Journal of Clinical & Translational Endocrinology 14 (2018) 5–11

Contents lists available at ScienceDirect

Journal of Clinical & Translational Endocrinology

journal homepage: www.elsevier.com/locate/jcte

Less known aspects of central hypothyroidism: Part 2 – Congenital etiologies

Salvatore Benvenga[a,b,c], Marianne Klose[d], Roberto Vita[a,*], Ulla Feldt-Rasmussen[d]

[a] Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[b] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy
[c] Interdepartmental Program of Molecular & Clinical Endocrinology, and Women's Endocrine Health, University Hospital Policlinico G. Martino, Messina, Italy
[d] Department of Medical Endocrinology and Metabolism, Rigshospitalet, National University Hospital, Copenhagen University, Copenhagen, Denmark

ARTICLE INFO

Keywords:
Hypopituitarism
Central hypothyroidism
Thyrotropin deficiency
Congenital hypothyroidism

ABSTRACT

Central hypothyroidism (CH) occurs approximately in 1:50,000, and therefore is expected to be one thousand times rarer compared with primary hypothyroidism. Despite its rarity in the general population, it is much more common in certain disorders, in which it is frequently associated with other pituitary hormone deficiencies. The aim of this paper is to provide an updated review on the frequency of congenital CH, which is < 1:50,000, and on its etiology, disregarding CH caused by other genetic defects, such as mutations of transcription factors involved in pituitary organogenesis or mutations of the genes encoding TRH or TRH receptor.

Introduction

Central hypothyroidism (CH) is biochemically diagnosed by the coexistence of low circulating free thyroxine (FT4) with low to normal circulating thyrotropin (TSH), also described as inappropriately low serum TSH concentrations [1]. Even if within normal limits when typically measured on blood drawn at daytime, the nocturnal TSH surge is diminished and the bioactivity of circulating TSH is low in patients with CH [2].

CH stems from disruption of the hypothalamus-pituitary axis that leads to insufficient stimulation of thyroid by TSH. TSH production by the thyrotrophs is induced by TSH-releasing hormone (TRH), a polypeptide synthetized from the 29 kDa pre-pro-TRH mainly in the hypothalamic paraventricular nuclei [3]. Thyrotroph cells are localized in the anteromedial region of the adenohypophysis and account for approximately 5% of the functional anterior pituitary cells [4]. In comparison, the somatotrophs account for approximately 35–50%, making the thyrotrophs the least common of the hormone-secreting pituitary cells [4]. This fact has by itself lead to the conclusion that TSH deficiency should be one of the rarest adenohypophyseal hormone insufficiencies [5]. TSH is a heterodimer glycoprotein consisting of two subunits, the α-subunit that is identical to the α-subunit of follicle-stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (HCG), and the β-subunit that is unique and confers biologic specificity. Bioactivity of TSH depends on its glycosylation and is influenced by the highly-conserved sequence 27CAGYC31 in the β-subunit [5,6].

CH occurs in less than 1 in 50,000 (0.002%) births [7]. Despite its rarity in the general population, CH is common in patients with certain disorders. In these patients TSH deficiency is frequently associated with other hormone deficiencies (multiple hypopituitarism or panhypopituitarism). The aim of this paper is to provide an updated review of such diseases, disregarding CH caused by other genetic defects, such as mutations of transcription factors involved in pituitary organogenesis or mutations of the gene encoding TRH or TRH receptor. Epidemiology and causes of acquired CH are addressed in a companion review.

Methods

A systematic literature search using PubMed and MEDLINE databases was performed using the strings "central hypothyroidism" and "congenital hypothyroidism". We excluded all the papers focusing on primary congenital hypothyroidism and CH resulting either from genetic defects in pituitary organogenesis or from TRH/TRH receptor mutations.

Abbreviations: ACTH, adrenocorticotropin hormone; ALGS, arteriohepatic dysplasia; CH, central hypothyroidism; DWS, Dandy-Walker syndrome; FT3, free triiodothyronine; FT4, free thyroxine; GH, growth hormone; HCG, human chorionic gonadotropin; IGDF1, immunogobulin superfamily member 1; PC1/3, proprotein convertase 1/3; PWS, Prader-Willi syndrome; ROHHAD, rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation; SCD, sickle cell anemia; SOD, septo-optic dysplasia; SMMCIS, solitary median maxillary central incisor syndrome; SWS, Sturge-Weber syndrome; TRH, TSH-releasing hormone; TSH, thyrotropin; TT3, total triiodothyronine; TT4, total thyroxine

* Corresponding author at: Department of Clinical and Experimental Medicine, University of Messina, Viale Gazzi, 98125 Messina, Italy.
E-mail address: rvita@unime.it (R. Vita).

https://doi.org/10.1016/j.jcte.2018.09.004
Received 6 June 2018; Received in revised form 12 July 2018; Accepted 25 September 2018

Table 1
Malformative syndromes associated to central hypothyroidism and relative frequency.

Malformative syndrome	Epidemiology	Rate of central hypothyroidism (CH)	Other endocrinological aspects
Immunoglobulin superfamily member 1 (IGSF1) deficiency	1:100,000	100% in males 33% in females	Hypoprolactinemia, GH deficiency, delayed pubertal testosterone production in males, macro-orchidism, obesity, metabolic syndrome
Congenital proprotein convertase 1/3 (PC1/3) deficiency	?	61%	Diabetes insipidus, central adrenal insufficiency, GH deficiency, gonadotropin deficiency, childhood obesity
Prader-Willi syndrome	1:8000–16000 newborns	5–30%	GH deficiency, central adrenal deficiency, obesity
Septo-optic dysplasia	1:10,000 newborns	45–80%	GH deficiency, central adrenal insufficiency, central diabetes insipidus, gonadotropin deficiency, central precocious puberty
Arteriohepatic dysplasia (Alagille syndrome)	1:30,000–50,000 newborns	≈30%	None
Solitary median maxillary central incisor syndrome	1:50,000 newborns	≈25%	Hypopituitarism, short stature, empty sella
Dandy-Walker syndrome	1:10,000–30,000	?	–
Edwards syndrome (Trisomy 18)	≈1:6000 newborns. [5–10% of them live past their first year]	See holoprosencephaly	See holoprosencephaly
Holoprosencephaly	1:16,000	11%	Central hypocortisolism, GH deficiency and diabetes insipidus
Genoa syndrome	?	See holoprosencephaly	See holoprosencephaly
Sturge-Weber syndrome	1:20,000–50,000 newborns	≈2.5%	GH deficiency, central hypogonadism
Rapid-onset Obesity with Hypothalamic Dysfunction, Hypoventilation, and Autonomic Dysregulation (ROHHAD) syndrome	≈100 cases reported in the literature	≈30%	Hypothalamic dysfunction, GH deficiency, ACTH deficiency, hyperprolactinemia

Results

As summarized in Tables 1 and 2, in a number of syndromes CH has a much higher frequency compared to the expected 0.002% (1 in 50,000 births) (see "Introduction") [7].

Immunogobulin superfamily member 1 (IGSF1) deficiency

This X-linked syndrome stands out because of the 100% prevalence of CH in males and 33% in females. Clinical presentation of this syndrome include obesity and macro-orchidism [8]. In a multicentric European study on 42 patients (24 males) from 10 families, male patients (age 0–87 years) showed CH in 100% of patients, hypoprolactinemia in 67%, and transient partial growth hormone (GH) deficiency in 13%) [8]. Even though testes grew at a normal age and then reached macro-orchid size, growth spurt, pubic hair development and testosterone production through puberty were delayed. Also, three-quarters of patients over 55 years of age had components of metabolic syndrome, and overall, waist circumference, fat percent and body mass index tended to be elevated [8]. Very recently, a novel IGSF1 mutation in a 14-year old Japanese boy presenting with CH, short stature and chronic constipation was reported [9]. It is predicted that the incidence of IGSF1 deficiency-related hypothyroidism is approximately 1:100,000 [10].

Congenital proprotein convertase 1/3 (PC1/3) deficiency

Another rare syndrome, inherited in an autosomal recessive mode, is congenital proprotein convertase 1/3 (PC1/3) deficiency [11]. PC1/3 is an endoprotease that processes many prohormones expressed in enteroendocrine, endocrine and neuronal cells. Martin et al. evaluated 13 children with PC1/3 deficiency [11]. All children were born at term with normal weights (3.4 ± 0.3 Kg), and all presented with evidence of dehydration, metabolic acidosis, and malabsorbitive diarrhea during the first two months of life [11]. Children managed to thrive only after nutritional support. However, as patients aged beyond early infancy, their weight increased significantly. From an endocrine perspective, it is noteworthy that pituitary deficiencies were highly prevalent (diabetes insipidus, postprandial hypoglycemia, adrenocorticotropic hormone (ACTH) deficiency and TSH deficiency in 61% of cases, and GH and gonadotropin deficiencies in less than 50%) (Table 1) [11]. These endocrine abnormalities are supposed to result from defective processing of pro-TRH to TRH, proopiomelanocortin to ACTH, and proinsulin to insulin. Other than GH, PC1/3 processes somatostatin and ghrelin, which in turn control GH secretion. Species differences in the cleavage site sequence of proGHRH may explain why humans are less prone to GH deficiency compared with mice [11]. Also, gonadotropin deficiency may results from altered kisspeptin precursor processing rather than an altered proGnRH to GnRH conversion. Finally, data assessing the involvement of PC1/3 in processing the human vasopressin is lacking. Different age-dependent expression of PC1/3 and PC2, that is is another proprotein convertase, may explain development of diabetes insipidus beyond early infancy [11].

Prader-Willi syndrome (PWS)

PWS is the most common syndromic form of obesity. The prevalence of PWS in the United States was reported between 1:16,062 and 1:25,000; outside the United States, the reported prevalence has ranged from 1:8000 in rural Sweden to 1:16,000 in Western Japan [12]. In regard to the presence of CH in patients with PWS, some studies are worth mentioning. One Canadian study described the response of TSH to TRH in children and adolescents (n = 21) with PWS, and compared TSH and total thyroxine (TT4) concentrations measured on neonatal

Table 2
Diseases associated to iron overload-related central hypothyroidism and relative frequency.

Disease	Epidemiology	Rate of central hypothyroidism (CH)	Other endocrinological aspects
Sickle cell disease (SCD)	1:500–1400	≈2%	Hyper-/hypogonadotropic hypogonadism, GH deficiency, primary hypothyroidism, osteopenia/osteoporosis, vitamin D deficiency
β-thalassemia	1:10,000–100,000	0–35%	Hypogonadotropic hypogonadism, diabetes mellitus, impaired glucose tolerance, hypoparathyroidism, vitamin D insufficiency, osteopenia/osteoporosis