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Transient Hypothyroxinemia of Prematurity and Associated Risk Factors: A Review

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Abstract

Preterm infants are greatly at risk of developing a handicap. Major risk factors of such infirmities are linked with low levels of thyroid hormones mostly seen in infants born before 34 weeks. It is referred as transient hypothyroxinemia of prematurity, which is a neonatal endocrine phenomenon that results in early thyroid insufficiency. Transient hypothyroxinemia of prematurity is an easily preventable cause of preemies mental retardation. It is an impermanent postnatal presence of an abnormal insufficient blood concentration of thyroid hormones with a decreased serum thyroxine and free thyroxine, with the exception of a normal thyroid-stimulating hormone level. Its occurrence concurs with the critical period for brain development. The diversity and multifactorial nature of the aetiology of transient hypothyroxinemia of prematurity, namely hypothalamic-pituitary immaturity, loss of maternal serum thyroxine, genetic factors, iodine deficiency and some critical illnesses are among the few of the most important factors that require to be addressed. An increasing collection of evidence has well established the relationship between transient hypothyroxinemia of prematurity and impairments of the growth and development of the brain, which necessitates the implementation of the preventive measure to halt this trend. However, there is an uncertainty among clinicians concerning the most efficient prevention and therapeutic strategies. In this article, we have tried to integrate the present knowledge of the role of thyroid hormones in the developing brain. Moreover, we presented the data linking thyroid hormone status of preterm infants to the neurodevelopment.

Introduction

Thyroid hormones are imperative for metabolism, inorganic ions, stimulation of growth and development of diverse tissues, especially the central nervous system, through specific time windows [1]. Preterm babies show a postnatal thyroid function qualitatively comparable, but quantitatively reduced in comparison to full-term infants. The decrease in the cord serum thyroxine (T4) is influenced by the age of gestation and the weight at birth [2]. The postnatal thyroid-stimulating hormone (TSH) is reduced and infants with impediments of prematurity, such as respiratory distress syndrome (RDS), experience a decline in the serum thyroxine (T4) in the first period of life [3]. Certain researchers have presented a dramatic surge in the survival of the preterm infants, including brain injury, cognitive delay, blindness, and mental retardation, etc. The challenge is to achieve healthy survival without the high prevalence of neurodevelopment [4].

Transient hypothyroxinemia of prematurity (THOP) is an endocrine disorder of thyroid deficiency frequently seen in preterm infants less than 34 weeks of gestation, but more common in those less than 30 weeks of gestation. It is usually the result of a combination of the loss of maternal contribution thyroid hormones and the hypothalamus-pituitary-thyroid axis. Clinically outlined by temporary postnatal low serum levels of thyroxine (T4) and free thyroxine (FT4), but usually with a normal TSH level [5], and when severe it is correlated with an increased risk of cerebral palsy and mental development [6]. A delayed thyroxine (T4) replacement in these infants may have a relatively significant impact on their neurodevelopment. THOP can be attributable to elements influencing iodine deficiency or excess, dual oxidase 2(DUOX2) mutations [7], maternal thyroid hormone receptor (TSHR) antibodies or prematurity, untreated maternal thyroid dysfunction, and dugs [8].

The studies conducted over the past few decades and reports of THOP associated with the maternal-placental thyroxine (T4) transfer withdrawal, immaturity of the hypothalamic-pituitary-thyroid, the synthesis and peripheral metabolism developmental constraints of iodothyronines, iodine deficiency, inflammatory mediators, infections as well as and critical illnesses have renewed interest in exploring with imaging or laboratory reports further into THOP [9]. This review discusses the implication of THOP risk factors and the need to dwell deep into it to pave the way for a novel or adjunctive management.

Epidemiology

Hypothyroidism disorder, maybe from birth or acquired [10]; full term babies experience a TSH surge immediately after birth, while thyroxine (T4) serum level in preterm babies is slightly lower but with a normal TSH. The detection of congenital hypothyroidism in most infants is done via newborn screening during the first week of life [11]. The achievements in neonatal management lately brought about a meaningful increase in the survival rates of both the extremely low birth weight (ELBW) and very low birth weight (VLBW) infants [12]. The neonatal screening programs indicate prevalence of congenital hypothyroidism of 1:3000 to 1:4000 infants worldwide [13]; The reported studies showed a lower prevalence in African-Americans compared to Asian-Americans and Pacific islanders, Hispanics, and Native Americans [14]; and twice as many girls are affected compared to boys [15].

In 1974, pilot screening programs for congenital hypothyroidism were developed in Quebec, Canada, Pittsburgh, and Pennsylvania, and currently, has been established all over the planet. In London, assay of TSH was done with a single Guthrie dried blood spot and the program succeeded in the early diagnosis and treatment of 22 babies, among whom eight were not earlier diagnosed on clinical examination [13]. In Sweden, a routine phenylketonuria (PKU) screening helped to determine thyroxine (T4) and TSH levels of newborns, the clinical investigation revealed with a follow-up that a significant number of babies might be misdiagnosed at the first screening [14]. Newborn screening is one of the major accomplishments in preventive medicine. Internationally, it has been carried out for the past 50 years; there has been a remarkable development in the recent years in neonatal screening to ensure an earlier detection of cognitive disorders [15]. However, this significant

variation in the incidences of THOP among different geographical locations may be due to the different methods applied in the management and screening and the level of neonatal care.

Development of the human thyroid system

How striking that the destiny of a new little life will be decided by the quantity of such a miniature molecule molded by a gland so little! The hormone thyroxine is the little molecule mentioned above, and during the fetal development, some of the thyroxine (T4) is produced by the baby around mid-gestation. Thyroid development is portrayed by initial formation of a small cluster of cells at the base of the tongue around the 20th day of gestation. The fetal thyroid gland is identified by the 7th week of gestation and, thyroid follicle cells with colloid formation are spotted at 10th-week gestation. Growth and differentiation happen as the thyroid achieves its structure of two lateral lobes joined by an isthmus, several thyroid transcription factors such as TTF-1 and PAX8 are important in thyroid gland morphogenesis and probably its caudal migration to its destination [16].

Thyroid hormones are essential for brain development, influencing neurogenesis, neuronal migration, neuronal and glial cell differentiation, myelination, and synaptogenesis. Thyroid action mechanism in the brain involves binding to nuclear thyroid protein receptors and in conjunction with other ligands, activates or deactivates critical neurodevelopmental genes. The regulation of gene expression and an active hormone triiodothyronine (T3) interaction with nuclear receptors mostly induce thyroid hormone actions. Thyroxine (T4) and triiodothyronine (T3) perform non-genomic actions. Monocarboxylate transporter 8(Mct8) and organic anion transporter polypeptide 1c1 (Oatp1c1), both transmembrane transporters, facilitate the entry of triiodothyronine (T3) and thyroxine (T4) in the brain. According to a study conducted on cerebral cortex in mice, a failure of an adequate amount of thyroid hormones to reach neural target cells in order to maintain normal brain development might be induced by a deficiency of monocarboxylate transporter 8(Mct8) [17].

Role of maternal thyroid hormone

Babies born from mothers with thyroid hormonal defect are at high risk of being affected by thyroid dysfunction. A strong fetal neuropsycho-intellectual development is mostly guaranteed by the essential role of the complex maternofetal thyroid gland [18]. The impairment of the brain development may originate from several clinical disorders and genetic factors involved in the formation and maturation of the pituitary glands. Firstly, in a matter of glandular development defect, the maternal thyroid hormones assistance to the fetal thyroxine (T4) is well done, thus, the possibly abnormal fetal thyroid gland hormonal production lead to brain damage. Secondly, regarding the maternal thyroid deficiency (autoimmune hypothyroidism) alone, the seriousness of maternal thyroid gland malfunction will lead to the impairment of the fetus neuro-development [19, 20]. During the early gestational period, this type of clinical conditions may obviously take place or appear only during late gestation due to untreated maternal hypothyroidism or autoimmune thyroid disorder (AITD). At roughly 12 weeks of gestation, fetus attains the capacity to synthesize thyroid hormones. In reference to several studies, maternal thyroid hormones (T3, T4) are substantially transferred through the placenta. Moreover, deiodinases, an enzyme contained in the placenta can convert thyroxine (T4) and tri-iodothyronine (T3) [21]. In an iodine deficiency predicament, both fetal and maternal thyroid functions are compromised and, therefore, it is mainly the precocity and degree of the maternal hypothyroxinemia during pregnancy that will define fetal neurological development potential repercussions [22].

There are serious consequences for the infants rising from maternal thyroid dysfunction. Female fertility, pregnancy outcomes, and offspring development are overtly affected by hypothyroidism and thyrotoxicosis. Stillbirths, preterm deliveries and low birth weight, which may induce the impairment of neuropsychological development, have been associated with maternal thyroid dysfunction by

countless research [23]. The maternal and fetal thyroid hormone synthesis is insured by a mandatory sufficient iodine delivery; this is especially important since thyroid hormones are vital factors in fetal brain development [20]. Hypothyroxinemia may be induced by an iodine deficiency and results in brain damage predominantly with irregular neurological sequelae. A meta-analysis regrouping 18 studies showed a loss in intelligence quotient (IQ) of 13.5 points, in areas with severe iodine deficiency [24]. Developmental abnormalities and poor scholarly achievements later in life have been observed to be linked with mild or borderline iodine deficiency. As stated in a study, "consistently, over half of the women with thyroid laboratory abnormalities would be missed if only high-risk women are examined" as a result, babies are lost prematurely [25]. Considering the importance of thyroxine (T4) for proper fetal development, a war should be declared against it, by the reason of hypothyroidism impose on the developing fetus.

Consequences and outcomes of THOP

The upsurge of morbidity and mortality correlate with lower thyroid hormone levels in newborn infants. Thyroid hormones are vital for normal brain, heart and lung maturation [26-28]. In the systema respiratorium, thyroid hormones take a major part in the synthesis of surfactant [28]. Moreover, a phenomenon of lower triiodothyronine (T3) and thyroxine (T4) levels is frequently seen in infants suffering from respiratory distress syndrome (RDS) [29, 30]. Similarly, in the case of cardiopulmonary bypass and extracorporeal life support, the levels of thyroid hormones are reduced, and with intravenous triiodothyronine (T3) during or after life support or cardiac surgery, there was an increase of cardiac functional parameters [31]. Furthermore, THOP is also related to the slowdown of the patent ductus arteriosus (PDA) closure [32].

In addition to their effects on the lungs and the heart, thyroid hormones play a vital role in the brain. Several studies on animals have demonstrated the fact that thyroid hormones are primordial for the early stage of brain maturation and are embroiled in numeral critical neurobiological and neuronal ontogenesis processes [33]. The low levels of thyroid hormones during the prime weeks of life lead to poor children neurodevelopment. Preterm with a gestational age less than 30 weeks disrupts the maternal contribution and transition in the first period of the pregnancy to a fully independent control system at birth. This may lead to the impairment of cognitive and motor development [34]. Den Ouden et al. [35] reported an association between thyroid dysfunction over the first weeks of life with diminished cognitive function at 5 and 9 years of age in preterm infants. From 18 to the 24 month period of children, a significant cognitive impairment is seen in those with THOP than those without THOP. According to the Bayley mental development scores, in younger children, the average IQ reduction ranges from 6.8 to 8.3 points, and in older children, the minimum IQ reduction is 8.6 points [36]. This correlation was found to stop or hold subsequent to the adjustment of assorted prenatal and postnatal risk factors that are noted to influence development. Besides, these mental delays were shown to persist with age and school failure in children with THOP [37]. Along with delayed mental development, THOP has also been related to the incidence of cerebral palsy [38], which is two to six folds in children with severe THOP.

Interestingly, many researchers have reported other consequences in case of thyroid deficiency. In a cohort study, infants born between 29 to 35 gestational weeks, low thyroid hormones levels were found to be related to poor visuomotor abilities at 12 and 18 months of age [39, 40]. In another similar study, lower free thyroxine (T4) levels between 2 and 4 weeks of life were linked with high incidence of retinopathy of prematurity (ROP), and at 3 months of age with poorer Bayley motor scores and bad visual attention [41]. These findings thus suggest that THOP is not only associated with generally poorer neurodevelopment overall, it is also related to sub-optimal development of visual and language abilities [42]. As we know preterm infants are affected by several and complicated illnesses which may develop into serious lasting disabilities; it makes uncertain whether this lack of development is due to THOP or whether THOP is a direct consequence of additional

factors causing the poor developmental outcome. In the case of thyroid deficiency, thyroid hormone replacement may improve respiratory and cardiac functions and lower the risk of neurodevelopmental deficits thus confirming the causal nature of this association. From the early 80s, several studies have investigated the effects of thyroxine (T4) and/or triiodothyronine (T3) supplement for preterm infants. At first, the purpose of these studies was to assess the connection of THOP with infant morbidity, mortality, and neurodevelopment. Thyroid supplement studies were carried out in the 1980s anteceding the surfactant era and antenatal steroid, indicating a decrease in pulmonary leaks and infant mortality in very preterm infants who have an immature lung structure, and an immature cardiovascular system. In the earliest trial of Schonberger et al. [43] on infants born less than 37 weeks or weighing less than 2.2 kg admitted to the intensive care unit (ICU) were given a daily those of 25 μg T4 and 5 μg T3. Among 126 preterm infants treated with thyroxine (T4) replacement, 12 died, resulting in a mortality rate of 9.5%; this revealed a significant reduction in mortality rate. In another randomized control trial of thyroid hormones treatment on respiratory outcomes in 253 preterm infants born less than 30 weeks; the first 7 days of life, 60 preterms received a placebo of 6 μg/kg/day T3 plus 1 mg/kg/day hydrocortisone via continuous intravenous infusion. Findings disclosed comparable respiratory parameters in the treatment, and low free thyroxine (FT4) and free triiodothyronine (FT3) levels were correlated with higher mortality rates and higher severity of lung disease [44]. Thyroid deficiency, thus, not only affect preterm lung or heart, it impairs visual disabilities; and could be accounted for some of the weak visual abilities.

The earliest trials concerning neurodevelopment also produced conflicting results. One among the first trial reported a non-significant 11.4 point reduction at 12 months of age with no difference at 24months in mental development scores in thyroxine (T4) treated of preterm infants [45]. Vanhole et al. [46] reported a study on thyroxine (T4) hormone replacement treated infants; a five point reduction in both motor and mental development scores, but the study was statistically nonsignificant. In van Wassenaer et al. [47] study, infants born at less than 28 weeks gestation, if treated with levothyroxine, had a stable heart rate in the first weeks of life; moreover, the study showed a lower incidence of patent ductus arteriosus (PDA). Around 200 infants born prior to 30 weeks of age were given 8 μg/kg/day T4 for six weeks and the other half received placebo, though they were no differences between groups who received the thyroxine (T4) treatment or the placebo, the research revealed that thyroxine (T4) hormone treatment was influenced by gestational age [47]. For instance, levothyroxine for preterm born infants before 27 weeks achieved an eighteen score higher on the Mental Development Index (MDI) than that given placebo up to age two. But at 5 and 10 years of age infants born at <27 weeks gestation treated with thyroxine (T4) had a higher cognitive and intelligence scores than those treated with the placebo [48]. Paul et al. [49, 50] investigated the preterm infants less than 1.5 kg and showed the association between thyroid hormones has an incidence rate of 85% and low thyroxine (T4) values with increased odds of death and intra-ventricular hemorrhage (IVH). Furthermore, in a research of 83 very preterm infants, thyroid hormone levels of free thyroxine (FT4) were examined every 2 and 6 weeks, and a neuropsychological follow-up at age 7. In this study, the results showed that, contrary to other earlier research, high level of free thyroxine (FT4) in very preterm infants could be an indicator of neuropsychological deficit in childhood [51]. On the contrary, levothyroxine supplement in preterm at a dose of 5 μg/kg/day did not affect free thyroxine (FT4) levels and showed no beneficial effect at 18 months of corrected age [52]. Van Wassenaer et al. [53] attempted to establish a guideline for the evaluation and treatment based on previous studies, but there was no correlation found between thyroid supplements and neurological outcomes in infants at 36 months age.

Conclusions

Different researchers have shown that thyroid dysfunction, especially transient hypothyroxinemia of prematurity (THOP) is one of the

neurodevelopment adverse aspects in children born prematurely with low thyroid hormone levels [54]. Thyroid hormones are essential throughout the lifetime of infants born before term, and if the required thyroid hormones are not fully supplied, a number of notable cognitive and motor sequelae arise. These problems may not be only due to the thyroid deficiency; there are many predisposing medical complications of prematurity, such as chronic lung disease, congenital heart disease, hyperbilirubinemia, nutritional deficiency, medications and long stay in the hospital which may induce long-term neurological defects. While it is known that prescribing thyroxine supplement for preterm infants in need, the strategy works if executed within the appropriate momentous time window. A comprehension of the physiological adaptation of the hypothalamus-pituitary-thyroidal axis facilitates the management of fetal and perinatal thyroid hormones deficiency cases, which may promote the minimization of complications and long-term effects of THOP. In other words, additional studies on neonatal outcomes of subclinical THOP are needed for a better care and management before conclusive guidelines.

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