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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 T4 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 ≤ or =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.
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Congenital hypothyroidism (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, Gsα, 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 dyshormonogenesis account for 15–20% of CH cases (20). In thyroid dyshormonogenesis (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 dyshormonogenesis is a genetically heterogeneous group of inherited disorders in the enzymatic cascade of thyroid hormone synthesis. The underlining genetic defects causing dyshormonogenesis 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 (DUOX2A)(30), pendrin (SLC26A4/PDS/(31), and iodotyrosine dehalogenase1(DEHAL1) (32). Mutations in the TPO or Tg are the most frequent genetic defects in thyroid dyshormonogenesis.

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

Thyroid hormones, thyroxine (T4) and triiodothyronine (T3), 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 T4 and T3. 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 (DUOX2A). 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 (T3) or thyroxine (T4). 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 T4 and T3, thyroglobulin is engulfed.
by the thyrocytes through pinocytosis, digested in lysosomes, and then secreted into the bloodstream. In contrast, monoiodotyrosine and diiodotyrosine are found only in minute amounts in the bloodstream. The major form of thyroid hormone in the blood is thyroxine (T<sub>4</sub>) (approximately 80%), which has a longer half life than T<sub>3</sub>. The ratio of T<sub>4</sub> to T<sub>3</sub> released in the blood is roughly 20 to 1. T<sub>4</sub> is converted to the active T<sub>3</sub> (three to four times more potent than T<sub>4</sub>) 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<sup>+</sup> down their electrochemical gradient to the simultaneous inward translocation of one I<sup>-</sup> against its electrochemical gradient (35). The driving force for NIS activity is the Na<sup>+</sup> gradient generated by the Na<sup>+</sup>/K<sup>+</sup> 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, M143-Q323, Q267E, C272X, T354P, G395R, 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<sub>4</sub> and T<sub>3</sub>) 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 dyshormonogenesis, 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<sup>2+</sup>/reduced nicotinamide adenine dinucleotide phosphate-dependent generation of H<sub>2</sub>O<sub>2</sub> (50, 51). In thyroid hormone synthesis, H<sub>2</sub>O<sub>2</sub> 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<sub>2</sub>O<sub>2</sub>, 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
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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 non-thyroidal 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 H2O2 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 T4), the main iodinated by-products of thyroid hormone synthesis by thyroidal iodothyrosine 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, Gαt, 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 dyshormonogenic 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 (Table 1) (27). The most common genetic defects are TG mutation, resulting in dyshormonogenesis 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 BRAFV600E, mutations of which are found in about 45% of papillary thyroid carcinomas (81). BRAFV600E-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, BRAFV600E induced oncogenic transformation of thyroid follicular cells is lost when TSH receptor is knockout, indicating the dependence of TSH mediated cAMP signaling in BRAFV600E 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 dyshormonogenic goitres. Although less frequently, genetic defects in the MAPK/ERK signaling pathway have been reported, for example, BRAFV600E 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.

<table>
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<th>Tumor</th>
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<th>Other genetic defects</th>
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<td>1.</td>
<td>FTC</td>
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<td>2.</td>
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<td>Truncated TPO</td>
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<td>3.</td>
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A New Look at Hypothyroidism

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<td>PTC</td>
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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.

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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 (T₃) or thyroxine (T₄), a process that involves only a small fraction of iodotyrosines. Thyroglobulin is then engulfed by thyrocytes through pinocytosis and digested in lysosomes, and T₄ and T₃ 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 $^{123}$I whole body scan. The scan was performed 24 h following the oral administration of 74 MBq (2 mCi) of $^{123}$I. Whole body images were acquired in anterior and posterior projections before $^{131}$I 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 $^{131}$I 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).
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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.

How to reference
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