LOW FREE T_4 LEVELS DURING PREGNANCY ARE A RED FLAG THAT NEEDS ATTENTION

Ramos HE, Morandini M, Carre A, Tron E, Floch C, Mandelbrot L, Neri N, De Sarcus B, Simon A, Bonnefont JP, Amiel J, Desguerre I, Valayannopoulos V, Castanet M, Polak M. **Pregnancy in women heterozygous for MCT8 mutations: risk of maternal hypothyroxinemia and fetal care.** Eur J Endocrinol 2011;164:309-14. Epub November 23, 2010.

SUMMARY

BACKGROUND

The Allan–Herndon–Dudley syndrome (AHDS) is a rare but very severe congenital X- linked disorder. Clinically, affected patients present with severe muscle hypotonia, with poor muscle development and, frequently, with severe mental retardation. Characteristic laboratory findings in these patients are increased serum total and free triiodothyronine (T_3) levels, low-normal or decreased serum total and free thyroxine (T_4) levels, and normal or borderline increased serum TSH (1). AHDS is caused by mutations of the thyroid hormone transporter, MCT8, that is crucial for a sufficient intracellular supply of thyroid hormones. This is particularly true for the central nervous system. The high expression of the MCT8 transporter in the placenta provides for the transfer of thyroid hormones from the mother to the fetus. Since it is possible that a poorly functioning placental MCT-8 transporter would limit the fetal supply of maternal T_4, the authors studied two mothers who were heterozygous for the AHDS gene.

METHODS AND RESULTS

Two mothers, each having given birth to a boy affected by AHDS, were carefully monitored during their second pregnancy. The first mother had moderate mental retardation and a history of transient hypothyroidism during her first pregnancy; she was now pregnant with twins, one female and one male. The second mother was euthyroid and mentally normal. She had a hitherto unknown mutation of the MCT8 gene. The male fetuses were tested for MCT8 mutations in utero, including direct sequencing of the fetal DNA from chorionic villi. Mutations of the MCT8 gene were excluded. In the first mother, thyroid function was tested every 2 weeks during the first trimester. In the second mother, the first thyrotropin (TSH) measurement was obtained at week 24. Fetal thyroid growth was assessed by ultrasonography, and thyroid function was indirectly monitored by following skeletal maturation, heart rate, mobility and growth.

During the first mother's first 12 weeks of pregnancy, free T_4 levels were decreased (5.6 to 7.6 pool/L; normal range, 11 to 19) without any variability of serum TSH (0.8 to 0.95 mU/L). The patient was treated with T_4 in increasing doses up to 150 µg per day starting at week 12 until after delivery. Despite this treatment, serum free T_4 levels remained below the normal range while serum TSH was invariably within the normal range. In the second mother, the free T_4 level at week 24 was 11 pool/L and the serum TSH 0.6 mU/L. The patient was treated with 50 µg of T_4. The three offspring were all normal at birth and during the first weeks postnatally.

CONCLUSIONS

MCT8 is an important transporter of T_4 into the cell. When mutated, such as in AHDS, cells are deficient in thyroid hormones and the affected children have severe hypotonia and mental retardation. Serum free T_4 levels are low and free T_3 levels high normal. MCT8 is strongly expressed in the placenta. In this article, two mothers heterozygous for an MCT8 mutation are described, one presenting with a spuriously low and the other with a frankly reduced serum free T_4 level without concomitantly increased serum TSH. The low free T_4 values were taken as an indication for thyroxine treatment during pregnancy. The nonaffected infants were normal.

COMMENTARY

It is unlikely that many endocrinologists will be confronted with the dilemma of treating mothers heterozygous for AHDS. The normal outcome of the pregnancies in two mothers heterogeneous for the AHDS gene, as reported in this article, does certainly not warrant the conclusion that T_4 treatment was beneficial. It was undoubtedly not harmful. Yet, this article stresses the importance of an isolated maternal low free T_4 level (in presence of a normal serum TSH level (<2.5 mU/L) for a possible delay in the cognitive functions of the offspring in early childhood. Endocrinologists and obstetricians are now well aware of the importance of closely monitoring thyroid function during pregnancy as well as in pregnant women with a history of present or past thyroid autoimmunity. These patients are likely to receive T_4 treatment, particularly if their serum TSH is above 2.5 mU/L. Less attention is given to serum T_4 levels. However, the remarkable experimental work of Obregon et al. focused on the pathogenic role of low maternal serum T_4 levels (2). Even without considering the special case of AHDS, the authors of this article were right in treating these mothers with thyroxine. In 1999, a clinical article appeared on the subject (3), and last year the first large scale study strongly emphasized the crucial role of low maternal free T_4 levels for the development of cognitive function in early childhood (4). At present, it is not yet clear whether the delayed maturation will be corrected in later life or whether it corresponds to a permanent defect. Nevertheless, endocrinologists and obstetricians must realize that a decreased or borderline low free T_4, despite normal serum TSH, in a pregnant woman needs attention and that treatment is recommended.

A technical note: The normal range of free T_4 values depend on the kit used in the laboratory. The differences between manufacturers can be substantial. Therefore, it is crucial that all laboratories report the origin of their material and their own normal range, which is still far from standard practice. Also pregnancy stage–dependent reference ranges for free T_4 are needed.

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