Evolution of Thyroid Function in Preterm Infants Detected by Screening for Congenital Hypothyroidism

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Objective To determine the evolution of congenital hypothyroidism in preterms and the clinical features of permanent forms.

Study design We retrospectively evaluated 24 preterm children detected by newborn screening for congenital hypothyroidism: first screening with blood-thyroid stimulating hormone cutoff ≥10 mU/L and second screening with blood-thyroid stimulating hormone cutoff ≥5 mU/L. After the age of 2 years, patients with eutopic thyroid had diagnostic reevaluations, including thyroid function testing and thyroid ultrasonography after L-thyroxine therapy withdrawal.

Results The first screening identified 21.7% of patients with thyroid stimulating hormone elevation, and the second screening identified 73.9% of patients. One patient (4.4%) was identified with a third screening test; 21 patients had an eutopic thyroid and 3 patients a thyroid dysgenesis. At reevaluation, 5 patients (23.8%) showed permanent hypothyroidism (serum-thyroid stimulating hormone [s-TSH] >10 mU/L) resulting in the need to reintroduce therapy, 5 patients (23.8%) showed persistent hyperthyrotropinemia (s-TSH 5-10 mU/L), and 11 infants (52.4%) transient hypothyroidism (s-TSH <5 mU/L). The main clinical features of patients affected by permanent hypothyroidism were 1 case of assisted reproduction, 2 twins, 2 small for gestational age, 1 maternal thyroiditis, and 2 patients with malformations/syndromes.

Conclusions Premature birth is a significant risk for congenital hypothyroidism with eutopic thyroid. In preterm infants, the evolution of congenital hypothyroidism remains difficult to predict. Our data emphasizes the high incidence of transient hypothyroidism in preterm infants, and the importance of diagnostic reevaluation to determine the definitive diagnosis. *(J Pediatr 2014;164:1296-302)*.

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Thyroid dysfunction is frequently observed among the comorbidities associated with prematurity. An immature hypothalamic-pituitary-thyroid axis, postnatal depletion of thyroid stores, non-thyroidal illness, and administration of drugs (such as dopamine and steroids) can all lead to derangement in thyroid function in preterm newborns.[1,2]

Insufficient or excessive iodine intake can also influence thyroid function. Despite a program of iodine prophylaxis, mild iodine deficiency is still prevalent in the Lombardy region of Italy.[3]

Congenital hypothyroidism is an important congenital endocrine disorder and one of the most preventable causes of intellectual disability. An increased incidence of referrals with blood-thyroid stimulating hormone (b-TSH) elevation on newborn screening has been observed in the past few decades.[4-7] Possible explanations for this include changes in screening programs with introduction of lower b-TSH screening cutoffs, changes in the ethnic composition of the screened population, and variable iodine supply. Another contributory factor may be preterm birth because the incidence of preterm births and survival of very low birth weight (VLBW) infants have increased by approximately 20% over the last 20 years.[8]

Thyroid function in VLBW infants, defined as having birth weight (BW) between 1000 and 1499 g, is characterized by a blunted and delayed thyroid stimulating hormone (TSH) surge at delivery, low circulating T3, T4, and free-thyroxine (FT4) levels, and low serum-thyroid stimulating hormone (s-TSH) concentration.

Preterm babies (born before 37 completed weeks of gestation) have a higher incidence of both primary congenital hypothyroidism and atypical hypothyroidism.[9,10] The prevalence of congenital hypothyroidism is higher in low birth

b-TSH	Blood-thyroid stimulating hormone	L-T4	L-thyroxine
BW	Birth weight	SGA	Small for gestational age
CPAP	Continuous positive airway pressure	s-TSH	Serum-thyroid stimulating hormone
FT4	Free-thyroxine	TSH	Thyroid stimulating hormone
GA	Gestational age	US	Ultrasound
IVF	In vitro fertilization	VLBW	Very low birth weight

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weight infants, defined as having BW between 1500 and 2499 g, and in VLBW neonates compared with the normal population (BW = 2500 g).[1,5,9,10]

Transient TSH elevation is common in preterm infants. Medda et al described preterm delivery as being an independent risk factor for transient congenital hypothyroidism,[11] Mengreli et al showed a higher prevalence of transient hypothyroidism in premature compared with full-term infants,[12] and according to Srinivasan, the incidence of congenital hypothyroidism in preterm infants was similar to term infants.[13] Our previous study[5] highlighted an increase in the prevalence of permanent hypothyroidism among the group of preterm babies (19/84 patients): 52.7% had permanent hypothyroidism, 21% had persistent hyperthyrotropinemia, and 26.3% had transient hypothyroidism.

At this time, it is not clear from the literature as to the relative prevalence of transient and permanent impairment of thyroid function in preterm infants.[12,13] Such inconsistency may stem from the small sample sizes of studies investigating treatment withdrawal in preterm and VLBW neonates with congenital hypothyroidism. The aim of our study, therefore, was to characterize neonatal features of preterm babies with congenital hypothyroidism, to establish the diagnosis of permanent hypothyroidism, persistent hyperthyrotropinemia, and transient hypothyroidism, and also to describe the clinical characteristics of the permanent forms of congenital hypothyroidism.

Methods

The newborn screening program for congenital hypothyroidism was started in Lombardy in 1979 and is primarily based on the measurement of b-TSH on neonatal Guthrie cards by automated fluoro-immunoassay (Autodelfia b-TSH; Perkin Elmer, Waltham, Massachusetts), centralized in the Regional Newborn Screening Laboratory. The blood sample is collected between days 2 and 4 after birth (day of birth = 0) in the newborns (both term and preterm) and the b-TSH cutoff value for referral is 10 mU/L. This cutoff is an age-specific threshold calculated at 99.5 percentile of the total at term reference newborn population (BW >2500 g).

Newborns included in the following special risk categories are rescreened for thyroid dysfunction: BW <2000 g, gestational age (GA) <33 weeks, Down syndrome, acutely ill infants, and maternal thyroid disease. Resampling is collected between days 15 and 30 of life[14] as a late rise in TSH is frequently observed in these at-risk newborns.[15] The age-adjusted b-TSH cutoff (at resampling) is 5 mU/L, and it is calculated at 99 percentile of the total at term reference newborn population.

Screening data were collected from the database of the Regional Newborn Screening Laboratory of Lombardy Region (Children's Hospital V. Buzzi, Milan) between 2007 and 2009. This is a retrospective study on 24 preterm infants detected by newborn screening in the years 2007-2009, referred to our center and treated with L-thyroxine (L-T4). We excluded a patient from the analysis of screening data (n = 23) because he was sampled for initial screening on day 17 (patient 6 in the **Table**).

Current confirmatory tests of congenital hypothyroidism are based on s-TSH and FT4 levels. s-TSH and FT4 reference ranges for 1- to 4-week-old preterm newborns were adopted from the study by Williams et al.[16] s-TSH and FT4 values after the first month were considered normal when included in the age-related reference intervals available in the literature.[17] Serum thyroglobulin and antibodies against thyroid peroxidase and TSH receptor were also measured.

Thyroid ultrasound (US) was performed in all patients at diagnosis by a sonographer with experience in pediatric thyroid US to ascertain the presence and the volume of thyroid gland and also to classify the etiology of congenital hypothyroidism (eutopic thyroid, athyreosis, and hemiagenesis). All patients had periodic investigations at our center in order to ascertain the correct L-T4 dosage. Results from clinical history and examinations, as well as possible associated abnormalities, were conveyed to the Italian National Registry of Infants with Congenital Hypothyroidism, where they were registered anonymously. Parents and/or legal guardians were appropriately informed, and they consented to anonymous data transmission and analysis. All parents had thyroid function testing, including the measurement of maternal thyroid antibodies. Institutional Review Board approval was not required by the institution because this is a retrospective study involving the anonymous review of medical records.

Diagnostic Reevaluation

According to international guidelines,[18] when the definitive diagnosis is not established in the neonatal period and there is a suspicion of transient hypothyroidism, a reevaluation of diagnosis is performed at age 2- to 3 years after a withdrawal of therapy to ascertain if there is persistence of congenital hypothyroidism. Subjects with eutopic thyroid glands had diagnostic reevaluation after 2 years of age (range 24-57 months; average 40 months) and 1 month post-L-T4 withdrawal.

The diagnostic reevaluation included measurements of s-TSH, serum-free thyroxine, thyroid antibodies, thyroglobulin, US of the thyroid gland and, only in selected cases, ^{123}I scintiscan with perchlorate discharge test was carried out. A reduction >10% of the ^{123}I uptake levels 2 hours after oral administration of sodium perchlorate was considered positive for an iodine organification defect. Iodine discharge of 10% to 90% was considered to represent a partial iodine organification defect, whereas iodine discharge >90% was considered to represent a total iodine organification defect. Genetic analyses were performed in selected cases: in 1 patient with partial iodine organification defect the dual oxidase 2 gene was analyzed and in 3 patients who were negative for iodine organification defects, but had permanent hypothyroidism, TSH-receptor gene was analyzed.

Depending on thyroid function tests 1 month post-L-T4 withdrawal and during the subsequent follow-up, hypothyroidism was classified as permanent hypothyroidism, persistent hyperthyrotropinemia, or transient hypothyroidism. Follow-up duration was at least 1 year in all cases. Permanent hypothyroidism was considered if thyroid function tests showed s-TSH levels above 10 mU/L on at least 2