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Congenital Hypothyroidism and Thyroid Cancer

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1. Introduction

Congenital hypothyroidism (CH) is a condition of thyroid hormone deficiency present at birth and can result in severe neurodevelopmental impairment, growth failure and permanent mental retardation if treatment is delayed for several months after birth (1-3). Girls are more frequently affected than boys (female to male ratios ranging from 2:1 to 4:1)(4). The mental retardation and neurodevelopmental impairment include poor motor coordination, ataxia, spastic diplegia, muscular hypotonia, strabismus, learning disability and diminished attention span (5). Consequently, most countries operate neonatal screening programs to enable early detection of cases and therapeutic intervention. Treatment consists of a daily dose of thyroid hormone (thyroxine) by mouth (6, 7). Because the treatment is simple, effective, and inexpensive, nearly all of the developed world practices newborn screening to detect and treat CH in the first weeks of life. The diagnosis is based on the measurement of TSH on the second or third day of life. If the TSH is high, the infant's doctor and parents are called and a referral to a pediatric endocrinologist is recommended to confirm the diagnosis and initiate treatment (6). Often a technetium (Tc-99m pertechnetate) thyroid scan is performed to detect a structurally abnormal gland. The Tc-99m pertechnetate exam will help differentiate thyroid dysgenesis from thyroid dyshormonogenesis. Most children born with CH and correctly treated with thyroxine grow and develop normally in all respects. Even most of those with athyreosis and undetectable T_4 levels at birth develop with normal intelligence. However, in some cases mild learning problems, subtle neurological dysfunctions, and subnormal IQ have been reported (2, 5). In a 5 year follow-up study of children with CH, Arenz et al reported that children with an initial thyroid-stimulating hormone (TSH) value of >200 mU/L performed significantly worse in motor skills than children with TSH value of ≤ 200 mU/L although intellectual development was normal (8). Glorieux et al reported that 27 patients with congenital hypothyroidism diagnosed by neonatal screening were examined at the age of 12 years. The 12 patients with severe hypothyroidism at diagnosis (thyroxine < 26 nmol/L, and area-of-the-knee epiphyses < 0.05 cm²) had a lower IQ than the 15 patients with less severe hypothyroidism (9). Salerno et al evaluate the intellectual outcome in 40 12-year-old patients with CH detected by neonatal screening, 13 patients showed subnormal IQ score (72.4 ± 4.9) compared with their siblings (86.7 ± 9.6 ; $P < 0.0001$) and with the other patients (96.1 ± 9.6 ; $P < 0.0001$). The low IQ score was associated with lower serum concentrations of thyroxine at

diagnosis, poor treatment compliance during follow-up and lower familial IQ. Interviews with parents of CH children revealed that a refusal to acknowledge the disease was linked to poor attention to the child's emotional life and to poor treatment compliance in some cases (11%) (10). These data suggest that neurodevelopmental impairment may be associated with inadequate treatment in some of CH cases.

2. Congenital hypothyroidism in Saudi Arabia

Since CH is the most common preventable cause of mental retardation, the newborn screening program for CH was started in 1988 at the Ministry of Health Maternity Hospitals in Saudi Arabia to detect and treat this disorder (11, 12). The prevalence of CH in Riyadh is 1 in 3,450 live births with 279,482 newborn infants screened (11, 12), the most common etiology shown by thyroid scan being thyroid ectopy (50%), followed by dyshormonogenesis (26%) and athyrosis (24%) (11). Two other studies showed a different rate of CH and dyshormonogenesis (13, 14). The study by Henry et al showed the prevalence of 1 in 2759 live births with 121,404 newborn infants screened in the same Central region (Riyadh), the predominant cause of congenital hypothyroidism found in the study being athyreosis (45%), followed by thyroid ectopia (24%) and dyshormonogenesis (17%) (13). The study by Majeed-Saidan et al showed the prevalence of 1 in 2096 live births with 44,778 newborn infants screened and 8/17 (47%) CH had dyshormonogenesis (14). However, the number of the newborn infants screened is smaller in these two studies. The prevalence of CH in other regions of Saudi Arabia is about 1 in 2931 live births in the South region with 100,000 newborn infants screened (Najran province) (15) although 1 in 1400 live births was reported in a separate study with 30810 newborn infants screened (16), 1 in 4200 live births with 193,613 infants screened in the North-West region (Madina Al-Munawara region) (17), and 1 in 5061 live births in the Eastern region (18). The overall prevalence of CH in Saudi Arabia is similar to those reported in the literature from other countries although the prevalence of dyshormonogenesis appears to be higher than other parts of the world. The nationwide efforts to promote neonatal screening programs in recent years in the Kingdom have likely prevented severe mental and growth retardation in newborn infants and also sparked the interest of researchers in CH (12, 13, 17-19). However, molecular characterization of underlying genetic defects has not been systematically conducted yet among the patients. There is also a paucity of data on clinical treatment and follow-up of the patients. Major misconceptions are still very common among young parents in Saudi Arabia. First, many do not fully understand the seriousness of the disease, refuse to participate in the neonatal screening or otherwise show poor compliance in diagnosis, treatment and follow-up. Second, others believe that the treatment of CH implies a life-long dependency on drug administration and therefore feel highly distressed when confronted with their child's disease. Inadequate treatment can lead to poor academic performance and learning problems which tend to be overlooked by the child's parents (2)

3. The etiology of congenital hypothyroidism

The etiology of congenital hypothyroidism is heterogeneous and is caused by either thyroid dysgenesis (75-80%) or dyshormonogenesis (15-20%) (1, 20). The most common cause of CH is thyroid dysgenesis, a spectrum of defective thyroid gland development leading to athyrosis (without visible thyroid tissue in imaging studies) (35-40%), thyroid ectopy

(frequently located in a sublingual position) (55–60%), and hypoplasia (a small-sized thyroid or remnants of thyroid tissue in the normal position) (5%) (21, 22). These forms represent 75–80% of all cases of CH (20). The pathogenesis of thyroid dysgenesis is largely unknown. The disorder is usually sporadic but up to 2% of familial cases have been reported (23–25). Genes associated with thyroid gland dysgenesis include the TSH receptor in non-syndromic congenital hypothyroidism, $G_{\alpha s}$, and the thyroid transcription factors (TTF-1, TTF-2, and Pax-8) (22, 24, 25). The extrathyroid genes involved in the control of migration of the median thyroid bud during embryogenesis, such as adhesion molecules, and vascular factors involved in the stabilization of the bi-lobed structure of the thyroid may also play a role (22). Thyroid dysmorphogenesis account for 15–20% of CH cases (20). In thyroid dysmorphogenesis (defects of thyroid hormone biosynthesis), patients have a normal sized or enlarged thyroid gland (goitre) in the normal position and are often recessively inherited (1). Thyroid dysmorphogenesis is a genetically heterogeneous group of inherited disorders in the enzymatic cascade of thyroid hormone synthesis. The underlying genetic defects causing dysmorphogenesis include gene mutations in the enzymatic cascade of thyroid hormone synthesis such as Na^+/I^- symporter (26), Tg (27), thyroperoxidase (TPO) (28), dual oxidase 2 (DUOX2 or THOX2)(29), dual oxidase maturation factor 2 (DUOXA2)(30), pendrin (SLC26A4/PDS/)(31), and iodotyrosine dehalogenase1(DEHAL1) (32). Mutations in the TPO or Tg are the most frequent genetic defects in thyroid dysmorphogenesis.

4. Thyroid hormone synthesis and the genes involved in the process

Thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3), are critical determinants of brain and somatic development in infants and of metabolic activity in adults; they also affect the function of virtually every organ system(33). They are tyrosine-based hormones produced by the thyroid gland. The synthetic process occurs in three major steps as shown in Figure 1(33, 34): production and accumulation of the raw materials, biosynthesis of the hormones on a backbone of Tg, release of the free hormones from Tg and secretion into blood. Tyrosines are provided from Tg, a large glycoprotein which is synthesized by thyroid epithelial cells and secreted into the lumen of the follicle forming colloid (essentially a pool of Tg). A molecule of Tg contains 134 tyrosines, although only a handful of these are actually used to synthesize T_4 and T_3 . Another important component in the synthesis of thyroid hormones is iodine, which is taken up from blood by sodium-iodide symporters located on the outer plasma membrane of thyroid epithelial cells. Once inside the cell, iodide is transported into the follicular lumen presumably in part by the anion transporter pendrin, and oxidized by the membrane-bound enzyme TPO. This oxidation requires the presence of hydrogen peroxide, which is generated by DUOX2, an enzyme that requires a specific maturation factor dual oxidase 2A (DUOXA2). The biosynthesis of thyroid hormones is conducted by TPO, an integral membrane protein present in the apical (colloid-facing) plasma membrane of thyroid epithelial cells. TPO catalyzes two important reactions: the iodination of selected tyrosine residues (also known as organification of iodide) on Tg which serves as the matrix for thyroid hormone synthesis, producing monoiodotyrosine and diiodotyrosine, and the intramolecular coupling reaction of iodinated tyrosines from two monoiodotyrosine or diiodotyrosine, leading to the formation of either triiodothyronine (T_3) or thyroxine (T_4). Only a small fraction of iodotyrosines are used in this process. Through the action of TPO, thyroid hormones accumulate in colloid, on the surface of thyroid epithelial cells, but are still tied up with Tg. To release T_4 and T_3 , thyroglobulin is engulfed

by the thyrocytes through pinocytosis, digested in lysosomes, and then secreted into the bloodstream. In contrast, moniodotyrosine and diiodotyrosine are found only in minute amounts in the bloodstream. The major form of thyroid hormone in the blood is thyroxine (T_4) (approximately 80%), which has a longer half life than T_3 . The ratio of T_4 to T_3 released in the blood is roughly 20 to 1. T_4 is converted to the active T_3 (three to four times more potent than T_4) within cells by deiodinases (5'-iodinase).

The transportation and concentration of iodide within the thyroid gland are mediated through the sodium iodide symporter (NIS) located in the basolateral membrane of the thyroid follicular cell. NIS, a specialized plasma membrane glycoprotein with 13 transmembrane domains, belongs to the family of sodium-dependent cotransporters and has most sequence similarity with the human sodium/glucose cotransporter 1(26). NIS couples the inward translocation of two Na^+ down their electrochemical gradient to the simultaneous inward translocation of one I^- against its electrochemical gradient (35). The driving force for NIS activity is the Na^+ gradient generated by the Na^+/K^+ ATPase. Human NIS is located on chromosome 19, consists of 15 exons, and encodes a protein of 643 amino acids with a predicted molecular mass of 68.7 kDa (36, 37). Although NIS mutation is relatively rare, up to 12 mutations have been reported (V59E, G93R, R124H, Δ M143-Q323, Q267E, C272X, T354P, G395R, Δ A439-P443, frame-shift 515X, Y531X, and G543E) (38-40).

Tg is a large 660-kD glycoprotein synthesized by the thyroid gland. It functions as a matrix where thyroid hormones (T_4 and T_3) are produced from the coupling of iodotyrosyl residues, catalyzed by TPO (41). The human TG gene is 270 kb and contains an 8307 bp coding sequence divided into 48 exons. The preprotein is composed of a 19-amino acid signal peptide, followed by a 2749-residue polypeptide (42). To date, up to 50 different TG gene mutations have been identified (43). These mutations lead to varying degrees of hypothyroidism.

TPO is a thyroid-specific glycosylated hemoprotein of 110 kDa with a short trans-membrane domain that binds it to the apical membrane of the thyrocyte (44), with the catalytic part facing inside the follicle. It consists of 933 amino acids that are encoded by an mRNA of 3048 nucleotides (44). The TPO gene spans over 150 kb on the short arm of chromosome 2, locus 2p25, and consists of 17 exons (45). TPO gene mutations are one of the most common causes of thyroid dysmorphogenesis, with several different inactivating mutations being identified in patients with total iodide organification defects (46-49).

The thyroid oxidase 2 (THOX) gene, known as dual oxidase 2 (DUOX2) is located at the apical membrane of thyrocytes and is involved in the Ca^{2+} /reduced nicotinamide adenine dinucleotide phosphate-dependent generation of H_2O_2 (50, 51). In thyroid hormone synthesis, H_2O_2 is used as a substrate by TPO to catalyze both the iodination of tyrosine residues and incorporation of iodine into TG (52). DUOX2 is located on chromosome 15 and consists of 33 exons encoding a mRNA of 6376 nucleotides long. The DUOX2 protein is a 1548-amino-acid polypeptide, including a 26-amino-acid signal peptide. Because defects in DUOX2 result in lack of H_2O_2 , this protein is essential for thyroid hormone synthesis. Evidence for the involvement of DUOX2 in thyroid hormonogenesis came from the identification of naturally occurring mutations; biallelic homozygous or compound heterozygous DUOX2 mutations lead to goitrous CH (29, 53, 54), whereas monoallelic nonsense defects cause transient CH (29, 31) although biallelic DUOX2 mutations have also

been reported recently in transient CH (55). Up to 23 DUOX2 mutations have been identified in patients with congenital hypothyroidism (29, 55-57). Recently, two novel genes, called DUOX maturation factors (*DUOXA1* and *DUOXA2*) were cloned (58). These genes are oriented head-to-head to the *DUOX* genes in the *DUOX1/DUOX2* intergenic region (58). The *DUOXA2* gene encodes an endoplasmic reticulum (ER) resident protein comprising five membrane-integral regions. *DUOXA2* mRNA is predominantly expressed in thyroid gland with lower levels in gastrointestinal epithelia, reminiscent of the expression profile of *DUOX2*. Whereas *DUOX2* expressed in nonthyroidal cells is completely retained in the ER (59), coexpression of *DUOXA2* rescues ER-to-Golgi transition, maturation, and translocation to the plasma membrane of functional *DUOX2* (58). A genetic defect in *DUOXA2* impairs expression of *DUOX2*, resulting in decreased H_2O_2 production by thyrocytes, and CH (30).

Pendred's syndrome (PS) is an autosomal recessive disease characterized by goitre without or with hypothyroidism, impaired iodide organification, and congenital sensorineural deafness (60), although studies on CH patients also show that a direct relation exists between the extent of hearing loss and the age at which treatment for CH was initiated (61). It is caused by biallelic mutations in the *SLC26A4* (solute carrier family 26, member 4), the PS gene (62), which contains an open reading frame of 2343 bp and encompasses 21 exons. The 780 amino acid transmembrane protein (pendrin) expressed in the thyroid gland, inner ear, endometrium, and kidney, where it is involved in iodide, chloride, formate, and nitrate transport (63). In the thyroid gland, pendrin acts at the apical pole of thyrocytes to transport intracellular iodide into the follicular lumen (64). Loss of pendrin function causes a failure in iodine supply and an organification defect often leading to euthyroid goitres (65). Because both TPO defects and PS may present with goitre, hypothyroidism, partial iodide organification defects, and a positive perchlorate test (31, 66), a definite etiologic diagnosis is impossible without molecular diagnosis.

Iodine is an essential component of thyroid hormone. To ensure that iodine is available for thyroid hormone biosynthesis, two highly specialized systems evolved in the thyroid gland. One accumulates iodide in thyroid cells by active membrane transport via the sodium-iodide symporter (67). The other recycles iodide through the deiodination of monoiodotyrosine and diiodotyrosine (but not T_4), the main iodinated by-products of thyroid hormone synthesis by thyroidal iodotyrosine dehalogenase (DEHAL1), a flavin mononucleotide-dependent enzyme (68). The gene is 36 kb and contains an 867 bp coding sequence divided into 5 exons and is located on chromosome 6 (6q24-25) (69-71). Mutation of the gene has been recently reported in patients with severe hypothyroidism (32).

5. Thyroid dysgenesis and the genes involved in the process

Thyroid dysgenesis is a defect in the organogenesis of the gland resulting in hypoplastic, ectopic or absent-thyroid gland and the underlying pathogenesis is largely unknown. Although the disorder is usually sporadic, a minority of cases are transmitted as Mendelian diseases (21-25, 72). Genes associated with thyroid gland dysgenesis include the TSH receptor in non-syndromic congenital hypothyroidism, $G_s\alpha$, and the thyroid transcription factors (TTF-1, TTF-2 or FOXE1, Pax-8, NKX2.1 and NKX2.5) (22, 24, 25, 73-75). The extrathyroid genes involved in the control of migration of the median thyroid bud during embryogenesis, such as adhesion molecules, and vascular factors involved in the stabilization of the bi-lobed structure of thyroid may also play a role (22).

6. Congenital hypothyroidism and thyroid cancer

Although rarely reported in the literature, malignant transformation from dysmorphonogenic goitres is one of the most serious complications of CH. More than 20 cases of thyroid cancer have been reported in the literature with similar frequency of either papillary or follicular cancer type (Table1) (27). The most common genetic defects are *TG* mutation, resulting in dysmorphonogenesis and CH. All the reported cases of thyroid carcinoma have long-standing congenital goitres and elevated thyroid stimulating hormone (TSH) (27, 76, 77), indicating that TSH plays a central role in the development and/or progression of thyroid carcinoma.

TSH is a well-known growth factor for thyroid epithelial cells, and can promote thyroid nodule formation and cancer progression (78). It has been suggested that constant and prolonged stimulation by TSH may result in the malignant transformation of thyroid follicular cells (76, 79), although a causal role for TSH in thyroid cancer initiation has not been conclusively demonstrated. In experimental studies, Morris *et al* found that prolonged exposure of transplanted thyroid tissue to excessive amounts of TSH in mice led to the development of malignant thyroid neoplasms with pulmonary metastases (79). Induction of papillary thyroid carcinoma following subtotal thyroidectomy has also been reported in rats (80). These data indicate that chronic TSH stimulation may be associated with thyroid cancer development. The significance of TSH in thyroid cancer initiation has recently been demonstrated in mice with a thyroid-specific knock-in of oncogenic *BRAF^{V600E}*, mutations of which are found in about 45% of papillary thyroid carcinomas (81). *BRAF^{V600E}*-expressing thyroid follicular cells become transformed and progress to invasive carcinomas with a very short latency. These mice also develop hypothyroidism with high TSH levels due to deregulation of genes involved in thyroid hormone biosynthesis. However, *BRAF^{V600E}* induced oncogenic transformation of thyroid follicular cells is lost when TSH receptor is knockout, indicating the dependence of TSH mediated cAMP signaling in *BRAF^{V600E}* induced papillary thyroid carcinoma initiation (81). Although the study by Franco *et al* (81) provides experimental support for a strong association between TSH levels and thyroid cancer incidence, it remains to be determined whether long-term TSH stimulation alone can induce thyroid cancer. It is likely that mutations in oncogenes or tumor suppressor genes may be needed for tumor initiation apart from long-term TSH stimulation.

Brewer *et al* have demonstrated that the mammalian target of rapamycin (mTOR/S6K1) signaling pathway is also involved in the TSH mediated proliferative signals (82). mTOR/S6K1 signaling pathway is the key effector of phosphoinositide 3-kinase (PI3K) initiated proliferative signals in the thyroid follicular cells (83). Constitutive activation of PI3K signaling has been frequently found in thyroid cancers including those with aggressive clinical behaviors (84). However, genetic defect in the genes involved in this signalling pathway has not been investigated in thyroid cancers derived from dysmorphonogenic goitres. Although less frequently, genetic defects in the MAPK/ERK signaling pathway have been reported, for example, *BRAF^{V600E}* and K601E mutations in one PTC and one FTC cases, respectively (85) as well as abnormal p53 expression in one case of follicular carcinoma with anaplastic transformation (77).

For CH caused by thyroid dyshormonogenesis, thyroid goitre can develop and, in rare cases, thyroid cancer occurs from dyshormonogenic goitre. In our previous studies, we have reported two cases of metastatic thyroid carcinoma derived from congenital dyshormonogenic goitres (Figure 2) from two consanguineal families (27, 86). They presented with large recurrent goitres and hypothyroidism since childhood. They were non-compliant with L-thyroxine treatment and had multiple surgeries since childhood due to recurrence of dyshormonogenic goitres and pressure problems. One of them eventually developed a metastatic FTC and the other metastatic FVPTC. The underlying genetic defects in these two cases are germline *TG* mutation. Other genes involved in the different signalling pathways are investigated such as mutations in the *RAS*, *BRAF* or *P53*, and *PAX8/PPAR-γ* rearrangement. All come negative and it remains to be seen whether other genetic defects leading to malignant transformation can be detected such as mutations in the genes involved in the PI3K/Akt and mTOR/S6K1 pathways. These findings suggest that many CH cases in remote areas may not be adequately treated. It is unfortunate to see goitres and cancer development in these patients given that these complications can be easily prevented if proper L-thyroxine treatment is given. The health care cost for treating these complications, and physical and mental sufferings for the patients are huge as compared to L-thyroxine replacement therapy.

In summary, the serious detrimental effect of CH on the child’s cognitive and motor development, which used to be a major feature of the disease, is now mostly prevented since the introduction of newborn screening program. However, inadequate treatment or poor compliant with treatment can lead to poor academic performance, and in severe cases, thyroid goitre and cancer. Education and close follow-up are warranted for patients with poor response to L-thyroxine replacement therapy. Adequate amounts of L-thyroxine treatment are essential to prevent cancer development.

Cases	Tumor	Major Genetic defects	Functional consequence	Other genetic defects
1.	FTC	g.279 del T in <i>PDS</i> ⁽⁷⁷⁾	Truncated pendrin	abnormal p53 expression
2.	FTC	g.2505_2506 ins C in <i>TPO</i> ⁽⁸⁷⁾	Truncated TPO	
3.	FTC	g.IVS5+1G>A in <i>TG</i> ⁽²⁷⁾	Truncated Tg	
4.	PTC	p.C1245R in <i>TG</i> ⁽⁸⁵⁾	Impaired intracellular Tg transport	
5.	PTC	p.C1245R in <i>TG</i> ⁽⁸⁵⁾	Impaired intracellular Tg transport	

Cases	Tumor	Major Genetic defects	Functional consequence	Other genetic defects
6.	PTC	p.C1245R/G2356R in <i>TG</i> ⁽⁸⁵⁾	Impaired intracellular Tg transport	
7.	FTC	p.C1977S in <i>TG</i> ⁽⁸⁵⁾	Impaired intracellular Tg transport	BRAF ^{K601E} mutation
8.	PTC	p.C1977S in <i>TG</i> ⁽⁸⁵⁾	Impaired intracellular Tg transport	
9.	PTC	p.C1958S in <i>TG</i> ⁽⁸⁵⁾	unknown	BRAF ^{V600E} mutation
10.	PTC	p.C1958S in <i>TG</i> ⁽⁸⁵⁾	unknown	
11.	FVPTC	p.R2223H in <i>TG</i> ⁽⁸⁸⁾	Impaired intracellular Tg transport	
12.	FTC	unknown ⁽⁷⁶⁾	unknown	
13.	FTC	unknown ⁽⁷⁶⁾	unknown	
14.	PTC	unknown ⁽⁸⁹⁾	unknown	
15.	PTC	unknown ⁽⁹⁰⁾	unknown	
16.	PTC	unknown ⁽⁹¹⁾	unknown	

- Note:
1. Cooper et al reported a large kindred of patients with congenital goitre, in which two siblings developed metastatic follicular thyroid carcinoma and a leak of nonhormonal iodide from the thyroid. However, the underlying genetic defect is unknown (76).
 2. Medeiros-Neto and Stanbury reviewed 109 patients with dyshormonogenesis, 15 patients had thyroid follicular cancer with unknown genetic defects (92). Based on rigid criteria of malignancy such as vascular invasion, 8 of the 15 reported cases in the literature appear to be clear examples of thyroid malignancy. Five of them had bone or lung metastases (87).

PDS: Pendred’s syndrome; PTC: papillary thyroid carcinoma; FTC: follicular thyroid carcinoma; FVPTC: follicular variant of papillary thyroid carcinoma

Table 1. Thyroid cancer cases developing from dyshormonogenic goitre.

Fig. 1. **Key Steps in Thyroid Hormone Synthesis.** Monoiodotyrosine and diiodotyrosine are synthesized from the iodination of tyrosyl residues within thyroglobulin. After organification, iodinated donor and acceptor iodotyrosines are fused in the coupling reaction to form either triiodothyronine (T_3) or thyroxine (T_4), a process that involves only a small fraction of iodotyrosines. Thyroglobulin is then engulfed by thyrocytes through pinocytosis and digested in lysosomes, and T_4 and T_3 are secreted into the bloodstream. Monoiodotyrosine and diiodotyrosine are deiodinated by iodotyrosine deiodinase, and the released iodide is recycled (68).

Fig. 2. Follicular variant of PTC (FVPTC) derived from thyroid dyshormonogenesis due to biallelic p.R2223H mutation in the *TG* gene. (A) Hematoxylin and eosin staining shows FVPTC with oncocytic features (A, x20; D, x40); Lymph node metastases were also observed (B, x 20; E, x 40). The non-tumor area shows hyperplastic thyroid micro-and macro-follicles without colloid, and cytological atypia, which are consistent with dyshormonogenesis (C, x20; F, x40). (B) Diagnostic 24 h ¹²³I whole body scan. The scan was performed 24 h following the oral administration of 74 MBq (2 mCi) of ¹²³I. Whole body images were acquired in anterior and posterior projections before ¹³¹I ablation. The scan showed large neck uptake and multiple foci in the chest, skull, and pelvis suggestive of lung and bone metastasis (a). The patient received a therapeutic dose of radioactive iodine ¹³¹I of 3,831.35 MBq (103.55 mCi). Six month later, a follow-up scan showed complete resolution of the neck, lung and bone uptakes (b).

7. References

- [1] Kopp P 2002 Perspective: genetic defects in the etiology of congenital hypothyroidism. *Endocrinology* 143:2019-24.
- [2] Moltz KC, Postellon DC 1994 Congenital hypothyroidism and mental development. *Compr Ther* 20:342-6
- [3] Peter F, Muzsnai A 2009 Congenital disorders of the thyroid: hypo/hyper. *Endocrinol Metab Clin North Am* 38:491-507
- [4] Lorey FW, Cunningham GC 1992 Birth prevalence of primary congenital hypothyroidism by sex and ethnicity. *Hum Biol* 64:531-8
- [5] Buyukgebiz A 2003 Congenital hypothyroidism clinical aspects and late consequences. *Pediatr Endocrinol Rev* 1 Suppl 2:185-90; discussion 190
- [6] LaFranchi SH, Austin J 2007 How should we be treating children with congenital hypothyroidism? *J Pediatr Endocrinol Metab* 20:559-78
- [7] Gruters A, Krude H 2007 Update on the management of congenital hypothyroidism. *Horm Res* 68 Suppl 5:107-11
- [8] Arenz S, Nennstiel-Ratzel U, Wildner M, Dorr HG, von Kries R 2008 Intellectual outcome, motor skills and BMI of children with congenital hypothyroidism: a population-based study. *Acta Paediatr* 97:447-50
- [9] Glorieux J, Dussault J, Van Vliet G 1992 Intellectual development at age 12 years of children with congenital hypothyroidism diagnosed by neonatal screening. *J Pediatr* 121:581-4
- [10] Salerno M, Militerni R, Di Maio S, Bravaccio C, Gasparini N, Tenore A 1999 Intellectual outcome at 12 years of age in congenital hypothyroidism. *Eur J Endocrinol* 141:105-10
- [11] Al-Jurayyan NA, Al-Nuaim AA, Redha MA, El-Desouki MI, Al Herbish AS, Abo Bakr AM, Al Swailem AA, Al Mazrou YY, Al Deress A 1996 Neonatal screening for congenital hypothyroidism in Riyadh: Analysis of six year's experience. *Ann Saudi Med* 16:20-3
- [12] Al-Jurayyan NA, Al-Herbish AS, El-Desouki MI, Al-Nuaim AA, Abo-Bakr AM, Al-Husain MA 1997 Congenital anomalies in infants with congenital hypothyroidism: is it a coincidental or an associated finding? *Hum Hered* 47:33-7
- [13] Henry G, Sobki SH, Othman JM 2002 Screening for congenital hypothyroidism. *Saudi Med J* 23:529-35
- [14] Majeed-Saidan MA, Joyce B, Khan M, Hamam HD 1993 Congenital hypothyroidism: the Riyadh Military Hospital experience. *Clin Endocrinol (Oxf)* 38:191-5
- [15] Ogunkeye OO, Roluga AI, Khan FA 2008 Resetting the detection level of cord blood thyroid stimulating hormone (TSH) for the diagnosis of congenital hypothyroidism. *J Trop Pediatr* 54:74-7
- [16] al-Jurayyan NA, Shaheen FI, al-Nuaim AA, el-Desouki MI, Faiz A, al Herbish AS, Bakr AM, al-Swailem AA, al Mazrou YY 1996 Congenital hypothyroidism: increased incidence in Najran province, Saudi Arabia. *J Trop Pediatr* 42:348-51
- [17] Al-Maghamsi MS, Al-Hawsawi ZM, Ghulam GN, Okasha AM 2002 Screening for congenital hypothyroidism in North-West region of Saudi Arabia. *Saudi Med J* 23:1518-21
- [18] Narchi HH, Kulaylat NA 1996 Congenital hypothyroidism screening program: A five-year experience at Saudi ARAMCO Al Hasa Health Center. *Ann Saudi Med* 16:47-9

- [19] Afifi AM, Abdul-Jabbar MA 2007 Saudi newborn screening. A national public health program: needs, costs, and challenges. *Saudi Med J* 28:1167-70
- [20] De Felice M, Di Lauro R 2004 Thyroid development and its disorders: genetics and molecular mechanisms. *Endocr Rev* 25:722-46
- [21] Topaloglu AK 2006 Athyreosis, dysgenesis, and dysmorphogenesis in congenital hypothyroidism. *Pediatr Endocrinol Rev* 3 Suppl 3:498-502
- [22] Deladoey J, Vassart G, Van Vliet G 2007 Possible non-Mendelian mechanisms of thyroid dysgenesis. *Endocr Dev* 10:29-42
- [23] Castanet M, Lyonnet S, Bonaiti-Pellie C, Polak M, Czernichow P, Leger J 2000 Familial forms of thyroid dysgenesis among infants with congenital hypothyroidism. *N Engl J Med* 343:441-2
- [24] Castanet M, Polak M, Leger J 2007 Familial forms of thyroid dysgenesis. *Endocr Dev* 10:15-28
- [25] Park SM, Chatterjee VK 2005 Genetics of congenital hypothyroidism. *J Med Genet* 42:379-89
- [26] Pohlenz J, Rosenthal IM, Weiss RE, Jhiang SM, Burant C, Refetoff S 1998 Congenital hypothyroidism due to mutations in the sodium/iodide symporter. Identification of a nonsense mutation producing a downstream cryptic 3' splice site. *J Clin Invest* 101:1028-35.
- [27] Alzahrani AS, Baitei EY, Zou M, Shi Y 2006 Clinical case seminar: metastatic follicular thyroid carcinoma arising from congenital goiter as a result of a novel splice donor site mutation in the thyroglobulin gene. *J Clin Endocrinol Metab* 91:740-6
- [28] Bikker H, den Hartog MT, Baas F, Gons MH, Vulsma T, de Vijlder JJ 1994 A 20-basepair duplication in the human thyroid peroxidase gene results in a total iodide organification defect and congenital hypothyroidism. *J Clin Endocrinol Metab* 79:248-52.
- [29] Moreno JC, Bikker H, Kempers MJ, van Trotsenburg AS, Baas F, de Vijlder JJ, Vulsma T, Ris-Stalpers C 2002 Inactivating mutations in the gene for thyroid oxidase 2 (THOX2) and congenital hypothyroidism. *N Engl J Med* 347:95-102.
- [30] Zamproni I, Grasberger H, Cortinovis F, Vigone MC, Chiumello G, Mora S, Onigata K, Fugazzola L, Refetoff S, Persani L, Weber G 2008 Biallelic inactivation of the dual oxidase maturation factor 2 (DUOXA2) gene as a novel cause of congenital hypothyroidism. *J Clin Endocrinol Metab* 93:605-10
- [31] Pfarr N, Borck G, Turk A, Napiontek U, Keilmann A, Muller-Forell W, Kopp P, Pohlenz J 2006 Goitrous congenital hypothyroidism and hearing impairment associated with mutations in the TPO and SLC26A4/PDS genes. *J Clin Endocrinol Metab* 91:2678-81
- [32] Moreno JC, Klootwijk W, van Toor H, Pinto G, D'Alessandro M, Leger A, Goudie D, Polak M, Gruters A, Visser TJ 2008 Mutations in the iodotyrosine deiodinase gene and hypothyroidism. *N Engl J Med* 358:1811-8
- [33] Van Herle AJ, Vassart G, Dumont JE 1979 Control of thyroglobulin synthesis and secretion. (First of two parts). *N Engl J Med* 301:239-49
- [34] Van Herle AJ, Vassart G, Dumont JE 1979 Control of thyroglobulin synthesis and secretion (second of two parts). *N Engl J Med* 301:307-14
- [35] Eskandari S, Loo DD, Dai G, Levy O, Wright EM, Carrasco N 1997 Thyroid Na⁺/I⁻ symporter. Mechanism, stoichiometry, and specificity. *J Biol Chem* 272:27230-8

- [36] Smanik PA, Liu Q, Furminger TL, Ryu K, Xing S, Mazzaferri EL, Jhiang SM 1996 Cloning of the human sodium iodide symporter. *Biochem Biophys Res Commun* 226:339-45
- [37] Smanik PA, Ryu KY, Theil KS, Mazzaferri EL, Jhiang SM 1997 Expression, exon-intron organization, and chromosome mapping of the human sodium iodide symporter. *Endocrinology* 138:3555-8
- [38] Pohlenz J, Refetoff S 1999 Mutations in the sodium/iodide symporter (NIS) gene as a cause for iodide transport defects and congenital hypothyroidism. *Biochimie* 81:469-76
- [39] Szinnai G, Kosugi S, Derrien C, Lucidarme N, David V, Czernichow P, Polak M 2006 Extending the clinical heterogeneity of iodide transport defect (ITD): a novel mutation R124H of the sodium/iodide symporter gene and review of genotype-phenotype correlations in ITD. *J Clin Endocrinol Metab* 91:1199-204
- [40] Reed-Tsur MD, De la Vieja A, Ginter CS, Carrasco N 2008 Molecular characterization of V59E NIS, a Na⁺/I⁻ symporter mutant that causes congenital I⁻ transport defect. *Endocrinology* 149:3077-84
- [41] Medeiros-Neto G, Targovnik HM, Vassart G 1993 Defective thyroglobulin synthesis and secretion causing goiter and hypothyroidism. *Endocr Rev* 14:165-83.
- [42] van de Graaf SA, Ris-Stalpers C, Pauws E, Mendive FM, Targovnik HM, de Vijlder JJ 2001 Up to date with human thyroglobulin. *J Endocrinol* 170:307-21.
- [43] Niu DM, Hsu JH, Chong KW, Huang CH, Lu YH, Kao CH, Yu HC, Lo MY, Jap TS 2009 Six New Mutations of the Thyroglobulin Gene Discovered in Taiwanese Children Presenting with Thyroid Dysmorphogenesis. *J Clin Endocrinol Metab*
- [44] Kimura S, Kotani T, McBride OW, Umeki K, Hirai K, Nakayama T, Ohtaki S 1987 Human thyroid peroxidase: complete cDNA and protein sequence, chromosome mapping, and identification of two alternately spliced mRNAs. *Proc Natl Acad Sci U S A* 84:5555-9
- [45] Kimura S, Hong YS, Kotani T, Ohtaki S, Kikkawa F 1989 Structure of the human thyroid peroxidase gene: comparison and relationship to the human myeloperoxidase gene. *Biochemistry* 28:4481-9
- [46] Bakker B, Bikker H, Vulsma T, de Randamie JS, Wiedijk BM, De Vijlder JJ 2000 Two decades of screening for congenital hypothyroidism in The Netherlands: TPO gene mutations in total iodide organification defects (an update). *J Clin Endocrinol Metab* 85:3708-12
- [47] Niu DM, Hwang B, Chu YK, Liao CJ, Wang PL, Lin CY 2002 High prevalence of a novel mutation (2268 insT) of the thyroid peroxidase gene in Taiwanese patients with total iodide organification defect, and evidence for a founder effect. *J Clin Endocrinol Metab* 87:4208-12
- [48] Pannain S, Weiss RE, Jackson CE, Dian D, Beck JC, Sheffield VC, Cox N, Refetoff S 1999 Two different mutations in the thyroid peroxidase gene of a large inbred Amish kindred: power and limits of homozygosity mapping. *J Clin Endocrinol Metab* 84:1061-71
- [49] Avbelj M, Tahirovic H, Debeljak M, Kusekova M, Toromanovic A, Krzisnik C, Battelino T 2007 High prevalence of thyroid peroxidase gene mutations in patients with thyroid dysmorphogenesis. *Eur J Endocrinol* 156:511-9

- [50] Dupuy C, Ohayon R, Valent A, Noel-Hudson MS, Deme D, Virion A 1999 Purification of a novel flavoprotein involved in the thyroid NADPH oxidase. Cloning of the porcine and human cdnas. *J Biol Chem* 274:37265-9
- [51] De Deken X, Wang D, Many MC, Costagliola S, Libert F, Vassart G, Dumont JE, Miot F 2000 Cloning of two human thyroid cDNAs encoding new members of the NADPH oxidase family. *J Biol Chem* 275:23227-33
- [52] Corvilain B, van Sande J, Laurent E, Dumont JE 1991 The H₂O₂-generating system modulates protein iodination and the activity of the pentose phosphate pathway in dog thyroid. *Endocrinology* 128:779-85
- [53] Vigone MC, Fugazzola L, Zamproni I, Passoni A, Di Candia S, Chiumello G, Persani L, Weber G 2005 Persistent mild hypothyroidism associated with novel sequence variants of the DUOX2 gene in two siblings. *Hum Mutat* 26:395
- [54] Varela V, Rivolta CM, Esperante SA, Gruneiro-Papendieck L, Chiesa A, Targovnik HM 2006 Three mutations (p.Q36H, p.G418fsX482, and g.IVS19-2A>C) in the dual oxidase 2 gene responsible for congenital goiter and iodide organification defect. *Clin Chem* 52:182-91
- [55] Maruo Y, Takahashi H, Soeda I, Nishikura N, Matsui K, Ota Y, Mimura Y, Mori A, Sato H, Takeuchi Y 2008 Transient congenital hypothyroidism caused by biallelic mutations of the dual oxidase 2 gene in Japanese patients detected by a neonatal screening program. *J Clin Endocrinol Metab* 93:4261-7
- [56] Moreno JC, Visser TJ 2007 New phenotypes in thyroid dysmorphogenesis: hypothyroidism due to DUOX2 mutations. *Endocr Dev* 10:99-117
- [57] Pfarr N, Korsch E, Kaspers S, Herbst A, Stach A, Zimmer C, Pohlenz J 2006 Congenital hypothyroidism caused by new mutations in the thyroid oxidase 2 (THOX2) gene. *Clin Endocrinol (Oxf)* 65:810-5
- [58] Grasberger H, Refetoff S 2006 Identification of the maturation factor for dual oxidase. Evolution of an eukaryotic operon equivalent. *J Biol Chem* 281:18269-72
- [59] De Deken X, Wang D, Dumont JE, Miot F 2002 Characterization of ThOX proteins as components of the thyroid H₂O₂-generating system. *Exp Cell Res* 273:187-96
- [60] Kopp P 2000 Pendred's syndrome and genetic defects in thyroid hormone synthesis. *Rev Endocr Metab Disord* 1:109-21
- [61] Wasniewska M, De Luca F, Siclari S, Salzano G, Messina MF, Lombardo F, Valenzise M, Ruggeri C, Arrigo T 2002 Hearing loss in congenital hypothalamic hypothyroidism: a wide therapeutic window. *Hear Res* 172:87-91
- [62] Everett LA, Glaser B, Beck JC, Idol JR, Buchs A, Heyman M, Adawi F, Hazani E, Nassir E, Baxevanis AD, Sheffield VC, Green ED 1997 Pendred syndrome is caused by mutations in a putative sulphate transporter gene (PDS). *Nat Genet* 17:411-22
- [63] Everett LA, Belyantseva IA, Noben-Trauth K, Cantos R, Chen A, Thakkar SI, Hoogstraten-Miller SL, Kachar B, Wu DK, Green ED 2001 Targeted disruption of mouse Pds provides insight about the inner-ear defects encountered in Pendred syndrome. *Hum Mol Genet* 10:153-61
- [64] Royaux IE, Suzuki K, Mori A, Katoh R, Everett LA, Kohn LD, Green ED 2000 Pendrin, the protein encoded by the Pendred syndrome gene (PDS), is an apical porter of iodide in the thyroid and is regulated by thyroglobulin in FRTL-5 cells. *Endocrinology* 141:839-45

- [65] Blons H, Feldmann D, Duval V, Messaz O, Denoyelle F, Loundon N, Sergout-Allaoui A, Houang M, Duriez F, Lacombe D, Delobel B, Leman J, Catros H, Journel H, Drouin-Garraud V, Obstoy MF, Toutain A, Oden S, Toubanc JE, Couderc R, Petit C, Garabedian EN, Marlin S 2004 Screening of SLC26A4 (PDS) gene in Pendred's syndrome: a large spectrum of mutations in France and phenotypic heterogeneity. *Clin Genet* 66:333-40
- [66] Gausden E, Armour JA, Coyle B, Coffey R, Hochberg Z, Pembrey M, Britton KE, Grossman A, Reardon W, Trembath R 1996 Thyroid peroxidase: evidence for disease gene exclusion in Pendred's syndrome. *Clin Endocrinol (Oxf)* 44:441-6
- [67] Dai G, Levy O, Carrasco N 1996 Cloning and characterization of the thyroid iodide transporter. *Nature* 379:458-60
- [68] Kopp PA 2008 Reduce, recycle, reuse--iodotyrosine deiodinase in thyroid iodide metabolism. *N Engl J Med* 358:1856-9
- [69] Moreno JC, Pauws E, van Kampen AH, Jedlickova M, de Vijlder JJ, Ris-Stalpers C 2001 Cloning of tissue-specific genes using serial analysis of gene expression and a novel computational subtraction approach. *Genomics* 75:70-6
- [70] Gnidehou S, Caillou B, Talbot M, Ohayon R, Kaniewski J, Noel-Hudson MS, Morand S, Agnangji D, Sezan A, Courtin F, Virion A, Dupuy C 2004 Iodotyrosine dehalogenase 1 (DEHAL1) is a transmembrane protein involved in the recycling of iodide close to the thyroglobulin iodination site. *Faseb J* 18:1574-6
- [71] Moreno JC 2003 Identification of novel genes involved in congenital hypothyroidism using serial analysis of gene expression. *Horm Res* 60 Suppl 3:96-102
- [72] Montanelli L, Tonacchera M 2010 Genetics and phenomics of hypothyroidism and thyroid dys- and agenesis due to PAX8 and TTF1 mutations. *Mol Cell Endocrinol* 322:64-71
- [73] Vilain C, Rydlewski C, Duprez L, Heinrichs C, Abramowicz M, Malvaux P, Renneboog B, Parma J, Costagliola S, Vassart G 2001 Autosomal dominant transmission of congenital thyroid hypoplasia due to loss-of-function mutation of PAX8. *J Clin Endocrinol Metab* 86:234-8
- [74] Meeus L, Gilbert B, Rydlewski C, Parma J, Roussie AL, Abramowicz M, Vilain C, Christophe D, Costagliola S, Vassart G 2004 Characterization of a novel loss of function mutation of PAX8 in a familial case of congenital hypothyroidism with in-place, normal-sized thyroid. *J Clin Endocrinol Metab* 89:4285-91
- [75] Moya CM, Perez de Nanclares G, Castano L, Potau N, Bilbao JR, Carrascosa A, Bargada M, Coya R, Martul P, Vicens-Calvet E, Santisteban P 2006 Functional study of a novel single deletion in the TITF1/NKX2.1 homeobox gene that produces congenital hypothyroidism and benign chorea but not pulmonary distress. *J Clin Endocrinol Metab* 91:1832-41
- [76] Cooper DS, Axelrod L, DeGroot LJ, Vickery AL, Jr., Maloof F 1981 Congenital goiter and the development of metastatic follicular carcinoma with evidence for a leak of nonhormonal iodide: clinical, pathological, kinetic, and biochemical studies and a review of the literature. *J Clin Endocrinol Metab* 52:294-306.
- [77] Camargo R, Limbert E, Gillam M, Henriques MM, Fernandes C, Catarino AL, Soares J, Alves VA, Kopp P, Medeiros-Neto G 2001 Aggressive metastatic follicular thyroid carcinoma with anaplastic transformation arising from a long-standing goiter in a patient with Pendred's syndrome. *Thyroid* 11:981-8.

- [78] Boelaert K 2009 The association between serum TSH concentration and thyroid cancer. *Endocr Relat Cancer*
- [79] Morris HP, Dalton AJ, Green CD 1951 Malignant thyroid tumors occurring in the mouse after prolonged hormonal imbalance during the ingestion of thiouracil. *J Clin Endocrinol Metab* 11:1281-95.
- [80] Goldberg RC, Lindsay S, Nichols CW, Jr., Chaikoff IL 1964 Induction of Neoplasms in Thyroid Glands of Rats by Subtotal Thyroidectomy and by the Injection of One Microcurie of I-131. *Cancer Res* 24:35-43
- [81] Franco AT, Malaguarnera R, Refetoff S, Liao XH, Lundsmith E, Kimura S, Pritchard C, Marais R, Davies TF, Weinstein LS, Chen M, Rosen N, Ghossein R, Knauf JA, Fagin JA 2011 Thyrotrophin receptor signaling dependence of Braf-induced thyroid tumor initiation in mice. *Proc Natl Acad Sci U S A* 108:1615-20
- [82] Brewer C, Yeager N, Di Cristofano A 2007 Thyroid-stimulating hormone initiated proliferative signals converge in vivo on the mTOR kinase without activating AKT. *Cancer Res* 67:8002-6
- [83] Yeager N, Brewer C, Cai KQ, Xu XX, Di Cristofano A 2008 Mammalian target of rapamycin is the key effector of phosphatidylinositol-3-OH-initiated proliferative signals in the thyroid follicular epithelium. *Cancer Res* 68:444-9
- [84] Saji M, Ringel MD 2010 The PI3K-Akt-mTOR pathway in initiation and progression of thyroid tumors. *Mol Cell Endocrinol* 321:20-8
- [85] Hishinuma A, Fukata S, Kakudo K, Murata Y, Ieiri T 2005 High incidence of thyroid cancer in long-standing goiters with thyroglobulin mutations. *Thyroid* 15:1079-84.
- [86] Raef H, Al-Rijjal R, Al-Shehri S, Zou M, Al-Mana H, Baitei EY, Parhar RS, Al-Mohanna FA, Shi Y 2010 Biallelic p.R2223H Mutation in the Thyroglobulin Gene Causes Thyroglobulin Retention and Severe Hypothyroidism with Subsequent Development of Thyroid Carcinoma. *J Clin Endocrinol Metab* 95:1000-6
- [87] Medeiros-Neto G, Gil-Da-Costa MJ, Santos CL, Medina AM, Silva JC, Tsou RM, Sobrinho-Simoes M 1998 Metastatic thyroid carcinoma arising from congenital goiter due to mutation in the thyroperoxidase gene. *J Clin Endocrinol Metab* 83:4162-6.
- [88] Raef H, Al-Rijjal R, Al-Shehri S, Zou M, Al-Mana H, Baitei EY, Parhar RS, Al-Mohanna FA, Shi Y 2010 Biallelic p.R2223H Mutation in the Thyroglobulin Gene Causes Thyroglobulin Retention and Severe Hypothyroidism with Subsequent Development of Thyroid Carcinoma. *J Clin Endocrinol Metab*
- [89] Kallel R, Mnif Hachicha L, Mnif M, Hammami B, Ayadi L, Bahri I, Ghorbel A, Abid M, Makni S, Boudawara T 2009 [Papillary carcinoma arising from dys hormonogenetic goiter]. *Ann Endocrinol (Paris)* 70:485-8
- [90] Drut R, Moreno A 2009 Papillary carcinoma of the thyroid developed in congenital dys hormonogenetic hypothyroidism without goiter: Diagnosis by FNAB. *Diagn Cytopathol* 37:707-9
- [91] Yashiro T, Ito K, Akiba M, Kanaji Y, Obara T, Fujimoto Y, Hirayama A, Nakajima H 1987 Papillary carcinoma of the thyroid arising from dys hormonogenetic goiter. *Endocrinol Jpn* 34:955-64
- [92] Medeiros-Neto G SJ 1994 Thyroid malignancy and dys hormonogenetic goiter. CRC Press, Boca Raton

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Hypothyroidism is the most common thyroid disorder. It can cause a variety of changes in women's menstrual periods, reduce their chances of becoming pregnant, as well as affect both the course of pregnancy and the neuropsychological development of babies. During pregnancy there is a substantially increased need for thyroid hormones and a substantial risk that a previously unnoticed, subclinical or latent hypothyroidism will turn into overt hypothyroidism. The thyroid inflammation caused by the patient's own immune system may form autoimmune thyroiditis (Hashimoto's thyroiditis). Congenital hypothyroidism (CH) occurs in approximately 1:2,000 to 1:4,000 newborns. Nearly all of the developed world countries currently practice newborn screening to detect and treat congenital hypothyroidism in the first weeks of life. "A New Look at Hypothyroidism" contains many important specifications and innovations for endocrine practice.

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