Euthyroid Graves’ Disease and TSH Receptor Antibody

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Euthyroid Graves’ disease (EGD) is defined as an ophthalmopathy of Graves’ disease in euthyroid subjects. Euthyroidism is defined as a thyroidal state showing serum TSH concentrations that are within the normal range as well as normal free T4 and free T3. Before a sensitive immunoradiometric assay for TSH became available, EGD was diagnosed based on normal free T4 and free T3 alone. We should, therefore, pay close attention to the diagnostic criteria, when we read articles on EGD.

Patients with overt hyperthyroidism due to Graves’ disease do not always manifest apparent ophthalmopathy, but they are always accompanied by detectable TSH receptor antibody (TRAb). There are several subclinically hyperthyroid patients with detectable stimulating-type TRAb without ophthalmopathy (1), who are considered to have EGD in a broad sense. I would therefore like to suggest that Graves’ ophthalmopathy in euthyroid subjects should be called euthyroid ophthalmic Graves’ disease (EOGD).

TRAbs such as thyroid stimulating antibody (TSAb) and TSH-binding inhibitor immunoglobulin (TBII) are detected in a majority of the patients with EOGD. Our EOGD patients demonstrating several eye signs corresponding to class II-IV according to the American Thyroid Association Classification, who were either euthyroid or subclinically hyperthyroid, showed a prevalence of TSAb, ranging from 86.8-100 %, while that of TBII tended to be low, ranging from 12.0-46.7% (2-4). Similar results were obtained from 35 mostly euthyroid patients that showed normal TSH levels in 32 (91.4%) cases, with the prevalence of TSAb and TBII, being 82.9% and 28.6%, respectively (5). Further studies on the prevalence of TSH receptor antibodies in euthyroid patients, as well as in those with subclinical hyperthyroidism, as determined by TBII, TSAb and other newly developed assays are thus required.

There arises a question as to why EOGD patients remain euthyroid in spite of detectable TRAb levels in their serum. In an effort to answer this question, Suzuki et al. examined the pathological findings of the thyroids that were surgically obtained from EOGD patients complicated with thyroid cancer, and observed a normal appearance devoid of findings suggesting Hashimoto’s thyroiditis or Graves’ disease (6). On the other hand, previous studies investigating thyroid tissue obtained by needle biopsy have revealed various findings including Hashimoto’s thyroiditis, slight inflammatory or degenerative changes, epithelial hyperplasia and normal thyroid tissue (2-4, 7-9). This patient was negative for TgAb and TPOAb, with normal TSH levels and weakly positive TBI and TSAb levels in the serum (6). Antithyroid antibodies were negative or weakly positive in most of the previously reported studies (2-4, 8). Therefore, destructive changes due to Hashimoto’s thyroiditis in spite of stimulation by TRAb appear unlikely to be responsible for the sustained euthyroidism observed in most of these cases.

We reported that 44% of EOGD patients showed scintigraphic hot or warm lesions which are resistant to T3 suppression. Interestingly, the patients with such an uneven uptake had increased ophthalmopathy index scores and a longer history of illness (4). There were two cases in which the pathological findings were determined by a needle biopsy from a hot or warm lesions, and they revealed the presence of epithelial hyperplasia.

TSAb, especially TSAb/TBII, is known to correlate with Graves’ ophthalmopathy, and TBII is related to hyperthyroidism (7). TBII is more closely correlated with the goiter size and the Tc-99m thyroidal uptake (3). We speculate that chronic, mild stimulation of the thyroid by TRAb, with positive findings for TSAb, but negative findings or weakly positive findings for TBII, is not potent enough to cause overt hyperthyroidism, but it can cause the formation of such lesions, and also subclinical hyperthyroidism in some cases. Although the authors discussed that a small thyroid is unlikely to be a cause of euthyroidism, all thyroidologists know that an increase in the goiter size is related to high TBI levels, resistance to antithyroid drug treatments and the disease activity itself. T3 non-suppressibility as well as a lower TSH response to TRH in EOGD is known to be asso-
associated with a more potent activity of TRAb (2). Therefore, as the authors pointed out, TSAb in the patient’s serum, which was much less than that in patients with HG, was not strong enough to cause hyperthyroidism or even subclinical hyperthyroidism and histological changes, such as epithelial hyperplasia. In this regard, the role of TBII, which was also very weakly positive, may thus have been very important.

Finally as the authors pointed out, there may also be some unknown factors that influenced the in vivo actions of TRAb as determined by in vitro assays.

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References