GRAVES’ DISEASE REVISITED

Genetic and Environmental Factors

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Graves' disease is a self-limited autoimmune hyperthyroid disorder caused by a combination of genes and environmental triggers. That is, patients with certain susceptibility genes develop Graves’ disease when they’re exposed to certain environmental triggers.

Autoimmune Nature

During the last few years, the autoimmune nature of Graves’ disease has been more clearly defined. Today, Graves’ disease is viewed as primarily a self-limited autoimmune disorder.

Genetic Factors

In 2002, Dr Shamael Waheed and colleagues at Bart's and the Royal London Hospital used molecular genetic technology to examine the genes of people with Grave's disease. These researchers found that the genes that control programmed cell death or apoptosis in thyroid cells are switched on in people with Graves’ disease. This results in these cells lasting longer and being more vulnerable to attack by the immune system.

Another gene, one that controls vitamin D absorption and transport by binding proteins has also been found to be defective in patients in Graves’ disease. This leads to the characteristically low vitamin D levels seen in Graves’ disease. Low vitamin D levels in Graves’ disease lead to poor absorption of calcium and symptoms of muscle wasting, bone loss, and nervous system disorders. A polymorphism to the CYP27B1 transporter gene has been demonstrated in a Polish population of Graves’ disease patients.

Polymorphisms in the CTLA-4 gene and in several genes for cytokines have also been demonstrated in Graves’ disease. The high incidence of genetic changes seen in Graves’ disease may account for the considerable variation seen in symptoms, signs and the disease course of patients with Graves’ disease.

Autoimmune Factors

The immune system in patients with Graves’ disease leans towards a Th2 rather than a Th1 response. The Th2 response promotes autoimmunity and is characteristically seen in many autoimmune diseases including Graves’ disease and type 1 diabetes.

Graves’ disease is considered an antibody-mediated autoimmune disorder. Here, stimulating TSH receptor antibodies (also known as thyroid stimulating immunoglobulins
or TSI) react with the TSH receptor protein on thyroid cells, ordering these cells to produce excess thyroid hormone. While the immediate goals in treating Graves’ disease are to reduce thyroid hormone levels and lessen the effects of hyperthyroidism, the long-term goals are to heal the immune system and reduce the production of TSI.

There is some variation in TSI. This explains why Graves’ patients with very high TSI levels can have mild symptoms and Graves’ patients with moderate TSI levels can have severe symptoms. It’s suspected that there are several subtypes of TSI. Presumably, these subtypes determine the type of epitopes or binding sites on the TSH receptor that TSI can bind to. TSI may bind to epitopes that result in stimulation of thyroid cells or they may bind to epitopes that are less potent.

Many patients with Graves’ disease also have blocking TSH receptor antibodies. These antibodies block both TSH and TSI from reacting with the TSH receptor, thereby preventing thyroid cells from producing excess thyroid hormone.

**Environmental Triggers**

Various environmental agents have been found to trigger the development of Graves’ disease. These include cigarette smoke, stress, allergens, infectious agents, estrogens, aspartame, low selenium levels, excess dietary iodine, iodine contrast dyes, interferon-beta, and interleukins. Other suspected triggers include: goserelin acetate, which is a gonadotropin-releasing hormone (GnRH) –agonist; various monoclonal antibodies; Resources:


DeGroot, Julius, Weetman, A, Thyroid Manager, accessed May 1, 2008

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