International Journal of
Neonatal Screening

MDPI

Article

Impact of Lower Screening TSH Cutoff Level on the Increasing Prevalence of Congenital Hypothyroidism

Violeta Anastasovska [1,*] and Mirjana Kocova [2]

[1] Laboratory for Neonatal Thyroid Screening, University Pediatric Clinic, Medical Faculty, Skopje 1000, Macedonia
[2] Department of Endocrinology and Genetics, University Pediatric Clinic, Medical Faculty, Skopje 1000, Macedonia; mirjanakcova@yahoo.com
* Correspondence: violeta_anastasovska@yahoo.com; Tel.: +389-75-500-542; Fax: +389-2-3129-027

Academic Editor: Harvey Levy
Received: 7 February 2017; Accepted: 30 March 2017; Published: 4 April 2017

Abstract: Lower cutoff levels in screening programs have led to an increase in the proportion of detected cases of transient hypothyroidism, leading to an increase in the overall prevalence of primary congenital hypothyroidism (CH) in several countries. We have performed a retrospective evaluation on the data from 251,008 (96.72%) neonates screened for thyroid-stimulating hormone (TSH) level in dried blood spot specimens taken 48 h after birth, between 2002 and 2015, using the DELFIA method. A TSH value of 15 mIU/L whole blood was used as the cutoff point until 2010 and 10 mIU/L thereafter. Primary CH was detected in 127 newborns (1/1976) of which 81.1% had permanent and 18.9% had transient CH. The prevalence of primary CH increased from 1/2489 before 2010 to 1/1585 thereafter (p = 0.131). However, the prevalence of permanent CH increased only slightly (p = 0.922), while the transient CH prevalence showed an 8-fold increase after lowering the TSH cutoff level (p < 0.001). In cases of permanent CH, we observed a lower prevalence of thyroid dysgenesis (82.7% vs. 66.7%) and a higher prevalence of a normal in situ thyroid gland (17.3% vs. 33.3%), for the period with a lower TSH cutoff value. Our findings support the impact of a lower TSH cutoff on the increasing prevalence of congenital hypothyroidism.

Keywords: congenital hypothyroidism; prevalence; neonatal screening; thyroid-stimulating hormone; cutoff level

1. Introduction

A reliable primary congenital hypothyroidism (CH) prevalence of 1/3000–1/4000 was reported when neonatal screening for CH was first introduced [1]. Over the past two decades, a higher prevalence of CH has been identified worldwide ranging from 1/1600 to 1/2800 live births [2–5]. Potential causes include environmental factors, changes in the ethnic composition of the population, modification of the screening program methodology and application of the lower thyroid-stimulating hormone (TSH) cutoff level at screening [5–8]. The shift from primary T4 to primary TSH screening strategies, and the lowering of the TSH cutoff levels have been attributed to the increasing CH prevalence worldwide, probably due to more frequent detection of the milder forms of CH. The majority of cases detected using a lower TSH cutoff tend to have milder hypothyroidism, with imaging often demonstrating an eutopic, "gland in situ". However, some cases turn out to have transient CH [5,7,9–11].

The aim of this study was to investigate the influence of a lower TSH cutoff level on the prevalence of CH as well as on the prevalence trend of different etiologies of CH.

2. Materials and Methods

CH screening has been mandatory in Macedonia since 2007, after a previous 5 year pilot study. There is a centralized screening center located at the University Pediatric Clinic in the capital of Macedonia with screening coverage of over 95% of the total neonatal population. The DELFIA method with the neonatal TSH kit (DELFIA, Perkin-Elmer, WallacOy, Turku, Finland) is used to measure the whole-blood thyroid-stimulating hormone (TSH) level as a primary screening test, as described previously [12]. Heel prick whole-blood samples were taken on filter paper Schleicher and Schuell Inc., Keene, NH, USA (Whatman 903), between 48 and 72 h of life. Preterm newborns (<37 weeks' gestation), babies with low birth weight (<2500 g), and sick newborns with a prolonged stay in the neonatal intensive care units were re-sampled two weeks after the first screening. Neonates who were discharged from the maternity hospital before 48 h of life were screened at the moment of discharge. A 14-year retrospective population-based study was performed on a total of 251,008 (96.72%) newborns, screened in the period between April 2002 and December 2015. A TSH value of 15 mIU/L whole blood was used as the cutoff until 2010 (period 1), and 10 mIU/L from 2011 onward (period 2). A total of 136,874 (54.5%) newborns were screened during period 1, and 114,134 (45.5%) during period 2. The indications for biochemical and clinical evaluation as well as the performed analysis to complete the CH diagnosis were described previously [13,14]. Neonates with a persistent deficiency of the thyroid hormone that requires life-long treatment were classified as babies with permanent CH. Transient CH was diagnosed whenever thyroid hormone levels returned to normal, after tapering down and discontinuation of the thyroxine therapy [15,16]. Newborns detected with CH underwent thyroid ultrasonography followed by scintigraphy.

Statistical analysis was done with Statistical Package for Social Sciences (version 20.0; SPSS Inc., Chicago, IL, USA). Descriptive analysis was performed on the obtained TSH/T4 values. Pearson χ^2 was used for the comparison of proportions, and statistical significance was set at $p < 0.05$.

The study was approved by Human Research Ethics Committees of University Pediatric Clinic, Medical Faculty, Skopje, and the the Local Ethics Committee. The authors declare that all investigations were carried out following the rules of the Declaration of Helsinki of 1975 and its later amendments. For this retrospective type of study, formal consent is not required.

3. Results

During the period 2002–2015, primary congenital hypothyroidism was detected in 127 newborns with an overall prevalence of 1/1976, and a female to male ratio of 1.35:1. Among neonates with primary CH, 103 (81.1%) had permanent CH, indicating a prevalence of 1/2437 and female predominance (female to male ratio 1.71:1) and 24 (18.9%) had transient CH with a prevalence of 1/10,459 and male predominance (female to male ratio 1:2), Table 1.

Table 1. Impact of a lower thyroid-stimulating hormone (TSH) cutoff level on the congenital hypothyroidism (CH) prevalence.

	Prevalence of CH (*n*)			
	Total	**Period 1**	**Period 2**	***p* Value**
Primary CH	1/1976 (127)	1/2489 (55)	1/1585 (72)	0.131
Permanent CH	1/2437 (103)	1/2632 (52)	1/2238 (51)	0.922
Transient CH	1/10,459 (24)	1/45,625 (3)	1/5435 (21)	< 0.001
Number of screened newborns	251,008	136,874 (54.5%)	114,134 (45.5%)	

The prevalence of primary CH confirmed at birth increased from 1/2489 live births in period 1 to 1/1585 in period 2 with an increment of 36.3% ($p = 0.131$; $\chi^2 = 2.276$), and the prevalence of permanent CH increased from 1/2632 to 1/2238 live births with an increment of 15% ($p = 0.922$; $\chi^2 = 0.10$)—both statistically non-significant. On the other hand, we revealed a significant, more than 8-fold increase in the prevalence of transient CH, from 1/45,625 live births in period 1 to 1/5435 in period 2 ($p < 0.001$; $\chi^2 = 13.50$), as shown in Table 1. The percentage of transient CH, among children with CH, was significantly higher in period 2 (29.2%) than in period 1 (5.5%), ($p < 0.001$).

We also evaluated the impact of lowering the TSH cutoff value on the prevalence trend of permanent CH caused by different etiologies, obtained with thyroid ultrasonography and/or scintigraphy. Thus, we observed a slightly lower prevalence of thyroid dysgenesis (athyreosis, ectopic gland, hemiagenesis, and hypoplasia in situ) in period 2 (66.7%) than in period 1 (82.7%), a decrement of 5.2%; and a higher prevalence of a normal in situ thyroid gland in period 2 (33.3%) compared to period 1 (17.3%), an increment of 55.9%; however, both are statistically non-significant (Table 2).

Table 2. Prevalence trend of permanent CH with different underlying etiologies.

	Prevalence of Permanent CH (*n*)		
	Period 1 (*n* = 52)	**Period 2 (*n* = 51)**	***p* Value**
Thyroid dysgenesis	1/3183 (43)	1/3357 (34)	0.305
Normal/hyperplastic thyroid	1/15,208 (9)	1/6714 (17)	0.117

4. Discussion

Over the years, lower TSH cutoffs have been adopted in some neonatal thyroid screening programs worldwide, leading to a progressive increase in the detection of additional mild forms of the disease and with that an increase in the overall prevalence of CH [3,7]. Our 14-year retrospective study showed a higher prevalence of CH confirmed at birth in Macedonia (1/1976) than previously reported (1/2591)—an increment of 23.7% [12]. In fact, the higher prevalence of CH was observed over period 2, thus indicating the impact of lowering the TSH cutoff level on the overall CH prevalence. Specifically, the prevalence of primary CH confirmed at birth increased from 1/2489 live births in period 1 to 1/1585 in period 2 (an increment of 36.3%). The latter is higher than the prevalence reported in Italy (1/1940) [6], Greece (1/1749) [3], and Serbia (1/1872) [17] for the period of lower TSH cutoff thresholds but lower than that reported in Turkey (1/650) [18]. However, a two-fold increase in the prevalence of CH has been reported by six Newborn Screening Programs around the world, after lowering the TSH cutoff [9]. In Iran, where the TSH cutoff is 5 mIU/L whole blood, the estimated birth prevalence of CH is as high as 1/307 live births [19].

In the present study, the prevalence of permanent CH showed an increment of 15% for period 2 (1/2238), (Table 1), which is within the range of CH prevalence rates reported in the literature (1/1600–1/2800) [2–5]. However, it was not in accordance with some reports stating that transient and permanent forms of CH have contributed jointly to the increased CH prevalence [10]. The increased prevalence of CH after reducing the cutoff point is not necessarily a single predictor of transient TSH elevation [3], but in our case the prevalence of transient CH increased more than 8-fold. Similarly, an approximate 5-fold increase in the prevalence of transient CH has been reported in Turkey after reducing the cutoff point (1/1154 vs. 1/6202) [10,20]. The percentage of transient CH within the entire CH group revealed in our study showed an increment from 5.5% of all CH to 29.2%, indicating the important contribution of the lower TSH cutoff level in detecting additional cases of transient CH. This rate is much higher than the expected rate of 5%–10% reported for iodine-sufficient populations [21,22]. A significant increase in the transient CH from none in the first period (30 mIU/L whole blood cutoff) to 35% of all CH patients in the last period (9 mIU/L whole blood cutoff), was recently reported in central Serbia with 30 years of experience in thyroid screening [17]. A similar finding was reported from Italy, for a period of 20 years [6]. Kara et al. revealed an increased rate of transient CH to 35% in 2008 (10 mIU/L whole blood cutoff) and 56% in 2009–2010 (7.5 mIU/L whole blood cutoff), compared to 27% in the period 2000–2002 (20 mIU/L whole blood cutoff) [10]. In general, lower cutoff levels in screening programs have led to an increase in the proportion of detected cases of transient hypothyroidism, leading to an increase in the overall prevalence of primary CH. Whether early detected mild CH cases by newborn screening can benefit from early thyroid hormone treatment is still controversial [23]. Some authors have reported that it may have beneficial effects on the full brain function of the affected children [24–27]. With this in mind, we believe that a TSH cutoff value of 10 mIU/L whole blood is acceptable. Further lowering of the cutoff value should be postponed until

clear data on the benefits for children versus family anxiety and additional cost are assessed by large international studies.

Another purpose of this study was to evaluate the impact of a reduced TSH cutoff point on the prevalence rate of permanent CH with different underlying causes. A lower rate of thyroid dysgenesis and higher proportion of a normal in situ thyroid gland were observed among children with permanent CH in period 2 compared to period 1, although the difference did not reach statistical significance. In Italy, a significant increase in permanent CH with normal in situ thyroid for the period with reduced TSH cutoff compared to the previous one has been reported [6]. Corbetta et al. reported a higher rate of newborns with a normally located thyroid gland which represents two-thirds of the overall CH population [7]. In Canada, Deladoey et al. found that lowering the cutoff point resulted in identifying more mild CH forms with a normally located thyroid gland [28].

Lowering the TSH cutoff is an important factor contributing to the higher prevalence of primary CH in Macedonia and, our results show a significant impact of transient CH on the increased prevalence of primary CH in the country. Further analysis is necessary to identify the other environmental and genetic factors associated with the occurrence of transient CH in our population.

Author Contributions: Both authors have contributed to the critical revision of the manuscript for important intellectual content. Violeta Anastasovska carried out the thyroid screening in the country, and contributed to the retrospective evaluation of the data, idea and concept of the manuscript as well as designing, writing and editing the manuscript. Mirjana Kocova contributed to diagnosis, ultrasound check-ups, treatment and follow-up of the patients with congenital hypothyroidism as well as designing and editing the manuscript.

Conflicts of Interest: The authors declare no conflict of interest. Both authors have reviewed the manuscript and agree to its submission and format.

References

1. Fisher, D.A.; Dussault, J.H.; Foley, T.P., Jr.; Klein, A.H.; LaFranchi, S.; Larsen, P.R.; Mitchell, M.L.; Murphey, M.H.; Walfish, P.G. Screening for congenital hypothyroidism: Results of screening one million North American infants. *J. Pediatr.* **1979**, *94*, 700–705.
2. Albert, B.B.; Cutfield, W.S.; Webster, D.; Carll, J.; Derraik, J.G.B.; Jefferies, C.; Alistair, J.; Gunn, A.J.; Hofman, P.L. Etiology of increasing incidence of congenital hypothyroidism in New Zealand from 1993–2010. *J. Clin. Endocrinol. Metab.* **2012**, *97*, 3155–3160.
3. Mengreli, C.; Kanaka-Gantenbein, C.; Girginoudis, P.; Magiakou, M.A.; Christakopoulou, I.; Giannoulia-Karantana, A.; Chrousos, G.P.; Dacou-Voutetakis, C. Screening for congenital hypothyroidism: The significance of threshold limit in false-negative results. *J. Clin. Endocrinol. Metab.* **2010**, *95*, 4283–4290.
4. Harris, K.B.; Pass, K.A. Increase in congenital hypothyroidism in New York State and in the United States. *Mol. Genet. Metab.* **2007**, *91*, 268–277.
5. Hetzberg, V.; Mei, J.; Therrell, B.L. Effect of laboratory practices on the incidence rate of congenital hypothyroidism. *Pediatrics* **2010**, *125*, S48–S53.
6. Olivieri, A.; Fazzini, C.; Medda, E. Multiple factors influencing the incidence of congenital hypothyroidism detected by neonatal screening. *Horm. Res. Paediatr.* 2015, *83*, 86–93.
7. Corbetta, C.; Weber, G.; Cortinovis, F.; Calebiro, D.; Passoni, A.; Vigone, M.C.; Beck-Peccoz, P.; Chiumello, G.; Persani, L. A 7-year experience with low blood TSH cutoff levels for neonatal screening reveals an unsuspected frequency of congenital hypothyroidism (CH). *Clin. Endocrinol.* **2009**, *71*, 739–745.
8. Kaiserman, I.; Maytal, A.; Siebner, R.; Sack, J. Effects of immigration on the incidence of congenital hypothyroidism. *Eur. J. Endocrinol.* **1997**, *137*, 356–359.
9. Ford, G.; LaFranchi, S. Screening for congenital hypothyroidism: a worldwide view of strategies. *Best Pract. Res. Clin. Endocrinol. Metab.* **2014**, *28*, 175–187.
10. Kara, C.; Gunindi, F.; Yılmaz, G.C.; Aydın, M. Transient congenital hypothyroidism in Turkey: An analysis on frequency and natural course. *J. Clin. Res. Pediatr. Endocrinol.* **2016**, *8*, 170–179.
11. Parks, J.S.; Lin, M.; Grosse, S.D.; Hintonn, C.F.; Drummond-Borg, M.; Borgfeld, L; Sullivan, K.M. The impact of transient hypothyroidism on the increasing rate of congenital hypothyroidism in the United States. *Pediatrics* **2010**, *125*, S54–S63.

12. Kocova, M.; Anastasovska, V.; Sukarova-Angelovska, E.; Tanaskoska, M.; Taseva, E. Clinical practice: Experience with newborn screening for congenital hypothyroidism in the Republic of Macedonia—A multiethnic country. *Eur. J. Pediatr.* **2015**, *174*, 443–448.
13. Anastasovska, V.; Kocova, M. Ethnicity and incidence of congenital hypothyroidism in the capital of Macedonia. *J. Pediatr. Endocrinol. Metab.* **2016**, doi:10.1515/jpem-2016-0178.
14. Zdraveska, N.; Anastasovska, V.; Kocova, M. Frequency of thyroid status monitoring in the first year of life and predictors for more frequent monitoring in infants with congenital hypothyroidism. *J. Pediatr. Endocrinol. Metab.* **2016**, *29*, 795–800.
15. Messina, M.F.; Aversa, T.; Salzano, G.; Zirilli, G.; Sferlazzas, C.; De Luca, F.; Lombardo, F. Early discrimination between transient and permanent congenital hypothyroidism in children with eutopic gland. *Horm. Res. Paediatr.* **2015,** *84,*159–164.
16. Rastogi, M.V.; LaFranchi, S.H. Congenital hypothyroidism. *Orphanet J. Rare Dis.* **2010**, *5*, 17.
17. Mitrovic, K.; Vukovic, R.; Milenkovic, T.; Todorovic, S.; Radivojcevic, J.; Zdravkovic, D. Changes in the incidence and etiology of congenital hypothyroidism detected during 30 years of a screening program in central Serbia. *Eur. J. Pediatr.* **2016**, *175*, 253–259.
18. Dilli, D.; Ozbaş, S.; Acıcan, D.; Yamak, N.; Ertek, M.; Dilmen, U. Establishment and development of a national newborn screening programme for congenital hypothyroidism in Turkey. *J. Clin. Res. Pediatr. Endocrinol.* **2013**, *5*, 73–79.
19. Dorreh, F.; Chaijan, P.Y.; Javaheri, J.; Zeinalzadeh, A.H. Epidemiology of congenital hypothyroidism in Markazi Province, Iran. *J. Clin. Res. Pediatr. Endocrinol.* **2014**, *6*, 105–110.
20. Simsek, E.; Karabay, M.; Kocabay, K. Neonatal screening for congenital hypothyroidism in West Black Sea area, Turkey. *Int. J. Clin. Pract.* **2005**, *59*, 336–341.
21. Fisher, D.A.; Grueters, A. Disorders of the thyroid in the newborn and infant. In *Pediatric Endocrinology*, 3rd ed.; Sperling, M.A., Ed.; Elsevier Saunders: Philadelphia, PA, USA, 2008; pp. 198–226.
22. Anastasovska, V.; Kocova, M. Newborn screening for thyroid-stimulating hormone as an indicator for assessment of iodine status in the Republic of Macedonia. *J. Med. Biochem.* 2016, *35*, 1–5.
23. Sağlam, H.; Buyukuysal, L.; Koksal, N.; Ercan, I.; Tarim, O. Increased incidence of congenital hypothyroidism due to iodine deficiency. *Pediatr. Int.* **2007**, *49*, 76–79.
24. Rapaport, R. Congenital hypothyroidism: Expanding the spectrum. *J. Pediatr.* **2000**, *136*, 10–12.
25. LaFranchi, S.H. Increasing incidence of congenital hypothyroidism: Some answers, more questions. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 2395–2397.
26. Cheetham, T. Congenital hypothyroidism: Managing the hinterland between fact and theory. *Arch. Dis. Child*. **2011**, *96*, 205.
27. Ehrlich, R.M. Thyroxin dose for congenital hypothyoidism. *Clin. Pediatr. (Phila)* **1995**, *34*, 521–522.
28. Deladoey, J.; Ruel, J.; Giguere, Y.; Van Vliet, G. Is the incidence of congenital hypothyroidism on the increasing really increasing? A 20-years retrospective population-based study in Quebec. *J. Clin. Endocrinol. Metab.* **2011**, *96*, 2422–2429.