T_3-PREDOMINANT GRAVES' DISEASE

Ito M, Toyoda N, Nomura E, Takamura Y, Amino N, Iwasaka T, Takamatsu J, Miyauchi A, Nishikawa M. Type 1 and type 2 iodothyronine deiodinases in the thyroid gland of patients with 3,5,3′-triiodothyronine-predominant Graves' disease. Eur J Endocrinol. October 11, 2010 [Epub ahead of print].

SUMMARY

INTRODUCTION

Triiodothyronine (T_3)-predominant Graves' disease is defined by elevation of the serum free T_3 level associated with normal or low free thyroxine (FT_4) level in patients with Graves' disease who are on antithyroid drug therapy (1). This contrasts with ordinary Graves' disease in which patients on antithyroid drugs usually attain normalization of both serum FT_4 and FT_3. The reasons for the predominance of T_3 secretion are unclear. In the euthyroid state, 80% of T_3 production is extrathyroidal, but in patients with Graves' disease, the majority of T_3 production is in the thyroid gland. This paper explores the basis for the increased production of T_3 in T_3-predominant Graves' disease.

METHODS

Studies were performed in 13 patients with T_3-predominant Graves' disease and 18 patients with "common-type" Graves' disease. The activity and mRNA of type 1 (D1) and type 2 (D2) iodothyronine deiodinase were measured in the thyroid glands removed at surgery from the group with T_3-predominant Graves' and the group with common-type Graves' disease.

RESULTS

The patients with T_3-predominant Graves' disease (GD) were significantly younger and had much larger thyroid glands as calculated by ultrasound measurements than the patients with common Graves' disease (Table 1). The thyrotropin (TSH)-receptor antibody levels of the T_3-predominant GD was 40-fold greater and the thyroid-stimulating antibody was 3-fold greater than in the patients with common GD. Deiodinase 2 activity in the thyroid tissue of T_3-predominant GD was much higher than in common GD tissue. Deiodinase 1 activity was also significantly higher in the T_3-predominant-GD as compared with the common-GD thyroid tissues. The activity of both deiodinase 2 and deiodinase 1 was positively correlated with the ratio of serum FT_3/FT_4 and with the TSH-receptor antibody or thyroid-stimulating antibody levels. The deiodinase type 1 mRNA was significantly greater in the T_3-predominant thyroid tissue as compared with the common GD tissue, but this was not found with regard to the deiodinase 2 mRNA. Deiodinase 1 activity was significantly correlated with the mRNA level.

The increased tissue activity of the thyroid deiodinases 1 and 2 explains the basis for the T_3 predominance as compared with ordinary GD. Presumably, the higher levels of the thyroid-stimulating antibody plays a role in this pathogenesis by stimulating the activity of both thyroid 5′-monodeiodinases, thus augmenting conversion of T_4 to T_3.

TABLE 1. Comparison of Various Parameters in 13 T_3-Predominant Graves' Disease and 17 Patients with Common Graves' disease.

	T_3-Predomant Graves' Disease	Common Graves' Disease
Age (yr)	36±12*	49±16
TSH (mU/L)	2.5±5.0	2.0±2.0
FT_4	0.89±0.79	0.87±0.15
FT_3	4.7±3.6*	2.4±0.4
FT_3/FT_4	6.6±3.0*	2.7± 0.5
TSH-receptor antibody	206±276*	5.0±4.7
TSI	1124±582*	350±338
Thyroid volume	227±126*	32±23
Thyroid D1 (pmol/mg/hr)	403±201*	321±152
D1 mRNA (U)	0.028±0.015*	0.016±0.014
Thyroid D2 (fmol/mg/hr)	824±596*	195±132
D2 mRNA (U)	0.545±0.276	0.404±234

* Indicates significant difference. TSI = Thyroid stimulating immunoglobulin

COMMENTARY

T_3-predominant Graves' disease was first described in 1984 by Junta Takamatsu (a coauthor of this study) et al., and shown to be a recalcitrant condition with regard to long-term cure by antithyroid drug therapy (1). The lack of remission can be predicted by the high level of TSH-receptor antibody. The frequency of this condition in relation to ordinary Graves' disease is unclear. I believe that it is relatively rare, but all of us have seen some of these patients in our practices. The current study explains the pathogenesis based on advances in our understanding of the two activating deiodinase enzymes that convert T_4 to T_3. However, gaps in our knowledge remain. Deiodinase 1 in peripheral tissues is stimulated by high levels of T_3, but this may contribute little to serum T_3 in this situation, since FT_4 is normal or low in T_3-predominant GD. The transcriptional regulation of D2 is stimulated by cyclic AMP that is generated in the thyroid by the TSH-receptor antibody (2). However, T_3 causes down-regulation of type 2 deiodinase by a posttranslational mechanism involving ubiquitin-mediated proteasomal degradation (2). The half-life of D2 is only 40 minutes; it is rapidly activated or suppressed. In hyperthyroidism, the activity of D2 is suppressed. The relative contribution of D1 and D2 to the thyroid's secretion of T_3 in hyperthyroidism is still unclear, and the relative contributions in this rare variant of Graves' disease still remain to be clarified. Nevertheless, the data of this recent contribution provide good evidence to show that thyroidal 5′-deiodinases are responsible for the elevated serum T_3 in T_3-predominant Graves' disease.

— Jerome M. Hershman, MD

References

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