Clin Thyroidol 2012;24:12–14.

Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

The Allan–Herndon–Dudley Syndrome: How Common Is It, and Does Normalizing Thyroid Function Tests in Such Patients Improve Any Clinical Parameters?

Stephen W. Spaulding

Visser WE, Vrijmoeth P, Visser FE, Arts WF, van Toor H, Visser TJ. Identification, functional analysis, prevalence and treatment of monocarboxylate transporter 8 (MCT8) mutations in a cohort of adult patients with mental retardation. Clin Endocrinol. August 28, 2012 [Epub ahead of print]. doi: 10.1111/cen.12023.

SUMMARY

Background

Thyroid hormone transporters are expressed on the plasma membranes of cells, where they can influence both the uptake and the efflux of thyroid hormones. The monocarboxylate transporter 8 (MCT8) is an important and widely expressed transporter of several thyronines. Patients with the Allan–Herndon–Dudley syndrome present in infancy with hypotonia, weakness, and failure to gain weight. They have global developmental delays in childhood, and they display spasticity and hyperreflexia as adults. Their thyroid-function tests show a characteristic pattern—high T_3, low-normal T_4, and high-normal TSH—that reflect mutations in MCT8 affecting its activities. The hypothalamic–pituitary axis seems to have reduced sensitivity to T_3, whereas the high circulating level of T_3 produces hyperthyroid responses in the kidney, liver, and cardiovascular system of these patients. (Interestingly, MCT8 is also expressed in the thyroid gland, where it is involved in the secretion of thyroid hormones). MCT8 is found on the X chromosome; female carriers generally are asymptomatic, but may display mild abnormalities on thyroid-function tests (1). The current study used less stringent thyroid hormone criteria to screen men institutionalized for mental retardation to look for additional patients with MCT8 mutations.

Methods

A study on the thyroid origin of psychomotor retardation recruited about 500 institutionalized men from centers throughout the Netherlands (2). The serum levels of T_4, FT_4, TSH, T_3, rT_3, and sex hormone binding globulin (SHBG) were determined. For patients whose T_3 was above the 80th percentile and whose T_4 was below the 20th percentile, the coding region of the MCT8 gene was sequenced. Mutant MCT8 genes were transfected into JEG3 cells, which do not express MCT8, and the percent of T_4, T_3, and rT_3 taken up was compared to the uptake of cells expressing the wild-type MCT8 gene. In one patient, the efficacy of combining antithyroid drug with L-T_4 was assessed.

Results

Eight patients were found to meet the less stringent limits on thyroid-function tests, and sequencing of their MCT8 genes uncovered two new mutations (L492P and a synonymous mutation, T162T). The synonymous T162T sequence did not affect the uptake of T_4, T_3, or rT_3 in JEG cells—as might have been anticipated—so this mutation was a coincidental finding, unrelated to the patient's neurologic condition. The L492P mutant, when expressed in JEG cells, had somewhat more active transport activity than most previously studied MCT8 mutations. A third patient was also uncovered: his mutation was a 3-base-pair deletion (F501del) that had previously been studied in that patient's nephew, who had a slightly milder phenotype, and whose fibroblasts showed more impairment of T_4 and T_3 efflux than their impairment in T_4 and T_3 uptake. Defective uptake was confirmed when the current patient's mutant MCT8 gene was expressed in JEG cells. This patient was initially treated

continued on next page

with PTU alone, which caused the serum T_3 level to fall to low-normal levels by 15 weeks, but the FT_4 fell below normal and the TSH rose, so L-T_4 was added to the PTU treatment. After about 20 weeks of treatment with L-T_4 plus PTU, the TSH, T_4, and T_3 levels normalized. A slight improvement in the patient's eating and aggressive behavior was also noted. The serum level of both bone-specific alkaline phosphatase and SHBG normalized, supporting the belief that the liver and bone behave as if they are hyperthyroid in untreated Allan–Herndon–Dudley patients.

Conclusions

Based on an estimate that 10% of males with developmental psychomotor retardation have X-linked mental retardation (XLMR), finding 2 patients out of about 500 institutionalized men with clinically significant mutations in MCT8 indicates that about 4% of patients with XLMR have MCT8 mutations. "Block and replace" treatment with L-T_4 plus PTU normalized the thyroid-function tests, but clinical responses were meager in an adult patient with a 3-base-pair deletion mutant.

ANALYSIS AND COMMENTARY

It is not clear from the text whether rT_3 levels were low in any of the eight patients, or whether any patients were taking thyroid medication, or drugs like carbamazepine, which can increase the T_3:rT_3 ratio and decrease the free T_4 level (2). It is difficult to establish which men with retarded psychomotor development have X-linked mental retardation. The estimate of 10% used by the authors is crucial for their estimate that 4% of patients with XLMR have MCT8 mutations: some other studies indicate the prevalence of MCT8 to be about 0.4% in patients with XLMR (1).

Attempting to treat patients with Allan–Herndon–Dudley by raising thyroid hormone levels in the hope that other thyroid hormone transporters (such as MCT10, organic anion transporter peptides [OATPs], and L-type amino acid transporters) would compensate for the loss of MCT8 activity did not cause much clinical improvement, and resulted in further weight loss. The current study with PTU combined with T_4 did normalize thyroid function, but it produced only minor clinical responses, similar to those previously reported in a 16-year-old boy (3).

Diiodothyropropionic acid (DITPA) is a weak agonist for both the alpha and beta thyroid hormone receptors, and it does not appear to depend on MCT8 for entry into cells. There is a new report on the use of DITPA for several years in four young children with MCT8 mutations, starting at the age of 8 to 25 months (4). Treatment with a combination of PTU plus L-T_4 had been tried previously in three of the children: one developed hypogranulocytosis (4). DITPA normalized the elevated serum T_3 and TSH levels, and raised T_4 and rT_3 levels into the borderline-low range. SHBG levels and sleeping heart rates improved in all four children, two gained weight, and all four showed a transient increase in skeletal muscle–derived creatine kinase. Although MCT8 knock-out mice have negligible neurologic impairment, some cerebral markers suggestive of hypothyroidism improved after giving them DITPA. Unfortunately, DITPA produced little improvement of psychomotor development in these children. It seems that therapy would need to be begun in early pregnancy to overcome the severe defects in central nervous system (CNS) development, but it would also be important that any thyroid analog that would be used prenatally would respond appropriately to CNS deiodinases, which are important for protecting cells from premature neuronal maturation.

continued on next page

References

1. Frints SG, Lenzer S, Bauters M, et al. MCT8 mutation analysis and identification of the first female with Allan–Herndon–Dudley syndrome due to loss of MCT8 expression. Eur J Hum Genet 2008;16:1029-37. Epub April 9, 2008.
2. Visser WE de Rijke YB, van Toor H, Visser TJ. Thyroid status in a large cohort of patients with mental retardation: the TOP-R (Thyroid Origin of Psychomotor Retardation) study. Clin Endocrinol 2011;75:395-401.
3. Wémeau JL, Pigeyre M, Proust-Lemoine E, d'Herbomez M, Gottrand F, Jansen J, Visser TJ, Ladsous MJ. Beneficial effects of propylthiouracil plus L-thyroxine treatment in a patient with a mutation in MCT8. J Clin Endocrinol Metab 2008;93:2084-8. Epub March 11, 2008.
4. Verge CF, Konrad D, Cohen M, Di Cosmo C, Dumitrescu AM, Marcinkowski T, Hameed S, Hamilton J, Weiss RE, Refetoff S. Diiodothyropropionic acid (DITPA) in the treatment of MCT8 deficiency. J Clin Endocrinol Metab. September 19, 2012 [E-pub ahead of print]. doi: 10.1210/jc.2012-2556.