Оригинальное исследование | Original study

Результаты скрининга неонатального ТТГ не совпадают с показателями оптимального йодного статуса у беременных женщин в Республике Грузия

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Обоснование. Грузия в прошлом была страной с умеренным и тяжелым дефицитом йода и высокой распространенностью эндемического зоба. Репрезентативное общенациональное обследование, проведенное в Грузии в 2017 г., подтвердило оптимальное обеспечение питания населения йодом с медианной концентрацией йода в моче 298 мкг/л у школьников и 211 мкг/л у беременных женщин.
Цель: оценить статус йодного питания населения Грузии.
Методы. Оценку проводили на основе частоты выявления ТТГ >5 и >20 мМЕ/л у новорожденных, а также путем сопоставления этих данных с результатами прямой оценки йодного статуса, выполненной в ходе национального обследования 2017 г.
Методы. С 2009 по 2015 г. доля новорожденных с ТТГ >20 мМЕ/л уменьшилась в три раза: с 0,45 до 0,15%. Эта тенденция наблюдалась во всех регионах страны с существенным различием между столицей, западной и восточной частями страны. Частота случаев обнаружения концентрации ТТГ >5 мМЕ/л у новорожденных в Грузии уменьшилась с 4,46% в 2009 г. до 3,5% в 2015 г. Однако только в Тбилиси частота обнаружения концентрации ТТГ >5 мМЕ/л у новорожденных была ниже 3% – уровня отсечения для адекватного питания йодом. В других регионах страны (Западная и Восточная Грузия) частота случаев выявления концентрации ТТГ >5 мМЕ/л у новорожденных составляла 3,8 и 4,4% соответственно, что можно было бы ложно интерпретировать как умеренный дефицит йода.
Заключение. Хотя неонатальный скрининг (определение концентрации ТТГ) полезен для выявления умеренной и тяжелой степени дефицита йода, его следует с осторожностью рекомендовать для оценки в регионах с оптимальным йодным обеспечением и при легком йодном дефиците.
Ключевые слова: *йод, неонатальный ТТГ, дети школьного возраста, беременные женщины, Грузия, Тбилиси, Глобальная сеть по йоду.*

The results of neonatal TSH screening do not agree with indicators of the optimal iodine status of pregnant women in the Republic of Georgia

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Background. Georgia historically was a country with moderate to severe iodine deficiency and high prevalence of endemic goiter. A representative countrywide iodine survey conducted in Georgia in 2017 confirmed optimal iodine nutrition of the population with median UIC 298 mcg/L in SAC and 211 mcg/L in PW.
Aim. The aim of this study was to assess status of iodine nutrition of population in Georgia.
Methods. The assesement based on the proportion of neonatal Thyroid-Stimulating Hormone (TSH) levels >5mIU/L from 2009 to 2015 and compare these data with the results of direct assessment of iodine status made during the 2017 national survey.
Results. From 2009 to 2015 the proportion of newborns with TSH >20 mIU/L decreased threefold: from 0.45 to 0.15%. This trend was observed in all regions of the country with significant difference between the capital city and Western in Eastern parts of the country. There has been also significant reduction of the prevalence of TSH >5 mIU/L in Georgia from 4.46% in 2009 to 3.5% in 2015. However, only in Tbilisi the frequency of elevated TSH was below 3% – the cutoff level for adequate iodine nutrition. In other regions (Western and Eastern Georgia) prevalence of TSH >5 mIU/L was 3.8% and 4.4% respectively that could be falsely interpreted as mild iodine deficiency.
Conclusions. Although neonatal TSH is useful to detect moderate to severe iodine deficiency, it should be cautiously recommended for the evaluation of iodine status in iodine sufficient to mildly iodine deficient regions.
Key words: *iodine, neonatal TSH, school-aged children, pregnant women, Republic of Georgia, Tbilisi, Iodine Global Network.*

Background

Georgia historically was a country with moderate to severe iodine deficiency and high prevalence of endemic goiter. After collapse of the Soviet system of endemic goiter prevention in 1991, legislation was passed in 2005 in Republic of Georgia mandating the iodization of all salt for human and animal consumption as a public health intervention to eliminate iodine deficiency in the country. In 2005, a national survey indicated that >90% of Georgian households used adequately iodized salt. The median urinary iodine concentration (UIC) in school-aged children (SAC) was 320.7 mcg/L. It was concluded that due to effective implementation of USI legislation, Georgia met the primary WHO criteria for the elimination of iodine deficiency [1].

The 2016 data indicated that 28,600 tones of iodized salt for human consumption were imported to Georgia annually (country does not have own salt industry). This amount is more than sufficient to meet the per capita needs of the population [2].

Starting from 2015, Iodine Global Network (IGN) established an alliance with a Georgian public health agency (NCDC), UNICEF and professional groups of physicians to strengthen iodine monitoring and update information on current status of iodine nutrition. IGN provided resources for launching UIC analysis in the Tbilisi laboratory and linked it with the Regional Iodine Reference laboratory in Almaty and US CDC in Atlanta.

A representative countrywide iodine survey was conducted in Georgia in 2017 and confirmed optimal iodine nutrition of the population with high coverage (over 90%) of households with quality iodized salt. Adjusted median UIC in SAC nationwide (298 mcg/L) was within the range (100–299 mcg/L) for optimum iodine nutrition of population. Median UIC findings in urban SAC were 29mcg/L higher than in rural SAC and the median UIC of SAC in the mountain regions was 51mcg/L lower than the median UIC in urban and rural SAC combined. The median UIC in the 634 pregnant women (PW) was 211 mcg/L, conveniently in the middle of the normative 150–250 mcg/L range. The median UIC in rural PW was 226 mcg/L and 205 mcg/L in urban PW. Given the high dispersion of UIC values that is typical for spot urine collections, these differences are minor [3].

While screening in developed countries is directed at detecting neonates with TSH elevations which are 20 mIU/L whole blood or higher, the availability of TSH assays sensitive to 5 mlU/L permits detection of mild elevations above normal. The neonatal thyroid has a low iodine content compared to that of the adult, and hence iodine turnover is much higher. This high turnover, which is exaggerated in iodine deficiency, requires increased stimulation by TSH. Hence, TSH levels are increased in iodine-deficient populations for the first few weeks of life – this phenomenon is called transient hyperthyrotopinemia [4, 5]. The prevalence of neonates with elevated TSH levels is therefore a valuable indicator of iodine deficiency in a given population.

Aim

Georgia has established nationwide screening for congenital hypothyroidism in the neonates covering all regions of the country and generated a large database of neonatal TSH results. The aim of this study was to assess status of iodine nutrition of population in Georgia based on proportion of neonatal TSH levels >5 mIU/L and compare it with direct assessment of iodine status (median UIC) made during the 2017 national survey.

Methods

From 2009 through 2015, 407,829 dried blood samples were collected in the Republic of Georgia from heel-prick of newborns as dried blood spots (DBS) on Whatman 903 filter paper. As a rule, these DBS were obtained between days 2 and 5 after delivery and used for neonatal TSH screening and further data analysis. DBS for measurement of TSH from participating maternity hospitals throughout the country were delivered to "Express Diagnostics" and "Test–Diagnostics" laboratories in Tbilisi where they were analyzed. TSH concentration was determined by the ELISA method using kits for neonatal TSH screening produced by "Monobind" company (USA). The results were recorded on the STAT FAX 2100 reader produced by "Awareness Technology, Inc." (USA). All records were de-identified. The results were grouped for the three geographical areas of the country: Tbilisi (capital city); Eastern Georgia; Western Georgia, as well as for the entire country. Ethical approval for this study was waived, as analysis of previously collected de-identified data was not considered human subjects research. Statistical analysis of the data was conducted using Excel electronic tables.

Results

From 2009 to 2015 407,829 records of neonatal TSH screening were obtained for further statistical analysis. On average, annual number of live birth in Georgia (excluding Abkhazia and South Ossetia) varied between 63,377 in 2009 (the highest) and 57,878 in 2013 (the lowest). Coverage of neonates with TSH screening varied from 92 to 98%. Infants with a TSH level more than the cut-off level of 20 mIU/L were referred to pediatricians and/or endocrinologists for further re-testing and clinical evaluation to determine the etiology of the elevated TSH.

From 2009 to 2015 the proportion of newborns with TSH >20 mIU/L decreased threefold: from 0.45 to 0.15% (Table 1). This trend was observed in all regions of the country with significant difference between the capital

Table 1. Prevalence (in percent, %) of neonatal TSH levels >20 mIU/L and >5 mIU/L in the Republic of Georgia, Tbilisi, Eastern (E. Georgia) and Western (W. Georgia) districts of the country

Year	Georgia TSH >20	Georgia TSH >5	Tbilisi TSH >20	Tbilisi TSH >5	E. Georgia TSH >20	E. Georgia TSH >5	W. Georgia TSH >20	W. Georgia TSH >5
2009	0.45	4.46	0.39	3.4	0.46	4.72	0.52	6.5
2010	0.39	4	0.4	3.85	0.33	3.8	0.44	4.5
2011	0.43	3.8	0.4	3.36	0.37	3.88	0.53	4.3
2012	0.35	3.76	0.31	3.48	0.34	3.7	0.42	4.2
2013	0.32	4	0.22	3.2	0.26	3.9	0.54	5.2
2014	0.3	4	0.19	3.2	0.3	4.1	0.48	5.2
2015	0.15	3.5	0.07	2.9	0.21	3.8	0.26	4.4

city Tbilisi, Western and Eastern parts of the country. In 2015 the prevalence of TSH >20 mIU/L was the lowest in Tbilisi (0.07%) and the highest in Western Georgia (0.26%).

There has been also significant but less dramatic reduction of prevalence of TSH >5mIU/L (Table 1, Fig. 1) in Georgia from 4.46% in 2009 to 3.5% in 2015. However, only in Tbilisi the frequency of elevated TSH was below 3% – the cut-off level for adequate iodine nutrition. In other regions (Western and Eastern Georgia) prevalence of TSH >5mIU/L was 3.8% and 4.4% respectively that could be falsely interpreted as mild iodine deficiency.

Discussion

Neonatal TSH screening is primarily directed to detect congenital hypothyroidism. To be broadly applicable in a population, the screening must be universal, and not omit children born in remote or impoverished areas. The availability of TSH assays sensitive to 5 mIU/L permitted detection of mild elevations above normal often called as transient hyperthyrotopinemia [5]. Other than infrequent cases of goitrogen exposure, iodine deficiency is the only significant factor to increase the incidence of transient hyperthyrotopinemia. The increase in the number of neonates with moderately elevated TSH concentrations (above 5 mIU/L) is proportional to the degree of iodine deficiency during pregnancy. It may be higher than 40% in severe endemic areas. When a sensitive TSH assay is used on samples collected 2 to 5 days after birth, a <3% frequency of TSH values >5 mIU/L indicates iodine sufficiency in a population [4].

According to the results of national iodine surveys conducted in 2005 and 2017, Republic of Georgia reached

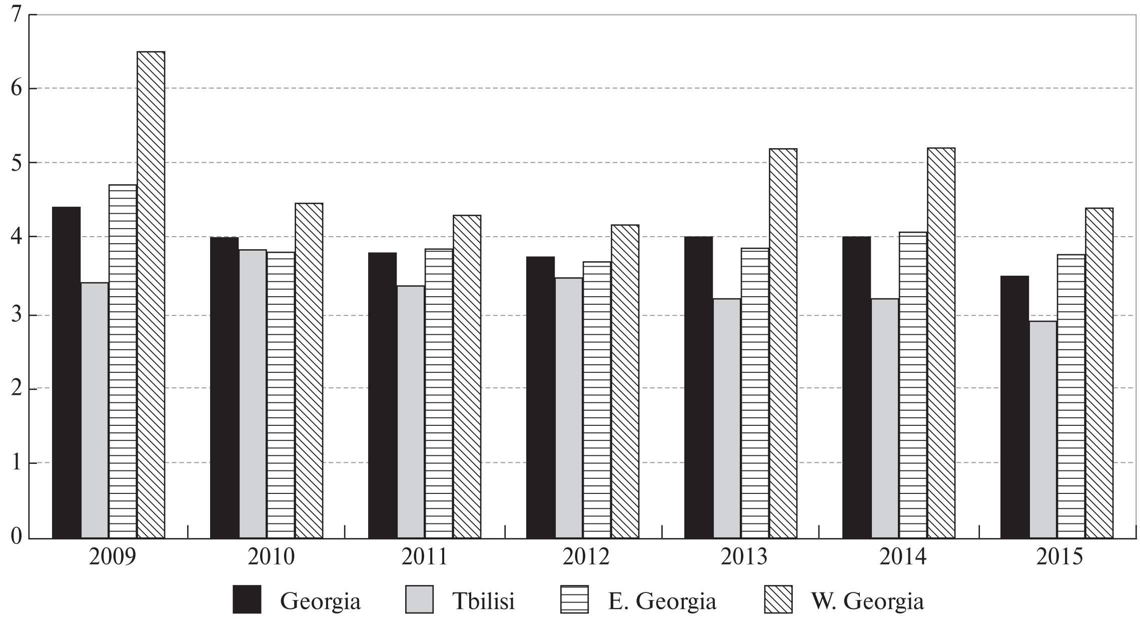

Fig. 1. Prevalence (%) of neonatal TSH levels >5 mIU/L in the Republic of Georgia, Tbilisi, Eastern and Western Georgia in 2009–2015.

sustainable optimum iodine nutrition of population due to effective salt iodization program. However, despite the fact that median UIC both in SAC and PW were in the optimal limits, the prevalence of TSH >5 mIU/L in the neonates in the national cohort was slightly above the cut-off level of 3%, except in capital city Tbilisi where it was 2.9%. More pronounced increase in TSH >5 mIU/L in the neonates was found in Eastern and Western districts of the country. However, median UIC levels were in the optimum range all over the country with minimal variations between the regions [3].

There are conflicting views on the validity of prevalence of TSH >5 mIU/L for the assessment of iodine nutrition. In Switzerland the frequency of neonatal TSH >5mIU/L decreased significantly from 2.9% to 1.7% with an increase in the median UIC in PW from 138 mcg/L to 249 mcg/L due to increase in salt iodine concentrations [6]. A study from Australia using a sensitive TSH assay found that only 2.2% of neonates had a TSH value <5 mIU/L despite a median UIC of 85 mcg/L among PW [7]. In Belgium iodine status is characterized by iodine sufficiency in SAC and mild iodine deficiency in PW and in women of childbearing age. Despite that PW in Belgium were mildly iodine deficient, the frequency of TSH values below 5 mIU/L from 2009 to 2012 was low: from 2.6 to 3.3%. The authors conclude that the sensitivity of the neonatal thyroid to small variations of iodine intake needs to be re-evaluated and compared to neonatal thyroglobulin concentrations that may be more sensitive to smaller variations of iodine intake during pregnancy [8].

Several factors, other than iodine intake, influence neonatal TSH concentration and may explain the conflicting results when applied for the monitoring of iodine status. It is possible that some of the conflicting results may arise from a cut-off derived from studies using different TSH assays. Neonatal TSH is also affected by the mode of delivery, multiple pregnancies and use of iodine-containing antiseptics during delivery [7]. Antiseptics containing betaiodine, such as povidone iodine, are used for cleaning the perineum prior to delivery or even the umbilical area of the baby. Betaiodine increases TSH levels in the neonate in both cord blood and heel prick specimens [4].

The limitation of this research was that we used only crude data for neonatal TSH: records with TSH >20 mIU/L were not removed, as well as those obtained outside the recommended window (2–5 days of life) and of infants possibly born premature. Recent study in the neighboring Armenia, country with optimum iodine nutrition of population and median UIC of 242 mcg/L in SAC and 226 mcg/L in PW, showed that exclusion of these records may decreased frequency of TSH values <5 mIU/L to less than 3% [9].

Conclusion

Despite optimum iodine nutrition of the Republic of Georgia population, including PW, the frequency of neonatal TSH <5 mIU/L was unexpectedly elevated over the 3% threshold. Although neonatal TSH is useful to detect moderate to severe iodine deficiency, it should be cautiously recommended for the evaluation of iodine status in iodine sufficient and mildly iodine deficient regions. Several issues need to be addressed before it can be recommended for this purpose. The sensitivity of neonatal TSH concentration in regions with optimum iodine nutrition needs to be reassessed in view of the conflicting data, suggesting that neonatal TSH may not beas sensitive as previously thought.

Additional information

Conflict of interests. Authors declare no explicit and potential conflicts of interests associated with the publication of this article.

Author's involvement. Nelli Barnabishvilli and Teimuraz Azikuri prepared the database, conducted statistical analysis of neonatal TSH in Georgia. Gregory Gerasimov compared results with other indicators of iodine nutrition and made the first draft of the manuscript. All authors reviewed and finalized the manuscript before submission.

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References

1. Suchdev PS, Jashi M, Sekhniashvili Z, Woodruff BA. Progress toward eliminating iodine deficiency in the Republic of Georgia. *Int J Endocrinol Metab*. 2009;7(3):200-207.
2. Parvanta I. *Design of the Georgia nutrition monitoring and surveillance system. Report to UNICEF*. 2015.
3. Gerasimov G, Sturua L, Ugulava T, van der Haar F. Georgia celebrates sustained optimal iodine nutrition. *IDD Newsletter*. 2018; 46(1):2-4.
4. World Health Organization, International Council for Control of Iodine Deficiency Disorders, UNICEF. *Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers*. 3rd ed. Geneva: WHO; 2008.
5. Delange F, Bourdoux P, Ermans A. *Transient disorders of thyroid function and regulation in preterm infants*. In: Delange F, Fisher D, Malvaux P, editors. *Pediatric Thyroidology*. Basel: S. Karger; 1985. p. 369-393.
6. Zimmermann MB, Aeberli I, Torresani T, Bürgi H. Increasing the iodine concentration in the Swiss iodized salt program markedly improved iodine status in pregnant women and children: a 5-y prospective national study. *Am J Clin Nutr*. 2005;82(2):388-392. doi: 10.1093/ajcn/82.2.388.

7. Travers CA, Guttikonda K, Norton CA, et al. Iodine status in pregnant women and their newborns: are our babies at risk of iodine deficiency? *Med J Aust*. 2006;184(12):617-620.
8. Vandevijvere S, Coucke W, Vanderpas J, et al. Neonatal thyroid-stimulating hormone concentrations in Belgium: a useful indicator for detecting mild iodine deficiency? *PLoS One*. 2012;7(10):e47770. doi: 10.1371/journal.pone.0047770.
9. Hutchings N, Gerasimov G. Salt iodization in Armenia: a model for sustained success. *IDD Newsletter*. 2017;45(4):2-4.

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