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The Phenotypes of TRα1 Mutations Can Greatly Vary

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Van Mullem AA, Chrysis D, Eythimiadou A, Chroni E, Tsatsoulis A, de Rijke YB, Visser WE, Visser TJ, Peeters RP. Clinical phenotype of a new type of thyroid hormone resistance caused by a mutation of the TRα1 receptor: consequences of LT_4 treatment. J Clin Endocrinol Metab 2013;98:3029-38. Epub April 30, 2013.

SUMMARY

Background

Since the description of T_3 receptors in 1987, many patients with T_3-receptor mutations have been described. These mutations were restricted to $T_3\beta$ receptor (TRβ) (1-3). It was only in 2012 that the first human case of a dominant mutation of the α1 receptor (TRα1) was described (4). The patient had clinically hypothyroidism, was mildly mentally retarded, was of short stature, and had skeletal dysplasias, while the predominant symptom was severe constipation. This is to be expected, since the intestine is highly endowed with TRα1. Biologically, the thyroid parameters were characterized by a normal serum TSH, a decreased free T_4 and increased T_3 and free T_3. In the present article, the authors review the cases of a daughter and her father who were affected by the mutation. The girl, the index case, has been followed clinically since the age of 6 years.

Methods

In vitro, the mutation was tested by functional analyses in cell cultures transfected with mutant TRα1 and/or nonmutant TRα1. The index patient was treated from the ages of 6 to 11 years with thyroxine. At the age of 8½ years, growth hormone treatment was begun. At age 11, thyroxine treatment was stopped for 35 days. While off treatment with thyroxine, and 7 months after restarting thyroxine, clinical analyses were performed. Thyroxine treatment for the father was also withdrawn for 35 days.

Results

In vitro, the mutated receptor was not only inactive but, in addition, it completely inhibited the activation of the normal TRα1 by T_3. The mutation is therefore of the dominant negative type. It also affected the functional activity of TRα1, but this could be overcome by higher T_3 doses.

The genetic analysis of the index case and her father revealed a heterozygotic mutation with an insertion of thymine at codon 397 (F397fs406X). The index patient had moderately impaired cognitive function; her mental age was retarded by 4 to 5 years. She was of short stature. Her pulse rate when off treatment was 88 beats per minute. The blood pressure and electrocardiogram were normal. Her pubertal age was 12. At the age of 3 years the patient was considered to have clinical hypothyroidism because of symptoms such as macroglossia, omphalocele, and congenital hip dislocation (5).

In the index patient and her father, thyroid hormone levels, when off thyroxine treatment, showed high serum T_3 and free T_3, a normal serum TSH, and a borderline decreased T_4 and free T_4. The T_3:T_4 ratio was clearly increased. When on thyroxine treatment, the index patient's serum T_4 levels normalized, as did the T_3:T_4 ratio, but serum TSH decreased to suppressed levels of 0.1 mU/L Before and after the interruption of thyroxine treatment, total and LDL cholesterol levels were clearly elevated despite high serum T_3 levels.

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Without thyroxine treatment, insulin-like growth factor I (IGF-I) levels tended to decrease and thyroxine treatment corrected the cholesterol and IGF-I values. In the index patient and her father, moderate constipation was present during thyroxine withdrawal but was corrected with treatment. The pulse rate in the index patient increased to 94 beats per minute while on thyroxine treatment.

Conclusions

Heterozygotic dominant negative mutations of TRα1 should be considered in a slightly retarded child with short stature and high serum T_3 levels but borderline low total and free T_4 levels. Serum TSH is not informative. When thyroxine treatment was withdrawn, constipation recurred but not in as severe a form as in the first case described. This indicates that the phenotype can be variable. Thyroxine treatment stimulated the TRβ-mediated effects (such as deiodinase type I, sex-hormone–binding globulin (SHBG), and TSH inhibition). Constipation is likely to be related to the mutated intestinal TRα1; unexpectedly, it seemed to respond to thyroxine treatment. The short period of thyroxine withdrawal did not allow obtain any information on possible cognitive effects of thyroxine.

ANALYSIS AND COMMENTARY

It is obvious that such cases should be discovered at birth in order for T_4 treatment to be started immediately. Only then would it be possible to see whether thyroxine has any beneficial effects on the most crucial of all TRα–mediated actions, that on brain development. Such treatment will, however, come with the price of overstimulating TRβ-dependent effects, such as TSH inhibition and stimulation of deiodinase type 1 activity; other effects, such as those on cholesterol and SHBG, are of minor consequence. Deiodinase type 1 activity is strongly dependent on TRβ-related effects, and this explains the high serum T_3 levels. Thus, it has been proposed to add PTU to the thyroxine to specifically inhibit deiodinase type I activity.

The thyroid hormone values (low T_4 and increased T_3) together with normal serum TSH should not be mistaken for other pathologies. Iodine deficiency and dyshormogenesis would have similar T_4 and T_3 levels, but serum TSH levels would be in the high normal range or increased. In the syndrome of resistance to TRβ, both T_4 and T_3 will be increased, while serum TSH is normal or slightly increased.

Most neonatal screening programs measure either serum TSH or T_4. In this particular situation, TSH screening will miss the mutation, as in the case of central hypothyroidism. Most children come to the attention of the pediatrician much later, when parents get worried about delayed development. Because of the nature of the mutation, a dominant negative one, treatment with thyroxine may be fraught with difficulties, even though these authors report that constipation, probably an α-dependent manifestation, was improved. In order to enhance the chances of an early diagnosis, a large-scale prospective study measuring both T_4 and TSH may be welcome.

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