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Hypothyroidism

Osama M. Ahmed[1] and R. G. Ahmed[2,3]
[1]*Physiology Division, Zoology Department, Faculty of Science, Beni-Suef University,*
[2]*Lab of Comparative Endocrinology, Catholic University, Leuven,*
[3]*Zoology Department, Faculty of Science, Beni-Suef University,*
[1,3]*Egypt*
[2]*Belgium*

1. Introduction

Hypothyroidism is caused by insufficient secretion of thyroid hormones by the thyroid gland or by the complete loss of its function. The share of hypothyroidism among other endocrine diseases is gradually increasing. It is encountered in females more than in males. The idiopathic form of hypothyroidism occurs mainly in females older than 40 years. Hypothyroidism is usually progressive and irreversible. Treatment, however, is nearly always completely successful and allows a patient to live a fully normal life (Potemkin, 1889; Thomas, 2004; Roberts and Ladenson, 2004).

2. History

Hypothyroidism was first diagnosed in the late nineteenth century when doctors observed that surgical removal of the thyroid resulted in the swelling of the hands, face, feet, and tissues around the eyes. The term myxoedema (mucous swelling; myx is the Greek word for mucin and oedema means swelling) was introduced in 1974 by Gull and in 1878 by Ord. On the autopsy of two patients, Ord discovered mucous swelling of the skin and subcutaneous fat and linked these changes with the hypofunction or atrophy of the thyroid gland. The disorder arising from surgical removal of the thyroid gland (cachexia strumipriva) was described in 1882 by Reverdin of Geneva and in 1883 by Kocher of Berne. After Gull's description, myxoedma aroused enormous interest, and in 1883 the Clinical Society of London appointed a committee to study the disease and report its findings. The committee's report, published in 1888, contains a significant portion of what is known today about the clinical and pathologic aspects of myxoedema (Wiersinga, 2010).

3. Causes and incidence

Many permanent or temporary conditions can reduce thyroid hormone secretion and cause hypothyroidism. About 95% of hypothyroidism cases occur from problems that start in the thyroid gland. In such cases, the disorder is called primary hypothyroidism (Potemkin, 1889). Secondary and tertiary hypothyroidism is caused by disorders of the pituitary gland and hypothalamus respectively (Lania et al., 2008). Only 5% of

hypothyroid cases suffer from secondary and tertiary hypothyroidism (Potemkin, 1889). The two most common causes of primary hypothyroidism are (1) Hashimoto's thyroiditis which is an autoimmune condition and (2) overtreatment of hyperthyroidism (an overactive thyroid) (Simon, 2006; Aminoff, 2007; Elizabeth and Agabegi, 2008). Primary hypothyroidism may also occur as a result of insufficient introduction of iodine into body (endemic goiter). In iodine-replete communities, the prevalence of spontaneous hypothyroidism is between 1 % and 2 %, and it is more common in older women and ten times more common in women than in men (Vanderpump, 2005 and 2009). Radioiodine therapy may lead to hypothyroidism (Potemkin, 1989). Primary hypothyroidism may also occur as a result of hereditary defects in the biosynthesis of thyroid hormones (due to defect in the accumulation of iodine by the thyroid gland or defect in the transformation of monoiodotyrosine and diiodotyrosines into triiodothyronine and thyroxine) or may be caused by hypoplasia and plasia of the thyroid gland as a result of its embryonic developmental defect, degenerative changes, total or subtotal thyroidectomy (Potemkin, 1889). Hypothalamic and pituitary hypothyroidism, or central hypothyroidism results from a failure of the mechanisms that stimulate thyroid-stimulating hormone (TSH) and TSH releasing hormone (TRH) synthesis, secretion, and biologic action (Thomas, 2004). The most prevalent cause of central hypothyroidism, including secondary and tertiary subtypes, is a defective development of the pituitary gland or hypothalamus leading to multiple pituitary hormone deficiencies, while defects of pituitary and hypothalamic peptides and their receptors only rarely have been identified as the cause of central congenital hypothyroidism (Grueters et al., 2002; Ahmed et al., 2008).

Type	**Origin**	**Description**
Primary	Thyroid gland	The most common forms include Hashimoto's thyroiditis (an autoimmune disease) and radioiodine therapy for hyperthyroidism.
Secondary	Pituitary gland	It occurs if the pituitary gland does not create enough thyroid-stimulating hormone (TSH) to induce the thyroid gland to produce enough thyroxine and triiodothyronine. Although not every case of secondary hypothyroidism has a clear-cut cause, it is usually caused by damage to the pituitary gland, as by a tumor, radiation, or surgery. Secondary hypothyroidism accounts for less than 5% or 10% of hypothyroidism cases.
Tertiary	Hypothalamus	It results when the hypothalamus fails to produce sufficient thyrotropin-releasing hormone (TRH). TRH prompts the pituitary gland to produce thyroid-stimulating hormone (TSH). Hence may also be termed hypothalamic-pituitary-axis hypothyroidism. It accounts for less than 5% of hypothyroidism cases.

Table 1. Classification of hypothyroidism according to the origin of cause (Simon, 2006; Aminoff, 2007; Elizabeth and Agabegi, 2008).

4. Grades of hypothyroidism

Hypothyroidism ranges from very mild states in which biochemical abnormalities are present but the individual hardly notices symptoms and signs of thyroid hormone deficiency, to very severe conditions in which the danger exists to slide down into a life-threatening myxoedema coma. In the development of primary hypothyroidism, the transition from the euthyroid to the hypothyroid state is first detected by a slightly elevated serum TSH, caused by a minor decrease in thyroidal secretion of T4 which doesn't give rise to subnormal serum T4 concentrations. The reason for maintaining T4 values within the reference range is the exquisite sensitivity of the pituitary thyrotroph for even very small decreases of serum T4, as exemplified by the log-linear relationship between serum TSH and serum FT4. A further decline in T4 secretion results in serum T4 values below the lower normal limit and even higher TSH values, but serum T3 concentrations remain within the reference range. It is only in the last stage that subnormal serum T3 concentrations are found, when serum T4 has fallen to really very low values associated with markedly elevated serum TSH concentrations (Figure 1). Hypothyroidism is thus a graded phenomenon, in which the first stage of subclinical hypothyroidism may progress via mild hypothyroidism towards overt hypothyroidism (Table 2) (Reverdin, 1882).

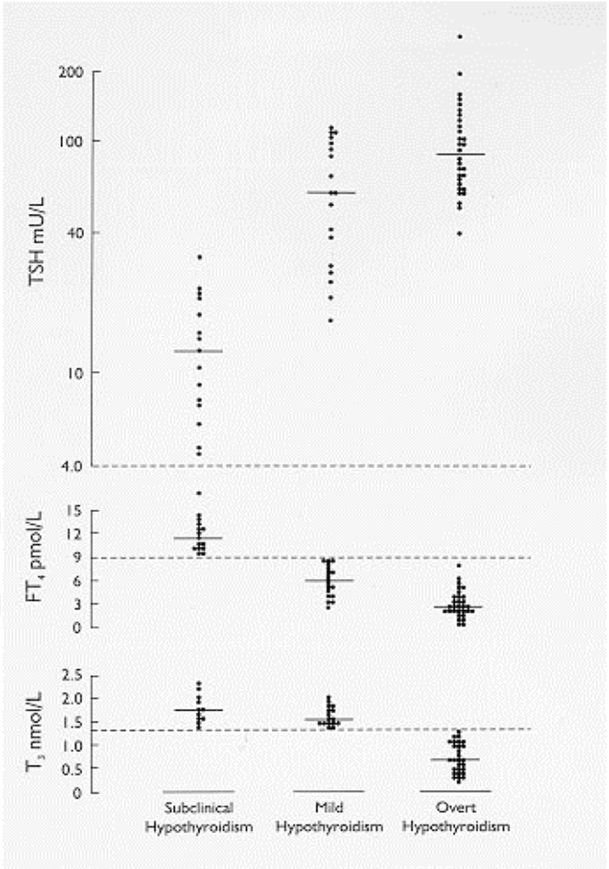

Fig. 1. Individual and median values of thyroid function tests in patients with various grades of hypothyroidism. Discontinuous horizontal lines represent upper limit (TSH) and lower limit (FT4, T3) of the normal reference ranges (Wiersinga, 2010).

Grade 1	Subclinical hypothyroidism	TSH +	FT4 N	T3 N(+)
Grade 2	Mild hypothyroidism	TSH +	FT4 -	T3 N
Grade 3	Overt hypothyroidism	TSH +	FT4 -	T3 -
+, above upper normal limit; N, within normal reference range; -, below lower normal limit.				

Table 2. Grades of hypothyroidism (Reverdin, 1882).

Taken together, hypothyroidism can be classified based on its time of onset (congenital or acquired), severity (overt [clinical] or mild [subclinical]), and the level of endocrine aberration (primary or secondary) (Roberts and Ladenson, 2004). Primary hypothyroidism follows a dysfunction of the thyroid gland itself, whereas secondary and tertiary hypothyroidism results from either defect in the development or dysfunction of pituitary gland and hypothalamus (Grueters et al., 2002; Ahmed et al., 2008).

5. Hypothyroidism and metabolic defects

The thyroid hormones act directly on mitochondria, and thereby control the transformation of the energy derived from oxidations into a form utilizable by the cell. Through their direct actions on mitochondria, the hormones also control indirectly the rate of protein synthesis and thereby the amount of oxidative apparatus in the cell. A rationale for the effects of thyroid hormone excess or deficiency is based upon studies of the mechanism of thyroid hormone action. In hypothyroidism, slow fuel consumption leads to a low output of utilizable energy. Many of the chemical and physical features of these diseases can be reduced to changes in available energy (Hoch, 1968 & 1988; Harper and Seifert, 2008).

Thyroid dysfunction is characterized by alterations in carbohydrate, lipid and lipoprotein metabolism, consequently changing the concentration and composition of plasma lipoproteins. In hyperthyroid patients, the turnover of low-density-lipoprotein apoprotein is increased, and the plasma cholesterol concentration is decreased. Hypothyroidism in man is associated with an increase in plasma cholesterol, particularly in low-density lipoproteins and often with elevated plasma VLD lipoprotein, and there is a positive correlation with premature atherosclerosis. Although it is known that myxoedemic patients have decreased rates of low-density lipoprotein clearance from the circulation, it is not known with certainty if the elevated concentration of VLD lipoprotein is due to increased secretion by the liver or to decreased clearance by the tissues (Laker and Mayes, 1981).

6. Symptoms associated with hypothyroidism

Hypothyroidism produces many symptoms related to its effects on metabolism. Physical symptoms of hypothyroidism-related reduced metabolic rate include fatigue, slowed heart rate, intolerance to cold temperatures, inhibited sweating and muscle pain. Depression is a key psychological consequence of hypothyroidism and slow metabolism as well. For women, slow metabolism can cause increased menstruation and even impair fertility. Weight gain and metabolic rate are intimately related. A slow metabolism interferes with

the body's ability to burn fat, so those with hypothyroidism often experience weight gain when their condition is not treated properly. Since the metabolism keeps muscles functioning properly and controls body temperature, hypothyroidism can impair these essential metabolic processes. The weight gain can then lead to obesity, which carries its own serious health risks, including for diabetes, heart disease and certain types of cancer. Other side effects include impaired memory, gynecomastia, impaired cognitive function, puffy face, hands and feet, slow heart rate, decreased sense of taste and smell, sluggish reflexes, decreased libido, hair loss, anemia, acute psychosis, elevated serum cholesterol, difficulty swallowing, shortness of breath, recurrent hypoglycemia, increased need for sleep, irritability, yellowing of the skin due to the failure of the body to convert beta-carotene to vitamin A, and impaired renal function (Onputtha, 2010).

Hypothyroidism is frequently accompanied by diminished cognition, slow thought process, slow motor function, and drowsiness (Bunevičius and Prange Jr, 2010). Myxedema is associated with severe mental disorders including psychoses, sometimes called 'myxematous madness'. Depression related to hypothyroidism, even subclinical hypothyroidism may affect mood (Haggerty and Prange, 1995). Thyroid deficits are frequently observed in bipolar patients, especially in women with the rapid cycling form of the disease (Bauer et al., 2008). Both subclinical hypothyroidism and subclinical hyperthyroidism increase the risk for Alzheimer's disease, especially in women (Tan et al., 2008). However, most hypothyroid patients do not meet the criteria for a mental disorder. A recent study evaluated brain glucose metabolism during T4 treatment of hypothyroidism (Bunevičius and Prange Jr, 2010). A reduction in depression and cognitive symptoms was associated with restoration of metabolic activity in brain areas that are integral to the regulation of mood and cognition (Bauer et al., 2009). In hypothyroidism, replacement therapy with T4 remains the treatment of choice and resolves most physical and psychological signs and symptoms in most patients. However, some patients do not feel entirely well despite doses of T4 that are usually adequate (Saravanan et al., 2002). In T4-treated patients, it was found that reduced psychological well being is associated with occurrence of polymorphism in the D2 gene (Panicker et al., 2009), as well as in the OATP1c1 gene (van der Deure et al., 2008). Thyroid hormone replacement with a combination of T4 and T3, in comparison with T4 monotherapy, improves mental functioning in some but not all hypothyroid patients (Bunevicius et al., 1999; Nygaard et al., 2009), and most of the patients subjectively prefer combined treatment (Escobar-Morreale et al., 2005). It was concluded that future trials on thyroid hormone replacement should target genetic polymorphisms in deiodinase and thyroid hormone transporters (Wiersinga, 2009).

7. Hypothyroidism and development

7.1 Congenital hypothyroidism

Traditionally, research on the role of the thyroid hormones in brain development has focused on the postnatal phase and on identifying congenital hypothyroidism, which is the final result of the deficiency suffered throughout the pregnancy (Pérez-López, 2007). Iodine deficit during pregnancy produces an increase in perinatal mortality and low birth weight which can be prevented by iodated oil injections given in the latter half of pregnancy or in other supplementary forms (European Commission, 2002). The

epidemiological studies suggest that hypothyroxinemia, especially at the beginning of pregnancy, affects the neurological development of the new human being in the long term (Pérez-López, 2007). Full-scale clinical studies have demonstrated a correlation between maternal thyroid insufficiency during pregnancy and a low neuropsychological development in the neonate (Haddow et al., 1999). Maternal hypothyroxinemia during the first gestational trimester limits the possibilities of postnatal neurodevelopment (Pop et al., 2003; Kooistra et al., 2006). The most serious form of brain lesion corresponds to neurological cretinism, but mild degrees of maternal hypothyroxinemia also produce alterations in psychomotor development (Morreale de Escobar et al., 2004; Visser, 2006). The thyroid function of neonates at birth is significantly related to the brain size and its development during the first two years of life (Van Vliet, 1999). Screening programs for neonatal congenital hypothyroidism indicate that it is present in approximately one case out of 3000 to 4000 live births (Klein et al., 1991). Seventy-eight percent were found to have an intelligence quotient (IQ) of over 85 when congenital hypothyroidism was diagnosed within the first few months after birth, 19% when it was diagnosed between 3 and 6 months, and 0% when the diagnosis was made 7 months after birth (Pérez-López, 2007). In a meta-analysis of seven studies (Derksen-Lubsen and Verkerk, 1996), a decrease of 6.3 IQ points was found among neonates who suffered hypothyroidism during pregnancy in comparison to the control group. Long-term sequelae of hypothyroidism also affect intellectual development during adolescence. The affected children show an average of 8.5 IQ points less than the control group, with deficits in memory and in visuospatial and motor abilities related to the seriousness of congenital hypothyroidism and due to inadequate treatment in their early childhood (Rovet, 1999).

Untreated congenital hypothyroidism (sporadic cretinism) produces neurologic deficits having predominantly postnatal origins (Porterfield, 2000). Although mental retardation can occur, it typically is not as severe as that seen in neurologic cretinism. Untreated infants with severe congenital hypothyroidism can lose 3-5 IQ points per month if untreated during the first 6-12 months of life (Burrow et al., 1994). If the children are treated with thyroid hormones soon after birth, the more severe effects of thyroid deficiency are alleviated (Porterfield, 2000). However, these children are still at risk for mild learning disabilities. They may show subtle language, neuromotor, and cognitive impairment (Rovet et al., 1996). They are more likely to show attention deficit hyperactivity disorder (ADHD), have problems with speech and interpretation of the spoken word, have poorer fine motor coordination, and have problems with spatial perception (Rovet et al., 1992). The severity of these effects is correlated with the retardation of bone ossification seen at birth. This would suggest that the damage is correlated with the mild hypothyroidism they experience in utero. Rovet and Ehrlich (1995) have proposed that the sensitive periods for thyroid hormones vary for verbal and nonverbal skills. The critical period for verbal and memory skills appears to be in the first 2 months postpartum, whereas for visuospatial or visuomotor skills it is prenatal (Porterfield, 2000). Thyroid hormone deficiency impairs learning and memory, which depend on the structural integrity of the hippocampus (Porterfield, 2000). Maturation and synaptic development of the pyramidal cells of the hippocampus are particularly sensitive to thyroid hormone deficiency during fetal/perinatal development (Madeira et al., 1992). Early in fetal development (rats), thyroid hormone deficiency decreases radial glial cell maturation and therefore impairs cellular migration (Rami and Rabie, 1988), which can lead to irreversible changes in the

neuronal population and connectivity in this region. Animals with experimentally induced congenital hypothyroidism show delayed and decreased axonal and dendritic arborization in the cerebral cortex, a decrease in nerve terminals, delayed myelination, abnormal cochlear development, and impaired middle ear ossicle development (Porterfield and Hendrich, 1993).

7.2 Endemic cretinism

The most severe neurologic impairment resulting from a thyroid deficiency is an endemic cretinism caused by iodine deficiency (Porterfield, 2000). In fact, iodine deficiency represents the single most preventable cause of neurologic impairment and cerebral palsy in the world today (Donati et al., 1992; Morreale de Escobar et al., 1997). These individuals suffer from hypothyroidism that begins at conception because the dietary iodine deficiency prevents synthesis of normal levels of thyroid hormones (Porterfield, 2000). It is more severe than that seen in congenital hypothyroidism because the deficiency occurs much earlier in development and results in decreased brain thyroid hormone exposure both before and after the time the fetal thyroid gland begins functioning (Porterfield, 2000). Problems with endemic cretins include mental retardation that can be profound, spastic dysplasia, and problems with gross and fine motor control resulting from damage to both the pyramidal and the extrapyramidal systems (Porterfield, 2000). These problems include disturbances of gait, and in the more extreme forms, the individuals cannot walk or stand (Pharoah et al., 1981; Donati et al., 1992; Stanbury, 1997). If postnatal hypothyroidism is present, there is growth retardation and delayed or absent sexual maturation (Porterfield and Hendrich, 1993). Damage occurs both to structures such as the corticospinal system that develop relatively early in the fetus and structures such as the cerebellum that develop predominantly in the late fetal and early neonatal period (Porterfield, 2000). The damage is inversely related to maternal serum thyroxine (T4) levels but not to triiodothyronine (T3) levels (Calvo et al., 1990; Donati et al., 1992; Porterfield and Hendrich, 1993). Delong (1987) suggests that the neurologic damage occurs primarily in the second trimester, which is an important period for formation of the cerebral cortex, the extrapyramidal system, and the cochlea, areas damaged in endemic cretins. Maternal T3 levels are often normal and the mother therefore may not show any overt symptoms of hypothyroidism (Porterfield, 2000). Early development of the auditory system appears to be dependent upon thyroid hormones (Bradley et al., 1994). The greater impairment characterized by endemic cretinism relative to congenital hypothyroidism is thought to result from the longer period of exposure of the developing brain to hypothyroidism in endemic cretinism (Donati et al., 1992; Porterfield and Hendrich, 1993; Morreale de Escobar et al., 1997).

7.3 Thyroid function during pregnancy and iodine deficiency

Glinoer and his group showed that, in conditions of mild iodine deficiency, the serum concentrations of free thyroxine decrease steadily and significantly during gestation (Glinoer, 1997a,b). Although the median values remain within the normal range, one third of pregnant women have free thyroxine values near or below the lower limit of normal. This picture is in clear contrast with thyroid status during normal pregnancy and normal iodine intake, which is characterised by only a slight (15%) decrease of free thyroxine by the end of gestation. After an initial blunting of serum thyroid stimulating hormone (TSH) caused by increased

concentrations of human chorionic gonadotrophin, serum TSH concentrations increase progressively in more than 80% of pregnant Belgian women, although these levels also remain within the normal range. This change is accompanied by an increase in serum thyroglobulin, which is directly related to the increase in TSH. This situation of chronic thyroid hyperstimulation results in an increase in thyroid volume by 20% to 30% during gestation, a figure twice as high as that in conditions of normal iodine supply. The role of the lack of iodine in the development of these different anomalies is indicated by the fact that a daily supplementation with physiological doses of iodine (150 µg/day) prevents their occurrence (Glinoer et al., 1995). In moderate iodine deficiency, the anomalies are of the same nature but more marked. For example, in an area of Sicily with an iodine intake of 40 µg/day, Vermiglio et al reported a decline of serum free thyroxine of 31% and a simultaneous increase of serum TSH of 50% during early (8th to 19th weeks) gestation (Vermiglio et al., 1995). Only a limited number of studies are available on thyroid function during pregnancy in populations with severe iodine deficiency (iodine intake below 25 µg iodine/day). Moreover, because of the extremely difficult conditions in which these studies were performed, the results are necessarily only partial. The most extensive data are available from New Guinea (Choufoer et al., 1965; Pharoah et al., 1984) and the Democratic Republic of Congo (DRC, formerly Zaire) (Thilly et al., 1978; Delange et al., 1982). The studies conducted in such environments show that the prevalence of goitre reaches peak values of up to 90% in females of child bearing age 20 and that during pregnancy, serum thyroxine is extremely low and serum TSH extremely high. However, it has been pointed out that for a similar degree of severe iodine deficiency in the DRC and New Guinea, serum thryoxine in pregnant mothers is much higher in the DRC (103 nmol/l) than in New Guinea (38.6–64.4 nmol/l) (Morreale de Escobar et al., 1997). The frequency of values below 32.2 nmol/l is only 3% in the DRC while it is 20% in New Guinea. This discrepancy was understood only when it was demonstrated that in the DRC, iodine deficiency is aggravated by selenium deficiency and thiocyanate overload (see later section) (Delange et al., 1982; Vanderpas et al., 1990; Contempre et al., 1991). Also, during pregnancy, iodine deficiency produces hypothyroxinemia which consequently causes (1) thyroid stimulation through the feedback mechanisms of TSH, and (2) goitrogenesis in both mother and fetus (Pérez-López, 2007). For this reason, it seems that moderate iodine deficiency causes an imbalance in maternal thyroid homeostasis, especially toward the end of pregnancy, leading to isolated hypothyroxinemia suggestive of biochemical hypothyroidism. Uncontrolled hypothyroidism in pregnancy can lead to preterm birth, low birth weight and mental retardation (Drews and Seremak-Mrozikiewicz, 2011).

7.4 Perinatal thyroid function and iodine deficiency

In mild iodine deficiency, serum concentrations of TSH and thyroglobulin are still higher in neonates than in mothers (Glinoer, 1997a,b), indicating that neonates are more sensitive than adults to the effects of iodine deficiency. Again, the role of iodine deficiency is demonstrated by the fact that neonates born to mothers who have been supplemented with iodine during pregnancy have a lower thyroid volume and serum thyroglobulin and higher urinary iodine than newborns born to untreated mothers (Glinoer et al., 1995). Other evidence of chronic TSH overstimulation of the neonatal thyroid is the fact that there is a slight shift towards increased values of the frequency distribution of neonatal TSH on day 5, which is the time of systematic screening for congenital hypothyroidism (Delange, 2001). The frequency of values above 5

mU/l blood is 4.5%, while the normal value is below 3%. In moderate iodine deficiency, the anomalies are of the same nature but more drastic than in conditions of mild iodine deficiency (Delange, 2001). Transient hyperthyrotrophinaemia or even transient neonatal hypothyroidism can occur. The frequency of the latter condition is approximately six times higher in Europe than in the United States where the iodine intake is much higher (Delange et al., 1983). The shift of neonatal TSH towards increased values is more marked and the frequency of values above 20–25 mU/l blood, that is above the cut off point used for recalling the neonates because of suspicion of congenital hypothyroidism in programmes of systematic screening for congenital hypothyroidism, is increased (Delange, 2001). There is an inverse relationship between the median urinary iodine of populations of neonates used as an index of their iodine intake and the recall rate at screening (Delange, 1994 & 1998). It has to be pointed out that these changes in neonatal TSH frequently occur for levels of iodine deficiency that would not affect the thyroid function in non-pregnant adults (Delange, 2001). The hypersensitivity of neonates to the effects of iodine deficiency is explained by their very small intrathyroidal iodine pool, which requires increased TSH stimulation and a fast turnover rate in order to maintain normal secretion of thyroid hormones (Delange, 1998). In severe iodine deficiency, as in the mothers, the biochemical picture of neonatal hypothyroidism is caricatural, especially in the DRC where mean cord serum thyroxine and TSH concentrations are 95.2 nmol/l and 70.7 mU/l respectively and where as many as 11% of the neonates have both a cord serum TSH above 100 mU/l and a cord thyroxine below 38.6 nmol/l, that is a biochemical picture similar to the one found in thyroid agenesis (Delange et al., 1993).

7.5 Hypothyroidism and brain development in humans

The neonatal period of development in humans is known to be sensitive to thyroid hormone, especially as revealed in the disorder known as congenital hypothyroidism (CH) (Krude et al., 1977; Dussault and Walker, 1983; Miculan et al., 1993; Foley, 1996; Kooistra et al., 1994; van Vliet, 1999; Rovet, 2000). CH occurs at a rate of approximately 1 in 3,500 live births (Delange, 1997). Because CH infants do not present a specific clinical picture early, their diagnosis based solely on clinical symptoms was delayed before neonatal screening for thyroid hormone (Zoeller et al., 2002). In fact, only 10% of CH infants were diagnosed within the first month, 35% within 3 months, 70% within the first year, and 100% only after age 3 (Alm et al., 1984). The intellectual deficits as a result of this delayed diagnosis and treatment were profound. One meta-analysis found that the mean full-scale intelligence quotient (IQ) of 651 CH infants was 76 (Klein, 1980). Moreover, the percentage of CH infants with an IQ above 85 was 78% when the diagnosis was made within 3 months of birth, 19% when it was made between 3 and 6 months, and 0% when diagnosed after 7 months of age (Klein, 1980; Klein and Mitchell, 1996). Studies now reveal that the long-term consequences of CH are subtle if the diagnosis is made early and treatment is initiated within 14 days of birth (Mirabella et al., 2000; Hanukoglu et al., 2001; Leneman et al., 2001), which can be accomplished only by mandatory screening for thyroid function at birth. This medical profile has become the principal example illustrating the importance of thyroid hormone for normal brain development (Zoeller et al., 2002). Recent studies indicate that thyroid hormone is also important during fetal development. Thyroid hormones are detected in human coelomic and amniotic fluids as early as 8 weeks of gestation, before the onset of fetal thyroid function at 10–12 weeks (Contempre et al., 1993). In addition, human fetal brain tissues express thyroid hormone receptors (TRs), and receptor occupancy by thyroid

hormone is in the range known to produce physiological effects as early as 9 weeks of gestation (Ferreiro et al., 1988). Finally, the mRNAs encoding the two known TR classes exhibit complex temporal patterns of expression during human gestation (Iskaros et al., 2000), and the mRNAs encoding these TR isoforms are expressed in the human oocyte (Zhang et al., 1997). These data indicate that maternal thyroid hormone is delivered to the fetus before the onset of fetal thyroid function, and that the minimum requirements for thyroid hormone signaling are present at this time (Zoeller et al., 2002). Two kinds of pathological situations reveal the functional consequences of deficits in thyroid hormone during fetal development (Zoeller et al., 2002). The first is that of cretinism, a condition usually associated with severe iodine insufficiency in the diet (Delange, 2000). There are two forms of cretinism based on clinical presentation: neurological cretinism and myxedematous cretinism (Delange, 2000). Neurological cretinism is characterized by extreme mental retardation, deaf-mutism, impaired voluntary motor activity, and hypertonia (Delange, 2000). In contrast, myxedematous cretinism is characterized by less severe mental retardation and all the major clinical symptoms of persistent hypothyroidism (Delange, 2000). Iodide administration to pregnant women in their first trimester eliminates the incidence of neurological cretinism (Zoeller et al., 2002). However, the initiation of iodine supplementation by the end of the second trimester does not prevent neurological damage (Cao et al., 1994; Delange, 2000). Several detailed studies of endemias occurring in different parts of the world have led to the proposal that the various symptoms of the two forms of cretinism arise from thyroid hormone deficits occurring at different developmental windows of vulnerability (Cao et al., 1994; Delange, 2000). Therefore, thyroid hormone appears to play an important role in fetal brain development, perhaps before the onset of fetal thyroid function (Zoeller et al., 2002). The second type of pathological situation is that of subtle, undiagnosed maternal hypothyroxinemia (Zoeller et al., 2002). The concept and definition of maternal hypothyroxinemia were developed in a series of papers by Man et al. (Man and Jones, 1969; Man and Serunian, 1976; Man and Brown, 1991). Low thyroid hormone was initially defined empirically - those pregnant women with the lowest butanol-extractable iodine among all pregnant women (de Escobar et al., 2000). This work was among the first to document an association between subclinical hypothyroidism in pregnant women and neurological function of the offspring. After the development of radioimmunoassay for thyroid hormone, Pop et al. (1995) found that the presence of antibodies to thyroid peroxidase in pregnant women, independent of thyroid hormone levels per se, is associated with significantly lower IQ in the offspring. Subsequent studies have shown that children born to women with thyroxine (T4) levels in the lowest 10th percentile of the normal range had a higher risk of low IQ and attention deficit (Haddow et al., 1999). Excellent recent reviews discuss these studies in detail (de Escobar et al., 2000). Taken together, these studies present strong evidence that maternal thyroid hormone plays a role in fetal brain development before the onset of fetal thyroid function, and that thyroid hormone deficits in pregnant women can produce irreversible neurological effects in their offspring (Gupta et al., 1995; Klett, 1997).

7.6 Hypothyroidism and brain development in experimental animals

Considerable research using experimental animals has provided important insight into the mechanisms and consequences of thyroid hormone action in brain development (Zoeller et al., 2002). The body of this work is far too extensive to review here but has been reviewed at critical times during the past 50 years (de Escobar et al., 2000; Oppenheimer et al., 1994;

Oppenheimer and Schwartz, 1997; Pickard et al., 1997). Several themes have emerged that provide a framework in which to begin to understand the role of thyroid hormone in brain development. First, the majority of biological actions of thyroid hormone appear to be mediated by TRs, which are ligand-dependent transcription factors (Mangelsdorf et al., 1995). There are two genes, encoding TRα and TRβ, although these two receptors do not exhibit different binding characteristics for T4 and for triiodothyronine (T3) (Zoeller et al., 2002). Second, based on considerable work in the cerebellum, there appear to be critical periods of thyroid hormone action during development. As originally defined (Brown et al., 1939), the critical period was that developmental stage where thyroid hormone replacement to CH children could improve their intellectual outcome. This definition was also applied to experimental studies to identify the developmental period during which thyroid hormone exerts a specific action (Zoeller et al., 2002). It is now generally accepted that there is no single critical period of thyroid hormone action on brain development, either in humans (Delange, 2000) or in animals (Dowling et al., 2000). Rather, thyroid hormone acts on a specific development process during the period that the process is active. For example, thyroid hormone effects on cellular proliferation would necessarily be limited to the period of proliferation for a specific brain area. Because cells in different brain regions are produced at different times (Bayer and Altman, 1995), the critical period for thyroid hormone action on cell proliferation would differ for cells produced at different times.

7.7 Thyroid hormone deficiency and neuronal development

Thyroid hormone deficiency during a critical developmental period can impair cellular migration and development of neuronal networks. Neuronal outgrowth and cellular migration are dependent on normal microtubule synthesis and assembly and these latter processes are regulated by thyroid hormones (Nunez et al., 1991). During cerebral development, postmitotic neurons forming near the ventricular surface must migrate long distances to reach their final destination in the cortical plate where they form a highly organized 6-layer cortical structure (Porterfield, 2000). Appropriate timing of this migration is essential if normal connectivity is to be established. This migration depends not only upon specialized cells such as the radial glial cells that form a scaffolding system but also on specific adhesion molecules in the extracellular matrix that are associated with the focal contacts linking migrating neurons with radial glial fibers (Mione and Parnavelas, 1994). These neurons migrate along radial glial fibers, and following neuronal migration, the radial glial cells often degenerate or become astrocytes (Rakic, 1990). Migration also depends on adhesive interactions involving extracellular matrix proteins such as laminin and the cell-surface receptor integrin (Porterfield, 2000). Disorders of neuronal migration are considered to be major causes of both gross and subtle brain abnormalities (Rakic, 1990). Hypothyroidism during fetal and neonatal development results in delayed neuronal differentiation and decreased neuronal connectivity (Nunez et al., 1991).

8. References

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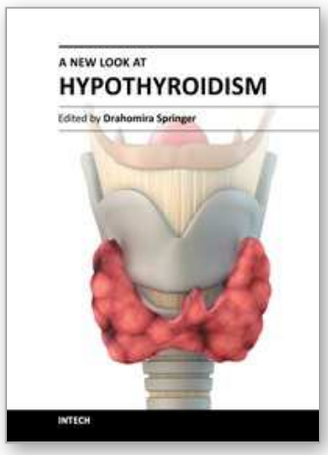

A New Look at Hypothyroidism

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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.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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