Can One Predict Resolution of Neonatal Hyperthyrotropinemia?

Luisa Aguiar, MD[1], Jane Garb, MS[2], Edward Reiter, MD[1], Paul Visintainer, PhD[2], Rachana Singh, MD[1], Holley Allen, MD, MSPH[1], and Ksenia Tonyushkina, MD[1]

Objective To identify predictors of transience vs permanence of neonatal hyperthyrotropinemia. We hypothesized that infants with greater severity of perinatal stress are more likely to have transient thyrotropin elevations.

Study design We retrospectively studied infants diagnosed with hyperthyrotropinemia between 2002 and 2014, following them for up to 12 years after diagnosis. Patients were divided into 3 groups: transient hyperthyrotropinemia (treatment was never prescribed), transient congenital hypothyroidism (treatment started but discontinued), and permanent congenital hypothyroidism (withdrawal unsuccessful or not attempted). We performed univariate and multiple logistic regression analyses, including and excluding infants with maternal thyroid disease.

Results We included 76 infants, gestational age mean (±SD) 34.2 (±5.7) weeks, evaluated for hyperthyrotropinemia. Thirty-five (46%) were never treated, and 41 (54%) received levothyroxine. Of the treated patients, 16 successfully discontinued levothyroxine, and for 25 withdrawal either failed or was not attempted. We found that male patients were almost 5 times more likely than female patients to have transient neonatal hyperthyrotropinemia (OR 4.85; 95% CI 1.53-15.37). We documented greater maternal age (31.5 ± 5.48 years vs 26 ± 6.76 years, mean ± SD, $P = .02$), greater rate of cesarean delivery (86.7% vs 54.2%; $P = .036$), and retinopathy of prematurity (37.5% vs 8%; $P = .02$) in the group with transient congenital hypothyroidism vs the group with permanent congenital hypothyroidism.

Conclusion The results show transience of neonatal thyrotropin elevations in a majority of patients and suggest a possible association of hyperthyrotropinemia with maternal and perinatal risk factors. *(J Pediatr 2016;174:71-7)*.

Congenital hypothyroidism, defined as thyroid hormone deficiency present at birth,[1] is a common cause of preventable neurocognitive impairment.[1,2] The clinical course has improved dramatically as a result of early detection and treatment, made possible after newborn screening (NBS) programs were introduced in the 1970s. Recent studies from the US and worldwide reported doubling of the incidence of congenital hypothyroidism in the last 3 decades, from 1:3000-1:4000 to 1:1600-2000.[3-7] This greater incidence has been attributed to the detection of mild elevations of thyrotropin (TSH) as well as a delayed TSH surge in premature infants.[8-10]

Neonatal hyperthyrotropinemia, defined here as elevated TSH with normal free thyroxine (T4),[11] often is used interchangeably with transient hyperthyrotropinemia and transient hypothyroidism, with no consensus on the best terminology. The proposed etiologies include delayed maturation of the hypothalamic–pituitary–thyroid axis, increased TSH response to thyrotropin-releasing hormone, presence of antithyroid antibodies, thyroid morphology abnormalities, or thyroperoxidase or TSH receptor gene-sequence variations.[4] Congenital hypothyroidism guidelines are available in the US and Europe[12,13] and help guide the treatment in the majority of the cases, especially if there is a clear TSH elevation (>40 μIU/mL) with low T4. The management of TSH elevation with normal T4/free T4 is still a subject of controversy, particularly in the neonatal intensive care setting. Clinicians are often faced with the dilemma of whether or not to treat these patients, as early treatment is crucial for cases of true congenital hypothyroidism but unnecessary therapy may lead to parental anxiety and overtreatment might be associated with negative effects on cognitive development.[14,15]

A variety of perinatal risk factors, such as prematurity, small for gestational age, birth asphyxia, and inflammation in extremely premature newborns have been associated with transient abnormalities in thyroid studies in infancy.[8,11,16-19] To our knowledge, there are no comprehensive studies that have assessed the relationship between maternal and perinatal risk factors with transient hyperthyrotropinemia. In the present study, we aimed to evaluate the natural course of hyperthyrotropinemia diagnosed in the

BW	Birth weight
GA	Gestational age
NBS	Newborn screening
NICU	Neonatal intensive care unit
ROP	Retinopathy of prematurity
T4	Thyroxine
TSH	Thyrotropin

From the [1]Department of Pediatrics, and [2]Department of Epidemiology and Biostatistics, Baystate Health, Springfield, MA

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newborn period. We hypothesized that children with greater severity of perinatal stress are more likely to have transient TSH elevations.

Methods

The study was performed at an academic tertiary health care system with a level III neonatal intensive care unit (NICU). The data were collected from a single pediatric endocrinology group that provides hospital consultations for neonatal thyroid disorders in the newborn nursery and NICU and also serves as a referral center for primary pediatric practices and community hospitals in western Massachusetts, southern Vermont, northern Connecticut, and eastern upstate New York. Screening for congenital hypothyroidism is performed by the New England Newborn Screening Program, which uses a whole blood primary T4 with backup TSH method. According to the Program protocol, all premature infants have repeat NBS testing every 2 weeks for 6 weeks. Abnormal results are confirmed by serum specimen performed by a hospital reference laboratory with the Electrochemiluminescene assay (Roche, Rotkreuz, Switzerland).

All infants evaluated by pediatric endocrinology for elevated TSH levels with normal T4/free T4 for age on initial or subsequent NBS or serum test were included. The normal ranges for T4/TSH on the NBS were based on the New England NBS state laboratory criteria, and normal serum free T4 levels in premature and sick infants were established according to published data.[20-22] We included the consults in the newborn nursery, NICU, and in our outpatient clinic during a 12-year period (2002-2014). Patients with known chromosomal abnormalities or those who died in the neonatal period were excluded. All infants who met inclusion criteria were divided into 3 groups on the basis of their clinical course: transient hyperthyrotropinemia, transient congenital hypothyroidism, and permanent congenital hypothyroidism. Transient hyperthyrotropinemia implies that TSH levels eventually normalized and levothyroxine therapy was never started. In the group with transient congenital hypothyroidism, treatment was started but successfully discontinued before study evaluation. In the group with permanent congenital hypothyroidism, levothyroxine withdrawal was unsuccessful or not attempted. The distribution of patients between groups is illustrated in **Figure 1** (available at www.jpeds.com). Given the lack of established guidelines for T4 supplementation in neonatal hyperthyrotropinemia, the treatment decision was dependent on the individual physician.

Retrospective chart review was performed with a pediatric endocrinology clinic database PEDRO Electronic Medical Record System (Pedrosoft LLC, Basking Ridge, New Jersey), Clinical Information System general hospital electronic medical records (Cerner, Kansas City, Missouri), and paper charts. Demographic data on the mother and infant comprising age, sex, ethnicity, and medical insurance type were collected to assess the differences among the groups. We also collected the data on the thyroid function tests leading to management decisions and levothyroxine doses throughout the years of observation. To answer the primary research question and identify predictors of transience vs permanence of the isolated TSH elevations, we collected maternal, perinatal, and neonatal variables.

Maternal/perinatal risk factors included maternal age, chronic maternal conditions, pregnancy complications, maternal thyroid disease and use of thyroid medications (levothyroxine and antithyroid drugs), type of delivery, gestational age (GA), birth weight (BW), Apgar score, and placental weight. The neonatal stress indicators collected comprised use of medications (dopamine, steroids, amiodarone, beta-blockers, phenobarbital, iodine contrast), infections, patent ductus arteriosus, necrotizing enterocolitis, intraventricular hemorrhage, retinopathy of prematurity (ROP), need for respiratory support, bronchopulmonary dysplasia, hypoxic–ischemic encephalopathy, 17-hydroxyprogesterone level on NBS, creatinine levels, and duration of hospital stay after birth. A risk score subsequently was developed for maternal/prenatal factors by simple addition of all individual risk factors. The study was approved and monitored by the institutional review board.

Statistical Analyses

Study data were collected and managed with REDCap[23] electronic data capture tools hosted at Tufts University Medical School. ANOVA and Student *t* test were used for continuous variables and Pearson χ^2 for categorical variables to compare study groups.

Multiple logistic regression model was used to identify the predictors of hyperthyrotropinemia resolution with and without treatment and all variables that revealed differences between groups at $P < .2$ on univariate analysis were included.[24] All results were also adjusted for sex, ethnicity, race, GA, and BW. A backward stepwise procedure was used, and variables with a significance of $P < .15$ were retained in the model. Only univariate analysis was performed to study the differences between the groups with permanent and transient congenital hypothyroidism due to small numbers. STATA (StataCorp, 2013, College Station, Texas) statistical software was used for all analyses.

Results

We analyzed 76 infants seen by our pediatric endocrinology group for hyperthyrotropinemia at various time points during infancy and the results are presented in **Table I**. All infants were younger than 3 months of age, with 2 outliers who presented at 5 and 7 months of age with persistence of TSH elevations; the mean age was 1 month, and there was no difference between groups. Thirty-four (44%) infants were first seen at our outpatient clinic and the rest were first evaluated in the NICU or newborn nursery. The distribution between the in- and outpatient groups did not change significantly over the years of data collection.