Congenital Hypothyroidism due to Defects of Thyroid Development and Mild Increase of TSH at Screening: Data From the Italian National Registry of Infants With Congenital Hypothyroidism

Antonella Olivieri, Carlo Corbetta, Giovanna Weber, Maria Cristina Vigone, Cristina Fazzini, Emanuela Medda, and The Italian Study Group for Congenital Hypothyroidism

Metabolism and Endocrinology Unit (A.O., C.F.), Department of Cell Biology and Neurosciences, and National Centre for Epidemiology Surveillance and Health Promotion (E.M.), Istituto Superiore di Sanità, 00161 Rome, Italy; Regional Newborn Screening Laboratory of Lombardia Region (C.C.), Children's Hospital V. Buzzi, 20154 Milan, Italy; and Department of Pediatrics (G.W., M.C.V.), Vita-Salute S. Raffaele University, IRCCS San Raffaele Hospital, 20132 Milan, Italy

Context: Over the years lower TSH cutoffs have been adopted in some screening programs for congenital hypothyroidism (CH) worldwide. This has resulted in a progressive increase in detecting additional mild forms of the disease, essentially with normally located and shaped thyroid. However, the question of whether such additional mild CH cases can benefit from detection by newborn screening and early thyroid hormone treatment is still open.

Objective: The aim of this study was to estimate the frequency of cases with mild increase of TSH at screening in the Italian population of babies with permanent CH and to characterize these babies in terms of diagnosis classification and neonatal features.

Methods: Data recorded in the Italian National Registry of infants with CH were analyzed.

Results: Between 2000 and 2006, 17 of the 25 Italian screening centers adopted a TSH cutoff at screening of $<$15.0 μU/mL. It was found that 21.6% of babies with permanent CH had TSH at screening of 15.0 μU/mL or less, whereas this percentage was 54% in infants with transient hypothyroidism. Among the babies with permanent CH and mild increase of TSH at screening ($\leq$15 μU/mL), 19.6% had thyroid dysgenesis with serum TSH levels at confirmation of the diagnosis ranging from 9.9 to 708 μU/mL. These babies would have been missed at screening if the cutoff had been higher.

Conclusions: Lowering TSH cutoff in our country has enabled us to detect additional cases of permanent CH, a number of which had defects of thyroid development and severe hypothyroidism at confirmation of the diagnosis. (***J Clin Endocrinol Metab*** **98: 1403–1408, 2013)**

Congenital hypothyroidism (CH) is 1 of the most common preventable causes of adverse neurodevelopmental outcome. Optimal management of CH requires early diagnosis and prompt treatment to avoid neurointellectual sequelae. This goal has been achieved by neonatal screening, which represents 1 of the most important results of preventive medicine in childhood (1, 2). Over the years the increased assay sensitivity and a more effective analysis of distribution of TSH values in the screened neonatal population have led to adopt lower TSH cutoffs in some screening programs. This has caused a progressive increase in detecting additional mild forms of the disease,

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received September 4, 2012. Accepted January 31, 2013.
First Published Online February 26, 2013

Abbreviations: b-TSH, whole blood TSH; CH, congenital hypothyroidism; INRICH, Italian National Registry of infants with CH.

essentially with normally located and shaped thyroid, with a consequent increase in CH incidence (3–5). However, the question of whether such additional mild CH cases can benefit from detection by newborn screening and early thyroid hormone treatment is still open. Some authors state that until there is good evidence of no intellectual impairment without treatment, detection and a precautional treatment of these milder cases is preferable (6, 7). Nevertheless, other authors underline that lowering TSH cutoff levels touches the central idea of newborn screening as both the target disease and possible benefits of treatment are still unknown (8).

The aim of this study was to estimate the frequency of cases with mild increase of TSH at screening in the Italian population of babies with permanent CH and to characterize these babies in terms of diagnosis classification and neonatal features. To this end data recorded in the Italian National Registry of infants with CH (INRICH), a population-based registry that performs the nationwide surveillance of permanent CH in Italy (9), were analyzed.

Materials and Methods

The data reported were derived from the INRICH in which the newborn screening results were collected. In Italy CH screening is mandatory and blood is generally taken between 3 and 5 days of life. All the Italian screening centers for CH (regional and interregional) use whole blood TSH (b-TSH) as a primary screening test, and 11 of these (accounting for about 40% of all screened babies every year) also test blood total T_4 at screening. The number of newborns screened yearly by each screening center differs among the regions (range 5000–100 000 newborns). Between 2000 and 2006, the TSH cutoff levels for detection in the various screening centers varied from 7 to 15 μU/mL, according to the different evaluation carried out by each screening laboratory on effectiveness/efficiency of the CH screening program. Specifically, 17 of the 25 centers adopted a screening cutoff of less than 15 μU/mL (2 with a 7 μU/mL cutoff, 11 with a 10 μU/mL cutoff, and 4 with a 12 μU/mL cutoff). The remaining 8 centers adopted a 15-μU/mL cutoff. In that period one third of the Italian screening centers performed the collection of a second blood specimen at 2–4 weeks of age in preterm, low birth weight, and acutely ill infants babies, as recommended (10) because of the late rise of TSH frequently observed in these infants (11).

Of approximately 3 500 000 infants screened in Italy between 2000 and 2006, 1792 babies were diagnosed with CH and started L-thyroxine replacement therapy. These babies were recorded in the INRICH. In general, babies with transient hyperthyrotropinemia on the basis of spontaneous normalization of TSH between screening and diagnosis are not recorded in the registry. Positive results of screening tests are confirmed by definitive tests of thyroid function on serum. These include TSH and free T_4 (FT4), which are considered normal when included in the age-related reference intervals available in the literature (12, 13). Thyroid ultrasound and/or scintigraphy are generally performed to complete the CH diagnosis. Infants with confirmed primary CH are then referred to the follow-up center of their region to start the replacement therapy. According to international guidelines (14), when the definitive diagnosis is not established in the neonatal period and a suspicion of transient primary hypothyroidism is present, a reevaluation of diagnosis is performed at the age of 2–3 years after a withdrawal of the replacement therapy to ascertain the persistence of CH. Information on new cases with CH are collected in the INRICH by means of 3 questionnaires filled in at diagnosis. These include anonymous data concerning CH infants such as screening and confirmatory laboratory tests; information on demographic data; details on the clinical state in the neonatal period; diagnostic investigations; information regarding pregnancy, birth, and family background; and start and dose of the replacement therapy. Details on the collection of information on CH cases and activities of the INRICH are described elsewhere (9).

Exclusion criteria

Babies with a diagnosis of in situ thyroid for whom results of reevaluation had not yet been obtained at the time of the study were not included in the analysis (n = 116). Moreover, to avoid the risk of thyroid agenesis misclassification, absent uptake (^{123}I or ^{99}Tc) on scintigraphy was classified as athyreosis when confirmed by absent thyroid tissue on ultrasound. Babies with an absent uptake on scintigraphy and no ultrasound confirmation were not included in the analysis. We can assume that the exclusion of these babies did not provide an underestimation of those with mild increase of TSH at screening because all of these babies had b-TSH greater than 15.0 μU/mL.

Statistical analysis

Results are expressed as the fifth, 50th, and 95th percentiles and means ± SD. A χ^2 test was used to compare frequency distributions. A $P < 0.05$ was considered significant. Statistical analyses were conducted using Intercooled STATA for Windows (version 8.0; StataCorp, College Station, Texas).

Results

Among the 1676 babies included in the analysis, 163 were diagnosed with transient hypothyroidism after a withdrawal of the replacement therapy at 3 years of age. Eighty-eight of these babies (54%) showed a b-TSH at screening of 15.0 μU/mL or less. The remaining 1513 babies had permanent CH. Stratification of both transient and permanent CH cases by b-TSH values at screening is reported in Table 1. Three hundred twenty-seven of 1513 babies with permanent CH (21.6%) had a milder increase of b-TSH at screening (≤15.0 μU/mL). Among these, 99 had b-TSH of less than 10 μU/mL (range 0.6–9.9). Among permanent CH infants with known gestational age, the frequency of preterm babies was significantly higher in the group of newborns with b-TSH at screening of 15.0 μU/mL or less than in those with values greater than 15 μU/mL (23.4% vs 12.1%, $P < .01$). With regard to additional congenital malformations, the frequency of major malformations (6.7% and 6.7%, respectively), as well as

Table 1. Distribution of Cases With Transient and Permanent CH Recorded in the INRICH (2000–2006) and Stratified by b-TSH Values at Screening

b-TSH at Screening, μU/mL	Babies, n (%) Transient CH, n = 163	Median Age at Screening Days (First and Third Quartiles)	Preterm/at Term/ Unknown, n
<10	20 (12.3)	4 (3, 5)	3/9/8
10–15	68 (41.7)	3 (3, 4)	11/50/7
>15	75 (46.0)	4 (3, 6)	25/49/1
b-TSH at Screening, μU/mL	**Permanent CH n = 1513**	**Median Age at Screening Days (First and Third Quartiles)**	**Preterm/at Term/ Unknown, n**
<10	99 (6.5)	3 (3, 4)	21/45/33
10–15	228 (15.1)	3 (3, 4)	41/158/29
>15	1186 (78.4)	3 (3, 4)	126/910/150

the frequency of multiple malformations (2.7% and 2.1%, respectively), were similar in both groups.

The relative contributions of the 7-, 10-, and 12-μU/mL cutoff laboratory values to the detection of the mild CH cases was calculated as the frequency of permanent CH babies with b-TSH at screening less than 15 μU/mL among all permanent CH cases diagnosed in each group of laboratories. This frequency was 40.7% (81 of 199) in the group of laboratories with a cutoff of 7 μU/mL, 25.3% (215 of 848) in the group with a cutoff of 10 μU/mL, and 10.0% (26 of 259) in the group with a cutoff of 12 μU/mL. A frequency of 2.4% (5 of 207) was also observed in the group of laboratory values with a cutoff of 15 μU/mL. These cases were preterm and derived from a laboratory that adopted a repeat sampling strategy at 2–4 weeks of age in special categories of neonates.

Information on thyroid ultrasound and/or scintigraphy was available in 70% (1054 of 1513) of babies with permanent CH. In Figure 1, the percent distributions of b-TSH at screening in babies with normal/hyperplastic thyroid and in those with thyroid dysgenesis are shown. As expected, both distributions were not normally distributed and, although overlapping, these skewed in opposite directions. The b-TSH distribution of babies with normal/hyperplastic thyroid skewed toward lower values (median 18.0 μU/mL), whereas the b-TSH distribution of babies with thyroid dysgenesis skewed toward higher values (median 130 μU/mL). However, among babies with CH due to thyroid dysgenesis, there were 7.3% of babies with mild increase of b-TSH at screening (≤15.0 μU/mL), although no baby with thyroid agenesis showed such a low b-TSH value. In Table 2 thyroid ultrasound and/or scintigraphy diagnoses stratified by b-TSH at screening are shown. Among 234 babies with a mild increase of b-TSH (<15.0 μU/mL), 80.3% (n = 188) had normal/hyperplastic thyroid, 18.8% (n = 44) had thyroid hypoplasia/hemiagenesis, and 0.9% (n = 2) had ectopic thyroid. Among 820 babies with b-TSH at screening greater than 15.0 μU/mL, 29.2% (n = 240) had normal/hyperplastic thyroid, 17% (n = 137) thyroid hypoplasia/hemiagenesis, 35% (n = 289) ectopic thyroid, and 18.8% (n = 254) thyroid agenesis.

In Figure 2, serum TSH (Figure 2A) and serum FT4 levels (Figure 2B) at confirmation of the diagnosis stratified by b-TSH values at screening are shown. The median age at which the diagnosis was confirmed was 21 days in the group with b-TSH at screening less than 10 μU/mL, 15 days in the group with b-TSH 10–15 μU/mL, and 15 days in the group greater than 15 μU/mL. The serum TSH median values in the 3 groups of babies were 21 μU/mL, 33 μU/mL, and 193 μU/mL, respectively, and the serum FT4 median values were 10.9 pM/L, 10.5 pM/L, and 5.1 pM/L, respectively. Both the TSH and the FT4 values were above the upper limit and below the low limit, respectively, of available reference ranges reported in relation to ages by Elminger et al (12) and Wil-

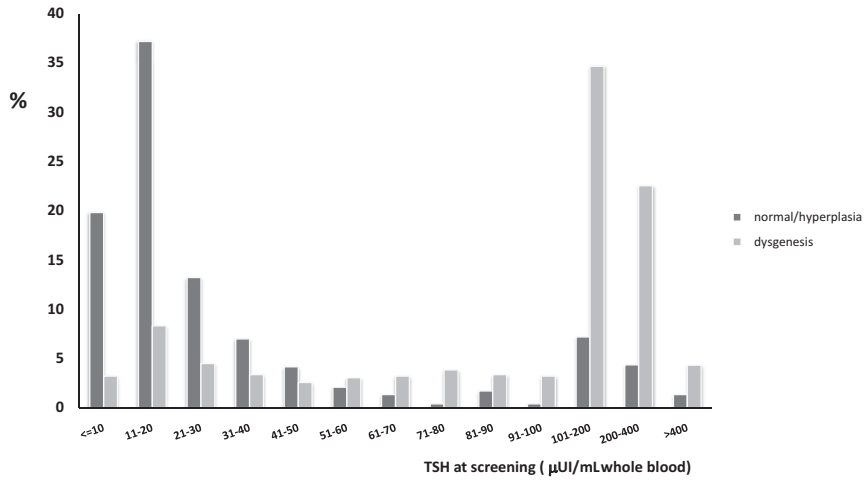

Figure 1. Percent distributions of TSH values at screening in babies with normal/hyperplastic thyroid and in those with thyroid dysgenesis recorded in the INRICH in the period 2000–2006.

Table 2. Thyroid Ultrasound and/or Scintigraphy Diagnoses in 1054 out of 1513 Babies With Permanent CH Recorded in the INRICH in the Period 2000–2006

b-TSH at Screening, μU/mL	Normal Thyroid, n (%)	Hyperplasia, n (%)	Hypoplasia, n (%)	Hemiagenesis, n (%)	Ectopy, n (%)	Agenesis, n (%)	Total, n
<10	36 (56.2)	13 (20.3)	14 (21.9)	1 (1.6)	0	0	64
10–15	118 (69.4)	21 (12.3)	26 (15.3)	3 (1.8)	2 (1.2)	0	170
>15	177 (21.6)	63 (7.7)	131 (16.0)	6 (0.7)	289 (35.2)	154 (18.9)	820

liams et al (13). It is worth noting that 19 of the 46 babies with b-TSH at screening less than 15 μU/mL and thyroid dysgenesis were severely hypothyroid at confirmation of the diagnosis with serum TSH levels ranging between 40 and 708 μU/mL.

The occurrence of maternal hypothyroidism and/or goiter during pregnancy was similar in the group with b-TSH less than 15 mU/L at screening (8.2%) and the group with b-TSH greater than 15 mU/L (7.7%). Also, the frequency of maternal hyperthyroidism was similar among babies with milder increase of TSH at birth and those with b-TSH greater than 15 μU/mL (2.3% and 1.2%, respectively).

Analysis in the subgroup of babies screened by TSH and TSH+T_4 screening strategies

To verify whether the detection of b-T4 at screening can help to identify babies with mild forms of permanent CH, an analysis on the subgroups of CH babies screened by primary TSH and by a combined TSH+T_4 strategy was performed. The percentage of babies with mild increase of b-TSH at screening (≤15.0 μU/mL) was 23% in the group screened by TSH strategy and 20% in that screened by TSH+T_4 strategy.

Discussion

In this study the analysis of the INRICH data has demonstrated that more than 20% of the Italian population of babies with permanent CH had a milder increase of TSH at screening (≤15.0 μU/mL), whereas in the group of infants with transient hypothyroidism, this percentage was 54%. Most of the babies with permanent CH and a mild increase of b-TSH at screening showed normal/hyperplastic thyroid. As known, this may be due to partial defects of genes involved in thyroid hormonogenesis or impairments in other thyroidal genes caused by epigenetic events or triggered by environmental factors (15). However, in the present study an association between defects of thyroid development and mild increase of b-TSH at screening was observed. Specifically, 19.6% of babies with a mild increase of b-TSH at screening had defects of thyroid development (thyroid hypoplasia, hemiagenesis, and ectopy). These babies would have been missed out at screening if the cut off had been higher.

It is interesting to note that the frequency of thyroid hypoplasia/hemiagenesis was similar in the group with b-TSH at screening of 15.0 μU/mL or less and in that with b-TSH greater than 15.0 μU/mL. In addition, the frequencies of major and multiple malformations were similar in the 2 groups. Although it is well known that a high frequency of extrathyroidal malformations is associated with CH (16), the results obtained in the present study seem to suggest that both severe and milder forms of hypothyroidism are associated with impairments of embryo development. Moreover, the high frequency of multiple malformations observed in both groups of infants further

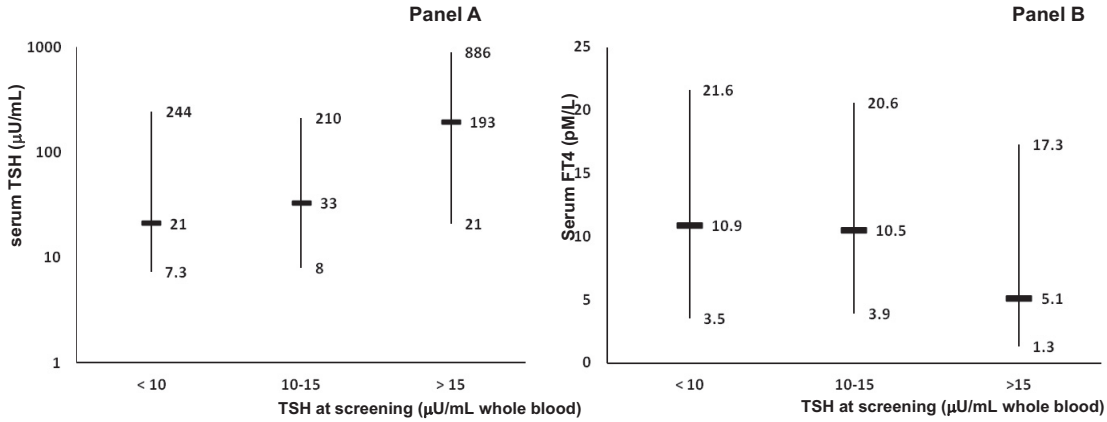

Figure 2. Distributions (fifth, 50th, and 95th percentiles) of serum TSH (A) and serum FT4 (B) at confirmation of the diagnosis grouped by b-TSH values at screening. For expected values see reference 12 and reference 13.

support the idea that in both groups a very early impairment may occur in the first stages of embryo development with a consequent involvement of different organs and structures. However, further studies are needed to elucidate this issue and to investigate the genes responsible for the first stages of embryo development and their sensitivity to the thyroid hormone.

In the present study, the global frequency of maternal thyroid dysfunction in pregnancy was higher than that reported in pregnant women (17) both in the group of infants with b-TSH at screening of 15.0 μU/mL or less and in that with b-TSH greater than 15.0 μU/mL. These findings are in accordance with our previous case-control study in which maternal thyroid dysfunction was demonstrated to be a risk factor for CH (18). Taken together, these observations suggest that thyroid dysfunction in pregnancy may be a risk factor both for mild and more severe forms of CH and also underline the importance of maternal euthyroidism during pregnancy for fetal growth and development.

With regard to the frequency of preterm babies, it was found to be significantly higher than that observed in the Italian population of newborns (~6.0%) both in the group of newborns with b-TSH at screening of 15.0 μU/mL or less (23.4%) and in those with values greater than 15 μU/mL (12.1%). Prematurity is known to affect thyroid function in the neonatal period as well as later in life (11, 19). In the first stages of life, hypothyroidism may result from a transient immaturity of the thyroid gland with respect to thyroid hormone biosynthesis and adaptation to variations in the external iodine supply. Moreover, premature babies may receive lower iodine than the recommended minimum of 30 μg/kg·d (20, 21), especially those hospitalized in the neonatal intensive care unit who are fed by parenteral nutrition, which has been demonstrated to provide almost no iodine (22).

Another finding obtained from this study is represented by the fact that a screening strategy using simultaneous TSH+T_4 testing does not seem to improve diagnosis of milder forms of primary permanent CH. Specifically, a similar frequency of CH babies with mild b-TSH increase at birth was found in the group of babies screened by TSH strategy and in that screened by combined TSH+T_4. Whether the combined TSH+T_4 screening strategy has more advantages than the TSH testing alone is not completely clear. It has recently been reported that in the 9 state screening programs in the United States using simultaneous TSH+T_4 testing, the rate of detection of CH in 2008 was 1:2520 vs an average US incidence of 1:2343. In the same year in the United States, 17 state screening programs used primary TSH and 26 primary T_4 test strategy (23, 24). The INRICH data analyzed in the present study have confirmed these observations because the incidence rate of permanent CH in Italy between 2000 and 2006 was 1:2135 live born in the regional screening programs using a TSH strategy and 1:2300 in those using simultaneous detection of TSH+T_4 testing.

In conclusion, our results show that lowering the TSH cutoff in our country has led to detect additional cases of permanent CH, a number of which had defects of thyroid development and severe hypothyroidism at confirmation of the diagnosis.

Acknowledgments

The authors are grateful to Daniela Rotondi for her technical support. The members of the Italian Study Group for Congenital Hypothyroidism are the following: R. Altamura, U. Angeloni, I. Antonozzi, M. Baserga, S. Bernasconi, G. Bona, I. Bucci, F. Calaciura, R. Caldarera, M. Camilot, M. Cappa, U. Caruso, M. R. Casini, A. Cassio, L. Cavallo, G. Cesaretti, F. Chiarelli, B. Ciannamea, R. Ciatti, M. Cicciò, R. Cordova, A. Correra, P. Costa, F. De Luca, C. De Santis, S. Di Maio, G. Gallicchio, R. Gastaldi, G. Grasso, R. Gurrado, A. Lelli, D. Leonardi, S. Loche, R. Lorini, G. Manente, F. Monaco, G. Minelli, P. Narducci, N. Oggiano, S. Pagliardini, G. Parlato, E. Pasquini, A. Pinchera, M. Pizzolante, G. Radetti, F. Righetti, A. Rizzo, G. Saggese, D. Sala, C. Salerno, L. Sava, D. Scognamiglio, V. Stoppioni, M. Tonacchera, R. Vigneri, and G. Vignola.

Address all correspondence and requests for reprints to: Antonella Olivieri, Department of Cell Biology and Neurosciences, Istituto Superiore di Sanità, Viale Regina Elena, 299, 00161 Rome, Italy. E-mail: antonella.olivieri@iss.it.

This study was supported by the Istituto Superiore di Sanità fund n. 2AQC.

Disclosure Summary: The authors have no conflict of interest to declare.

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