Use of thyroid stimulating hormone receptor antibodies test in an outpatient endocrinology clinic for differential diagnosis of hyperthyroidism

Abstract. Objective. Antibodies (Abs) to the thyroid stimulating hormone receptor (TSHR) play an important role in the pathogenesis of autoimmune thyroid disease (AITD). We define the complex terminology that has arisen to describe TSHR-Abs, and discuss significant advances that have been made in the development of clinically useful TSHR-Abs assays. Methods. Literature review and discussion. Results. TSHR-Abs may mimic or block the action of TSH or be functionally neutral. Stimulating TSHR-Abs are specific biomarkers for Graves’ disease and responsible for many of its clinical manifestations. TSHR-Abs may also be found in patients with Hashimoto thyroiditis in whom they may contribute to the hypothyroidism. Measurement of TSHR-Abs in general, and functional Abs in particular is recommended for the rapid diagnosis of Graves’ disease, differential diagnosis and management of patients with AITD, especially during pregnancy, and in AITD patients with extrathyroidal manifestations such as orbitopathy. Measurement of TSHR-Abs can be done with either immunoassays that detect specific binding of Abs to the TSHR or cell-based bioassays, which also provide information on their functional activity and potency. Application of molecular cloning techniques has led to significant advances in methodology that have enabled the development of clinically useful bioassays. When ordering TSHR-Abs, clinicians should be aware of the different tests available and how to interpret results based on which assay is performed. The availability of an international standard and continued improvement in bioassays will help promote their routine performance by clinical laboratories and provide the most clinically useful TSHR-Abs results. Conclusion. Measurement of TSHR-Abs in general, and functional (especially stimulating) Abs in particular is recommended for the rapid diagnosis, differential diagnosis, and management of patients with Graves hyperthyroidism, related thyroid eye disease, during pregnancy, as well as in Hashimoto thyroiditis patients with extrathyroidal manifestations and/or thyroid-binding inhibiting immunoglobulin positivity. Keywords: Graves’ disease; hyperthyroidism; thyroid stimulating hormone receptor antibody
It is expected that the presence of TSHR-Ab is diagnostic of GD. Other causes of hyperthyroidism in clinical practice include various forms of thyroiditis, autonomously functioning thyroid nodule (AFTN), toxic multi-nodular goiter, gestational thyrotoxicosis, and exogenous intake of levothyroxine. In iodine-sufficient areas, the most common cause of hyperthyroidism is GD, followed by nodular thyroid disease and thyroiditis. However, according to the age and iodine sufficiency, a higher proportion of subjects may have toxic nodular goiter or silent thyroiditis [4].

The distinction between various causes of hyperthyroidism is important because the treatment differs with the etiology. The differential diagnosis of hyperthyroidism is performed with a combination of history, clinical examination, biochemical investigations, thyroid scintigraphy, TSHR-Ab test, ultrasound thyroid with Doppler, and follow-up of the patient through the natural history of the disease [5].

Unlike ultrasound and thyroid scintigraphy, which require specialized equipment, the TSHR-Ab test can be performed with automated hormone analyzer platforms with short turnaround times. This has made the TSHR-Ab test an effective method to diagnose GD. A meta-analysis showed that the overall pooled sensitivity and specificity of the second- and third-generation TSHR-Ab assays are above 97 % [6].

The incorporation and early utilization of TSHR-Ab into current diagnostic algorithms conferred a 46 % shortened time to diagnosis of GD and a cost saving of 47 % [7]. The American Thyroid Association and the European Thyroid Association recommend the use of TSHR-Ab for the diagnosis of GD [8, 9].

However, there are various limitations in the interpretation of TSHR-Ab. This includes the types of assays used, bioactivity of TSHR-Ab, and the presence of TSHR-Ab in people with other autoimmune diseases, thyroid diseases, and even non-autoimmune diseases. Further, the cut-offs of TSHR-Ab for optimum diagnosis vary according to the type of the assay and manufacturer, leading to variable sensitivity and specificity of the assays.

In subjects with suppressed TSH, diagnosing GD will make a difference in management.

M. John et al. [10] assessed the utility of TSHR-Ab to differentiate GD from non GD in subjects with suppressed TSH. The TSHR-Ab test performed with an electrochemiluminescence immunoassay using the cut-off recommended by the manufacturer (1.75 IU/l) had a high sensitivity for diagnosis of GD. However, at this cut-off, the specificity of the assay was 62.9 %. Using an ROC curve analysis, authors derived an optimal cut-off of 3.37 IU/L, which gave an overall pooled sensitivity of 89.9 % and specificity of 91.1 %, respectively .

The sensitivity of TSHR-Ab for diagnosis of GD has improved with the use of third-generation assays. However, at this cut-off, the specificity of the TSHR-Ab was less likely to be positive beyond the initial period of diagnosis. It is well known that the serum levels of TRab reduce in subjects with prolonged illness because of GD on autoimmune thyroid diseases. This has been suggested to be because of waning autoimmunity [11]. The cut-offs recommended by the manufacturer are usually used for various tests. In six subjects with GD (4.1 %), the TSHR-Ab levels were less than 1.75 U/l.

Although the sensitivity of TSHR-Ab for diagnosis of GD has improved with the use of third-generation assays, GD subjects with negative TSHR-Ab are documented in various studies. In a study involving 440 subjects with various forms of thyrotoxicosis, 18 % of the subjects with GD were found to be negative for TSHR-Ab. Subjects negative for TSHR-Ab had lower levels of free T3 and free T4, a lower probability of smoking, higher antithyroid peroxidase, and a higher risk of orbitopathy [12].

In another study using multi-modality imaging for the diagnosis of GD, the sensitivity and specificity of TSHR-Ab were 93 % and 91 %, respectively [13]. Studies have also shown that there is a reduced risk of relapse of GD after stopping therapy in people who were TSHR-Ab-negative at diagnosis and throughout treatment in comparison with TSHR-Ab-positive GD [14]. Histological studies have shown that there is a distinct histological pattern in TSHR-Ab-negative GD characterized by less severe papillary hyperplastic epithelia and enlarged colloid and more lymphocytic infiltration [15].

In general, TSHR-Ab-negative GD seems to be a less severe form of GD in comparison to TSHR-Ab-positive GD [15]. Diffuse technetium uptake in scintigraphy with thyrotoxicosis with absent TSHR-Ab may be seen in germ-line mutation of the TSH receptor or in a sub-set of subjects with toxic multi-nodular goiter. In a series of 89 subjects with TSHR-Ab-negative thyrotoxicosis and diffuse goiter, 4.5 % had germline mutations in the TSH receptor. In this study, 10 % of TSHR-Ab-negative patients without mutations subsequently became TSHR-Ab-positive [16].

TSHR-Ab may mimic or block the action of TSH or be functionally neutral. Stimulating TSHR-Ab are specific biomarkers for GD and responsible for many of its clinical manifestations.
Conclusion
The TSHR-Ab test is a sensitive test to differentiate between subjects with GD and non GD presenting with hyperthyroidism. In subjects with discordance between clinical features and TSHR-Ab, thyroid scintigraphy should be considered.

References
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Результати. AT-rТТГ можуть імітувати або блокувати дію ТТГ чи бути функціонально нейтральними. Стимулюючі AT-rТТГ є специфічними біомаркерами хвороби Грейвса (ХГ) і відповідають за її клінічні прояви. AT-rТТГ також можуть бути виявлені у пацієнтів з тиреоїдитом Хашімoto, у яких вони можуть сприяти виникненню в подальшому гіпотиреозу. Визначення AT-rТТГ можна проводити за допомогою імунологічних аналізів, які виявляють специфічне зв'язування AT з rТТГ, або аналізів, які також надають інформацію про їх функціональну активність і ефективність. Застосування методів молекулярного клонування призвело до значного прогресу в методології, що дозволило розробити клінічно корисні біологічні аналізи. Рецептори до ТТГ внаслідок взаємодії з тиреостимулювальними антитілами при ХГ або з надлишком ТТГ при первинному гіпотиреозі відіграють роль автоантигена, ініціюючи автоімунний процес. Існують свідчення, які вказують на пряму кореляцію рівнів AT-rТТГ із клінічною активністю автоімунного процесу, що визначає тяжкість та прогноз захворювання. Рецептор ТТГ містить домен і для стимулюючих, і для блокуючих антитіл. При ХГ стимулюючі імуноглобуліни, зв'язуючись із rТТГ, імітують стимуляцію щитоподібної залози за допомогою ТТГ, що призводить до гіпертиреоїду. Частка стимулюючих антитіл становить близько 60–80 %, проте при сумарному визначенні антитіл поєднання ефекту стимулюючих та блокуючих анти- тіл може призводити до розбіжностей клініко-лабораторних даних у пацієнта. Висновок. Вимірювання AT-rТТГ (особливо стимулюючих) рекомендується для швидкої діагностики, диференційної діагностики і лікування пацієнтів з ХГ, ендокріною орбітопатією.

Ключові слова: хвороба Грейвса; гіпертиреоз; антитіла до рецептора тиреотропного гормона