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

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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 T₃, low-normal T₄, and high-normal TSH—that reflect mutations in MCT8 affecting its activities. The hypothalamic–pituitary axis seems to have reduced sensitivity to T₃, whereas the high circulating level of T₃ 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 T₄, FT₄, TSH, T₃, rT₃, and sex hormone binding globulin (SHBG) were determined. For patients whose T₃ was above the 80th percentile and whose T₄ 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 T₄, T₃, and rT₃ 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-T₄ 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 T₄, T₃, or rT₃ 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 T₄ and T₃ efflux than their impairment in T₄ and T₃ uptake. Defective uptake was confirmed when the current patient’s mutant MCT8 gene was expressed in JEG cells. This patient was initially treated...
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with PTU alone, which caused the serum T₃ level to fall to low-normal levels by 15 weeks, but the FT₄ fell below normal and the TSH rose, so L-T₄ was added to the PTU treatment. After about 20 weeks of treatment with L-T₄ plus PTU, the TSH, T₄, and T₃ 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-T₄ 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 rT₃ 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 T₃:rT₃ ratio and decrease the free T₄ 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 T₁ 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-T₄ had been tried previously in three of the children: one developed hypogranulocytosis (4). DITPA normalized the elevated serum T₃ and TSH levels, and raised T₄ and rT₃ 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.

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

References


