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The multiple genetic causes of central hypothyroidism

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An insufficient stimulation by thyrotropin (TSH) of an otherwise normal thyroid gland represents the cause of Central Hypothyrodism (CeH). CeH is about 1000-folds rarer than Primary Hypothyroidism and often represents a real challenge for the clinicians, mainly because they cannot rely on adequately sensitive parameters for diagnosis or management, as it occurs with circulating TSH in PH. Therefore, CeH diagnosis can be frequently missed or delayed in patients with a previously unknown pituitary involvement. A series of genetic defects have been described to account for isolated CeH or combined pituitary hormone defects (CPHDs) with variable clinical characteristics and degrees of severity. The recently identified candidate gene IGSF1 appears frequently involved. This review provides an updated illustration of the different genetic defects accounting for CeH.

Definition and epidemiology

Central hypothyroidism (CeH) is a condition characterized by a hypothyroid state originating from a defective stimulation of an otherwise normal thyroid gland. This condition is the consequence of anatomic or functional disorders affecting the pituitary thyrotrope cells or the hypothalamic TRH neurons and eventually causing a defective TSH secretion [1,2].

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An isolated failure of thyrotrope cells is possible, but the TSH defect is more frequently part of combined pituitary hormone defects (CPHDs), which indeed complicate both diagnosis and clinical management of CeH. Diagnosis is usually based on the association of low free T4 (FT4) with low/normal TSH levels in the serum. Therefore, CeH represents the major false negative result of the "reflex TSH strategy", a worldwide diffuse method to screen thyroid function [3]. Differently from primary hypothyroidism, CeH is classically associated with a small thyroid of normal structure at ultrasound [1,2].

CeH most frequently occurs as a sporadic condition and, differently from primary hypothyroidism, there is no female prevalence. Its incidence was estimated to range from 1:16,000 to about 1:160,000 in different neonatal populations [3–5]. Such variable frequency is probably depending upon several factors, such as ethnicity and diagnostic strategies. The combined determination of total T4, Thyroxine-Binding Globulin (TBG) and TSH constitute the basis of the more sensitive diagnostic strategy used by the Dutch national health system [5] allowing the detection of milder forms of neonatal CeH that are not uncovered by the combination of low total T4 and normal/low TSH in Japan and USA [3,4].

It is worth noting that the typical manifestations of congenital hypothyroidism are rarely present at birth since thyroid hormone requirements during fetal life are lower than after birth and, differently from a primary thyroid defect, the CG can stimulate the fetal thyroid.

The mechanisms underlying CeH pathogenesis variably involve both hypothalamic and pituitary cells but they are still undetermined in several cases. The major causes of CeH are listed in Table 1, but the main cause of CeH in young age is probably represented by genetic defects.

Genes involved in CeH

The various genes so far linked to CeH are illustrated in Fig. 1. The inheritable forms of CeH are classically divided in two: those included among the CPHDs and the isolated CeH [1,2,6–8] (Table 2). In recent years, several other genes and syndromes have been variably associated with thyrotropin defects (Table 3).

TSHβ *gene*

In 1971, Miyai et al. [9] reported a consanguineous family affected with CeH due to an isolated TSH defect. About 20 years later, *TSHβ* gene mutations were the first genetic defect described to cause congenital CeH in Japan and Greece [10,11]. Up-to-date, less than 10 mutations of *TSHβ* gene have been reported [7].

The most frequently reported mutation (c.373delT or p.C125Vfs*10) was originally described in a Brazilian family [12], but since then it has been reported worldwide in several, non-consanguineous families, including three German kindreds [13–17]. A funder effect was also recently reported for this *TSHβ* deletion in Ireland [18]. This variant demonstrates the important role of the C-terminal portion of the TSHβ-subunit, the so-called seat belt stabilizing the hetero-dimerization with the α-subunit [9,19].

Table 1
Main causes of central hypothyroidism (CeH) in pediatric age.

Type of causes	Specific conditions
Inheritable defects	Mutations causing CPHDs or isolated CeH
Invasive or compressive lesions	Craniopharyngiomas
	Pituitary macroadenomas
	Empty sella
	Meningiomas or gliomas
	Rathke cleft cysts
Iatrogenic causes	Cranial surgery or irradiation
	Drugs (anti-cancer treatments, RXR agonists, dopamine)
Injuries	Head traumas, traumatic delivery
Autoimmune diseases	Lymphocytic hypophysitis
Infiltrative lesions	Iron overload
	Sarcoidosis or Histiocytosis X
Infective diseases	Tuberculosis or Mycoses

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