Transient Neonatal Hypothyroidism

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Transient neonatal hypothyroidism is defined as a temporary abnormality of the thyroid function discovered at birth, which later reverts to a normal status. It may or may not require replacement therapy [1]. Recovery to euthyroidism typically occurs in the first few months or years of life [2].

Transient hypothyroidism is much more common in preterm infants but may occur in apparently healthy term infants [3].

Causes of transient neonatal hypothyroidism include

- Maternal and neonatal iodine deficiency or excess
- Drugs
- Intrauterine exposure to maternal antithyroid drugs
- Transplacental passage of maternal TSH receptor blocking antibodies
- Genetic mutations
- Prematurity – critically ill newborn
- Congenital hemangioma/hemangioendothelioma

In many cases, an underlying etiology may not be determined.

8.1 Maternal and Neonatal Iodine Deficiency or Excess

Iodine is essential for the production of thyroid hormones.

Worldwide, *iodine deficiency* resulting in hypothyroidism is the most important preventable cause of cognitive impairment in children [4]. Iodine deficiency in the newborn is mainly due to *maternal iodine-deficient diets* [2].

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Iodine deficiency is more common in preterm infants than in term infants. Preterm infants, in fact, have low iodine and thyroid hormone stores [5] and require relatively more iodine than full-term infants and older children to maintain a positive iodine balance [6, 7] putting them at risk for deficiency without an adequate *iodine dietary intake*. The Committee on Clinical Practice Issues of the American Society of Clinical Nutrition recommended parenteral intakes of iodine of 1 μg/kg/day for the preterm infant, even though this might be below their requirements. It should be considered that in recent years exposition to iodine excess in obstetrics and neonatology units has been reduced. Therefore, iodine excess should not be considered anymore as a valuable source of iodine [8].

Studies on healthy preterm and full-term newborns lead to believe that the iodine intake required to maintain a positive balance is at least 15 μg/kg/day in full-term newborns and 30–60 μg/kg/day in preterm babies [8].

It has long been recognized that *iodine excess* leads to a paradoxical inhibition of the first step of thyroid hormone synthesis. Thyroid hormone synthesis decreases transiently over a period of 24 to 48 h as a result of an increased concentration of intrathyroidal iodine, "termed the acute *Wolff–Chaikoff effect.*" The mechanism for the acute Wolff–Chaikoff effect is not completely understood but is thought to be at least partially explained by the generation of several inhibitory substances on thyroid peroxidase activity [9]. In a few days, escape from the acute Wolff–Chaikoff effect occurs with resumption of normal thyroid function. Excess iodine results in hypothyroidism if the acute Wolff–Chaikoff effect persists. Newborns cannot adapt to iodine excess in the blood and can be affected with neonatal transient hypothyroidism related to the Wolff-Chaikoff effect [10]. Neonates are particularly sensitive to iodine excess because their skin is especially permeable, iodine trapping processing in the thyroid gland is very active, and iodine renal clearance is low. Premature babies are more susceptible, and lower iodine overload may impair their thyroid function [11].

Iodine exposure occurs because of the use of iodine-containing antiseptics, drugs such as amiodarone, or radiocontrast agents [12–14] in the mother or in the newborn. A recent study showed no abnormal thyroid functions in the infants of 21 mothers given iodide contrast during pregnancy, suggesting that thyroid dysfunction may be related to the type and duration of exposure [15].

Urinary iodine concentration is the recommended method to assess iodine status of a certain population in a specific time point; thyroglobulin may be a biomarker of iodine status [16, 17]. Further studies are required to confirm the utility of thyroglobulin as a biomarker of iodine status. Typically in case of iodine excess, the urinary iodine concentration is high. The raised urinary iodine levels confirm the exposure to iodine but are not always associated with greatly elevated TSH levels [18]. In the review by Aitken J [18], the incidence of transient hypothyroidism/hyperthyrotropinaemia in the exposed infants in the cohort studies ranged from 12 per 100 to 33 per 100.

The evaluation at birth of urinary iodine excretion would be helpful in detecting the transitory nature of TSH elevation since iodine excess causes transient hypothyroidism [19].

8.2 Drugs

Some anticonvulsant agents (carbamazepine and sodium valproate) can cause transient mild hypothyroidism.

Aminophylline and caffeine used as respiratory stimulants in preterm infants with recurrent apnea can transiently alter thyroid function. *Steroids and dopamine*, used in critically ill babies, can interfere with the hypothalamic-pituitary-thyroid axis, causing transient central hypothyroidism with low FT4 concentrations and a low or normal TSH level [1].

8.3 Intrauterine Exposure to Maternal Antithyroid Drugs

During pregnancy, the use of *antithyroid drugs* (ATDs) can temporarily alter the function of the thyroid gland in the fetus and newborn. Propylthiouracil, methimazole, and carbimazole all cross the placenta. The smallest possible dose of ATDs should be used in order to avoid a deleterious fetal impact [20]. Overtreatment should be avoided because of the possibility of inducing fetal goiter and/or fetal hypothyroidism [21]. ATDs are able to cross the placenta resulting in a blockade of thyroid function of the fetus, leading to fetal and neonatal transient hypothyroidism. The T4 and TSH values tend to return to normal within 1–3 weeks after birth without treatment [3].

8.4 Transplacental Passage of Maternal TSH Receptor Blocking Antibodies

Maternal autoimmune thyroid disease is a common disorder. Thyroid peroxidase antibodies (TPOAb) have been found in 10 % of women during or shortly after pregnancy [22].

Although antithyroglobulin (TGAb) and TPOAb apparently have no pathogenetic effect on fetal and neonatal hypothyroidism, transient mild elevation of serum TSH above the normal reference value for age is frequently observed in the first month of life in infants born from mothers affected by autoimmune thyroiditis [23].

Maternal autoimmune thyroid disease, in rare cases, may be associated with the production of *thyrotropin receptor blocking antibodies* (TRBAb).

The TRBAb can cross the placenta and block the TSH receptor in the neonatal thyroid, leading to transient congenital hypothyroidism. Scintigraphy may show no uptake despite the presence of a eutopic thyroid gland with maternal TRBAb. Hypothyroidism can last up to 3–6 months after birth as maternal antibody levels fall. In some cases, it might be necessary to start therapy with L-T4, planning a reevaluation of therapy at a later time.

The incidence of transient congenital hypothyroidism due to maternal TRBAb in North America is 1 in 180.000 healthy infants or approximately 2 % of babies with congenital hypothyroidism [24]. As autoimmune thyroiditis characterized by the

presence of TRBAb is a relatively rare disorder, Rastogi and LaFranchi only recommend TRBAb determinations in a case where a previous child has had transient congenital hypothyroidism and the mother has a diagnosed autoimmune thyroid disease and is pregnant again [2].

The newborn screening program for congenital hypothyroidism of Lombardy region, Italy, considers newborns of mothers affected by thyroid disease a special risk category and provides a second sampling. The resampling is collected between days 15 and 30 of life. If neonatal screening for congenital hypothyroidism is positive, serum TSH and FT4 are sampled. In this case, we also suggest testing TGAb, TPOAb, and TSH receptor antibodies.

8.5 Genetic Mutations

Genetic mutations, mostly in heterozygosity, may contribute to the development of a transient thyroid dysfunction detected by neonatal screening.

Mutations in the genes *dual oxidase 2* (DUOX2) and *dual oxidase maturation factor 2* (DUOXA2), involved in the etiology of dyshormonogenesis, can lead to transient or permanent congenital hypothyroidism, with a high intra- and interfamilial phenotypic variability [25, 26]. Heterozygous mutations in DUOX2 usually lead to transient congenital hypothyroidism [27].

The possible hypotheses to explain the variability of the DUOX2/A2 phenotype are the existence of other H(2)0(2) generating systems, the different requirements for thyroid hormones according to age, the ethnicity, and the iodine intake [25].

The most significant features to select patients for the DUOX2 analysis are goiter, partial iodide organification defect, low free T4, and high TSH concentrations at the first postnatal serum sampling, despite borderline blood spot TSH [28].

A defect in *thyroid peroxidase* (TPO) is one of the causes of dyshormonogenesis of the thyroid gland.

Niu et al. suggested that the presence of heterozygous TPO gene mutations contributes to development of neonatal transient hypothyroidism [29]. The authors suggest as possible pathogenetic explanations the effect of the stress of extrauterine adaptation during labor on an immature pituitary-thyroid axis in genetically predisposed individuals, combined with environmental triggers.

Subjects who are heterozygous for *TSHR gene mutations* can show various phenotypes, from mild hypothyroidism to the euthyroid condition [30–33]; they are not always identified during neonatal screening. The use of a low TSH spot threshold allows the detection of more cases with mild thyroid dysfunction that are generally associated with monoallelic defects [34].

The thyroid dysfunction caused by monoallelic defects of TSHR gene is usually a permanent condition; however, as TSH values fluctuate from mild hypothyroidism to euthyroidism, this condition may erroneously suggest a transient hypothyroidism.

The need for therapy with L-T4 in patients with partial TSH resistance is still a matter of debate.

8.6 Prematurity – Critically Ill Newborn

Children born prematurely compared with children born at term have a greater spectrum of thyroid dysfunction. *Premature infants* are characterized by hypothalamic-pituitary immaturity, a premature loss of the contribution of transplacental T4 and iodine, limited thyroid gland reserve, immaturity of the mechanism of thermogenesis mediated by brown adipose tissue, a persistent fetal thyroid hormone metabolism, and a high morbidity predisposing to euthyroid sick syndrome [35]. As a consequence, premature babies may face multiple variations of thyroid function, such as transient hypothyroxinemia of prematurity, persistent hyperthyrotropinemia, and congenital hypothyroidism, which can occur with delayed TSH rise and euthyroid sick syndrome. In addition, *very low birth weight infants* usually have various systemic diseases and are administered drugs that can alter the hypothalamic-pituitary-thyroidal axis, such as dopamine, morphine, and caffeine [36].

The European Society for Paediatric Endocrinology suggests a *strategy of second screening* in preterms, low birth weight and very low birth weight neonates, and ill and preterm neonates admitted to neonatal intensive care unit.

In our previous study from Lombardy region, Italy, on 24 preterm infants affected by congenital hypothyroidism and treated with L-thyroxine, we found that only 23,8 % of patients with gland in situ at reevaluation showed permanent hypothyroidism requiring therapy reintroduction. There do not appear to be any obvious clinical or laboratory features that predict which infants will or will not recover normal thyroid function [37].

8.7 Congenital Hemangioma/Hemangioendothelioma

The majority of *hemangiomas* are small and require no therapy. It is likely that only patients with both high levels of type 3 iodothyronine deiodinase activity and large tumor burdens are at risk for hypothyroidism. Congenital liver hemangiomas can produce large amounts of the enzyme type 3 iodothyronine deiodinase, producing a consumptive type of hypothyroidism in which high doses of thyroxine are required to maintain euthyroidism. Serum T4 levels are low, TSH is elevated, and reverse T3 levels are also increased. Hypothyrodism resolves as the tumor involutes or is treated [38, 39].

8.8 Starting Treatment with L-T4 and Reevaluation of the Thyroid Axis

Since the transient nature of the hypothyroidism will not be recognized clinically or through laboratory tests in some infants, initial treatment will be similar to that in any infant with permanent congenital hypothyroidism [3].

If TSH concentration remains between 6 and 20 mU/L with an FT4 concentration within the normal limits for age for more than 3–4 weeks, it can be decided

in discussion with the family either to start L-T4 supplementation immediately and retesting, off treatment, at a later stage, or retest 2 weeks later without treatment [40].

It is not known whether or not babies with mild, transient hypothyroidism do or do not benefit from *thyroid hormone treatment*. Until these data are available, it might be prudent to treat infants with this atypical form of hypothyroidism, with reevaluation of thyroid function after age 2 years [41]. In these cases, it is important to distinguish at some later point between permanent and transient congenital hypothyroidism.

Reevaluation of the thyroid axis is recommended [40]

- When no etiological diagnostic assessment was carried out during early infancy and/or when treatment was started in the context of the infant being ill (e.g., preterm)
- When initial evaluation has shown a normally located gland with or without goiter
- In neonates with positive thyroid antibodies
- In children who have required no increase in L-T4 dose since infancy
- In children in whom no enzyme defect has been identified (either because no molecular genetic investigations have been carried out or because investigations have proved negative for all mutations tested)

Reevaluation should be performed in case of athyreosis diagnosed on the basis of isotope scanning alone when there is a condition of

- Excess iodine exposure
- Maternal antibodies blocking the TSH receptor
- Iodine transport defects

Reevaluation should be performed in case of DUOX2 mutation.

Diagnostic reevaluation consists of a trial off therapy of 4 weeks followed by measuring TSH and FT4 levels.

According to ESPE guidelines [40], reevaluation of the thyroid axis, off treatment, should normally take place after the age of 3 years. *Earlier reevaluation* (from 1 year of age) can be considered if transient increases in TSH concentration are likely.

8.9 Transient Neonatal Hyperthyrotropinemia and Thyroid Function in Childhood

Leonardi et al. [42] studied the *long-term outcome* of thyroid function in children with very short-lasting neonatal hyperthyrotropinemia ("false positive" at neonatal screening) in an observational, prospective study. Thyroid function and morphology were evaluated in 44 "false-positive" children up to 8 years of age. In these children, a high prevalence (50 %) of subclinical hypothyroidism in early childhood

(2.8 ± 0.5 years) had already been described [43]. At an average of 5.3 years, subclinical hypothyroidism persisted in 43.2 % of children, and at 8 years of age, subclinical hypothyroidism persisted in 31.8 % of children. This study confirms that newborns who resulted "false positive" at neonatal screening have a high risk to develop persistent subclinical hypothyroidism. *Thyroid morphology abnormalities* found at ultrasound evaluation, during more advanced childhood, were frequent. Thyroid morphology abnormalities were present both in children with normal serum TSH in childhood and in children with slightly elevated TSH but were more frequent in the latter group. Common TPO and TSHR polymorphism were present with similar frequency in the two groups. The authors conclude that a "false-positive" result at screening allows to identify subjects at risk for subsequent subclinical hypothyroidism.

According to the review by Monzani et al. [44], subclinical hypothyroidism in children is usually a remitting process with a low risk of evolution toward overt hypothyroidism.

Conclusion

The pathogenesis of neonatal transient hypothyroidism includes both *environmental and genetic factors*.

In the future, further studies might better explain if the presence of mutations in heterozygosity of genes involved in the synthesis of thyroid hormones during critical periods such as extrauterine adaptation can cause neonatal transient hypothyroidism.

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