Diagnostic and therapeutic challenges of acquired thyrotropic deficiency

Diagnostic et prise en charge du déficit thyréotrope acquis

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Abstract

The acquired thyrotropic deficiency (TD) is a hypothyroid condition due to an insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland. This disease can be the consequence of disorders affecting either the pituitary gland or the hypothalamus, but most frequently both of them, and is generally called central hypothyroidism (CH). CH is about one thousand folds rarer than primary hypothyroidism (PH) and the thyroid hormone defect is often less severe than in primary forms. Differently to PH, the TD is most frequently characterized by low/normal TSH levels and thyroid hormone replacement is associated with the suppression of residual TSH secretion. Thus, CH diagnosis and management often represent a clinical challenge because physicians cannot rely on the systematic use of the reflex TSH determination. The clinical challenge of CH is further amplified by the frequent combination with other pituitary deficiencies.

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Résumé

Le déficit thyréotrope acquis est une hypothyroïdie en rapport avec la stimulation insuffisante par la TSH d’une thyroïde par ailleurs normale. Cette maladie peut être la conséquence de pathologies touchant soit l’hypophyse, soit l’hypothalamus, soit, et c’est le plus fréquent, les deux, et est généralement appelée hypothyroïdie centrale (HC). L’HC est environ 1000 fois plus rare que l’hypothyroïdie périphérique et les troubles des hormones thyroïdiennes sont souvent moins sévères que dans les hypothyroïdies périphériques. À la différence des hypothyroïdies périphériques, le déficit thyréotrope est le plus souvent caractérisé par des concentrations normales ou basses de TSH et le traitement substitutif thyroidien est associé à une suppression de la sécrétion résiduelle de TSH. Le diagnostic de l’hypothyroïdie centrale et sa prise en charge représentent donc souvent un défi clinique car les médecins ne peuvent pas utiliser, comme ils le font pour l’hypothyroïdie périphérique, le dosage de TSH. Le défi clinique de l’hypothyroïdie centrale est amplifié par la combinaison fréquente avec d’autres déficits hypophysaires hormonaux.

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1. Central hypothyroidism epidemiology and pathogenesis

The frequency of central hypothyroidism (CH) is estimated to range in the general population from 1:20,000 to 1:80,000. CH can affect patients of all ages and, contrary to what is found in primary hypothyroidism (PH) patients, without a female prevalence. CH itself does not reduce life expectancy, though quality of life can be severely worsened [1].

The etiopathogenesis of CH is quite heterogeneous [2–4]. Depending on the underlying organic or genetic cause, either sporadic or familial forms of CH have been described. In most of the acquired forms of the disease, CH is combined with other pituitary hormone deficiencies (CPHD). The major causes of CH are reported in Table 1.

The thyrotropic deficiency (TD) is frequently both quantitative and qualitative in acquired CH [5]. A quantitative defect in the amount of functional pituitary thyrotrope cells is probably the pathogenic mechanism accounting for most of the CH cases. This quantitative defect in TSH producing cells is frequently associated with a qualitative defect in the secreted TSH isoforms, which conserve immunoreactivity but display an impaired ability to stimulate TSH receptors on thyroid cells.
Lack of accurate parameters for therapy adjustment

Nonthyroidal illnesses

Treatments of other CPHDs

Clinical manifestations of central hypothyroidism can be masked by high circulating levels of bioinactive TSH. Circulating TSH levels are generally low/normal.

Factors challenging the diagnosis and clinical management of central hypothyroidism. The etiopathogenesis of acquired central hypothyroidism.

Idiopathic forms

Infective diseases (tuberculosis, syphilis, mycoses)

Infiltrative lesions (sarcoidosis, hemochromatosis, histiocytosis X)

Autoimmune hypophysitis

Vascular accidents (pituitary apoplexy, post-partum Sheehan’s syndrome, sub-arachnoidal hemorrhage and infarction)

Head traumas

Iatrogenic causes (cranial surgery or irradiation, drugs)

Invasive lesions (pituitary macroadenomas, craniopharyngiomas, hypothalamic lesions, pituitary tumors, breech delivery, external sub-arachnoidal hemorrage and infarction)

The secretion of bioinactive TSH was documented in CH due to hypothalamic lesions, pituitary tumors, breech delivery, external head irrigation and Sheehan’s syndrome. In these conditions, an abnormal control of TSH synthesis and secretion by TRH, and other neuroendocrine or paracrine factors, may be associated with alterations of post-translational processing of the molecule, resulting in the release of TSH forms with altered glycosylation and variable bioactivity [6]. The existence of this qualitative defect in TSH secretion provides an explanation for the lack of correlation between circulating thyroid hormone and TSH concentrations in patients with CH.

2. Diagnostic challenges

The hypothyroid state is generally milder in CH than in PH patients; in addition, manifestations can be masked by signs and symptoms of CPHDs. Therefore, the diagnosis of CH is generally obtained on biochemical basis either incidentally or in patients under evaluation for hypothalamic or pituitary diseases.

The diagnosis of CH cannot be reached by the sole TSH determination (Table 2), and the combined evaluation of TSH and thyroid hormone is required for the diagnosis of whatever form of CH [7]. The hallmark of CH is the finding of serum FT4 concentrations into the hypothyroid range associated with low/normal TSH levels. Indeed, some CH patients with a prevalent hypothalamic defect may have high serum TSH levels, a finding potentially leading to misdiagnose these patients as having a PH. Measurement of anti-thyroid autoantibodies may help in differentiating CH from primary hypothyroidism. The diagnostic flow-chart of CH should also include the exclusion of factors that may interfere in TSH measurement methods by performing appropriate tests of dilution and recovery. The measurement of different parameters of peripheral thyroid hormone action, such as sex hormone-binding globulin, ferritin, bone markers, serum lipids and others, does not appear diagnostically useful. Moreover, patients with CPHDs may have additional pituitary hormone deficiencies that may complicate the interpretation of many parameters of peripheral thyroid hormone action.

In most of the cases, only manifest forms of CH, but not the subclinical defects characterized by FT4 levels still within the normal range, can be recognized. It has been reported that the diagnosis of hidden CH in survivors of childhood cancer may be reached by evaluating nocturnal TSH surge. Furthermore, Alexopoulou and coworkers [8] gave a diagnostic value to time-related decreases in circulating T4 concentrations larger than 20% as compared with the basal T4 values. This approach would then allow the diagnosis and treatment of mild hypothyroid states of central origin, analogous to the subclinical forms of primary hypothyroidism.

The presence of abnormal TSH responses to TRH may be of help to confirm the suspect of CH and TRH testing may suggest the differential diagnosis of the central defect, being hypothalamic defects associated with exaggerated, prolonged or delayed TSH responses [1,6]. Nevertheless, both pituitary and hypothalamus are affected in most CH patients.

In every patient with CH, CT scan or MRI study of the pituitary region should be carried out.

Finally, patients with nonthyroidal illness (NTI) have values of thyroid function testing that largely overlap with those of CH patients, suggesting NTI as a form of CH whose outcome might be susceptible to be improved by thyroid hormone treatment. Therefore, the presence of comitant diseases at the time of blood withdrawal should always be excluded before suspecting true CH (Table 2).

3. Therapeutic challenges

Treatment of CH is aimed to restore normal serum concentrations of circulating thyroid hormones [1,7–9]. Levo-thyroxine (L-T4) therapy is easily tuned in PH by evaluating circulating TSH levels, but this measurement is unable to guide L-T4 treatment in CH patients, though the finding of unsuppressed TSH levels during L-T4 treatment strongly indicate under-treatment.

Therefore, the evaluation of circulating free thyroid hormones acquires a major role in the monitoring of L-T4 treatment in such a clinical condition. Nonetheless, several recent papers dealing with substitutive L-T4 therapy in patients with CH have underlined the pitfalls in achieving optimal replacement [9]. CH patients are generally undertreated and L-T4 dosage should be targeted in order to obtain FT4 values at the middle of the laboratory range of normal values. In this context, the FT3 measurement may be of help mainly in detecting overtreatment. This may also be suggested by the concomitant evaluation of clinical and biochemical indices of peripheral thyroid hormone action.

In patients at risk of CPHDs, concomitant central adrenal insufficiency must always be excluded before starting L-T4
therapy, because of the risk to precipitate an adrenal crisis. If adrenal function cannot be assessed prior to the start of L-T4, a prophylactic treatment with steroids is advised and assessment of adrenal function can be postponed. Significant differences in L-T4 doses are also depending on the concomitant treatments for CPHDs. Recombinant growth hormone (GH) treatment interferes with the activity of the thyroid axis and may either unmask a state of central hypothyroidism or render a L-T4 substitutive therapy insufficient. Moreover, estrogens had been reported to increase L-T4 requirement. Since this is mainly a consequence of an increase in thyroxine-binding globulin (TBG) levels, the effect of estrogens and the required adjustment of L-T4 should be transient in order to saturate the increased T4-binding capacity of plasma proteins.

Disclosure of interest

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

References