A NEW THYROID DISORDER

MCT8 Mutations and Thyroid Hormone Resistance

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Recent studies show what many patients with thyroid disorders already realize—that thyroid function test results can be misleading. In a recently discovered MCT8 mutation, hypothyroidism occurs but the typical thyroid function pattern seen in hypothyroidism (high TSH, low FT4 and/or FT3) isn’t seen.

Thyroid Hormone

Thyroxine (T4) and triiodothyronine (T3) are our major thyroid hormones. These hormones are best measured in their free forms, called free T4 (FT4) and free T3 (FT3). It’s long been presumed that thyroid hormone circulating within the plasma is readily available to react with our cells. Thyroid hormone must enter our cells before it can cause the effects it’s associated with. Normally, our thyroid hormone levels provide a good idea of our thyroid status.

TSH

Normally, the pituitary gland regulates thyroid hormone levels by its secretion of thyroid-stimulating-hormone (TSH or thyrotropin). Normally, the pituitary secretes more TSH when thyroid hormone levels are low. TSH, in turn, orders thyroid cells to produce more thyroid hormone, helping prevent hypothyroidism.

Hypothyroid Symptoms, Normal Labs

High plasma levels of thyroid hormone cause hyperthyroidism, and low levels cause hypothyroidism. Normally, in hypothyroidism, TSH levels are elevated and in hyperthyroidism, TSH levels are low. However, plasma levels may not reflect what’s happening at the cellular level.

Many individuals with classic symptoms of hypothyroidism, such as low body temperature, joint pain, and depression, are discouraged when they’re told that their thyroid hormone levels are within the normal range. The question of whether they might be resistant to their body’s own thyroid hormone is seldom considered. Yet, a disease known as thyroid hormone resistance can prevent thyroid hormone from reaching our cells.

The New Thyroid Disease—the MCT8 Mutation

Until recently, it was believed that thyroid hormone entered the body’s cells passively by diffusion across the plasma membrane. Recent studies show that thyroid hormone
actually crosses the plasma membrane and enters cells by using specific transporter proteins. An important thyroid hormone transporter is monocarboxylate transporter 8 (MCT8).

MCT8 is encoded by the gene SLC16A2, which is located at Xq13.2. Based on the gene sequence MCT8 has been found to have 12 transmembrane domains. In addition, the transporter MCT10 has been found to transport iodothyronines and aromatic amino acids and seems to be more preferential than MCT8 in transporting T3 over T4 (normally more T4 is transported) across plasma membranes.

**Thyroid Hormone Resistance**

MCT8 mutations cause a form of thyroid hormone resistance. Two other causes of thyroid hormone resistance also exist: 1) defects in the intra-nuclear thyroid hormone receptor-beta (TR-beta) and 2) defects in thyroid hormone metabolism manifested as deficient conversion of T4 to T3. In 1) resistance to thyroid hormone leads to elevations in TSH, FT4, T4, FT3 and T3. Patients with this type of resistance vary from euthyroid to mildly hypothyroid and goiter is typically present. In 2) a mutation in the sequence-binding protein 2 (gene called SECISBP2) that influences the synthesis of the enzyme deiodinase needed for conversion of T4 into T3 (by removing an iodine from T4’s outer ring). In this condition, T3/FT3 levels decline in the blood stream and cells. This defect in thyroid hormone metabolism can cause short stature and delayed bone age.

**Effects of the MCT8 Mutation**

Loss of function mutations in MCT8 cause a rare form of X-linked mental retardation, similar to fragile X syndrome. If MCT8 doesn’t transport thyroid hormone into neurons (cells of the brain and nervous system), the nervous system cannot properly develop. Males with MCT8 mutations manifest mental retardation, hypotonia, and an unusual pattern of thyroid function test abnormalities, including an increased T3, normal to decreased T4 and FT4 and a normal to elevated TSH level. If tested, the reverse T3 result is low.

This unusual pattern can be explained by the mutation. Evidence shows that not all tissues display equivalent defects in their uptake of thyroid hormone. However, the defective uptake of thyroid hormone in the central nervous system leads to mental retardation in affected males. Defective uptake of T3 can cause elevated T3 levels in the blood. If the pituitary gland is insensitive to thyroid hormone, levels of TSH rise even when T3 is high. The elevated TSH can, in turn, cause increased T3 production by the thyroid gland. T4 and reverse T3 are low because tissues that respond to elevated T3 such as the liver, recognize the elevated T3 concentrations. This causes an increased clearance of T4 and reverse T3, causing their blood concentrations to decline.

The discovery of MCT8 mutations explains laboratory discrepancies, that is, cases in which the lab results didn’t fit a particular pattern. It also explains how thyroid hormone resistance can cause TSH to appear normal even with a low FT4. In many instances only
the TSH test is performed. If the TSH result is normal, and symptoms of hypothyroidism are observed, tests for FT4, FT3 and T3 should all be performed.

Resource:

William Winter and Neil Harris, A New Type of Thyroid Disease, Advance for Administrators of the Laboratory, June, 2008: 46-50.

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