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A New Form of Congenital Hypothyroidism with Normal Serum TSH Values Has Been Reported

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SUMMARY

Background

Thyroid hormone receptors are encoded by two genes that undergo alternative splicing. The known subtypes of thyroid hormone receptors are TRα1 (predominantly present in bone, the gastrointestinal [GI] tract, myocardium, and the central nervous system [CNS]), TRβ1 is predominant in hepatic and renal tissue and TRβ2 in the hypothalamus, pituitary, cochlea, and retina. Thyroid hormone resistance is a rare congenital disease (present in 1 in 40,000 total population), due, in most cases, to dominant negative mutations of the TRβ gene. In a few cases, the gene defect could not be identified (1).

Until now, no clinical case of mutation of the TRα gene has been reported, and it was suggested that these mutations were lethal. However, animal models indicated that the complete absence of TRα had only minimal effects in otherwise normal mice. Homozygous dominant negative mutations of the TRα receptor were lethal; the tissues depending on TRα stimulation were greatly affected. In contrast, heterozygous animals survived, although they had significant but varying phenotypes. The authors of this article describe the first human case of a de novo TRα mutation acting in a dominant negative manner, similar to the severely affected mutated mice.

Methods and Results

A 6-year-old girl of Caucasian origin, born to unrelated parents, presented with many of the stigmata of severe congenital hypothyroidism, including growth and developmental retardation, skeletal dysplasia, and extremely severe constipation. Physical examination revealed a large head and short legs. She had had delayed tooth eruption and, at 6 years of age had no secondary dentition. Her gait was slow, broad-based, and clumsy. The size of the thyroid was not mentioned. Radiographs showed multiple extra bone pieces (wormian bones) of the skull with a patent sagittal suture and alterations of the hip typical for hypothyroidism. X-rays indicated a markedly dilated bowel. Her heart rate was below the 10th percentile and her blood pressure was also low. The biochemical parameters showed a markedly decreased total and FT_4 and a high total T_3 and FT_3, and reverse T_3 was practically absent. The ratio of T_4 to T_3 was very low. Most interestingly, serum TSH was strictly normal (1.04 mU/L). As a marker of TRβ overactivity, serum hormone binding globulin was clearly increased even before treatment with thyroxine. Attempts at treating the patient with thyroxine were not successful, since the TRα-dependent parameters, such as heart rate, blood pressure, and metabolic rate responded poorly or not at all. However, serum TSH was completely suppressed, reflecting the normal functioning of TRβ-mediated thyroid hormone effects.

The mutation was identified by a method called "whole exome capture," rather than the cumbersome sequencing of the whole genome. A heterozygous nonsense mutation (E403X) was identified in TRα1, which was not present in either parent. Transfection studies in JEG-3 cells revealed the dominant negative character of this receptor. In other words, in the presence of a mutated receptor, the normal TRα could not be activated by T_3.

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Conclusions

The clinical presentation of this 6-year-old child could easily be confounded with the appearance of classical hypothyroidism characterized by growth and developmental retardation, skeletal dysplasia and extremely severe constipation. However, the biochemical data showed a normal serum TSH with low normal FT_4 and a high normal FT_3. Similar biochemical data can be found in the Allan–Herndon–Dudley syndrome, but the phenotype is completely different. This syndrome is due to a defect of a thyroid hormone transporter (2). The disease described here is due to a dominant negative mutation of the TRα gene (E403X). The patient was a heterozygote. The clinical phenotype could not be improved by L-T_4 treatment. It is likely that this syndrome is extremely rare. Interestingly, patients with thyroid hormone resistance due to TRβ mutations have a completely different clinical picture, often with some signs of tissue hyperthyroidism, such as rapid heart rate.

ANAYLSIS AND COMMENTARY

It is amazing how accurately genetic studies in mice predicted the human disease, in particular the TRα1(PV) mutant mouse, which shows marked growth retardation (3). While the absence of a functioning TRα gene has few phenotypic and biochemical consequences in mice (4), some dominant negative mutants produced mouse phenotypes similar to the human case (5). In mice, the homozygotes were lethal, whereas the heterozygotes were viable.

In the present patient, the lack of response to relatively high doses of L-T_4 is astonishing. It indicates that the mutation has a strong dominant effect. In patients with TRβ mutations, L-T_4 and/or Triac may improve the hyperthyroid state, but only in some cases. This indicates that the expression of the defect can vary greatly.

Can we make any deductions from this case concerning the treatment of the average patient with hypothyroidism? One may think about tissue-specific effects, but for the moment this remains speculative.

— Albert G. Burger, MD

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