Less known aspects of central hypothyroidism
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Congenital hypothyroidism

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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 adenohypophysial 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, immunoglobulin 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

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

### Table 1

| 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 (Torsosy 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 | ≈ 30% | Hypothalamic dysfunction, GH deficiency, ACTH deficiency, hyperprolactinemia |
| Rapid-onset Obesity with Hypothalamic Dysfunction, Hyperventilation, and Autonomic Dysregulation (ROHHAD) syndrome | 100 cases reported in the literature | | |

### 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].

### Immunoglobulin 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 endopeptidase that processes many prohormones expressed in endocrine, 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 malabsorptive 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, adenocorticotrophic 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 result 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 another proprotein convertase, may explain development of diabetes insipidus beyond early infancy [11].

### Prader-Willi syndrome (PWS)

PWS is the most common syndrome 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
screening for congenital hypothyroidism in children with PWS (n = 23) and controls [13]. In the first group, 1/21 patients (4.8%) had CH (tertiary hypothyroidism). However, mean FT4 concentration (10.4 pmol/L; range, 8.2–13.5 pmol/L) was in the lower one-third of the normal range in 18 of 20 remaining subjects. In these 20 patients, mean TSH level was 1.9 mU/L (range, 0.8–4.2 mU/L) at baseline and 21.8 mU/L (range, 10.0–46.7 mU/L) at 20 min (peak). Serum levels of TSH and TT4 at birth were not significantly different between PWS neonates and controls. The authors concluded that, because of the low prevalence (1/21) of hypothyroidism, L-T4 treatment should not be routinely prescribed to youth with PWS [13].

One Dutch study evaluated thyroid function in 75 children with PWS (median age = 4.7 years) at baseline and one year later during GH treatment (1 mg GH/m²/day; n = 34) or without GH treatment (n = 23, controls) [14]. At baseline, median (interquartile range) TSH, TT4, FT4 and TT3 levels were −0.1 SDS (−0.5 to 0.5), −0.6 SDS (1.7 to 0.0), −0.8 SDS (−1.3 to −0.3) and 0.3 SDS (−0.3 to 0.9), respectively. Median TT4 and FT4 levels were significantly lower than 0 SDS, while TT3 was significantly higher than 0 SDS. In untreated PWS children thyroid function tests were unchanged. After one year of GH treatment, FT4 decreased significantly from −0.8 SDS (−1.5 to −0.2) to −1.4 SDS (−1.6 to −0.7), while TT3 was unchanged at 0.3 SDS (0.1 to 0.8). Because T3 levels were relatively high or normal, both before and during GH treatment, PWS children had increased T4 to T3 conversion. Peripheral T4 to T3 conversion by deiodinase type 2 might compensate for the relatively lower FT4. Furthermore, increased leptin levels and GH treatment may contribute to enhance this conversion [14].

The aforementioned 5% (1/21) rate of CH in PWS, was challenged by a recent French paper [15]. Data from 154 patients (68 men), with a median age of 27 years (range 16–54), revealed that, with a rate of 26% matching the 25% rate of type 2 diabetes mellitus, hypothyroidism was one of the most prevalent disorders. Noteworthy, no information on the level of hypothyroidism (primary, central) was provided [15]. This 26% rate is consistent with that of a recent review [16]. The review states that hypothyroidism is reported in approximately 20–30% of children with PWS and, similar to other endocrinopathies in PWS, the etiology is thought to be central in origin [16]. By comparison, depending on the diagnostic criteria used, the reported prevalence of GH or ACTH deficiency in PWS ranged from 40 to 100% or 0 to 60%, respectively [16].

Septo-optic dysplasia (De Morsier syndrome) (SOD)

Septo-optic dysplasia (SOD) is a disorder of early brain development with an incidence of 1 in 10,000 newborns [17]. Although its signs and symptoms vary, this condition is traditionally defined by three characteristic features: underdevelopment (hypoplasia) of the optic nerves, abnormal formation of structures along the midline of the brain, and pituitary hypoplasia [17].

A retrospective chart review was conducted on a cohort of children with optic nerve dysplasia or SOD between January 2005 and March 2013 [18]. During the study period, of the 101 patients evaluated (median age: 2.3 years, range: 0.76–6.5), 73 (72.3%) had hypopituitarism, with GH deficiency (62%) and CH (54%) being the most common abnormalities. Gonadotropin deficiency was diagnosed in half of adolescents evaluated (4/8). Magnetic resonance imaging (MRI) pituitary abnormalities predicted hypopituitarism with sensitivity and specificity of 54% and 92%, respectively. Thus, a normal pituitary gland did not exclude endocrinopathy [18].

In a retrospective electronic medical record chart review of a tertiary care center’s pediatric endocrinology clinic, 80 patients with SOD were selected [19]. SOD was diagnosed in patients fulfilling at least two of the following criteria: optic nerve hypoplasia, agenesis/hypoplasia of septum pellucidum and/or corpus callosum, and hypothalamic-pituitary dysfunction. Hypothalamic-pituitary dysfunction was present in half (51%) of subjects with optic nerve hypoplasia with (36%) or without (15%) dysgenesis of septum pellucidum and/or corpus callosum as compared to dysgenesis of septum pellucidum and/or corpus callosum alone (4%). Overall, 55% of SOD patients had hypothalamic-pituitary dysfunction, which had been diagnosed within 2 years of age. CH, GH deficiency, central adrenal insufficiency and diabetes insipidus were the most frequent endocrinopathies with a rate of 70%, 55%, 50% and 30%, respectively [19].

The prevalence of CH in SOD may differ geographically or ethnically, as indicated by the following two studies: one study on 10 Saudi children with SOD who were observed from October 1999 through to May 2004 [20], and one on 18 German children who were observed between 1976 and 1992 [21]. Age of Saudi patients ranged from 18 months to 5 years. The mean age of initial presentation for endocrine evaluation was 14 months. The rates of GH deficiency, TSH deficiency, ACTH deficiency and diabetes mellitus were 100%, 80%, 80%, and 10%, respectively. Finally, two patients (20%) were suspected to have gonadotropin deficiency. At neuroradiological evaluation, 3 patients had pituitary gland hypoplasia, 2 had pituitary stalk dysplasia with pituitary stalk either attenuated or not visualized [20]. In the German study [21], mean age at initial presentation was 1.9 years (range: 1 day–13 years). In contrast to the Saudi study in which only a basal hormonal evaluation was performed [20], in the German study endocrinological investigation consisted of basal and dynamic evaluation of hypothalamic-pituitary-thyroid, -gonad -adrenal axis, as well as GH-IGF-1 axis [21]. Particularly, 5 of the 11 patients (45%) tested with TRH had CH. Two patients (2/9, 22%) had insufficient gonadotropin response to GnRH. One of the two patients challenged with CRH had insufficient ACTH response. GH stimulation tests revealed 1 to 7 patients with GH deficiency, based on the test used. Finally, one patient suffered from diabetes insipidus. Overall, multiple pituitary deficiency was present in 7 patients [21]. An empty sella with or without an ectopic pituitary was seen in 4 cases [21].

The high frequency of CH in SOD is also demonstrated by a study from the Indiana University School of Medicine (Indianapolis, USA) [22]. In this study, medical records of children with CH observed from 1990 to 2006 were reviewed. Forty-two subjects (22 boys) were identified, with 57% having SOD, and 98% had multiple pituitary hormone deficiencies, including GH deficiency (76%), ACTH deficiency (81%) and central diabetes insipidus (21%) [22].

Arteriohepatic dysplasia (Alagille syndrome) (ALGS)

Approximately 5 times rarer than SOD is ALGS, an autosomal dominant disorder that most often (94%) results from mutations of the JAG1 gene (type 1 ALGS). ALGS primarily affects the liver, heart, skeleton, eye, face, kidney and vasculature. The incidence of ALGS is 1 in 30,000–50,000 live births, but due to the variable phenotype it is likely to remain underdiagnosed [23]. At least two case reports of CH can be retrieved in the literature. One article describes panhypopituitarism in a young woman [24], while the other article describes a young man with GH and TSH deficiency [25]. Very recently Italian researchers wished to verify the involvement of JAG1 variants in the pathogenesis of congenital thyroid defects and the frequency of unexplained hypothyroidism in a series of ALGS1 patients (n = 21) and 100 unrelated patients with congenital hypothyroidism (controls) [26]. This research was complemented by a study of JAG1 variants in vitro and in the zebrafish. In this article, De Fillipis et al. report a previously unknown nonautoimmune hypothyroidism in 6/21 (29%) ALGS1 patients, 2 of them with thyroid hypoplasia. Two JAG1 variants in the heterozygous state were found in 4% of controls (4/100) [26]. The role of JAG1 gene in the pathogenesis of congenital hypothyroidism was demonstrated in zebrafish, in which a primary thyroid defect resulted from knocking down jag1a/b (orthologous of the human JAG1) expression [26].
Solitary median maxillary central incisor syndrome (SMMCIS)

SMMCIS is as rare as ALGS, as it occurs in 1:50,000 live births [27]. SMMCIS includes severe to mild intellectual disability, holoprosencephaly, congenital heart disease, and midline defects such as congenital nasal malformation, solitary median maxillary central incisor, cleft lip and/or palate, abnormal pituitary morphology, hypopituitarism, hypothyroidism and short stature [27,28].

Dandy-Walker Syndrome (DWS)

DWS is a congenital brain malformation involving the cerebellum and the fluid filled spaces around it, occurring in 1 in 10,000-30,000 newborns [29]. There are three main DWS features: i) partial or complete absence of the cerebellar vermis; ii) enlargement of the fourth ventricle with or without increased intracranial pressure; iii) cyst formation near the base of the skull. Absence of the corpus callosum and noncerebral malformations (heart, face, limbs) may occur. Clinical presentation ranges from progressive enlargement of the skull and symptoms of intracranial hypertension to slow motor development [29]. Ten to 20% percent of patients are diagnosed in late childhood or in adulthood because of headaches, facial palsy, muscular hypertonicity and unsteady walking gait. DWS is associated with trisomy of chromosome 13, 18 (see below), and 21 [30]. There is at least one report of CH in DWS, a 3-month-old Saudi boy [31].

Trisomy 18 (Edwards syndrome), holoprosencephaly and Genoa syndrome

Edwards syndrome is the second most common trisomy after Down syndrome, as it occurs in approximately 1 in 5000 live-born infants. Although most cases result in termination or fetal loss, live births have been documented in 5%. Five to 10 percent of children with trisomy 18 live past their first year [32]. A few patients (especially girls) can live into their twenties or thirties although they need full time caregiving. The first year is a period of rapid development and the parents expect a fully normal baby. The majority of children do not live past their twenties or thirties although they need full time caregiving.

Trisomy 18 (Edwards syndrome), holoprosencephaly and Genoa syndrome needs to be considered in all pediatric cases of early- and rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD)

ROHHAD is a rare syndrome that affects the autonomic nervous system (such as inability to regulate body temperature, slow heartbeat, excessive sweating, altered pupil response to light, strabismus, and/or intestinal abnormalities), hyper- or hyponatremia, and the endocrine system [47]. As cited by Kocaay et al. [48], at the time of their case reports there were only 78 patients described in the literature. An article published one year later, stated “fewer than 100 case reported in the literature” [49].

As the name suggests, the most characteristic features include dramatic weight gain over a six- to 12-month period in the first 10 years of life followed by hypothalamic dysfunction, dysregulation of the autonomic nervous system, and alveolar hypoventilation. The exact underlying cause of ROHHAD, including a precise genetic basis, is currently unknown [49]. The endocrine disorders include TSH deficiency, GH deficiency, ACTH deficiency, hyperprolactinemia, early or late puberty. The long-term prognosis for people with ROHHAD varies. ROHHAD children are at increased risk for certain types of tumors including ganglioneuromas and ganglioneuroblastomas, and sudden death for cardiac arrest occurs due to alveolar hypoventilation [47]. Due to the occurrence of ganglioneuromas (located in the abdomen and lungs) and neuroendocrine tumors, such as ganglioneuroblastoma, in about 40% of the patients, the disease is now also called ROHHAD-neuroendocrine tumors (ROHHADNET). ROHHAD may fail to be diagnosed early [48]. In a 13-year-old female patient who was reported to be healthy until the age of 3 years, CH, hyperprolactinemia, Raynaud phenomenon and electrolyte disorders were all findings that had been identified three years before the patient’s presentation to the authors’ clinic, but these findings were not interpreted together to reach a diagnosis. The authors underscore that the possibility of ROHHAD syndrome needs to be considered in all pediatric cases of early- and rapid-shaped epiphyses and hypoplastic terminal phalanges of fingers. Genetics of Genoa syndrome is still unknown [37].

Encephalotrigeminal angiomatosis (Sturge-Weber syndrome) (SWS)

SWS is a congenital, non-familial disorder of unknown incidence and cause. A somatic c.548G>C mutation in GNAQ (encoding guanine nucleotide-binding protein, q polypeptide (MIM600998)) was indeed identified in 88% and 92% of patients with SWS and non-syndromic port-wine stains, respectively [38]. SWS is a neurocutaneous disorder characterized by port-wine birthmark in the distribution of the ophthalmic branch of the trigeminal nerve, and venous-capillary abnormalities of the leptomeninges and the eye. Stasis results in ischemia and necrosis. Neurological manifestations are variable, including seizures, stroke and mental retardation. Glaucousemia is also common [38-40].

The incidence of SWS is estimated at 1 person per 20,000-50,000 [41]. Comi et al. [42] described two children out of 83 (2.4%) with SWS and CH. The authors concluded that, because the 2.4% prevalence of CH is much greater than in the general population, thyroid function testing is important in SWS patients despite no symptoms of hypothyroidism [42]. Another two cases of SWS with low FT4 and presumable CH were reported elsewhere [43]. Very recently, CH was reported in a 11-yr old boy with SWS [44]. He was familiarly predisposed to hypothyroidism in both his maternal and paternal grandmother. The patient had a positive history for convulsions, but did not take any anticonvulsants. Thyroid function tests were performed, and were consistent with CH. Indeed, FT4 was 0.62 ng/dl (normal range, 0.7–1.6 ng/dl), TT4 was 4.5 μg/dl (normal range 5.5–11.0 μg/dl) and TSH 2.69 IU/ml (normal range, 0.47–4.68 IU/ml) [44]. Finally, GH deficiency and hypogonadotropic hypogonadism have been also reported in SWS patients [45,46].

Rapid-onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD)
onset obesity associated with hypothalamic-pituitary endocrine dysfunction [48], a message that is echoed in another case report [50]. This second article describes two girls who presented with rapid weight gain, at the age of 5 and 9 years respectively. The first was admitted due to obesity and CH. After two months she developed autonomic nervous system dysregulation (thermal dysregulation), alveolar hypoventilation, hypopidipsia, severe hypernatriemia, and hypertriglyceridemia. The second case was admitted three months after diagnosis of mild hyperprolactinemia associated with rapid-onset obesity, due to seizures, hypothermia, and electrolyte disorders (hyponatriemia followed by severe hypernatriemia). CH and ACTH deficiency were also diagnosed [50]. In another case report, the first in Southeast Asia, CH was diagnosed at age 5 while ACTH deficiency at age 11 [51]. The authors also reviewed the 52 ROHHAD cases previously reported in literature, in whom CH and GH deficiency were diagnosed in ≈ 30% and ≈ 50%, respectively [51].

Sickle cell anemia (SCD)

SCD is an autosomal recessive inherited hemolytic anemia. SCD is the most common inherited blood disorder in the United States. Indeed, SCD is most common in Mediterranean people, Arabs, Indians, and in all the people descending from African ancestors [52]. Endocrine complications of SCD result from either iron overload or ischemia due to vaso-occlusive crisis occurring within endocrine glands [53].

In one paper, 50 Turkish children and adolescents with SCD were evaluated for endocrine problems [53]. Mean age of patients was 13.1 ± 2.9 years, and 50% of patients had at least one endocrine abnormality. Hypergonadotropic hypogonadism was detected in 3 patients (6%), hypogonadotropic hypogonadism in 1 female patient (2%), and small testicular volume in respect to age in 3 male patients (8.5%). GH deficiency was detected in 1 (2%) female patient, while CH and primary hypothyroidism in 1 (2%) and 2 cases (4%), respectively [53]. American authors reported the occurrence of hypothyroidism in three adult patients (> 45 years of age at time of diagnosis) with SCD [54]. All three patients had received multiple units of transfused red blood cells and had serum ferritin levels of greater than 6000 ng/mL. All patients were critically ill at the time of the diagnosis of hypothyroidism and died shortly after for congestive heart failure. Postmortem examination in one patient revealed fibrosis of the thyroid together with iron deposition [54].

β-thalassemia

Thalassemia is the most common hereditary anemia, which is transmitted in an autosomal recessive manner, and β-thalassemia major is its most severe form. Thousands of infants with β-thalassemia are born each year [55]. Approximately 1.5% of the global population are carriers of β-thalassemia, with an annual incidence of 1 in 100,000 across the world and 1 in 10,000 in Europe. Cyprus, Sardinia and Southeast Asia are the regions with the highest frequency of β-thalassemia carriers. According to Thalassemia International Federation, approximately 200,000 patients with β-thalassemia major are alive [56]. Iron overload-related complications, including the endocrine ones, depend on the use of iron chelation, since patients who are regularly treated with iron chelation therapy have less severe complications and live beyond their 40s [56].

A multicentric study from USA, Canada and United Kingdom compared iron-overloaded subjects with thalassemia (group I, n = 142, age 25.8 ± 8.1 years) and transfused SCD (group II, n = 199, 24.9 ± 13.2 years) to non-transfused SCD subjects (group III, n = 64, 25.3 ± 11.3 years) [57]. In group I, diabetes, hypogonadism, hypothyroidism and growth failure were more frequent compared to group II (13% vs. 2%, P < 0.001; 40% vs. 4%, P < 0.001; 10% vs. 2%, P < 0.001; 33% vs. 7%, P < 0.001, respectively) [57]. It is noteworthy to say that hypothyroidism was defined as ongoing thyroid hormone replacement therapy, thus irrespective of the etiology. Overall, the rate of multiple endocrinopathy (≥2) was four or seven times greater in group I than group II or group III (56% vs. 13% or 8%, P < 0.001). At multivariate analysis, group I patients had 9.4 times higher odds of overall endocrinopathy, with the duration of chronic transfusion being a predictor of endocrine failure. In contrast, iron overload did not increase the risk of endocrinopathy in group II, suggesting a role of the underlying disease in the pathogenesis of the endocrine injury [57].

De Sanctis et al. performed a cross-sectional analysis on 339 β-thalassemia major patients. All patients were on chelation therapy from the prepubertal or peripubertal age. Twenty-six out of 339 (7.6%) were diagnosed with CH [58]. Particularly, the rate of CH in pre-pubertal age (< 11 years), peri-pubertal age (11–16 years) and pubertal age (> 16 years) was 0%, 22% and 7.8%, respectively. Furthermore, 12/26 (46.1%) CH patients had an associated hypogonadotropic hypogonadism, 4/26 (15.3%) short stature, 2/26 (7.7%) insulin-dependent diabetes mellitus, and 1/26 (3.8%) hypoparathyroidism [58]. Even though serum ferritin did not differ significantly between hypothyroid and euthyroid patients, the authors did not exclude the role of iron overload in the pathogenesis of CH. In addition, normal ferritin may not rule out iron overload in some tissue [58]. Concomitant hepatitis C infection, which was present in three-quarters of patients, increased collagen deposition secondary to increased activity of the iron-dependent protocollagen proline hydroxylase enzyme, and the hypoxic effect of chronic anemia have been proposed also for the hypothalamic-pituitary dysfunction [58].

A study from Qatar investigated thyroid function in 48 patients with thalassemia major between 5 and 18 years of age [59]. Over a 12-year follow-up hypothyroidism was diagnosed in 35% (17/48) of patients, who all except one were > 10 years old. Thirteen out of 17 patients (13/48, 27%) had CH. FT4, but not TSH, correlated negatively with age (r = -0.595, P < 0.0001) suggesting a progressive hypothalamic-pituitary dysfunction over time [59]. In an Iranian cross-sectional study on 77 patients with β-thalassemia major (mean age 21.26 ± 4.53 years; range 15-36) rates of impaired puberty, short stature, hypothyroidism, diabetes mellitus, impaired glucose tolerance, hypoparathyroidism, vitamin D deficiency and vitamin D insufficiency were 46.8%, 33.8%, 18.2%, 16.9%, 13.0%, 7.8%, 45.5% and 24.7%, respectively [60]. No details are given in regard to the level of hypothyroidism (primary, secondary), since all patients with reduced FT4 or increased TSH or on levothyroxine were included [60].

In a multicenter study from Cyprus on 435thalassemic patients, the most prevalent endocrine complications were short stature (35%) and hypogonadotropic hypogonadism (32.5%), followed by hypothyroidism (5.9%), hypoparathyroidism (1.2%) and diabetes mellitus (9.4%). Type of hypothyroidism (primary or central) was not specified, although the authors clarify that primary thyroid dysfunction occurs in most cases before hypothalamic-pituitary disruption by hemosiderosis [61]. Thus, CH is much less common compared to primary hypothyroidism [61,62]. This observation was confirmed by a Greek study on 200 β-thalassemia patients regularly transfused and desferrioxamine chelated [63]. In this study, all the 33 patients (16.5%) with thyroid dysfunction had either overt primary hypothyroidism (i.e. increased TSH levels, low FT4 and/ or FT3; n = 8, 4%) or subclinical primary hypothyroidism (increased basal TSH levels, normal FT4 and FT3, exaggerated TSH response after TRH infusion; n = 25, 12.5%). No case of CH was observed [63]. Primary thyroid hypofunction usually appears in the second decade of life and may be reversible upon intensive and precocious chelation [61,62]. In a multicentric Italian study on a large cohort of β-thalassemia patients, primary hypothyroidism occurred as frequently (6.2%) as in the Cyprost study mentioned above, although earlier (mean age 15.8 years) [64].

Discussion

The prevalence of hypothyroidism in the general population ranges
from 0.3% to 3.7% in the United States, and from 0.2% to 5.3% in Europe, with an average overall prevalence of 2–3%. CH is a rare case of thyroid hormone deficiency, since it is expected to occur around one thousand times less frequently compared to primary hypothyroidism [65].

In this review we have shown that, despite its rarity in the general population, CH is much common in certain disorders. These disorders can be divided into either malformative syndromes characterized by an anatomical defect, or disorders that were acquired in the neonatal period. CH can be associated with certain congenital anomalies, such as cardiovascular defects, genitourinary anomalies, and various endocrine defects [14].

Concluding remarks

In this review we have shown that, despite its rarity in the general population, CH is much common in certain disorders. These disorders can be divided into either malformative syndromes characterized by an anatomical defect, or disorders that were acquired in the neonatal period. CH can be associated with certain congenital anomalies, such as cardiovascular defects, genitourinary anomalies, and various endocrine defects [14].

In conclusion, all the patients with the disorders mentioned above should be screened for CH. Indeed, thyroid function testing should not be limited to TSH, since it can be normal, but should include also FT4 and rT3, since they can be abnormal in some of these disorders. In patients with Down syndrome, CH should be considered in the differential diagnosis of cognitive impairment, developmental delay, and feeding difficulties [39].

Declaration of interest

This article is based on the S Benvenga et al. (2015) article entitled “Interactions between Hypothalamic Pituitary Thyroid Axis and Other Pituitary Dysfunction” that was held at the 15th International Thyroid Congress, Lake Buena Vista, FL, USA (October 18–23, 2015).

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