INTRODUCTION

Thyroid-stimulating hormone (TSH) is the major regulator of thyroid growth and function in the adult. The lack of TSH or its ability to activate TSH receptors (TSHR) mutations impairs the thyroid functions leading to hypothyroidism. In contrast, pathologically elevated serum TSH levels, TSHR stimulating antibodies or constitutively activating TSHR mutations stimulate thyroid hormone production and thyroid growth, leading to hyperthyroidism and goiters. TSH regulates the thyroid function via its G-protein-coupled TSH receptors (TSHR). Data from patients with TSHR mutations, in vitro and in vivo studies have shown that TSHR function is often impaired in the absence of the stimulatory or inhibitory binding partners (i.e., the activating or inactivating mutations) and increases the intracellular cyclic AMP (cAMP) pathway. However, higher TSHR concentrations can also activate the inhibitory signaling, resulting in the activation of phosphatase, cAMP, and an increase in intracellular calcium levels. This signaling pathway has been suggested to play a role in some pathologies of patients with TSHR resistance or in receptor-gene development, but unlike demonstrated in other GPCRs the exact physiological impact of the TSHR mutations remains unclear. In humans, the TSHR is located in a wide range of tissues. It is also a target of thyroid stimulating or blocking antibodies, which can be detected in “Graves’ disease” and autoimmune hyperthyroidism. The mutations in TSHR, either in humans or in rodents, provide a novel model to study and lead to constitutively hyperfunctioning TSHR (NAHT) with minimal interference in a variable degree of TSH resistance (SNAHT), especially in GPR. The gain of function due to constitutively activating mutations (CAM) in the TSHR presents the most common cause for NAHT. The TSHR CAMs can be identified from a spectrum of hyperthyroid phenotypes including familial constitutively activating dominant hyperthyroidism (FNAHT), sporadic congenital constitutively hyperthyroidism (SNAHT), and in rare cases of cases NAHT with SNAHT have been published. These TSHR CAMs typically lead to increased basal production of cAMP and eventually also to a simultaneous increase in thyroid hormone production in thyroids. This thyroid independent TSHR activity stimulates thyroid hormone synthesis and leads to hyperthyroidism, which is usually manifest and requires ablation therapy to avoid thyrotoxicosis. Therefore, it is recommended that all patients with non-autoimmune hyperthyroidism should be evaluated for the TSHR activating mutations.

Family with NAHT

CONCLUSIONS

1. In the event of non-autoimmune hyperthyroidism in a patient, it is worthwhile to deepen the family history and perform genetic tests to identify a possible gene mutation in the TSHR receptor.

2. Proper diagnosis determines the application of effective radical treatment.

3. The diagnosis of activating mutation at the TSH receptor will allow for careful observation of the patient and possible early implementation of appropriate treatment.