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Maternal Iodine Deficiency and Brain Disorders

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Abstract

Thyroid Hormones (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 iodine deficiency is considered the most common cause of fetal TH deficiency, but the problem may also arise in the fetus/neonates. 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 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. Thus, iodine defenses programmes can avoid adverse neurodevelopmental consequences in mothers and their offspring.

Keywords: Thyroid hormones; Iodine deficiency; Development; Brain; Hypothyroidism

Introduction

Several reports are listed on the harmful effect of Thyroid Hormone (TH) deficiency during the development [1-7]. Iodine is essential for pregnant and lactating women, as well as infants [8]. Pregnant women in USA have been shown to have mild iodine deficiency [9]. Marginal iodine deficiency is a common health problem in pregnant women [10]. Iodine deficiency disease is the most common cause of preventable mental deficiency in the world today [11]. Maternal hypothyroxinemia can induce neurodevelopmental impairments in the developing fetus [12]. In rodents, several neural populations have been shown to be sensitive to hypothyroidism during the pre- and postnatal periods [13]. In rats, TH deficiency during fetal and neonatal periods produces deleterious effects, such as reduced synaptic connectivity, delayed myelination, disturbed neuronal migration, deranged axonal projections, decreased synaptogenesis and alterations in levels of neurotransmitters [14,15]. In addition, a lack of TH in the postnatal period of rats causes an irreversible mental retardation, characterized by a slowing of thoughts and movements accompanied by prolonged latencies of several evoked potentials and slowed electroencephalographic rhythms [16]. Therefore, this review will deal with several important topics, sometimes controversial and which still are not completely settled: what is the effect of maternal iodine deficiency on the fetal and neonatal thyroid state, and its effect on the brain and neural development. Also, the goal of this review is to place the exciting advances that have occurred by the previous authors.

Maternal Iodine Deficiency

Iodine is a key component of the THs, which are critical for healthy growth, development and metabolism [17]. Adequate iodine is important during pregnancy to ensure optimal growth and development of the offspring [18,19]. Also, adequate levels of iodine during pregnancy are essential for fetal neurodevelopment, and mild iodine deficiency is linked to developmental impairments [17,20]. The factors responsible for a higher requirement of iodine [11] are: (a) increased requirement of Thyroxin (T4) to maintain a normal global metabolism in the mother, (b) transfer loss of T4 and iodide from the mother to the fetus and (c) increased loss of iodide through the kidney due to an increase in the renal clearance of iodide in pregnancy. During pregnancy, iodine deficit produces an increase in perinatal mortality and low birth weight which can be prohibited by iodated oil injections given in the latter half of pregnancy or in other supplementary forms (European Commission, 2002) [21]. It is known that iodine deficiency during pregnancy can interfere with normal fetal growth and development [10]. The epidemiological studies recommend that hypothyroxinemia, especially at the beginning of gestation, affects the neurological development of the new human being in the long term [22,23]. Full-scale clinical studies have confirmed a connection between maternal thyroid insufficiency during gestation and a low neuropsychological development in the neonate [24]. In fact, the most severe neurologic injury resulting from a thyroid deficiency is in endemic cretinism initiated by iodine deficiency [4,25,26]. During the first gestational trimester, maternal hypo-thyroxinemia limits the possibilities of postnatal neurodevelopment [27-37]. The most serious form of brain lesion links to neurological cretinism, but mild degrees of maternal hypo-thyroxinemia also produce variations in psychomotor development [38-41]. The neurologic impairment happens primarily in the second trimester, which is a vital period for formation of the cerebral cortex, the extrapyramidal system, and the cochlea, areas damaged in endemic cretins [42]. Iodine deficiency in fetus results in miscarriages, stillbirths, brain disorders, retarded psychomotor development, speech and hearing impairments [43]. Iodine deficiency in infants can damage the developing brain and increase mortality [44].

On the other hand, Zhang et al. (2015) [45] reported that iodine supplement in early stage of pregnancy could improve the cell migration of cerebral cortex and neurodevelopment of offspring. The oral administration of a single dose of iodized oil is capable of correcting iodine deficiency both clinically and endocrino-logically in mothers and neonates [46,47]. Iodine supplementation has the potential to positively impact the birth weight of newborns. For mothers, consumption of iodized salt, iodized fish sauce, and iodine fortified food can improve iodine status of mothers while for infants, initiating breastfeeding soon after birth and maintaining exclusive breastfeeding can help infants achieve optimal nutritional status [8]. Sukkhojaiwaratkul et al. (2014) [48] recorded that maternal iodine supplementation improved iodine nutrition in their breast-fed offspring. A trend toward declining in cord serum Thyrotropin (TSH) values after iodine supplementation indicates improvement

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of iodine status during pregnancy.

TH Deficiency and Neuronal Development

TH insufficiency during a critical developmental period can damage 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 [4,49]. During fetal and neonatal development, hypothyroidism results in delayed neuronal differentiation and diminished neuronal connectivity [33-37,49]. Interestingly, deficient cellular maturation in the cerebral cortex of hypothyroid rats is characterized by [4,50] the following: (a) Smaller neuronal cell bodies that are more tightly packed than those in euthyroid animals; (b) Diminished axonal and dendritic outgrowth, elongation, and branching; (c) Reduced numbers of dendritic spines. Inadequate cellular differentiation results in markedly reduced synaptogenesis; (d) Diminished myelination of neuronal axons; (e) Changes in callosally projecting neurones, which may be due to the maintenance of a juvenile pattern of projections [51]; and (f) Alterations in dendritic morphology and structure in several cell types, including pyramidal cells in the cortex (decrease in dendritic spine number) [52].

On the other hand, in cerebellum, a hypothyroid rats exhibit a persistent External Granule cell Layer (EGL), reduced proliferation of granule cells of rat brain in the EGL [53,54] and slowed migration of granule cells into the internal granule cell layer (IGL) [55,56]. Also, the absence of TH during the first postnatal weeks causes profound Purkinje cell hypoplasia [57]. In addition, ectopic localization of neonatal Purkinje cells is a typical abnormality found in the hypothyroid cerebellum, which remarkably also occurs to much higher extent in reeler mice [58]. Anderson (2001) [59] depicted in the hypothyroid rat cerebellum that: (a) A reduction in Purkinje cell dendritic arborization; (b) A delay in granule cell migration from the EGL to the IGL and cell death is increased; and (c) A reduction in parallel fiber outgrowth and migration of the granule cells. Concurrently, the effects of hypothyroidism in the hippocampus [60] include: (a) A reduction in the number of dentate gyrus granule cells [61]; (b) A decrease in pyramidal cell spine densities [62]; (c) Changes in kainate-induced gene expression [63]; (d) A decrease in the number and size of dendritic spines of Purkinje cells [64]; and (e) A decrease in the branching of apical and basal dendrites granule and pyramidal cells [65]. Also, iodine deficiency causes an impaired maturation of hippocampal radial glial cells, which are involved in neuronal migration [66]. Specific alterations in dendritic morphology have been identified in the granule and pyramidal cells in the hippocampus due to TH deficiency [52,65-70].

Defects in synaptic architecture induced by TH insufficiencies, as well as deficiencies in protein substrates involved in complex signaling pathways serious for synaptic plasticity, culminate to disturb hippocampal neurophysiological function [67]. An irregular laminar distribution has been described in the auditory cortex of hypothyroid rats, including an increased number of neurons in layers V/VI, a concomitant diminution in layers II to IV, and the abnormal presence of neurons in the subcortical white matter [33,69-76]. Finally, a reduction, or absence, of TH during brain maturation yields molecular, morphological and functional alterations in hippocampus [34,60,74-77]. Interestingly, the neurodevelopmental impairments induced by hypothyroxinemia suggest an independent role of T4 [12].

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). The resolution of this review will require additional evidence at a molecular level either demonstrating a direct action of the THs on the fetal brain or additional evidence supporting the suggestion that the observed effects of maternal iodine deficiency on fetal development are explained by impaired gestation [78-81]. Thus, the adverse effects of maternal hypothyroidism on fetal development are mediated directly by loss of the maternal hormones contribution to the fetus, indirectly by metabolic impairment of gestation, or both. In addition, future attention should be focused on identifying a non-genomic approach because of there is scant evidence and these actions of TH differ across the developmental time and brain region [82,83].

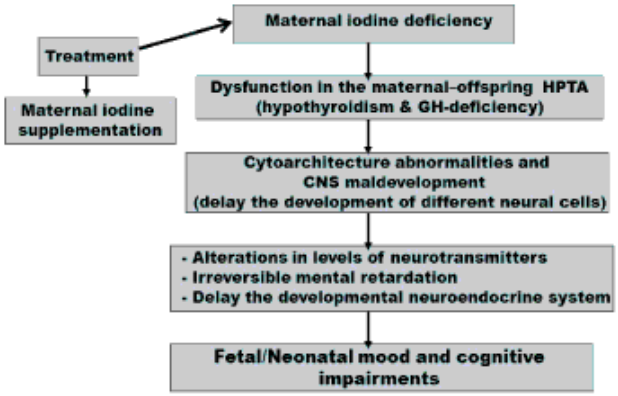

Figure 1: Schematic diagram for the interaction between the maternal iodine deficiency and CNS development. Where, GH is growth hormone and HPTA is hypothalamic-pituitary-thyroid axis.

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