# Beneficial Effects of Propylthiouracil plus L-Thyroxine Treatment in a Patient with a Mutation in *MCT8*

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**Context:** Mutations of the monocarboxylate transporter 8 (MCT8) gene determine a distinct X-linked phenotype of severe psychomotor retardation and consistently elevated $T_3$ levels. Lack of MCT8 transport of $T_3$ in neurons could explain the neurological phenotype.

**Objective:** Our objective was to determine whether the high $T_3$ levels could also contribute to some critical features observed in these patients.

**Results:** A 16-yr-old boy with severe psychomotor retardation and hypotonia was hospitalized for malnutrition (body weight = 25 kg) and delayed puberty. He had tachycardia (104 beats/min), high SHBG level (261 nmol/liter), and elevated serum free $T_3$ ($FT_3$) level (11.3 pmol/liter), without $FT_4$ and TSH abnormalities. A missense mutation of the MCT8 gene was present. Oral overfeeding was unsuccessful. The therapeutic effect of propylthiouracil (PTU) and then PTU plus levothyroxine ($LT_4$) was tested. After PTU (200 mg/d), serum $FT_4$ was undetectable, $FT_3$ was reduced (3.1 pmol/liter) with high TSH levels (50.1 mU/liter). Serum SHBG levels were reduced (72 nmol/liter). While PTU prescription was continued, high $LT_4$ doses (100 $\mu$g/d) were needed to normalize serum TSH levels (3.18 mU/liter). At that time, serum $FT_4$ was normal (16.4 pmol/liter), and $FT_3$ was slightly high (6.6 pmol/liter). Tachycardia was abated (84 beats/min), weight gain was 3 kg in 1 yr, and SHBG was 102 nmol/liter.

**Conclusions:** 1) When thyroid hormone production was reduced by PTU, high doses of $LT_4$ (3.7 $\mu$g/kg·d) were needed to normalize serum TSH, confirming that mutation of *MCT8* is a cause of resistance to thyroid hormone. 2) High $T_3$ levels might exhibit some deleterious effects on adipose, hepatic, and cardiac levels. 3) PTU plus $LT_4$ could be an effective therapy to reduce general adverse features, unfortunately without benefit on the psychomotor retardation. (***J Clin Endocrinol Metab* 93: 2084–2088, 2008**)

Monocarboxylate transporter 8 (MCT8), encoded by a gene located on human chromosome Xq13.2 is an active transporter facilitating cellular entry of thyroid hormone (TH) (1). MCT8 is expressed in numerous human tissues, especially brain, heart, placenta, lung, kidney, skeletal muscle, and liver. Mutations of the *MCT8* gene result in a distinct X-linked phenotype of severe psychomotor retardation and strongly elevated $T_3$ levels (2, 3). Lack of MCT8 transport of $T_3$ in neurons could explain the neurological phenotype (4). Currently, no therapy is available to improve the condition of the patients.

The aims of our study were to determine whether the high $T_3$ levels could also contribute to some critical features observed in patients with *MCT8* mutations, also known as the Allan-Herndon-Dudley syndrome (AHDS) (5), and whether treatment aimed at reducing circulating $T_3$ levels could be of benefit to these patients.

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Abbreviations: AHDS, Allan-Herndon-Dudley syndrome; D3, type 3 deiodinase; $FT_3$, free $T_3$; $LT_4$, levothyroxine; MCT8, monocarboxylate transporter 8; PTU, propylthiouracil; REE, resting energy expenditure; RQ, respiratory quotient; Tg, thyroglobulin; TH, thyroid hormone.

## Case Study

A 16-yr-old boy with severe psychomotor retardation and hypotonia was hospitalized for malnutrition (weight 25 kg, height 142 cm, body mass index 12.4 kg/m$^2$) and delayed puberty (Tanner stage 1). Since birth, mental development was severely disturbed; he had no hearing loss but was unable to speak and showed few reactions to external stimuli and little communication with the parents and the medical personnel. Moreover, he exhibited severe hypotonia, with no possibility of standing, of sitting without being belted, or of keeping his head upright. A divergent strabismus was present and a cleft palate. Permanent tachycardia (104 beats/min) was observed. Testicular glands were of low volume (4 ml); penis was prepubertal. Pubic hair was according to Tanner stage P1.

In contrast with the low $T_3$ syndrome expected in an undernourished patient, serum free $T_3$ ($FT_3$) level was elevated (11.3 pmol/liter; normal, 3.3–6.2 pmol/liter), without $FT_4$ (14.5 pmol/liter) or TSH (1.54 mU/liter) abnormality. The clinical phenotype and isolated high $FT_3$ levels were suspicious for an *MCT8* mutation, which was thus investigated. A missense mutation 812G→A (Arg271His) was detected in exon 3 of the *MCT8* gene. Both his mother and one of his three sisters were found to be carriers of this mutation.

Table 1 summarizes the initial biological data of the patient. Serum cholesterol and retinol binding protein were decreased, whereas the SHBG level was high (261 nmol/liter; normal, 15–45 nmol/liter). Testosterone level was low without an increase of serum gonadotropins.

Malnutrition was one of the reasons that the patient was referred to our medical clinic. Oral overfeeding (1600 kcal/d) was unsuccessful (gain of weight 200 g/yr). Gastrostomy was advised by the nutritionists of our hospital. However, considering the putative effect of high $T_3$ serum levels on the adipose and muscular tissues, we tested the therapeutic effect of propylthiouracil (PTU), first alone and subsequently in combination with levothyroxine ($LT_4$) replacement. Written informed consent of both parents was obtained. After 12 and 24 wk of PTU treatment (200 mg/d), serum $FT_4$ was undetectable (<2.9 pmol/liter), $FT_3$ was reduced (2.7, 3.1 pmol/liter), and TSH levels were high (25.3–50.1 mU/liter). Thyroglobulin (Tg) levels were increased (from 11.4 to 874 ng/ml). An increase in thyroid volume was concomitantly measured by ultrasonography (from 5 to 25 ml). Serum SHBG levels were reduced (46.8 and 72 nmol/liter). While PTU prescription was continued, high $LT_4$ doses (100 $\mu$g/d) were needed to normalize serum TSH levels (3.18 mU/liter). At this time, serum $FT_4$ was normal (16.4 pmol/liter), and $FT_3$ was slightly high (6.6 pmol/liter). Tachycardia abated (84 beats/min), gain of weight was 3 kg in 1 yr, and SHBG was 102 nmol/liter (Fig. 1).

Resting energy expenditure (REE) was measured by indirect calorimetry at diagnosis and then after PTU and on PTU plus $LT_4$ treatment. Inspired oxygen flow ($VO_2$), expired carbon dioxide flow ($VCO_2$), and the respiration quotient (RQ) were noted. REE was calculated every minute from oxygen consumption ($VO_2$ in milliliters per minute), as was production of carbon dioxide ($VCO_2$ in milliliters per minute). Continuous respiratory exchange measurements were conducted for a minimum period of 30 min. Coefficients of variation were less than 10% for $VO_2$ and dilution airflow and less than 5% for RQ (6). Predicted REE was calculated using the Schofield equation (7) and compared with the REE measured by indirect calorimetry. REE increased from 881 kcal (predicted 931 kcal) at baseline to 1160 kcal (predicted 1164 kcal) 3 months after PTU treatment and 1207 kcal (predicted 1158 kcal) on PTU plus $LT_4$. RQ remained stable (0.82, 0.81, and 0.80, respectively) during treatment.

**TABLE 1.** Initial biological features

| | Patient | Normal |
|---|---|---|
| Thyroid status | | |
| $FT_4$ (pmol/liter) | 14.8 | 10.5–25.5 |
| $FT_3$ (pmol/liter) | 11.3 | 3.3–6.1 |
| TSH (mU/liter) | 1.54 | 0.4–3.6 |
| Tg (ng/ml) | 13.7 | 1.5–43 |
| Endocrinology | | |
| GH (ng/ml) | 0.32 | 0–10 |
| Peaks during circadian rhythm | | |
| 22 h (ng/ml) | 17.4 | |
| 2 h (ng/ml) | 32.8 | |
| IGF-I (IU/liter) | 0.62 | 0.74–2.4 |
| Testosterone (nmol/liter) | 4.9 | 9.0–55.2 |
| SHBG (nmol/liter) | 261 | 15–45 |
| LH (ng/ml) | 1.2 | 2–12 |
| FSH (ng/ml) | 3.1 | 1.5–10 |
| Peaks after GnRH (100 $\mu$U) | | |
| LH (ng/ml) | 9.2 | |
| FSH (ng/ml) | 5.1 | |
| Biochemistry | | |
| Erythrocyte sedimentation rate (mm) | 11 | 1st hour |
| Blood cell counts | Normal | |
| Plasma glucose (mg/liter) | 84 | 70–115 |
| Creatinine (mg/liter) | 4 | 6–12 |
| Cholesterol (mg/dl) | 114 | 115–200 |
| Triglycerides (mg/dl) | 54 | 35–150 |
| $HCO_3^-$ (mEq/liter) | 32 | 24–30 |
| Ferritin (ng/ml) | 57 | 20–300 |
| Proteins (g/liter) | 73 | 60–75 |
| Albumin (g/liter) | 40.9 | 30–48 |
| Prealbumin (g/liter) | 0.13 | 0.21–0.41 |
| Retinol-binding protein (g/liter) | 0.02 | 0.03–006 |
| Acetoacetate (mmol/liter) | 0.03 | 0–0.2 |
| $\beta$-Hydroxybutyrate (mmol) | 0.03 | 0–0.3 |
| Lactate (mg/liter) | 226.9 | 50–220 |
| Pyruvate (mg/liter) | 12.7 | 5–15 |
| Lactate/pyruvate | 17.9 | 10–20 |

## Discussion

The AHDS was described in 1944 as inherited sex-linked idiocy and microcephaly (8). Only male subjects were affected, suggesting an X-linked disease. Patients exhibit hypotonia with feeding difficulties and inability to sit or stand up and walk in most of the cases. Development of rigidity and contractures of the limbs are usual. Some choreoathetosis movements or paroxysmal dyskinesias can be observed. Cognitive functions are severely affected (5, 8–10). In 2004, mutations of *MCT8* gene were identified by two groups in seven families in which males exhib-

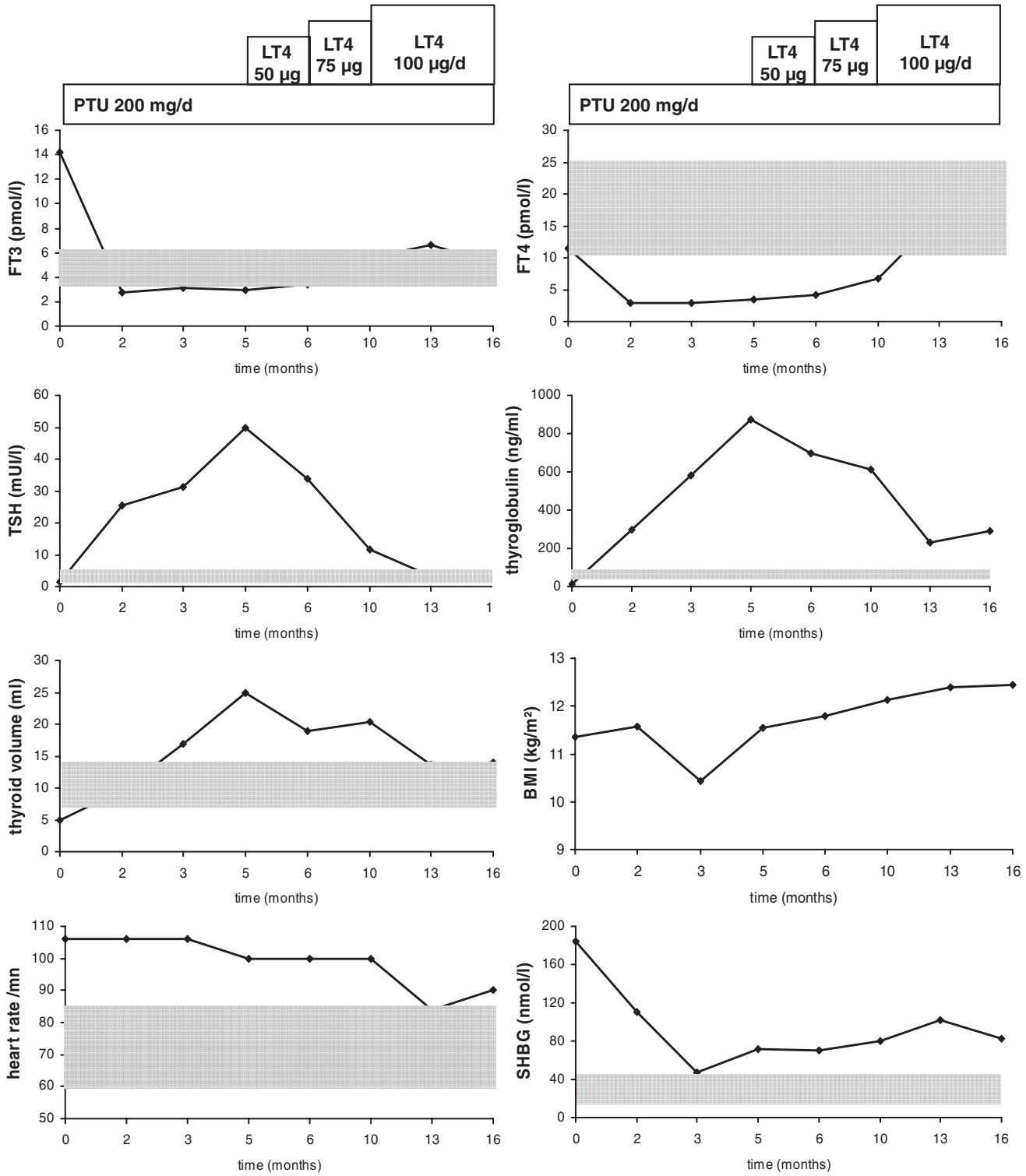


**FIG. 1.** Evolution of serum $FT_3$, $FT_4$, TSH, and Tg, of thyroid volume, body mass index (BMI), heart rate, and SHBG concentrations after therapy with 200 mg/d PTU and then PTU plus $LT_4$ at 50, 75, and 100 $\mu$g/d. PTU alone reduced $FT_4$, normalized $FT_3$, and increased TSH, Tg levels, and thyroid volume. When high doses of $LT_4$ were added, in comparison with initial values, TSH and $FT_4$ levels were similar, whereas a weighty reduction of $FT_3$ concentration was obtained. Therapy improved body mass index and reduced heart rate and SHBG levels.

ited severe psychomotor retardation and hypotonia coexisting with high serum $T_3$ levels (2, 3). One year later, a mutation of *MCT8* was identified in the family originally described in 1944 and in other families previously reported with AHDS (5, 11).

Because MCT8 is importantly involved in the neuronal transport of $T_3$ (1), lack of $T_3$ supply to these cells during brain development probably explains the severe mental deficiency and the low psychomotor development of the patients. One could expect that high $T_3$ level is related to reduction of metabolic clearance of $T_3$, because its intracellular entrance is reduced and

thus its access to neuronal type 3 deiodinase (D3). However, in male *MCT8* knockout mice, after injection of $^{125}$I-labeled iodothyronines, $T_3$ disappears from serum quite at the same rate as in wild-type mice (12), and $T_3$ generation by D1 and D2 is increased, which has also a consumptive effect on $T_4$ levels (13). These mice also show a reduced $T_3$ feedback at the hypothalamic and/or pituitary level (12). Furthermore, $T_4$ is required to maintain the high $T_3$ level (13).

The patient who was referred to us exhibited all the clinical and biological features of AHDS and, not surprisingly, had a familial transmitted *MCT8* mutation.

The patient had a permanent tachycardia (100–120 beats/min). He had no evidence of cardiac insufficiency, and cardiac acoustic and echocardiographic examinations were normal. Moreover, despite correct nursing, malnutrition was a preoccupant immediate problem of the patient. Therefore, we suspected deleterious effects of high $T_3$ levels at the cardiac level and on adipose and muscular tissues.

In a first step, reduction of TH levels was obtained by an antithyroid drug. PTU was chosen preferentially to methimazole in view of the additional inhibition of D1 by PTU. PTU was given in a dose of 200 mg/d to the patient weighing 25 kg. No side effect was observed. Both $T_4$ and $T_3$ concentrations were reduced. TSH level increased, resulting in the development of a goiter with high serum Tg concentrations. Although the PTU regimen was not modified, the patient was additionally treated with progressive doses of $LT_4$ to increase TH levels. High doses of $LT_4$ (100 $\mu$g/d, corresponding to 3.7 $\mu$g/kg·d) were needed to normalize the TSH levels and to reduce the goiter and serum Tg. This is in keeping with a state of partial resistance to TH.

In parallel, the general status of the patient improved. The cardiac frequency abated to 84 beats/min. The weight gain was 3 kg/yr *vs.* 200 g/yr with the conventional oral overfeeding. For this reason, the nutritionists decided to renounce the gastrostomy initially planned for the patient. Treatment with PTU alone or with PTU plus $LT_4$ did not significantly influence REE in our patient. The 32% increase in REE we observed 1 yr after PTU treatment can be explained by the improvement of nutritional status; indeed, measured REE remained closely correlated to predicted REE according to weight and height, whatever the treatment.

Unfortunately, the combined treatment with PTU and $LT_4$ had no effect on the cerebral disturbances of the disease and the psychomotor retardation of the young patient.

Definitely, the MCT8 deficiency syndrome constitutes a novel etiology of resistance to TH. In this situation, conventional doses of TH fail to produce the usual effect. This was obvious, because when the endogenous production was totally reduced by PTU, high doses of $LT_4$, twice higher than usual, were needed to restore normal TSH concentrations. This suggests that not only cellular $T_3$ entry but also that of $T_4$ is reduced. This gives an explanation of one of the most surprising features of the disease: TSH concentrations are normal or even increased despite high $T_3$ levels (3).

Interestingly, in AHDS, the effect of a high $T_3$ level seems to be expressed at the cardiac, muscular, adipose, and hepatic levels, as suggested by tachycardia, weight loss, and high SHBG concentrations. Some patients with resistance to TH due to TH receptor-$\beta$ mutations exhibit tachycardia or cardiac disorders (14) and hyperkinetic behavior and hyperactivity (15), related to the influence of high TH concentrations on tissues with a normal TH receptor-$\alpha$ function. In patients with *MCT8* mutations, tissues in which MCT8 does not play an important role in $T_3$ uptake are exposed to high $T_3$ levels and may be in a thyrotoxic state. Low cholesterol and very high SHBG levels were also observed in a 4-yr-old boy, carrying an *MCT8* mutation described by Biebermann *et al.* (16), in whom only high doses of $LT_4$ (100 $\mu$g) plus $LT_3$ (30 $\mu$g/d) were able to reduce significantly TSH and increase SHBG levels with no change of the mental and psychomotor development.

## Conclusions

1) In our patient with all the phenotypic and genetic characteristics of AHDS, when TH production was reduced by PTU, high doses of $LT_4$ (3.7 $\mu$g/kg·d) were needed to normalize serum TSH. Definitely, this gives clinical evidence that mutation of *MCT8* is a cause of resistance to TH, affecting not only $T_3$ but also $T_4$ cellular entrance. 2) In contrast, high $T_3$ levels might exhibit some deleterious effects at the adipose, hepatic, and cardiac levels. As the two faces of Janus, lack of intraneuronal $T_3$ explains severe psychomotor deficiency, while at the same time, an excess of circulating $T_3$ could explain some peripheral features of the patients. 3) PTU plus $LT_4$ treatment could be an effective therapy to improve the general condition of these patients, unfortunately without benefit on the psychomotor retardation.

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