CLINICAL THYROIDOLOGY **FOR THE PUBLIC**

A publication of the American Thyroid Association

AMERICAN THYROID ASSOCIATION
FOUNDED 1923
www.thyroid.org

HYPERTHYROIDISM

Some patients with apparent Graves' disease do not have an autoimmune thyroid disorder

BACKGROUND

One of the most common causes of hyperthyroidism is Graves' disease, an autoimmune process in which the patient's immune cells make antibodies against the thyroid stimulating hormone (TSH) receptor on the thyroid gland cells. These autoantibodies stimulate the thyroid to grow, resulting in a diffuse enlargement (goiter), and to produce excessive amounts of thyroid hormone, resulting in hyperthyroidism. Graves' disease with hyperthyroidism is characterized by the presence of diffuse thyroid enlargement, suppression of pituitary TSH, elevations of thyroxine (T_4) and/or triiodothyronine (T_3), the presence of TSH receptor antibodies in the blood, an elevated radioactive iodine uptake by the thyroid gland and clinical symptoms such as weight loss, increased perspiration, anxiety, tremor, rapid heart rate and frequent bowel movements. Some patients with Graves' disease may have subclinical (mild) hyperthyroidism without symptoms but with a goiter, suppressed TSH, TSH receptor antibodies, but with normal T_4 and T_3. Although TSH receptor antibodies are detected in the majority of patients with Graves' disease, there are some patients in whom such antibodies cannot be detected, but yet appear to have typical Graves' disease. Some of the antibody negative patients may actually have Graves' disease but the antibody levels are too low to detect initially. A small number of the patients may have a mutation of the TSH receptor resulting in the receptor being chronically turned on causing diffuse enlargement of the thyroid and clinical or subclinical hyperthyroidism. This would resemble the clinical and biochemical findings with Graves' disease but without the antibodies.

The present study was designed to look at a large number of patients with hyperthyroidism, diffuse goiters, but no measurable TSH receptor antibodies to see if the cause of the hyperthyroidism could be determined.

THE FULL ARTICLE TITLE

Nishihara E et al, The prevalence of TSH receptor germline mutations and clinical courses in 89 hyperthyroid patients with diffuse goiter and negative anti-TSH receptor antibodies. Thyroid. November 26, 2013 [Epub ahead of print].

SUMMARY OF THE STUDY

Over a 10 year period, close to 25,000 patients with hyperthyroidism were evaluated at Kuma Hospital in Japan. From this group, 89 patients had diffuse goiters with negative TSH receptor antibodies. About 10% of the 68 patients who were followed for more than a year developed TSH receptor antibodies and another 6% had weakly positive antibody levels, suggesting that they actually had mild Graves' disease when first seen and then evolved into more typical Graves' disease. A total of 4 of the 89 patients were found to have mutations in the thyroid TSH receptor that was responsible for the goiter and hyperthyroidism. Screening of family members of these patients identified an additional 7 patients with the mutations and all had subclinical or overt hyperthyroidism, while the other family members without the mutation had normal thyroid function. Patients with the mutations did not have a spontaneous remission of the hyperthyroidism with or without antithyroid drugs, unlike some patients with Graves' disease who may go into remission either spontaneously or after a course of antithyroid drug treatment.

WHAT ARE THE IMPLICATIONS OF THIS STUDY?

In this series of patients, about 5% of the 89 adult patients who clinically appeared to have Graves' disease but did not have TSH-receptor antibodies in their blood had activating mutations of the TSH receptor causing the hyperthyroidism and some of these mutations were found in other family members indicating that the disorder runs in families. Approximately 10-15% of the 89 patients actually had Graves' disease that became apparent over time. Thus, the cause of the hyperthyroidism in the majority of the patients remained undefined. Nevertheless, the standard therapies of antithyroid drugs, radioactive iodine, or surgery can be used in these patients irrespective of the cause. Importantly, the antithyroid drugs will not bring about a remission for those with TSH receptor mutations.

— Glenn D. Braunstein, M.D.

AMERICAN THYROID ASSOCIATION
FOUNDED 1923
www.thyroid.org

HYPERTHYROIDISM, continued

ATA THYROID BROCHURE LINKS

Hyperthyroidism: http://www.thyroid.org/what-is-hyperthyroidism

Graves' disease: http://www.thyroid.org/what-is-graves-disease

ABBREVIATIONS & DEFINITIONS

Autoimmune thyroid disease: a group of disorders that are caused by antibodies that get confused and attack the thyroid. These antibodies can either turn on the thyroid (Graves' disease, hyperthyroidism) or turn it off (Hashimoto's thyroiditis, hypothyroidism).

Goiter: a thyroid gland that is enlarged for any reason is called a goiter. A goiter can be seen when the thyroid is overactive, underactive or functioning normally. If there are nodules in the goiter it is called a nodular goiter; if there is more than one nodule it is called a multinodular goiter.

TSH receptor: A molecule (protein) located on the thyroid cell surface that binds TSH and stimulates the production of the thyroid hormones within the thyroid cell.

Hyperthyroidism: a condition where the thyroid gland is overactive and produces too much thyroid hormone. Hyperthyroidism may be treated with antithyroid meds (Methimazole, Propylthiouracil), radioactive iodine or surgery.

Subclinical Hyperthyroidism: a mild form of hyperthyroidism where the only abnormal hormone level is a decreased TSH.

Graves' disease: the most common cause of hyperthyroidism in the United States. It is caused by antibodies that attack the thyroid and turn it on.

Genetic hyperthyroidism: A rare form of hyperthyroidism caused by genetic mutations in the TSH receptor that cause it to be permanently in the "on" position (activating mutations).

Mutation: a permanent change in one of the genes.

Genes: a molecular unit of heredity of a living organism. Living beings depend on genes, as they code for all proteins and RNA chains that have functions in a cell. Genes hold the information to build and maintain an organism's cells and pass genetic traits to offspring.

Triiodothyronine (T_3): the active thyroid hormone, usually produced from thyroxine.

Triiodothyronine (T_3): the active thyroid hormone, usually produced from thyroxine, available in pill form as Cytomel™.

TSH: thyroid stimulating hormone – produced by the pituitary gland that regulates thyroid function; also the best screening test to determine if the thyroid is functioning normally.

Radioactive iodine uptake (RAIU): this is a measurement of activity of the thyroid gland and is reported as the percent of a dose of radioactive iodine that is retained in the thyroid gland 24 h after the dose is given. An increase in RAIU usually indicates hyperthyroidism.

Antibodies: proteins that are produced by the body's immune cells that attack and destroy bacteria and viruses that cause infections. Occasionally the antibodies get confused and attack the body's own tissues, causing autoimmune disease.