The expanding spectrum of thyroid hormone resistance concerns the entire medical field

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L’extensif domaine des résistances aux hormones thyroïdiennes concerne désormais la totalité du domaine médical

In 1967, Samuel Refetoff, Loren Dewind and Leslie DeGroot reported in Chicago a familial syndrome combining deaf-muteness, stippled epiphyses and goitre, in occurrence with an increase in protein-bound iodine (PBI) [1]. At that time, concentrations of iodothyronines were not measured, and the PBI was the reflection of the iodine bound to the thyroid hormones. Despite this biological evidence of hormonal inflation, the concerned subjects expressed no signs of thyrotoxicity. For this reason, the authors sensed that this new entity might have arisen from thyroid hormones that were refractory to exerting their usual tissue effects in the target organs. Indeed, in this observation, inability of supplementary doses of thyroid hormones to exert their usual effects on TSH secretion and the metabolic state was established. In the family, in which the parents were blood relatives and the mode of transmission was autosomal recessive, it was secondarily established that the genetic abnormality originated from a homozygous complete deletion of the TRB gene, responsible for the absence of β receptor formation [2]. In fact the effect of the active T3 and T4 thyroid hormones is expressed at the TRα1 and TRα2 nuclear receptors coded by the TRα genes located on chromosome 17, and at the TRβ1 and TRβ2 receptors coded by TRβ on chromosome 3. In reality only TRα1, TRβ1 and TRβ2 bind thyroid hormones. Additionally TRα1 and TRβ1 are ubiquitous. TRα1 is predominant in the myocardium, skeletal muscle and brown adipose tissue. TRβ1 is highly expressed in the liver, kidneys, bone and cochlea, while TRβ2 is present in the anterior pituitary and cochlea. This original model of resistance to iodothyronines has remained a unique example. Beginning in the 1970s however, the widespread use of assays for T3 and T4 thyroid hormones and TSH led to the discovery of a growing number of instances of inappropriate TSH secretion, in which...

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normal or moderately increased values of TSH occurred with elevated blood levels of thyroid hormone. Well over 3000 cases have now been reported [3]. The hormonal changes related to the states of resistance of the pituitary gland and the peripheral tissues to the action of the thyroid hormones should be differentiated from methodological artefacts, and thyrotropin-secreting adenomas [4]. The resistance is generally partial, generalized so that the majority of affected patients have a eumetabolic state, and normal concentrations of sex hormone-binding protein (SBP), a sensitive marker of the action of thyroid hormones. The resistance can however be more selectively pituitary, so that the individuals establish a hypermetabolic state, suffering from nervousness or cardiac hyperexcitability. Up until now no studies have demonstrated any difference in these populations in the genetic basis for resistance. Transmitted by dominant autosomal mode, this results from a heterozygous point mutation of the TRB gene, which leads to inhibition of the wild-type gene, according to the so-called dominant negative mechanism [5] negative mechanism. Our team was among the first to show that the familial states of resistance to thyroid hormones can occur in the absence of identifiable TRB mutation, at an estimated proportion of 15 to 20% of cases. This suggests the implication of other genetic alterations, involving co-activation or co-repression [6,7]. The majority of clinically stable cases can benefit from monitoring or sometimes beta-blocker medication, although therapeutic trials have emphasized the possible benefit of D-Thyroxine or triiodothyroacetic acid on slowing TSH and thyroid production [8].

A description was made in 2004 of states in which hormonal resistance did not result from an alteration of the thyroid hormone nuclear receptors, but from an impairment of intracellular transport [9,10]. This latter uses organized anion transporters, including OATP (organic anion-transporting polypeptide) expressed in the various tissues (hepatocyte, kidney, muscle, brain); it also uses monocarboxylated transporters, which are specifically involved in the transport of thyroid hormones MCT10, and MCT8, the gene of which is located in Xq13.2. MCT8 mutations determine extremely severe X-linked mental retardation, which only affects boys and is transmitted by phenotypically unaffected mothers. It is associated with major hypotonia, with muscle hypotrophy and possible dyskinesias, without auditory disorders. The identity of this state with the Allan-Herndon-Dudley syndrome described in 1944 has been established [11]. We showed that the general and nutritional state of this disorder could be improved through the combination of propylthiouracil (which reduces the activity of type 1 deiodinase and reduces the level of T3) and high doses of levothyroxine for re-establishing hormonal equilibrium, though without improving the psychoneuromotor condition [12]. This supports current efforts in testing the benefits of thyromimetics (DITPA, TETRAC, TRIAC) [3].

Up until now, there have never been reports of impaired sensitivity to thyroid hormones involving genetic alterations of deiodinases (type 1 and 2), which contribute in the peripheral tissues and pituitary gland to the activation of thyroxine to triiodothyronine. In 2004 however, mutations were described on the SBP2 (selenocysteine insertion sequence-binding protein 2, or SEISBP2) genes coding for selenoproteins, which are co-factors of deiodinases [13]. In the initial family, the parents who were from the same Bedouin family, had a heterozygous R540Q mutation. Three of the seven children were homozygotes for the mutation, had growth delay, low T3 levels, increased T4 and rT3 and slightly increased TSH. The condition was also observed in other families from Ghana, Brazil or mixed African-European heritage with analogous phenotypes, often with intellectual developmental and auditory disorders and some original features. The therapeutic effects of T3 seem to be more significant than that of selenium [3].

For a long time TRA gene mutations remain undiscovered. They were considered probably fatal, or of a bone phenotype without alterations of the hormonal state, since the α receptor is scarcely expressed in the anterior pituitary gland. The first observation, reported in 2012, concerned a small 4-year-old girl with growth and severe intellectual delays, along with constipation and osteoporosis. This led the clinicians to consider congenital hypothyroidism, a diagnosis that was ruled out due to the normal hormone results. Complete genome sequencing led to recognition of the TRA1 gene mutation. The review here presented in this issue of the Presse Médicale, identified the 19 patients from 9 families nowadays published [14]. They all had dysmorphic syndrome comprised of small stature, with relative sparing of the trunk and head, often accompanied by alterations in psychomotor development, and anemia. The hormone work-up was nearly normal, with no evident alteration of FT3, FT4 or TSH. This contrasted with the clinical presentation, which in addition showed consistently high normal concentrations of FT4 and low normal results for FT3. The observation of TRA1-TRA2 mutations reported in Lille is somewhat distinctive due to the severity of the ostearticular involvement, the state of slimness, the intellectual sharpness, the appearance of chronic motor diarrhea since adult age, and finally the coincidental of recurrent primary hyperparathyroidism [15].

Thus over a nearly 40-year period, various genetic states of partial insensitivity to thyroid hormones have been gradually identified [16]. These are the result of either an alteration of the β or α nuclear receptors, an alteration of an intracellular transporter (MCT8), or a defect in their activation in the peripheral tissues due to failed activation of deiodinases by selenoproteins (SBP2). It should be emphasized that the recognition of these states is evidently endocrinologic when goitre or hormonal abnormalities are obvious (TRA mutations). The genetic origin and the familial risk of X-linked mental retardation related to MCT8 mutations can be missed, if T3 is not measured as was...
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Table 1

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Phenotype</th>
<th>FT3</th>
<th>FT4</th>
<th>TSH</th>
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</thead>
<tbody>
<tr>
<td>TRB</td>
<td>Goitre, possibly: hypermetabolism, tachycardia, attention deficit hyperactivity disorder</td>
<td>↑</td>
<td>↑</td>
<td>N (or ↑)</td>
</tr>
<tr>
<td>TRA</td>
<td>The Allan-Herndon-Dudley syndrome: skeletal dysplasia, macrocephaly, short lower limbs, placid behavior, constipation, anemia</td>
<td>High normal</td>
<td>Low normal</td>
<td>N (or ↓)</td>
</tr>
<tr>
<td>MCT8</td>
<td>Severe weakness, hypotonia, poor head control, difficulty sitting independently, paroxysmal dyskinesia</td>
<td>↑↑</td>
<td>N (or ↓)</td>
<td>N (or ↓)</td>
</tr>
<tr>
<td>SBP2</td>
<td>Intellectual and growth delay, hearing impairment, myopathy, immunodeficiency, azoospermia</td>
<td>↓</td>
<td>↑</td>
<td>↑ (or N)</td>
</tr>
</tbody>
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The states of partial insensitivity to thyroid hormones are no longer the domain of highly specialized thyroidologists, but have to be considered more generally by any physician faced with situations of statural growth, skeletal, neuromuscular, sensory and intellectual alterations; anemia; cardiac or gastrointestinal disorders, etc. Careful and critical assessment of unusual hormone measurements is therefore imperative, before specific genetic determination.

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References