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TRIAC May Ameliorate T₃ Thyrotoxicosis in the Allan–Herndon–Dudley Syndrome with MCT8 Deficiency

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SUMMARY

Background

The Allan–Herndon–Dudley syndrome (AHDS) was described in 1944; in 1990, its mutational pathogenesis was mapped to the MCT8 gene (1). The syndrome occurs predominantly in males because of its X-linked nature and is characterized by severe intellectual disability and central muscle weakness. A recent study affirms the nature of its psychomotor disabilities but extends the spectrum to somewhat milder, still very serious, phenotypes (2). It is now generally accepted that impaired psychomotor development in AHDS is related to deficiency of intracellular thyroid hormone in developing neuronal tissues, due for the most part to dysfunctional expression of mutated monocarboxylate-8 transporter (MCT8), a major transporter of T₄ and T₃ into brain and other tissue cells (3).

Although the most apparent features of AHDS relate to mental and motor disabilities, it is evident that this is a systemic disease, based in part on the very unusual serum thyroid-function test profile (2–4) and from features consistent with thyroid hormone deprivation in some tissues and excess in others.

The most striking aspect of thyroid-function testing is the marked elevation in serum total and free T₃ concentrations. In contrast, serum total and free T₄ concentrations are low or occasionally low normal. Belying the likely “perfect storm” of aberrant intracellular T₃ and T₄ concentrations in various sites, circulating thyroid-stimulating hormone (TSH) concentrations are normal or sometimes slightly above normal.

In addition to impaired psychomotor development, patients with AHDS suffer from generalized weakness and are underweight owing to reduced muscle mass. They are also more susceptible to stress and sepsis and have elevated heart rates and systolic hypertension. These features may be due to T₃ thyrotoxicosis in some organs (rather than intracellular thyroid hormone deficiency) resulting from the very high circulating T₃ concentrations. Theoretical and other considerations have suggested that the T₃ analog, 3,3 α ,5-triiodothyroacetic acid (TRIAC), might be effective in reducing circulating T₃ concentrations in patients with the AHDS (5,6). Therefore, in this study (4), TRIAC was administered to patients

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with AHDS to determine whether this would lower serum T₃ concentrations and ameliorate muscle weakness, weight loss, and other features consistent with T₃ thyrotoxicosis.

Methods

This was a multicenter, open-label, single-arm, phase 2 study in male patients with MCT8 deficiency. Eight sites in Europe and one in South Africa enrolled 46 patients. MCT8 deficiency was confirmed by the presence of a mutation in the *SLC16A2* gene. Candidates were selected either through the authors' awareness of patients with MCT8 deficiency or their inclusion in a ClinicalTrials.gov registered study. Patients were excluded if they had a major illness or had had major surgery within 4 weeks before the trial, were enrolled in other randomized clinical trials, were allergic to the components of TRIAC, or a parent or guardian declined for them to participate. Patients were also excluded from some aspects of the trial if there was a failure in compliance or follow-up.

Antithyroid drugs and/or levothyroxine, if being administered, were discontinued before starting TRIAC. TRIAC was begun at an initial oral dose of 350 µg per day with individualized dose escalation that followed a protocol to achieve a goal serum total T₃ concentrations from 1.4 to 2.5 nmol/L. This range was similar to the reference range for serum T₃ at the Erasmus Medical Center.

Study outcomes were assessed at baseline and after 12 months. A subset of the patients were also included in a long-term (median, 40.4 months) treatment-extension period. The primary end point of the study was the change in serum T₃ concentrations between baseline and month 12. Multiple blood components, clinical signs and symptoms relating to thyroid status, neuropsychological tests, and bone and cardiovascular parameters were assessed and

analyzed post hoc. Serum sex-hormone-binding globulin (SHBG) was measured because it is positively regulated by T₃ and has been used as a marker of thyroid hormone action. Other than the target range for serum T₃, the reference ranges provided in this review were obtained from standard sources, but the authors' data interpretation was based on reference ranges from Erasmus Medical Center.

Results

In the course of a 32-month period, 50 male patients who were eligible for the study were identified; all had severe intellectual and motor disability. Agreement to participate in the study was obtained from 46 of the 50 parents. Based on satisfactory compliance, 45 patients were included in the primary efficacy and safety analyses. An additional patient was not compliant, and thus his data were used only for the safety analyses.

Patients ranged in age from less than four years (24 percent) to >18 years (11 percent). The age ranges for the remaining patients were 41 percent for those who were 4 to 10 years and 24 percent for those who were 11 to 18 years. Forty patients completed the study. Those who did not withdrew for a variety of reasons, including parental or guardian request and severe comorbidities such as death from sepsis in one patient. Ten patients continued taking TRIAC during the treatment-extension period.

Baseline thyroid function tests revealed markedly elevated serum T₃ concentrations of 4.97 ± 1.55 nmol/L (mean $\pm$ SD, Reference range = 1.2 – 2.8 nmol/L). Serum T₄ concentrations were low or borderline low, 56.0 ± 13.0 nmol/L (Reference range = 57 – 159 nmol/L) as were serum free T₄ (fT₄) concentrations, 9.5 ± 2.5 pmol/L (Reference range = 10.4 – 17.4 pmol/L). Mean serum TSH concentrations were normal (2.91 ± 1.68 mU/L, Reference range = 0.63–3.9 µL). Serum T₃ concentrations declined sig-

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nificantly after the initiation of TRIAC. The median time to achieve serum T₃ concentrations within the target range was 2.5 months. Serum T₃ decreased by 3.15 nmol/L (95% CI, 2.68–3.62; P<0.0001) during a median treatment period of 13 months, a reduction of 61% from baseline. Post hoc analysis revealed that 85% of patients who completed 12 months of treatment had achieved the target range for serum T₃ concentrations of 1.4 to 2.5 nmol/L and the remaining patients had serum T₃ concentrations just above this range. This required a mean daily TRIAC dose of 38 µg/kg of body weight. Serum free T₄, total T₄, reverse T₃, and TSH concentrations also declined significantly (P<0.0001 for all); mean changes were 6.1 pmol/L, 31.6 nmol/L, 0.08 nmol/L, and 1.89 mU/L, respectively (P<0.0001 for all changes).

Sixty-five percent of the patients were underweight for age at baseline (z-score, < 2), and all patients had severe intellectual and motor disability. The resting heart rate was greater than the 90th percentile in 43% of the patients, and systolic hypertension was present in 12 of the 35 patients who had baseline blood pressure measurements. In patients who completed the 12-month treatment period, there was a significant mean increase in weight for age (2.7 kg; range, 1.9 to 3.5 kg; P<0.0001). Mean systolic blood pressure decreased from the 78th to the 61st percentile, and the proportion of patients with systolic hypertension decreased from 34 percent to 9 percent at month 12. The resting heart rate declined in all patients whose baseline rate

was greater than 100 per minute. SHBG concentrations decreased from 212±91 nmol/L at baseline to 178±76 nmol/L after TRIAC treatment (P = 0.0013) and serum creatine kinase increased significantly (consistent with changes that occur when muscle mass increases) by a mean of 53 U/L from the baseline concentration of 112±98 U/L (P<0.0001). Mean total serum cholesterol concentrations increased, but not significantly (3.2 to 3.4 mmol/L, P = 0.056). Gross motor function improved slightly in most patients but remained severely depressed in all patients. The greatest increment in this change was noted in patients who were started on TRIAC before age 4.

Seven adverse events, which included transient increases in perspiration and irritability, were noted and suspected to be due to TRIAC administration. All were mild, occurred at the start of TRIAC therapy, and resolved spontaneously after a few days. All serious adverse events were considered to be secondary to MCT8 deficiency.

Conclusions

Administration of TRIAC in patients with the AHDS is associated with normalization of markedly elevated serum T₃ concentrations, increased body weight, and reductions in systolic blood pressure, resting heart rate, and premature atrial complexes without serious adverse events not attributable to the AHDS per se. These changes, in the setting of AHDS, are likely to reduce premature mortality and enhance quality of life.

COMMENTARY

The discovery of the T₃ and T₄ transporting properties of MCT8 and its linkage to the pathogenesis of AHDS has revolutionized concepts of thyroid hormone action. The first study pointing to an

energy-dependent process for thyroid hormone transport into cells was published in 1954, when Christiansen et al. (7) reported that the concentration of T₃ by ascites carcinoma cells was inhibited

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by KCN. Despite a number of subsequent studies with results consistent with this observation, it was not until much later in the century that there was acceptance of the notion that T₃ and T₄ entry into cells was not simply passive diffusion, but rather was mediated by membrane transporters. Several publications, appearing within 4 years after Hennemann's review in 2001 (8), were pivotal in establishing thyroid hormone transporters as an essential aspect of thyroid hormone action. The first of these, in 2003, identified MCT8 as a specific thyroid hormone transporter (9). The following year, Dumitrescu et al. (10) and Friesema et al. (11) demonstrated the association of mutations in MCT8 with severe X-linked psychomotor retardation. In 2005, Schwartz et al. (1) reported that mutational analysis of six families with Allan–Herndon–Dudley syndrome (AHDS) identified one truncating mutation, one in-frame deletion, and four missense mutations in the MCT8 gene.

It is now well recognized that MCT8 gene mutations are associated with severely impaired psychomotor development in humans, consistent with intracellular thyroid hormone deprivation in neuronal tissues. The study reviewed here (4) is important for a number of reasons, one of which is that it should greatly increase awareness that AHDS is accompanied by clinically important features consistent with chronic T₃ thyrotoxicosis in cardiovascular, skeletal, and other tissues. That serum T₃ concentrations are actually markedly elevated in patients with AHDS and that a regimen that decreased serum concentrations to reference range values resulted in amelioration of these signs is consistent with the hypothesis that they are due, at least in part, to T₃ thyrotoxicosis. A limitation of the study, albeit one that is probably ethically appropriate, is that it did not include a control group of patients with AHDS who did not receive TRIAC. However, the hormonal and beneficial findings reported with TRIAC treatment in the

study do not occur spontaneously in patients with this syndrome.

The broad impressions regarding the AHDS and the effects of TRIAC treatment noted to date await more detailed refinement and a better understanding of their pathogenesis. The circulating thyroid hormone profile in AHDS has now been well characterized, but what is needed is more information about intracellular T₄, T₃, and rT₃ concentrations; the regulation of TSH secretion (3,12); and the effect of TRIAC treatment on these parameters (including intracellular TRIAC levels). This is certainly the case as it relates to a better understanding of clinical–molecular correlations. The findings reported in this study might suggest, on cursory consideration, that skeletal and cardiac tissue is less affected by MCT8 dysfunction than brain. However, in some studies at least, MCT8 mRNA is actually equally or more abundant in heart and muscle as in brain. Even the observation by Groeneweg et al. that the beneficial effects of TRIAC treatment on body weight and cardiovascular parameters appear to be due entirely to amelioration of T₃ thyrotoxicosis is cause for reservation, as some of these might relate to thyromimetic effects, per se, of TRIAC.

As far as the potential that thyromimetic effects of TRIAC in patients with AHDS are important, a tantalizing observation that is still very preliminary was that very modest improvements in motor function were more prominent in the youngest group of patients who received TRIAC (4). Therefore, the authors have planned “a future clinical trial” (ClinicalTrials.gov no. NCT 02396459) in young infants to determine whether better effects of TRIAC on neurocognitive development can be achieved. Regardless of the findings relating TRIAC treatment to neuromotor function at earlier stages of development, the study reviewed here is important because of its potential to improve quality of life and reduce

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suffering in patients with AHDS. Although AHDS is very rare, clinicians should be familiar with it in order to expand their understanding of the complexity of thyroid hormone action. In the event that they

encounter a patient with a persistently high serum T₃/T₄ ratio, they should follow up with appropriate action such as seeking input from experts who publish in this field.

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