Chapter 1

Hypothyroidism and Development Interactions

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Abstract

THs (THs) play an essential role in development and hormone deficiency during critical phases in fetal life may lead to severe and permanent brain damage. Maternal hypothyroidism is considered the most common cause of fetal TH deficiency, but the problem may also arise in the fetus. In the case of congenital hypothyroidism due to defects in fetal thyroid gland development or hormone synthesis, clinical symptoms at birth are often mild as a result of compensatory maternal TH supply. A shortage of THs starting at the early stages of pregnancy, such as in cretinism, results in neurological deficits that cannot be rescued by exogenous TH addition at later stages. Neonates are more sensitive than adults to the effects of iodine deficiency. Thus, these disturbances may lead to abnormalities in the neuronal network and may result in mental retardation and other neurological defects, including impaired motor skills and visual processing.

Keywords

THs; Development; Brain; Hypothyroidism

Hypothyroidism

Hypothyroidism is frequently accompanied by diminished cognition, slow thought process, slow motor function, and drowsiness [1-7]. Myxedema is associated with severe mental disorders including psychoses, sometimes called 'myxematous madness'. Depression is especially related to hypothyroidism; even subclinical hypothyroidism

may affect mood [8,9]. Thyroid deficits are frequently observed in bipolar patients, especially in women with the rapid cycling form of the disease [10,11]. Both subclinical hypothyroidism and subclinical hyperthyroidism increase the risk for Alzheimer's disease, especially in women [12]. However, most hypothyroid patients do not meet the criteria for a mental disorder. A recent study evaluated brain glucose metabolism during thyroxine (T4) treatment of hypothyroidism [2]. 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 [13,14]. 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 [15]. In T4-treated patients, it was found that reduced psychological well being is associated with occurrence of polymorphism in the deiodinase 2 (D2) gene [16], as well as in the organic anion transporter family OATP1c1 gene [17]. Thyroid hormone replacement with a combination of T4 and triiodothyronine (T3), in comparison with T4 monotherapy, improves mental functioning in some but not all hypothyroid patients [18,19], and most of the patients subjectively prefer combined treatment [20]. It was concluded that future trials on thyroid hormone replacement should target genetic polymorphisms in deiodinase and thyroid hormone transporters [21].

Congenital Hypothyroidism (CH)

Traditionally, research on the role of the THs in brain development has focused on the postnatal phase and on identifying CH, which is the final result of the deficiency suffered throughout the pregnancy [1,3,5,22-24]. 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 [25]. 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 [22,26]. Full-scale clinical studies have demonstrated a correlation between maternal thyroid insufficiency during pregnancy and a low neuropsychological development in the neonate [27]. Maternal hypothyroxinemia during the first gestational trimester limits the possibilities of postnatal neurodevelopment [1,5,9,23,28-33]. The most serious form of brain lesion corresponds to neurological cretinism, but mild degrees of maternal hypothyroxinemia also produce alterations in psychomotor development [34-37]. The thyroid function of neonates at birth is significantly related to the brain size and its development during the first two years of life [26]. Screening programs for neonatal congenital hypothyroidism indicate that it is present in approximately one case out of 3000 to 4000 live births [38]. 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 [25]. In a meta-analysis of seven studies [39], 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 controlgroup, 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 [40].

Untreated congenital hypothyroidism (sporadic cretinism) produces neurologic deficits having predominantly postnatal origins [1,5,23,41]. 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 [42]. If the children are treated with THs soon after birth, the more severe effects of thyroid deficiency are alleviated [41]. However, these children are still at risk for mild learning disabilities. They may show subtle language, neuromotor, and cognitive impairment [43]. 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 [44]. 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) [45] have proposed that the sensitive periods for THs 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 [41]. Thyroid hormone deficiency impairs learning and memory, which depend on the structural integrity of the hippocampus [41,46]. Maturation and synaptic development of the pyramidal cells of the hippocampus are particularly sensitive to thyroid hormone deficiency during fetal/perinatal development [47]. Early in fetal development (rats), thyroid hormone deficiency decreases radial glial cell maturation and therefore impairs cellular migration [1,33,48-50], 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 osside development [,1,33,49,51].

Endemic Cretinism

The most severe neurologic impairment resulting from a thyroid deficiency is in endemic cretinism caused by iodine deficiency [1,41,52-54]. In fact, iodine deficiency represents the single most preventable cause of neurologic impairment and cerebral palsy in the world today [55,56]. These individuals suffer from hypothyroidism that begins at conception because the dietary iodine deficiency prevents synthesis of normal levels of THs [41,57]. 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 begins functioning [41]. 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 [41]. These problems include disturbances of gait, and in the more extreme forms, the individuals cannot walk or stand [55,58,59]. If postnatal hypothyroidism is present, there is growth retardation and delayed or absent sexual maturation [51]. 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 [41]. The damage is inversely related to maternal serum T4 levels but not to T3 levels [51,55,60]. Delong (1987) [61] 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 [41]. Early development of the auditory system appears to be dependent upon THs [62]. 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 [51,55,56].

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 [63,64]. 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 (150μg/day) prevents their occurrence [65]. 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 (8thto 19thweeks) gestation [66]. Only a limited number of studies are available on thyroid function during pregnancy in populations with severe iodine deficiency (iodine intake below 25μg 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 [67,68] and the Democratic Republic of Congo (DRC, formerly Zaire) [69-72]. 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) [73]. 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) [70,71,75,76]. 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 [22]. 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 [77-79].

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 CH [1,5-7,80-87]. CH occurs at a rate of approximately 1 in 3,500 live births [88,89]. 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 [90-92]. 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 [93]. The intellectual deficits as a result of this delayed diagnosis and treatment were profound. One meta-analysis found that the mean full-scale IQ of 651 CH infants was 76 [94]. 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 [94,95]. 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 [96-98], 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 [90]. Recent studies indicate that thyroid hormone is also important during fetal development. THs 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 [99]. 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 [100]. Finally, the mRNAs encoding the two known TR classes exhibit complex temporal patterns of expression during human gestation [101], and the mRNAs encoding these TR isoforms are expressed in the human oocyte [102]. 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 [90]. Two kinds of pathological situations reveal the functional consequences of deficits in thyroid hormone during fetal development [90]. The first is that of cretinism, a condition usually associated with severe iodine insufficiency in the diet [103,104]. There are two forms of cretinism based on clinical presentation: neurological cretinism and myxedematous cretinism [103]. Neurological cretinism is characterized by extreme mental retardation, deaf-mutism, impaired voluntary motor activity, and hypertonia [103]. In contrast, myxedematous cretinism is characterized by less severe mental retardation and all the major clinical symptoms of persistent hypothyroidism [103]. Iodide administration to pregnant women in their first trimester eliminates the incidence of neurological cretinism [90]. However, the initiation of iodine supplementa-

tion by the end of the second trimester does not prevent neurological damage [103,105]. 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 [103,105]. Therefore, thyroid hormone appears to play an important role in fetal brain development, perhaps before the onset of fetal thyroid function [90]. The second type of pathological situation is that of subtle, undiagnosed maternal hypothyroxinemia [90]. The concept and definition of maternal hypothyroxinemia were developed in a series of papers by Man et al. [106-108]. Low thyroid hormone was initially defined empirically-those pregnant women with the lowest butanol-extractable iodine among all pregnant women [109]. 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) [110] 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 T4 levels in the lowest 10th percentile of the normal range had a higher risk of low IQ and attention deficit [27]. Excellent recent reviews discuss these studies in detail [109]. 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 [111,112].

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 [1,3,5-7,37,46,52,79,90,113-116]. The body of this work is far too extensive to review here but has been reviewed at critical times during the past 50 years [109,117-119]. 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 [120]. There are two genes, encoding TRα and TRβ, although these two receptors do not exhibit different binding characteristics for T4 and T3 [90]. Second, based on considerable work in the cerebellum, there appear to be critical periods of thyroid hormone action during development. As originally defined [121], 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 [90]. It is now generally accepted that there is no single critical period of thyroid hormone action on brain development, either in humans [103] or in animals [122]. 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 [123], the critical period for thyroid hormone action on cell proliferation would differ for cells produced at different times.

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 THs [1,6,7,124]. 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 [41]. Appropriate timing of this migration is essential if normal connectivity is to be established. This migration depends not only upon spe-

cialized 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 [125]. These neurons migrate along radial glial fibers, and following neuronal migration, the radial glial cells often degenerate or become astrocytes [126]. Migration also depends on adhesive interactions involving extracellular matrix proteins such as laminin and the cell-surface receptor integrin [41].Disorders of neuronal migration are considered to be major causes of both gross and subtle brain abnormalities [126]. Hypothyroidism during fetal and neonatal development results in delayed neuronal differentiation and decreased neuronal connectivity (1,33,49,50,124].

Future Direction

Whatever the mechanisms, the reported data require a reevaluation of which disturbance could result in irreversible and permanent damage to the developing thyroid-brain axis (Figure 1 and Figure 2). The resolution of this review will require additional evidenceat a molecular level either demonstrating a direct action of the THs on the fetal brain or additional evidencesupporting the suggestion that the observed effects of maternalhypothyroidism on fetal development are explainedby impaired gestation. Thus, whether the adverse effects of maternal hypothyroidism on fetal development aremediated directly by loss

of the maternal hormones contributionto the fetus, indirectly by metabolic impairment ofgestation, or both. In addition, future attention should befocused on identifying a nongenomic approach because of thereis scant evidence and these actions of TH differ across thedevelopmental time and brain region.
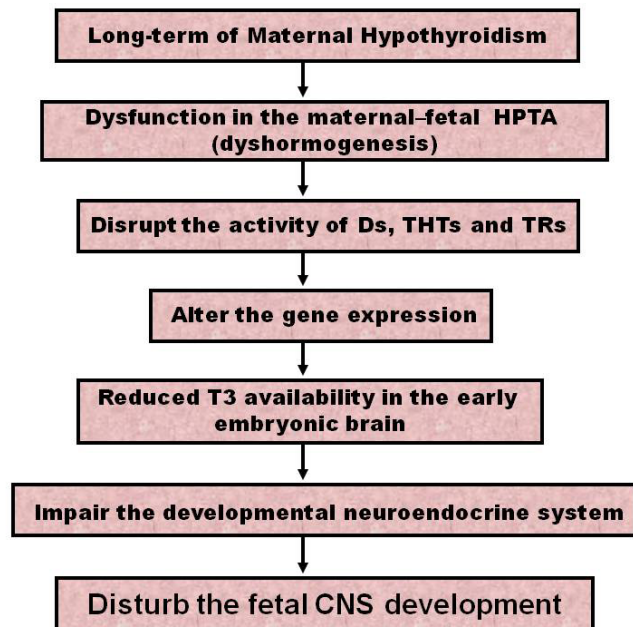

Figure 1: The interaction between the hypothyroidism and development. Where, HPTA is hypothalamic-pituitary-thyroid axis, THTs are thyroid transporters, Ds are deiodinases, TRs are thyroid receptors and CNS is central nervous system.
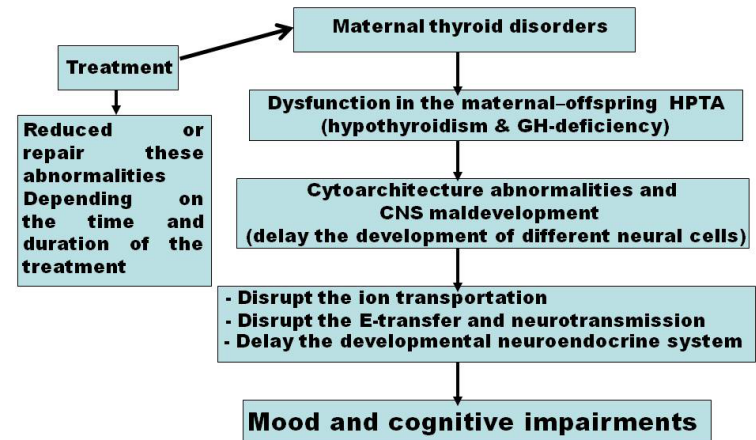

Figure 2: Schematic diagram for the interaction between the hypothyroidism and development. Where, GH is growth hormone and HPTA is hypothalamic-pituitary-thyroid axis.

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