Syndromes of resistance to TSH

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Résumé

La résistance à l’action de la TSH est une affection génétique se caractérisant par des altérations moléculaires compromettant la transmission à l’intérieur des thyrocytes du signal stimulant de la TSH. En principe, chacune des étapes de la cascade d’événements suivant la liaison de la TSH à son récepteur (R-TSH) est susceptible d’être défaillante. L’expression phénotypique de la résistance à TSH est très variable: depuis l’hypothyroïdie congénitale sévère avec hypoplasie, jusqu’à l’accroissement isolé et discret de la TSH coïncidant avec une apparence de parfaite euthyroïdie. Les formes sévères résultent d’une transmission héréditaire récessive et s’observent chez les patients exprimant des mutations dialleliques à l’origine d’une perte de fonction sévère du récepteur de TSH. En ces circonstances, il importe d’exclure toute autre cause de dysgénésie thyroïdienne isolée. À l’inverse, les formes les plus discrètes surviennent chez les patients exprimant une altération monoallélique, liée à une transmission héréditaire dominante. Dans ces situations, nous avons décrit l’effet de dominance négative qu’exercent certains mutants sur l’activité du récepteur codé par l’allèle sauvage. Ce sont les situations de thyropathies autoimmunes et aussi de pseudohypoparathyroïdie impliquant des altérations du gène GNAS qu’il convient alors de distinguer. Le projet de cette revue est de préciser la variabilité d’expression de la maladie.

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Mots clés : Hypothyroïdie congénitale ; Récepteur de TSH ; Résistance à TSH

Abstract

The resistance to TSH action is a genetic disease characterized by molecular defects hampering the adequate transmission of TSH stimulatory signal into thyroid cells. In principle the defect may affect every step along the cascade of events following the binding of TSH to its receptor (TSHR) on thyroid cell membranes. The phenotypic expressivity of TSH resistance is highly variable going from severe congenital hypothyroidism (CH) with thyroid hypoplasia to mild hyperthyrotropinemia (hyperTSH) associated with an apparent euthyroid state. More severe forms follow a recessive pattern of inheritance and occur in patients with biallelic mutations both causing a severe loss of TSHR function. Differential diagnosis in these cases includes the exclusions of other causes of isolated thyroid dysgenesis. Mildest forms may instead occur in patients with monoallelic TSHR defects following a dominant mode of inheritance. In these cases we described the dominant negative effect exerted by some mutants on the activity of the receptor encoded by the wild type allele. In these cases, differential diagnosis involves the exclusion of autoimmune thyroid disease or pseudohypoparathyroidism associated with defects at the GNAS locus. This review will focus on the variable clinical expression of this disease.

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1. Clinical and biochemical phenotypes of thyroid stimulating hormone resistance

TSH resistance (OMIM # 275200) is a condition of thyroid refractoriness to TSH stimulation [1–3]. Loss-of-function (LOF) TSHR mutations have been recognized as the molecular defect in most familial cases of TSH resistance. TSH resistance is characterized by high levels of serum TSH, normal or reduced levels of serum thyroid hormone and normal or hypoplastic thyroid gland. Depending on the degree of TSH insensitivity, the presentation may be extremely variable, ranging from severe congenital hypothyroidism (CH) to only mild elevations of TSH in the absence of hypothyroidism (Table 1).

TSH resistance was considered a rare condition. However, a Japanese group very recently reported the systematic analysis of TSHR gene in CH [7]. Hypothesizing that the frequency of TSHR mutations follows a Hardy-Weinberg distribution, the prevalence of heterozygous TSHR mutation carriers was calculated to be as high as 1:172. Though a major role seems to be played by a particular variant allele (R450H), these data indicate LOF TSHR mutations as one of the most frequent genetic causes of CH. Accordingly, several groups including ours are observing that LOF TSHR mutations may be a frequent finding in juvenile non autoimmune hyperthyrotropinemia (hyperTSH) [3].

As TSH is the major physiological stimulus of both thyroid function and proliferation, a profound reduction of thyroid sensitivity to TSH, as observed in patients with complete TSH resistance, leads to severe hypothyroidism with a hypoplastic thyroid gland. Because of reduced thyroid hormone feedback, TSH is markedly elevated and positive at the neonatal screening for congenital hypothyroidism. In the first description by Abramowicz et al. [4], thyroid hypoplasia was so profound and radioiodine uptake so impaired that thyroid agenesis was diagnosed at scintigraphy. However, the presence of thyroid tissue was disclosed by detectable serum thyroglobulin levels.

When thyroid refractoriness to TSH is incomplete, a condition known as partial TSH resistance, TSH elevation can somewhat compensate for the reduced sensitivity of the thyroid and milder forms of hypothyroidism are seen [5]. Patients typically have a thyroid gland of normal/reduced size, high TSH levels, but concentrations of free thyroid hormones in the normal range.

More recently, we described some families with mild elevations of TSH levels and a normal thyroid gland, in which the defect was caused by heterozygous TSHR mutations [6]. Similar alterations can be found in heterozygous relatives of patients with biallelic TSHR mutations [1–3,8]. Although such cases can be positive at neonatal TSH screening, they are generally diagnosed later on in life when they can be easily confounded with the more prevalent condition of subclinical hypothyroidism due to autoimmune thyroid disease (AITD).

2. Differential diagnosis

The occurrence of elevated TSH serum levels in the presence of low/normal free T4 concentration and thyroid volume is rather frequent in the general population. However, only a minority of these patients are affected with TSH resistance. So, the diagnostic workup should exclude other potential causes such as AITD, defects in TSH molecule and biological activity or other forms of congenital primary hypothyroidism, including abnormalities in thyroid transcription factors.

Differential diagnosis with AITD, by far the most frequent cause of TSH elevations in the adult population, is based on clinical history, biochemical evaluation of anti-thyroid antibodies and thyroid ultrasound. The positivity of anti-thyroid antibodies and/or the presence of the typical heterogeneous hypoechoic pattern at ultrasound are strongly suggestive of AITD. Other elements in favor of AITD are diagnosis reached in adult/advanced age as well as progressive evolution from subclinical toward overt disease. The only exception is represented by the accidental association of TSH resistance with AITD [9].

Some patients with central hypothyroidism may have elevated serum TSH levels. These alterations are generally found in patients with hypothalamic hypothyroidism but can also occur in the presence of TSHβ mutations. Despite high serum concentrations of the immunoreactive hormone, TSH biological activity is reduced which explains the condition of hypothyroidism [10]. The presence of TSH molecules with decreased bioactivity may be revealed by testing their potency in vitro.

Complete TSH resistance due to LOF TSHR mutations can lead to CH with thyroid gland in situ. Other known causes are defects in thyroid transcription factors, such as NKK2.1 or PAX8 [11]. Due to the expression of these transcription factors in tissues other than the thyroid, complex phenotypes have been reported in these cases. Patients with NKK2.1 mutations generally have typical neurological manifestations (choreoathetosis) and may also have pulmonary disease (respiratory distress or recurrent infections). PAX8 mutations generally cause isolated forms of CH but can be suspected in the presence of kidney abnormalities. The eventual involvement of these factors can be excluded by genetic analysis.

TSH resistance can also occur in the context of the multiple hormone resistance syndrome (Albright’s Hereditary Osteodystrophy) caused by inactivating mutations or reduced expression of the GNAS gene encoding the Gsα protein [12]. The presence of high PTH levels associated with hypocalcaemia and hyperphosphatemia, as well as the typical facies (i.e., obesity, short stature) are suggestive of this disorder.

3. Molecular genetics

About 50 different TSHR LOF mutations have been documented to be responsible for TSH resistance [3]. However, some cases of TSH resistance not associated with TSHR or GNAS mutations have been reported suggesting the probable involvement of other still not identified genes. Indeed, candidate genes include those belonging to the TSHR dependent intracellular pathways (Fig. 1).

In the earlier studies in which only probands with large TSH elevations were screened for mutations, the disease was linked to homozygous or compound heterozygous mutations and was described to follow a recessive pattern of inheritance. More
Table 1
Classification of TSH resistance upon the degree of thyroid refractoriness to TSH stimulation.

<table>
<thead>
<tr>
<th>Degree of resistance</th>
<th>Inheritance</th>
<th>TSH levels</th>
<th>Free T4 levels</th>
<th>Original reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>Recessive</td>
<td>↑↑↑</td>
<td>Low</td>
<td>Abramowicz et al., 1997 [4]</td>
</tr>
<tr>
<td>Moderate</td>
<td>Recessive</td>
<td>↑↑</td>
<td>Normal</td>
<td>Sunthornthepvarakul et al., 1995 [5]</td>
</tr>
<tr>
<td>Mild</td>
<td>Dominant</td>
<td>↑</td>
<td>Normal</td>
<td>Alberti et al., 2002 [6]</td>
</tr>
</tbody>
</table>

recently, we described patients with a mild form of partial TSH resistance due to heterozygous TSHR mutations. In these cases, the defect had a dominant pattern of inheritance. Such genetic heterogeneity is well reflected by diversity of clinical presentation.

Natural mutations leading to resistance to TSH action are distributed all along the receptor backbone and affect either the extracellular or transmembrane domains. Most of these mutations are associated with a defective cAMP response to TSH stimulation. However, two receptor variants affecting predominantly the Gq transduction pathway have also been reported [3].

The molecular mechanisms responsible for the loss of receptor function are probably multiple. Lack of receptor expression on the plasma membrane, ligand binding or coupling with G-proteins may be expected in case of mutations causing the synthesis of a truncated receptor. Initially, all missense mutations located in the extracellular domain were thought to alter ligand binding. However, several exceptions to this rule have now been reported. For instance, mutations C41S and I167N lead to a profound alteration of TSHR native conformation which hampers receptor targeting to the cell membrane. In contrast, mutations located in the transmembrane domain may result either in defective transmission of the stimulatory signal or in deranged routing of mutant TSHR to the cell plasma membrane. The mechanism of TSH resistance in patients with heterozygous TSHR mutations is less obvious. We recently demonstrated the presence of an in vitro dominant negative effect exerted by some of these mutants at the level of wild-type receptor maturation and routing to the cell membrane [8]. In fact, in cells co-transfected with wild type and mutant TSHRs, we observed a reduction of both basal and TSH-stimulated cAMP production as compared to that of cell transfected with wild type receptor alone. In addition, the co-expression of mutant TSHRs caused intracellular entrapment, mainly in the endoplasmic reticulum of wild-type receptor. Finally, we documented, by fluorescence resonance energy transfer and co-immunoprecipitation, the existence of a physical interaction between wild type and mutant receptors. Based on these data, the occurrence of TSH resistance in these cases appears to be due to a reduction of the amount of wild-type TSHR present at the cell membrane caused by oligomerization with intracellularly retained TSHR mutants [8,13].

4. Concluding Remarks

Several issues about TSH resistance remain to be addressed. First, some well-documented cases are not associated with mutations in TSHR coding regions. In these cases, one can propose the involvement of various mechanisms:

- variations of TSHR gene not detectable by conventional sequencing;
- genetic variations affecting the elements downstream to TSHR along the intracellular pathways stimulated by TSH;
- abnormal expression of TSHR gene.

Another debated point is whether to treat or not patients with apparently well-compensated TSH resistance. Several clinical evidences suggest that treatment may not be necessary. In fact, most of these patients were diagnosed in childhood or adult age and had quite a normal somatic and neurological development despite untreated since neonatal age. Moreover, one patient reported by our group was diagnosed at neonatal TSH screening but was not treated with L-thyroxine because of thyroid hormone levels close to the upper limit of the normal range. His growth and neurological performances are excellent without L-thyroxine supplementation. However, no general rule can be derived from these limited observations and a decision about starting or not therapy should be made in every single patient. In case no therapy is established, we advise a close clinical and biochemical follow-up, including skull MRI in order to disclose a possible pituitary hyperplasia. However, no pituitary hyperplasia was so far reported in untreated patients with TSH resistance diagnosed during adulthood. In addition, particular attention should be given to conditions in which thyroid hormone requirements are increased, such as puberty or pregnancy, as well as to
any insult to the thyroid gland, e.g. AITD that may easily turn euthyroid hyperthyrotropinemia into overt hypothyroidism.

Disclosures of interest

The authors declare that they have no conflicts of interest concerning this article.

References