Ö, Şimşek DG, Darcan S**. Clinical course of Hashimoto's thyroiditis and effects of levothyroxine therapy on the clinical course of the disease in children and adolescents. *J Clin Res Pediatr Endocrinol*. 2011;3(4):192-7. doi: 10.4274/jcrpe.425. PubMed PMID: 22155461; PubMed Central PMCID: PMC3245492.
20. **Lorini R, Gastaldi R, Traggiai C, Perucchin PP**. *Hashimoto's Thyroiditis. Pediatr Endocrinol Rev*. 2003 Dec;1 Suppl 2:205-11; discussion 211. Review. PubMed PMID: 16444160.

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