

HEREDITARY ACTIVATING MUTATIONS OF THE TSH RECEPTOR LEAD TO HYPERTHYROIDISM

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SUMMARY ●●●●●●●●●●●●●●●●

BACKGROUND

Hereditary activating mutations of the TSH receptor can lead to hyperthyroidism. In 1982, the first description of a familial form of hyperthyroidism (familial nonautoimmune hyperthyroidism, in short: familial form) was published. The first author of the original article is now the senior author of the article under discussion. In 1995, sporadic forms of hyperthyroidism due to activating mutations of the thyrotropin (TSH) receptor were described. Many other cases of both forms have been added since then. They are characterized by diffuse hyperactivity of the whole thyroid. To this list can be added autonomous adenomas, well known to the clinician and often referred to as warm and/or toxic nodules and rare cases of hot thyroid carcinomas. In many of these adenomas, activating mutations have been discovered. Occasionally, these tumors do not bear a TSH-receptor mutation but have a constitutive activation of Gs proteins leading by this pathway to an activation of the cAMP pathway. This mechanism is also responsible for hyperthyroidism in the McCune-Albright syndrome. This is, however, a multiorgan disease, the mutations also being expressed in other cell types.

Finally, mutations of the TSH receptor have been reported that are not constitutively activating but have a higher affinity for luteinizing hormone and human chorionic gonadotropin. Hyperthyroidism develops in women during pregnancy.

RESULTS

The authors concentrate mainly on the familial and sporadic form of nonautoimmune hyperthyroidism. By 1997, five families comprising 49 patients with an activating germline mutation of the TSH receptor had been identified. The present review comprises the medical history of 152 patients with the familial form coming from 27 families and 15 sporadic cases.

The familial forms have an autosomal dominant inheritance with no sexual predominance. In recent years, the clinical identity of both forms is becoming better known, since the number of cases described has been increasing at an accelerated speed. The supplementary tables are particularly interesting to study. Familial hyperthyroidism is rarely present at birth. The clinical picture develops occasionally in infancy but most frequently during adolescence and up to 30 years of age. An initial presentation of a familial form has even been described at the age of 48. When investigated, there was diffuse increased uptake of the thyroid and the volume of the thyroid was not always increased; in 26 of 97 cases, thyroid volume was even normal. In some rare cases, thyroid nodularity was seen. The clinical manifestations of hyperthyroidism are variable, even within different members of the same family bearing the same mutation.

In contrast to the familial form, sporadic cases occur without exception at birth or during the first year of life. They are clinically more severe than the familial forms, yet the severity is not uniform but widely variable. One explanation concerns the activity of the mutated TSH receptors. The mechanisms are, however, likely to be more complex.

In familial forms, exophthalmos was never described. Interestingly, the sporadic forms show some signs of eye changes that could be confused with exophthalmos. Prominence of the eyes, exophthalmia, and staring eyes are likely to be slightly different forms of description of the same sign: a protrusion of the eyes in the small orbits of neonates. It is nevertheless interesting that for unknown reasons, hyperthyroidism in neonates seems to increase the volume of the orbital tissues.

At present, most cases described have been in Europe and only two in the United States. The authors believe that this may be due to the more definitive treatment in the United States. When conservatively treated,

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recurrences can be expected in nearly all cases. Absence of autoimmune parameters may have been the major trigger for more detailed investigation of these cases.

The identified mutations are described in detail in the tables and shown in one figure. The localization of most of these mutations is in the transmembrane part of the receptor protein, even though two mutations are described in the extracellular component. It is interesting to see that the localization of some mutations of the sporadic form coincides with the familial form. The missing information is the number of cases that have shown in vitro that the mutation plays the dominant role in activation of the thyroid cell.

By definition, autoimmunity is absent; by light microscopy, diffuse hyperplasia without any infiltration is seen. Circulating antibodies are absent in the familial form even though in the sporadic form antithyroid peroxidase and antithyroglobulin

antibodies have occasionally been detected. In one case TSH-receptor-inhibiting antibodies were borderline positive.

In the 14 of 15 cases of the sporadic form, there was either prematurity, low birth rates, small goiter at birth, occasional craniosynostosis, and in approximately 60% mental retardation. Survival of these children means that the disease will be inherited by their offspring.

The underlying biologic defects of the familial and sporadic forms and of the autonomous adenomas are supposed to be indistinguishable: it consists in an activation of the cAMP cascade that is responsible for cell growth. Yet there are important quantitative differences since for diffuse goiter, one needs only one or two replications for increasing the functional mass and developing a small goiter while for adenoma one single cell needs to replicate many times in order to create a little tumor.

COMMENTARY ●●●●●●●●●●●●●●●●

In 1982, the first publication regarding the syndrome of familial nonautoimmune hyperthyroidism encountered a lot of skepticism. At that time, it was still difficult to measure thyroid-stimulating antibodies and in many patients with Graves' disease the antibodies could not be detected. Today, the two forms of genetic hyperthyroidism are well accepted, but despite the marked increase in reported cases, these forms of hyperthyroidism remain rare. The autonomous adenomas are a separate entity having in common the underlying biologic mechanisms: stimulation of the cAMP cascade by presumably constitutively active TSH receptors. Recent studies indicate, however, that the relation between the clinical presentation and the in vitro activity of the constitutively active TSH receptor is poor (1,2). It has been suggested that additional concomitant mutations and/or environmental factors (e.g., iodine supply) may have to be taken into consideration.

In the Caucasian population, toxic adenomas with activating mutations are found in 40 to 50% of patients, and it is likely that this percentage is lower in the Asian population. Other mechanisms of constitutive activation in adenomas need to be discovered.

The clinical findings that the familial forms appear not at birth but between adolescence and 30 years is puzzling. The authors suggest that this can be explained by a slow replication of the mutated cells leading slowly to an increased number of autonomous cells. The clinician would therefore expect a progressive and slow decrease of serum TSH, but this clinical information is known for warm nodules evolving to toxic ones but not for the diffuse forms of hereditary forms of hyperthyroidism.

Chronic stimulation of thyroid cells favors the appearance of papillary cancers. At present, the number of cases is too small to lend support to this hypothesis. With increased numbers of cases, these forms of hyperthyroidism may yield important new information.

For the clinician, the sporadic forms are easy to differentiate from neonatal Graves' disease. Clinical history and positive tests for TSH-receptor antibodies as well as the self-limited duration of neonatal Graves' disease allow the differential diagnosis. For the familial form with later onset, the family history is always crucial. Yet in Graves' disease we can also find parents with a history of hyperthyroidism. Even today, we still encounter patients with hyperthyroidism who have diffuse goiter and no TSH-receptor antibodies, and thyroid histology, if available, does not always show

evidence of autoimmune disease. Are these cases that we missed? What could be the clinical consequences? Patients certainly are eager to know about any familial risk, and they are entitled to this information. Fortunately, in the familial forms the severe neonatal forms are most uncommon. The sporadic forms survive now, and future generations may be at risk. In these very rare cases, it seems to me that genetic counseling is desirable.

— Albert Burger, MD

References

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