HYPOGLYCEMIA IN GRAVES’ DISEASE

A Look at Hirata’s Disease

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Conditions of insulin autoimmune syndrome (Hirata's disease), which causes transient conditions of hypoglycemia, are known to occur in patients with Graves' disease.

Insulin Autoimmune Syndrome

Insulin autoimmune syndrome (Hirata Disease) is a condition of spontaneous hypoglycemia (low blood glucose level) that can occur in patients with Graves' disease. First described by the Japanese physician Yukimasa Hirata in 1970, insulin autoimmune syndrome is characterized by trembling, numbness in the extremities, low levels of blood sugar, high levels of total serum insulin, and high titers of insulin autoantibodies. Insulin antibodies are a well-documented feature of insulin dependent diabetes mellitus prior to the administration of insulin and in patients with reactive hypoglycemia, which is technically known as the insulin autoimmune syndrome.

Insulin Antibodies

Because most patients with Graves’ disease are treated with anti-thyroid drugs, early publications in the medical literature stated that insulin autoimmune syndrome was caused by the antithyroid medications methimazole and carbimazole, but not propylthiouracil (PTU). However, subsequent studies have shown that insulin antibodies are also seen in untreated Graves’ disease patients. Furthermore, studies of patients before and after receiving antithyroid medications conclusively showed that antithyroid medications do not cause insulin antibody production. The same patients with insulin antibodies before starting treatment had insulin antibodies after starting treatment. In one small study, no Graves’ disease patients who tested negative for insulin antibodies later developed insulin antibodies after starting anti-thyroid drugs.

Symptoms

Conditions of insulin autoimmune syndrome can occur independently of Graves’ disease and typically cause fasting glucose levels below 40 mg/dl. Symptoms and characteristics of insulin autoimmune syndrome are identical in patients with and those without Graves’ disease. The peak age of onset is 60-69 years and peak duration of hypoglycemic attacks is usually more than 1 month and less than 3 months.

Approximately 82 percent of patients with Graves’ disease and insulin autoimmune syndrome achieved spontaneous remission without any specific treatment. Because patients on methimazole and carbimazole experienced complete remission of insulin autoimmune syndrome after stopping these medications, some experts feel that these medications may contribute to the development of insulin autoimmunity. Additional
studies show the development of insulin autoimmunity in Graves’ disease patients taking mercaptopropionyl glycine for cataracts, liver disease or arthritis or glutathione for liver disease, all of which, like the antithyroid drugs, are sulfhydryl compounds. Consequently, there is speculation that medications with sulfhydryl groups may contribute to insulin autoimmune syndrome.

**Recurrent Attacks**

Studies show that both Graves’ disease patients who have never used anti-thyroid medications and those who have used them can have recurrent attacks of hypoglycemia and insulin autoimmunity approximately one year after the initial condition of insulin autoimmunity resolved. Similar to the first attacks, the second attacks resolved within several months, indicating that insulin autoimmune syndrome is a transient condition, which can cause recurring episodes. Additional studies have shown that multiple recurring attacks and extended periods of hypoglycemia lasting up to three years can also occur in patients with Graves’ disease and insulin autoimmune syndrome. Higher titers of insulin autoantibodies are seen in patients with prolonged periods of hypoglycemia.

**Autoimmune Features**

Patients with Graves’ disease who develop insulin autoimmune syndrome have been found to possess certain immune system genes, notably HLA-Bw62/C4/DR4, DRB1*406, and DQA1. In one study of 50 patients with Graves’ disease only one patient who had these genetic markers had not yet developed insulin autoimmune syndrome. As in Graves’ disease, the pattern of predominance in HLA markers differs among different ethnic groups. In addition, the pattern differs in patients with autoimmune insulin syndrome who do not have Graves’ disease. Changes in HLA patterns have also been noted in patients before and after taking medications with sulfhydryl groups, which suggests that in some Graves’ disease patients, methimazole and carbimazole may trigger the development of insulin autoimmune syndrome. Some researchers propose that the autoimmune insulin syndrome is caused by the clustering of autoantibodies that occurs in autoimmune disease. This theory is supported by reports of a patient with Graves’ disease and insulin autoimmune syndrome in Osaka City, Japan whose hypoglycemia resolved and insulin antibodies titers fell after beginning treatment with methimazole.

**Who is Affected?**

Although insulin autoimmune syndrome in Graves’ disease has been reported in China, the United States, Italy, Switzerland, and Korea, it appears to be most prevalent in Japan, with 197 cases reported in the 20 years since it was first reported compared to about 20 cases in Caucasians. However, insulin autoimmune syndrome is suspected of being under-reported particularly in patients who only report sporadic symptoms related to hypoglycemia.
Because many of the symptoms in insulin autoimmune syndrome such as tremor are similar to those seen in hyperthyroidism, testing for hypoglycemia after the initial diagnosis of Graves’ disease is not routinely performed.

Resources:
