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Hypothyroidism associated with parathyroid disorders

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Hypothyroidism may occur in association with congenital parathyroid disorders determining parathyroid hormone insufficiency, which is characterized by hypocalcemia and concomitant inappropriately low secretion of parathormone (PTH). The association is often due to loss of function of genes common to thyroid and parathyroid glands embryonic development. Hypothyroidism associated with hypoparathyroidism is generally mild and not associated with goiter; moreover, it is usually part of a multisystemic involvement not restricted to endocrine function as occurs in patients with 22q11 microdeletion/DiGeorge syndrome, the most frequent disorders. Hypothyroidism and hypoparathyroidism may also follow endocrine glands' damages due to autoimmunity or chronic iron overload in thalassemic disorders, both genetically determined conditions. Finally, besides PTH deficiency, hypocalcemia can be due to PTH resistance in pseudohypoparathyroidism; when hormone resistance is generalized, patients can suffer from hypothyroidism due to TSH resistance. In evaluating patients with hypothyroidism and hypocalcemia, physical examination and clinical history are essential to drive the diagnostic process, while routine genetic screening is not recommended.

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Introduction

Parathyroid glands are endocrine organs devoted to the control of calcium and phosphate metabolism. They release the hypercalcemic hormone parathormone (PTH) in response to changes of the extracellular calcium, which regulates PTH synthesis and release from parathyroid cells through activation of the G protein-coupled calcium sensing receptors (CASR) expressed at the membrane levels. PTH targets bone and kidney cells regulating calcium and phosphate mobilization from bone and calcium reabsorption associated with phosphate wasting at kidney level. Parathyroid disorders are related to alterations of PTH release from parathyroid cells or alterations of PTH action, including conditions of PTH deficiency (hypoparathyroidism), PTH excess (hyperparathyroidism) and PTH resistance (pseudohypoparathyroidism).

Hypothyroidism occurs in parathyroid disorders when common genes involved in thyroid and parathyroid embryonic development are affected or when congenital destructive mechanisms occur in the adult life, such as autoimmunity or haemocromatosis.

Hypoparathyroidism is an uncommon disorders characterized by low serum calcium, increased serum phosphorus, and deficient production of PTH. Congenital hypoparathyroidism is definitely rarer than congenital hypothyroidism. The estimated prevalence of non-surgical hypoparathyroidism is 2.3/100,000 person-year [1].

Indeed, congenital parathyroid diseases may occur as hyperparathyroid disorders, characterized by elevated serum PTH levels. Congenital hyperparathyroid disorders are determined by inactivating mutations of key genes involved in embryonic parathyroid glands development, namely the calcium sensing receptor (*CASR*), *GNA11* and *AP1S1* genes, whose heterozygotic inactivating mutations cause familial hypocalciuric hypercalcemia (HHC1, OMIM#145980) and homozygotic mutations cause neonatal severe primary hyperparathyroidism (NSHPT, OMIM#239200) [2], and the vitamin D receptor (*VDR*) gene, whose inactivating mutations cause type 2A vitamin D resistant rickets (VDDR2A, #277440) [3]. Nonetheless, congenital hypothyroidism is not part of the phenotypes of these syndromes. Lastly, among hyperparathyroid conditions, genetic alterations of the GNAS gene determining PTH resistance in pseudohypoparathyroidism, is associated also with features of hypothyroidism.

Genetic and developmental aspects

Parathyroid embryonic development

In humans, parathyroid glands develop between the fifth and the twelfth week of gestation from the third and fourth pharyngeal pouches [4]. The superior parathyroid glands are derived from the endoderm of the dorsal portion of the fourth branchial pouches, which shares a common origin with the lateral thyroid [5]. The inferior parathyroid glands originate from the endodermal cells of the third pharyngeal pouches and develop from two common parathyroid/thymus primordia [6]. Indeed, besides the foregut endoderm, cells originating from the neural crest of rhombomeres 6 and 7 may contribute to the anlage of parathyroid glands [7]. During development, inferior parathyroid glands separate from the thymus and migrate caudal to thyroid and superior parathyroid glands. Therefore, parathyroid glands development can be distinguished into three phases: 1) formation of the parathyroid anlage, 2) migration toward their final destination, and 3) differentiation into PTH-secreting cells. Parathyroid embryogenesis and the genes involved in its regulation have been investigated mainly in mouse models, though mice have two parathyroid glands derived from the third pharyngeal pouches; here, the main findings in mice are summarized (Fig. 1A): 1) the third pharyngeal pouches are detectable by embryonic day (E) 9.5–10, corresponding to human embryo of 5 weeks of gestational age; in each third pharyngeal pouch, an epithelial outgrowth forms the bilateral parathyroid/thymus common primordia, which is divided in a dorsal and anterior presumptive parathyroid domain and in a ventral and distal presumptive thymus domain. Parathyroid gland and thymus can be recognized at E12.5–13, though *Pth* gene expression initiates at as early as E11.5 and is maintained throughout the development [8]. 2) Separation of parathyroid glands from the thymus occurs by E14–14.5, when both structures caudally migrate, the parathyroid glands locate behind the thyroid lobes, while thymus migrate down towards the cardiac structures. 3) Chief cells differentiate during the embryonic