Thyroid Functions in Healthy Infants during the First Year of Life

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Objective To study the pattern of thyroid function testing in healthy newborns during the first year of life.
Study design We used the computerized database of a health management organization. Among the 18 507 infants insured by the Clalit Health Services born in the Sheba Medical Center between 2002 and 2007, 652 full-term healthy newborns with birth weight >2 kg and no significant perinatal morbidity underwent thyrotropin (TSH) determination as outpatients in their first year of life. The Clalit Health Services database provided demographic data, laboratory results, and dispensed medications for the newborns and their mothers.
Results Initial serum TSH levels were within normal range (0.35-5.5 mIU/L) in 91.1%, elevated (>5.5-≤10 mIU/L) in 8.3%, and highly elevated (>10 mIU/L) in 0.6% of the studied cohort. The 97.5 and 2.5 percentile values were 7.4 and 0.74 mIU/L, respectively. TSH measurements were repeated in 34.2%, 72.2%, and 100% of children with normal, elevated, and highly elevated initial levels, respectively; results were normal in 96%, 74%, and 50% of patients with initial normal, elevated, and highly elevated TSH, respectively; repeated TSH levels were >97.5 percentile in 35% of patients with initial TSH >97.5 percentile compared with 1% with first results <97.5 percentile (P = .005). Only 4 (0.6%) of the 652 newborns included in the study received thyroxin treatment.
Conclusion The normal TSH levels found in most healthy infants with normal thyroid screening and the spontaneous normalization of TSH values below 7.4 mIU/liter, substantiate the reliability of the screening, reduce unnecessary work-up and unnecessary thyroxin treatment of neonates meeting these criteria. *(J Pediatr 2016;170:120-5)*.

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Newborn screening (NBS) for congenital hypothyroidism has become routine since the mid-1970s after the development of a radioimmunoassay capable of measuring thyroxin (T4) in dried blood spotted on filter paper.[1-4] Screening programs, either T4 or thyrotropin (TSH), performed within 48 hours after birth, have led to the early detection and treatment of infants with congenital hypothyroidism,[5] preventing morbidity, particularly intellectual disability and developmental disorders.[2] Yet, NBS has limitations; 5%-10% of newborns with congenital hypothyroidism have normal screening results irrespective of the type of the screening approach used.[1] Hence, and given the importance of early and prompt diagnosis of congenital hypothyroidism, thyroid function tests (TFTs) often are repeated by primary care pediatricians (PCPs) during the first year of life when subtle clinical signs and symptoms are suggestive of hypothyroidism regardless of NBS results. Nevertheless, there are few available data on the pattern of TFT in the first year of life of healthy children without previously documented congenital hypothyroidism and the subsequent evolution of results.[6-14]

A previous study by our group of the natural history of TFT in adults, based on a large computerized database, showed that 95% of the initial TSH levels measured were normal (0.35-5.5 mIU/L).[15] In yet another study carried out by our group, a large pediatric population showed a similar pattern of initial serum TSH concentrations, with normal values in 96.5%.[16] In the adult study subsequent testing done within 5 years showed that TSH remained normal in 98% of adult patients with normal initial TSH levels and became normal in 62.1% of the patients with hyperthyrotropinemia (an elevated TSH in the presence of normal levels of thyroid hormones) without treatment. A similar pattern was found in the pediatric population.

Hyperthyrotropinemia or subclinical hypothyroidism (SCH) is a common disorder, with a prevalence of 4%-8.5% in the general population.[17,18] There are no clear clinical guidelines regarding treatment of SCH. The strongest argument for levothyroxine (LT4) therapy is the high risk of progression to overt hypothyroidism over time[19,20] and the possible consequences of hyperthyrotropinemia itself.[10] In both adult and pediatric populations, the initi-

BW	Birth weight
CHS	Clalit Health Services
FT4	Free T4
LT4	Levothyroxine
NBS	Newborn screening
PCP	Primary care pediatrician
SCH	Subclinical hypothyroidism
T4	Thyroxin
TFT	Thyroid function test
TSH	Thyrotropin

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ation of LT4 replacement therapy is recommended for all patients with a TSH level greater than 10 mIU/L, even if the free T4 (FT4) concentration is within the normal laboratory range[1]; however, treatment of patients with TSH levels between 5 and 10 mIU/L remains controversial, especially in children, because of the lack of studies on outcomes of children with SCH treated with LT4 vs those receiving no therapy. Special attention should be given to the possibility of SCH in the first year of life, as the natural history of this condition is not well established, and published results are controversial regarding the percentage of patients requiring permanent LT4 therapy.[6-14]

The aim of this study was to assess the pattern of testing of thyroid function in healthy newborns during the first year of life and the evolution of results on follow-up.

Methods

This study was an observational study of an historical cohort based on review of data obtained from the Clalit Health Services (CHS) computerized database, a comprehensive state-of-the-art computerized data warehouse that stores demographic and medical data. Data are aggregated by continuous real-time input from physicians and health service providers and include anthropometric measurements, vital signs, laboratory data, and pharmaceutical information. Data can be queried to the level of an individual member.

Between the years 2002 and 2007, 18 507 infants born in the Sheba Medical Center were insured by the CHS. Included in this study were all children who had undergone at least one test of thyroid function in their first year of life after the initial NBS. The blood tests were ordered by PCPs during their routine clinical care of outpatients only. Inclusion criteria were: full-term infants with a birth weight (BW) greater than 2 kg and no significant perinatal morbidity (defined as discharge before 8 days of life). Excluded from the study were infants who fulfilled one of the following criteria: (1) major congenital malformation; (2) genetic abnormalities; (3) diagnosis of congenital hypothyroidism by neonatal screening; and (4) treatment with LT4, or with medications that may interfere with thyroid function (propylthiouracil, methimazole, alpha interferon or steroids). The study was approved by our institutional ethics committee. Because there was no identification of the patients for whom data were retrieved, there was no need for informed consent by the parents.

The computerized data for the years 2002-2007 of the patients fulfilling the aforementioned criteria were reviewed to provide demographic data (age, sex); maternal thyroid disease; the specific referral diagnosis for further TFT ordered by the PCP during a routine visit; age at first and recurrent tests; TFT results (TSH, FT4, total triiodothyrnine, free triiodothyronine), and thyroid antibodies; imaging of thyroid gland (ultrasound and/or scan); LT4 treatment for longer than 2 months. Assessment of the evolution of TSH was based on the results of repeated TSH measures made in the untreated patients within the course of 5 years compared with the initial TSH levels.

Laboratory Analysis

Serum TSH (normal range 0.35-5.5 mIU/liter) and FT4 (normal range 10.3-20 pmol/liter) determinations were performed by the use of a continuous random access analyzer (Immulite 2000; Diagnostic Products Corp., Los Angeles, California) and an immunoassay apparatus (ADVIA Centaur; Bayer HealthCare LLC, Diagnostics Division, Tarrytown, New York). Antithyroid antibodies (antiperoxidase and antithyroglobulin [normal reference 75 IU/mL and 150 IU/mL, respectively]) were measured by enzyme-linked immunosorbent assay (Orgentec Diagnostika GMBH, Mainz, Germany).

Statistical Analyses

Continuous normal distributed numerical data are expressed as mean (±SD), continuous parametric distributed data are expressed as median (IQR, range), and categorical data are expressed as number and percentages. The 2-tailed Pearson χ^2 test and Fisher exact test were used to compare categorical variables. The *t* test was used to compare numerical variables. A logistic regression model was used to examine the association between a second TSH measurement with a result greater than 10 mIU/L (as the dependent variable) and patient's characteristics when the initial TSH concentration was between 5.5 and 10 mIU/L. *P* values and 95% CIs were calculated for the analyses. Variables analyzed were age (divided into groups), sex, and time (months) between tests. All analyses were performed using SPSS statistical software (release 20; SPSS Inc, Chicago, Illinois). A *P*-value of ≤.05 was considered significant.

Results

Of the 18 507 infants born in the Sheba Medical Center and insured by the CHS between the years 2002 and 2007, 2491 (13.5%) underwent further TFT subsequent to the initial NBS; in 712 infants, the additional blood tests were obtained during the first year of life. Of these, 60 were excluded from the final analysis: 29 (4%) because testing was done during inpatient hospitalization; 23 (3%) due to congenital anomalies or genetic syndromes; and 8 (1.1%) who were diagnosed with congenital hypothyroidism, as confirmed by repeatedly elevated TSH and low FT4 levels. Thus, the cohort studied comprised 652 children (333 [51.1%] boys and 319 [48.9%] girls), representing 3.5% of the total number of infants subjected to the initial analysis of the data base (**Figure 1**; available at www.jpeds.com). In most of the patients the cause for TSH measurement was not specified (n = 446, 68.4%). The documented diagnoses were "observation of growth" (n = 86, 13%), neurologic problems (n = 96, 14.7%), and other diagnoses (n = 24, 7.5%).