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

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Abstract: Lower cutoff levels in screening programs have led to an increase in the proportion of detected cases with transient hypothyroidism, leading to increase of the overall incidence of primary congenital hypothyroidism (CH) in several countries. We have performed 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 hours after birth, between 2002 and 2015, using DELFIA method. A TSH value of 15 mIU/L 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 incidence of primary CH was increased from 1/2489 until to 2010 to 1/1585 thereafter (p=0.131). However, the incidence of permanent CH was slightly increased (p=0.922), while the transient CH incidence had 8-fold increasing after lowering the TSH cutoff level (p<0.001). In cases with permanent CH, we observed lower frequency for thyroid dysgenesis (82.7 vs. 66.7%) and higher frequency for normal in-situ thyroid gland (17.3 vs. 33.3%), for the period

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with reduced TSH cutoff value. Our findings support the impact of lower TSH cutoff on the increasing incidence of congenital hypothyroidism.

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

1. Introduction

Reliable congenital primary hypothyroidism (CH) incidence of 1:3,000 - 1:4,000 was reported when neonatal screening for CH was first introduced [1]. Over the past two decades, an increased incidence of CH has been described worldwide with a rate ranging between 1:1,600 and 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 TSH cutoff level at screening [5-8]. Shift from primary T4 to primary TSH screening strategies, and the lowering of the TSH cutoff levels have been attributed to the increasing CH incidence worldwide probably due to more frequently detection of the milder forms of CH. Majority of cases detected using 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 reduced TSH cutoff level on the incidence of CH as well as the incidence trend of different etiologies of CH.

2. Materials and Methods

In Macedonia CH screening is mandatory since 2007, after 5 years pilot study. There is a centralized screening center located at the University Pediatric Clinic in the capital of Macedonia with more than 95% screening coverage of the total neonatal population. DELFIA method is used to measured whole-blood thyroid-stimulating hormone (TSH) level as a

primary screening test, with the neonatal TSH kit (DELFIA, Perkin-Elmer, Wallac Oy, Turku, Finland), as described previously [12]. Heel prick whole-blood samples were taken on filter paper Schleicher and Schuell (Whatman 903), between 48 and 72 hours of life. Preterm newborns (<37 weeks' gestation), babies with low birth weight (<2,500 g), and sick newborns with a prolonged stay in the neonatal intensive care units were re-sampled at 2 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 total of 251,008 (96.72%) newborns, screened in the period April 2002 and December 2015. TSH value of 15 mIU/L was used as the cutoff until 2010 (period 1), and a 10 mIU/L cutoff thereafter (period 2). During the period 1, 136,874 (54.5%) newborns were screened, and the rest of 114,134 (45.5%) during the period 2. The indications for biochemical and clinical evaluation as well as the performed analysis to complete the CH diagnosis are described previously [13,14]. Neonates with persistent deficiency of thyroid hormone that requires life-long treatment were classified as babies with permanent CH. Transient CH, on the other hand, was diagnosed whenever thyroid hormone levels returned to normal, after tapering down and discontinuation of the thyroxine therapy [15,16]. Detected newborns with CH underwent thyroid ultrasonography and later on 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 $\chi 2$ 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

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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 overall incidence of 1/1976 (5.1/10,000), and female to male ratio 1.35:1. Among neonates with primary CH, 103 (81.1%) had permanent CH with incidence of 1/2437 (4.1/10,000) and female predominance (female to male ratio 1.71:1) and 24 (18.9%) had transient CH with incidence of 1/10,459 (0.96/10,000) and male predominance (female to male ratio 1:2), Table 1.

Table 1. Impact of reduced TSH cutoff level on the CH incidence

	Incidence per 10,000 (n)			
	Total	Period 1	Period 2	P Value
Primary CH	5.1 (127)	4.0 (55)	6.3 (72)	0.131
Permanent CH	4.1 (103)	3.8 (52)	4.5 (51)	0.922
Transient CH	0.96 (24)	0.2 (3)	1.8 (21)	<0.001

Interestingly, the incidence of primary CH confirmed at birth has increased from 1/2489 (4/10,000) live births in period 1 to 1/1585 (6.3/10,000) in period 2 with an increment of 36.3% ($p=0.131$; $\chi2=2.276$), whereas the incidence of permanent CH increased from 1/2632 (3.8/10,000) to 1/2238 (4.5/10,000) live births with an increment of 15% ($p=0.922$; $\chi2=0.10$). On the other hand, we revealed more than 8-fold increasing in the incidence of transient CH which was increased from 1/45,625 (0.2/10,000) live births in period 1 to 1/5435 (1.8/10,000) in period 2 ($p<0.001$; $\chi2=13.50$), Table 1. The frequency of transient CH observed in our

study showed an increasing from 5.5% in the period 1 to 29.2% of all CH patients in the period 2 ($p<0.001$).

We also evaluated the impact of lowering TSH cutoff value on the incidence trend of permanent CH caused by different etiologies, obtained with thyroid ultrasonography and/or scintigraphy. The incidence trend of permanent CH caused by thyroid dysgenesis (athyreosis, ectopic gland, hemiagenesis, and hypoplasia in situ) was slightly decreased from 1/3183 (3.1/10,000) in period 1 to 1/3357 (3.0/10,000) in the period 2 ($p=0.305$), a decrement of 5.2%. On the contrary, incidence of permanent CH with normal in-situ thyroid gland showed increasing from 1/15,208 (0.7/10,000) in the period 1 to 1/6714 (1.5/10,000) in the period 2 ($p=0.117$), an increment of 55.9% (Table 2).

Table 2. Incidence trend of permanent CH caused by different etiologies

	Incidence per 10,000 (n)		
	Period 1 (n=52)	Period 2 (n=51)	P Value
Thyroid dysgenesis	3.1 (43)	3.0 (34)	0.305
Normal/hyperplastic thyroid	0.7 (9)	1.5 (17)	0.117

Thus, we observed lower frequency for thyroid dysgenesis in period 2 (66.7%) than in the previous one (82.7%), and a higher frequency for normal in-situ thyroid gland in the period 2 (33.3%) compared with the period 1 (17.3%), Figure 1.

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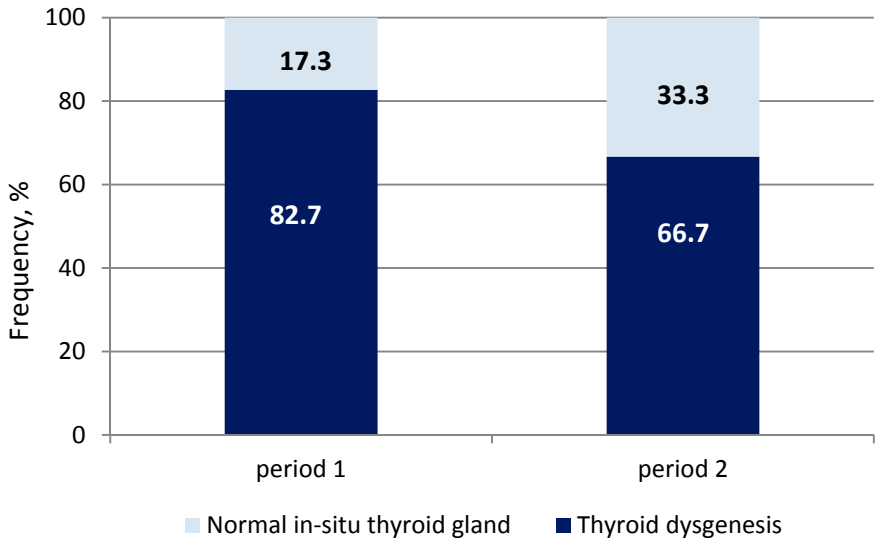

Figure 1. Frequency of permanent CH caused by the different etiologies

4. Discussion

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

In the present study, the incidence of permanent CH showed an increment of 15% for the period 2 (1/2238), (Table 1), which is within the range of CH incidence 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 incidence [20]. The increased incidence of CH after reducing the cutoff point is not necessarily a single predictor of transient TSH elevation [3], although we found that the impact of lowering of the TSH cutoff on the incidence of transient CH has been dramatic, with more than 8-fold increasing in the period 2, $p<0.001$. Similarly, an approximate 5-fold increase in incidence of transient CH has been reported in Turkey after reduced cutoff point (1/1154 vs. 1/6202) [20,21]. The frequency of transient CH revealed in our study showed an increasing from 5.5% of all CH to 29.2%, indicating important contribution of the lower TSH cutoff level in detecting additional cases of transient CH. This frequency is much higher than expected rate of 5-10% reported for iodine sufficient population [22], including our country [23], taking into account that transient CH is a heterogeneous disorder which can be caused both by iodine deficiency or excess. Significant increase in the transient CH from none in the first period (30 mIU/L cutoff) to 35% of all CH patients in the last period (9 mIU/L cutoff), $p<0.001$, was recently reported in central Serbia with 30 years experience in thyroid screening program [17]. Similar finding was reported from Italy, over the period of 20 years [6]. Kara et al. revealed increased frequency of transient CH to 35% in 2008 (10 mIU/L cutoff) and 56% in 2009-2010 (7.5 mIU/L cutoff), $p=0.05$, compared with 27% revealed in the period 2000-2002 (20 mIU/L cutoff) [20,24]. In general, lower cutoff levels in screening programs have led to an increase in the proportion of detected cases with transient hypothyroidism, leading to increase of the overall incidence of primary CH. Whether early detected mild CH cases by newborn screening can benefit from early thyroid hormone

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treatment is still controversial [24]. Some authors have reported that it may have beneficial effects on full brain function of the affected children [25-28].

Another purpose of this study was evaluation of impact of reduced TSH cutoff point on the incidence rate of permanent CH caused by different etiologies. A lower frequency of permanent CH with thyroid dysgenesis (66.7 vs. 82.7%) and higher frequency of permanent CH with normal in-situ thyroid gland (33.3 vs. 17.3%) were observed in the period 2 than in the period 1 (Figure 1), however, with no statistical significance. In Italy, a higher frequency of permanent CH with normal in-situ thyroid for the period with reduced TSH cutoff compared to the previous one has been reported (42 vs. 18%, $p<0.001$) [6]. Corbetta et al. reported a higher frequency of newborn with normally located thyroid gland which represents 2/3 of the overall CH population [7]. In Canada, Deladoey et al. found that lowering cutoff point resulted in identifying more mild CH forms with normally located thyroid gland [29].

Lowering of the TSH cutoff is important factor contributing to the increase of primary CH incidence in Macedonia, especially of the transient CH. Our results showed significant impact of transient CH on the increased incidence of primary CH in the country. Further analysis is necessary to identify the other environmental and genetic factors associated with the occurrence of transient forms in our CH population.

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

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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 MA, Christakopoulou I, Giannoulia-Karantana A, Chrousos GP, 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. (Oxf)* **2009**, *71*, 739-45.

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 Practice 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. Metabol*. **2016**, Sep 22, 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. 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. DOI: 10.4274/jcrpe.2345

21. 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.

22. Fisher, D.A.; Grueters, A. Disorders of the thyroid in the newborn and infant. In *Sperling MA*, ed.; Pediatric Endocrinology, 3rd ed.; Elsevier Saunders: Philadelphia, PA, USA, 2008; pp. 198-226.

23. 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.

24. 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.

25. Rapaport, R. Congenital hypothyroidism: expanding the spectrum. *J. Pediatr.* **2000**, 1*36*, 10-12.

26. LaFranchi, S.H. Increasing incidence of congenital hypothyroidism: some answers, more questions. *J. Clin. Endocrinol. Metab*. **2011**, *96*, 2395-2397.

27. Cheetham, T. Congenital hypothyroidism: managing the hinterland between fact and theory. *Arch. Dis. Child*. **2011**, *96*, 205-205.

28. Ehrlich, R.M. Thyroxin dose for congenital hypothyoidism. *Clin. Pediatr. (Phila)* **1995**, *34*, 521-522.

29. 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.