A Large Goiter in a Euthyroid Child Due to a Thyroglobulin Gene Defect

Arnold H. Slyper MD
Lehigh Valley Health Network, Arnold_H.Slyper@lvhn.org

Pia Hermanns MS, PhD

Jessica Okamoto RN
Lehigh Valley Health Network, Jessica.Okamoto@lvhn.org

Leeyat Slyper
Lehigh Valley Health Network

Published In/Presented At

Slyper, A., Hermanns, P., Okamoto, J., & Slyper, L. (2011, May). *A large goiter in a euthyroid child due to a thyroglobulin gene defect.* Poster presented at: The Society for Pediatric Research Annual Meeting, Denver, CO.

A Large Goiter in a Euthyroid Child Due to a Thyroglobulin Gene Defect

Arnold H Slyper, MD[1], Pia Hermanns, MSc, PhD[2], Jessica Okamato, RN[1], Joachim Pohlenz, MD[2] , Leeyat Slyper[1], and Samuel Refetoff, MD[3]

[1]Pediatric Endocrinology, Lehigh Valley Hospital, Allentown, PA, United States; [2]Pediatric Endocrinology, Johannes Gutenberg Children's Hospital, Mainz, Germany and [3]Medicine, Pediatrics and Genetics, University of Chicago, Chicago, Illinois, United States.

Abstract

Background: A large goiter in a euthyroid child is an unusual presentation for thyroid dyshormonogenesis.

Objective: To describe a euthyroid child with a large goiter due to a thyroglobulin gene defect.

Design/Methods: Genetic testing for a thyroglobulin gene defect.

Results: This 10 year old Pakistani female presented with a large goiter. She had been on levothyroxine (L-T4) since age 6, but hormonal replacement had been discontinued 2 years previously for financial reasons. As a consequence, her thyroid gland had enlarged. The parents are first cousins. Her thyroid gland was extremely enlarged, having a volume of approximately 96 cc. Initial laboratory tests showed: T4 1.6 ug/dL (5-12), free T4 0.47 ng/dL (0.71-1.63), free T4 by equilibrium dialysis 0.6 ng/dL (0.8-2.6), T3 2.37 ng/mL (0.6-1.81), free T3 5.05 pg/mL (2.3-4.2), TSH 2.84 ulu/mL, thyroglobulin 1 ug/L (2-30), thyroxine binding globulin 14 mcg/mL, thyroglobulin and thyroid peroxidase antibodies negative, plasma iodine 30 ug/L (40-92), and 24-hour urine for iodine 115 mcg (100-460). A thyroid ultrasound showed a markedly enlarged hypervascular gland, with a solid, less vascular nodule measuring 1.3 x 1.6 x 1.3 cm nodule in the lower pole of the left lobe. Because of the low free T4 with normal TSH she was evaluated for hypopituitarism with levels of IgF-1, IgF-BP3 and an ACTH stimulation test, and this testing was normal. She was placed on levothyroxine (L-T4) 75 mcg once daily, and a 3-month course of iodine because of her low plasma iodine. Over the next 1 years her thyroid gland decreased only slightly in size. While off L-T4 for 4 weeks, 4-hour radioiodide uptake was 93.8% and 24 hour uptake 91.3% (10-30). The nodule previously detected in the left lower lobe was shown to be cold on scanning. Genetic testing revealed a splice donor site mutation in intron 30 (IV30 SD 1G>C) of the thyroglobulin gene. The patient was a homozygote for this mutation, and her parents, two sisters and 1 brother were heterozygous carriers. A fine needle aspiration of her thyroid nodule was carried out because of the risk of malignancy in this condition and this showed changes suggestive of nodular hyperplasia.

Conclusions: Thyroid dyshormonogenesis needs to be considered in a euthyroid child with a goiter.

Introduction:

Patients with thyroid dyshormonogenesis usually present with congenital hypothyroidism in the neonatal period. However, thyroid dyshormonogenesis can also present later in childhood with a large goiter. A euthyroid patient is described who presented with a large goiter and was shown to have a thyroglobulin gene defect.

Case Presentation:

This 10 year old Pakistani female presented with a large goiter. She had been on levothyroxine (L-T4) since age 6, but hormonal replacement had been discontinued 2 years previously for financial reasons. As a consequence, her thyroid gland had enlarged. The parents are first cousins.

On physical examination her thyroid gland was extremely enlarged, having a volume of approximately 96 cc. The physical examination was otherwise unremarkable.

Initial laboratory testing: T4 1.6 ug/dL (5-12), free T4 0.47 ng/dL (0.71-1.63), free T4 by equilibrium dialysis 0.6 ng/dL (0.8-2.6), T3 2.37 ng/mL (0.6-1.81), free T3 5.05 pg/mL (2.3-4.2), TSH 2.84 ulu/mL, thyroglobulin 1 ug/L (2-30), thyroxine binding globulin 14 mcg/mL, thyroglobulin and thyroid peroxidase antibodies negative, plasma iodine 30 ug/L (40-92), and 24-hour urine for iodine 115 mcg (100-460).

Because of her low free T4 with normal TSH she was evaluated for hypopituitarism with levels of IgF-1, IgF-BP3 and an ACTH stimulation test, and this testing was normal. She was placed on levothyroxine (L-T4) 75 mcg once daily, and a 3-month course of iodine because of her low plasma iodine. Over the next 1 years her thyroid gland decreased only slightly in size, although with TSH suppression to slightly below the normal range a further decrease in size was achieved.

Her thyroid ultrasound showed a markedly enlarged hypervascular gland, with a solid, less vascular nodule in the lower pole of the left lobe measuring 1.3 x 1.6 x 1.3 cm.

A radioiodine scan was also performed. While off L-T4 for 4 weeks, her 4-hour radioiodide uptake was 93.8% and 24 hour uptake 91.3% (10-30). The nodule previously detected in the left lower lobe was cold (figure 1).

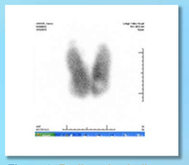

Figure 1. Radioactive iodine thyroid scan showing a very large goiter with a cold nodule in the left lower lobe.

Because of the risk of malignancy in this condition, a fine needle aspiration of her thyroid nodule was carried out and this showed changes of nodular hyperplasia.

Genetic Testing:

Genetic testing revealed a splice donor site mutation in intron 30 (IV30 SD 1G>C) of the thyroglobulin gene. The patient was a homozygote for this mutation, and her parents, two sisters and one brother were heterozygous carriers.

Discussion:

The clinical spectrum of patients with a thyroglobulin gene defect ranges from severe hypothyroidism to euthyroidism. The majority of patients present with a goiter at or shortly after birth. A number of euthyroid patients with this defect have been described.1-4 The partial splicing defect in this patient would have prevented the development of hypothyroidism.

A number of features in this patient are suggestive of a thyroglobulin gene defect. Blood levels of thyroglobulin are usually low to low-normal, whereas elevated levels are frequently found in other forms of thyroid dyshormonogenesis. Also typical is a low level of free T4 with an elevated free T3 level resulting in an elevated free T3/free T4 ratio. This abnormal ratio is probably due to increased type 2 iodothyronine deiodinase activity. Radionucleotide uptake is typically increased, and in this patient was extremely high.

Conclusions:

Thyroid dyshormonogenesis should be considered in a euthyroid child with a large goiter and no evidence of autoimmune thyroiditis. Basic laboratory testing can be helpful in diagnosis.

References:

1 Rivolta CM, Targonik HM. Molecular advances in thyroglobulin disorders. Clin Chim Acta 2006;374;8-24.

2 Corral J, Martin C, Perez R et al. Thyroglobulin gene point mutation associated with non-endemic simple goiter. Lancet 1993; 341:462-464.

3 Perez-Centeno C, Gonzalez-Sarmiento R, Mories MT et al. Thyroglobulin exon 10 gene point mutation in a patient with endemic goiter. Thyroid 1996;6:423-427.

4 Gonzalez-Sarmiento R, Corral J, Mories MT, Corrales JJ et al. Monoallelic deletion in the 5' region of the thyroglobulin gene as a cause of sporadic nonendemic simple goiter. Thyroid 2001;11:789-793.