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Estimating neonatal screening for congenital hypothyroidism test performance

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ABSTRACT

Introduction: Newborn screening (NBS) is a system of organized search in the entire neonatal population for specific diseases. In Bosnia and Herzegovina, two diseases are included in NBS, congenital hypothyroidism (CH), and phenylketonuria. The screening for CH is based on determination of thyroid stimulating hormone (TSH) levels in blood obtained by heel prick method. The aim of this study is to evaluate the effectiveness of NBS program for CH based on TSH and establish the mean age of diagnosis of CH.

Methods: TSH was measured by time - resolved fluoroimmunoassay (DELFIA Neonatal hTSH kit). The TSH cutoff value was 9 μU/mL. Neonates with TSH < 9 μU/mL had a negative NBS result. Neonates with TSH ≥ 9 μU/mL were recalled for a confirmation test and thyroid hormones were determined from venous blood to establish diagnosis of CH.

Results: A total of 24,351 neonates were subjected to NBS in our institution. A total of 164 newborns with TSH ≥ 9 μU/ml were sent to additional testing (mean recall rate of 0.68%) at a mean age of 11.4 ± 0.5 days of life. In this group, diagnosis of CH was confirmed in 22 neonates (13.41%). The mean rate of false positive results of NBS was 0.59%. The incidence of CH in Sarajevo Canton ranged from 1/2477 in 2018 to 1/641 in 2020. The mean incidence of CH over a 5-year period was 1/1085, while the mean age at the time of diagnosis was 16.5 ± 1.2 days.

Conclusion: The analysis of NBS on congenital hypothyroidism data showed the satisfactory recall and false positive rate and indicated well selected TSH cutoff value. The mean age at the time of diagnosis assures early treatment and good neurological outcome in neonates with CH.

Keywords: Congenital hypothyroidism; Neonatal screening; Thyrotropin

INTRODUCTION

Newborn screening (NBS) as a method appeared in the 1960s and is an example of secondary prevention. It means early detection of the disease in its preclinical or at very early stage. The disease which candidates to be included in neonatal screening should meet some public health conditions: Reasonably high incidence, late clinical presentation, availability of treatment, and appropriate laboratory test (1). Furthermore, ethical, medical, and economic aspects should be considered.

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At present, based on the above criteria two diseases are included in the newborn screening in Bosnia and Herzegovina (BiH) – congenital hypothyroidism (CH) and phenylketonuria. There is a need to expand the program on congenital adrenal hyperplasia and cystic fibrosis in near future, especially since the same technology (time-resolved fluoroimmunoassay) could be used (2).

CH is a deficiency of thyroid hormones at birth and was the leading cause of mental retardation in the pre-screening era. It is the most common congenital endocrine disorder. The incidence of CH ranges from 1:2000 and 1:4000 and varies in different geographical regions (3). In the last decades, there is a trend of increasing incidence of CH, and the reported worldwide rate is now ranging between 1:1,660 and 1:2,828 live births (4,5).

The neonatal screening programs for CH are based either on a single determination of TSH or by simultaneous

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determination of TSH and free or total T4 in neonatal blood samles taken by heel prick method (6,7).

At the beginning of NBS most centers were using higher TSH cutoff values, ranging between 10 and 20 μU/mL. Nowadays, there is a trend to use lower TSH cut-off values to improve sensitivity of the test. There is a variation in practice in different centers, and most of them use TSH cutoff values between 5 and 10 μU/ml. We use TSH cutoff point of 9 μU/mL (8,9).

The previous studies on incidence of CH in different regions in BiH showed the incidence between 1 in 2445 and 1 in 3957 (10,11).

Since the year 2012, there has been no recent data on incidence of CH in neonates born in Federation of BiH, nor any data from Sarajevo region.

Our aim was to evaluate the NBS program for CH based on TSH, calculate basic epidemiological indicators for CH and establish the mean age of diagnosis in all neonates tested in Clinical Center University of Sarajevo.

METHODS

The sampling for NBS was done at the maternity wards or at neonatal intensive care unit in two hospitals by educated healthcare workers. The blood samples were taken on filter papers by heel prick method between 2nd and 7th day of life. The analysis of TSH value in collected dried blood spots was performed at Biochemical Laboratory of Clinical Center University of Sarajevo and TSH levels were determined by time-resolved fluoroimmunoassay (DELFIA Neonatal hTSH kit). If TSH was ≤ 9 μU/mL, the neonates were considered as negative. Neonates with TSH values higher than 9 μU/mL were subjected to a confirmatory venous blood sampling (confirmation test), in which the values of TSH, free T4 or total T4, and T3 were analyzed by Elecsys Thyroid Tests (Roche Diagnostics). The diagnosis was based on reference values of thyroid hormones in neonatal age (Table 1). Study is approved by Ethical board of Clinical center of Sarajevo University.

RESULTS

A total number of 24,351 neonates were screened in the period 2016–2020. This was more than the total number of live births in Sarajevo Canton (22,578) and resulted from including neonates born outside of Sarajevo region transferred to our institution as a tertiary level of care. The neonates with TSH levels lower than 9 μU/ml on NBS were considered negative for CH. A total of 164 neonates (0.67%) had a positive result on the screening test (TSH ≥ 9 μU/mL) and were recalled for testing of thyroid hormones in venous blood (confirmation test) (Table 2). The mean age at the confirmation test was 11.4 ± 0.5 days of life. CH was confirmed in 22 out of 164 neonates (13.41%) who were subjected to the confirmatory test (Figure 1.). As our institution is a tertiary level health-care facility for pediatric care, no cases were referred after hospital discharge for suspicion on hypothyroidism, resulting in no false negative results. The average incidence of CH in the studied population of neonates was 1/1085 and ranged from 1/2,477 to 1/641 (Table 2).

Finally, 142 neonates were falsely positive on neonatal screening, which gives the mean false positive rate of 0.58% over a 5-year period. The mean age at the time of diagnosis of CH was 16.5 ± 1.2 days (Table 3).

TABLE 1. Reference values of thyroid hormones in neonates and infants (age<3 months) (17)

Analysis	Units	Age	Reference value
Total T4	nmol/L	<6 days	64.9–239
		6 days–3 months	69.6–219
Total T3	nmol/L	<6 days	1.12–4.43
		6 days–3 months	1.23–4.22
TSH	μIU/mL	<6 days	0.70–9.00
		6 days–3 months	0.72–11.0
Free T4	pmol/L	<6 days	11.0–32.0
		6 days–3 months	11.5–28.3
Free T3	pmol/L	<6 days	2.7–9.7
		6 days–3 months	3.0–9.3
Thyroglobulin	ng/mL	<6 days	<307
		6 days–3 months	<228

DISCUSSION

Immediately after birth, there is a physiological elevation of TSH due to the stress of the delivery and exposure to the extrauterine environment. The neonatal serum TSH raises up to 70 μU/ml within the 1st 24 h of life, and then rapidly drops to <10 μU/ml within the first 3 days of life (12). This explains why the timing of the NBS is crucial. The ideal time for NBS is 3–5 days of life. In neonates who are screened too early, the recall and false positive may be increased. The other factor which may influence the NBS output data is TSH cutoff value. If TSH cutoff level is lower, the sensitivity of the test is higher but also the false positive and recall rate may rise (13). The appropriate cutoff level of TSH is balancing between these two goals of NBS, the high sensitivity and low recall and false positive rate. The American Academy of Pediatrics (AAP) recommends a recall rate of 0.05%. Worldwide reported recall rates are ranging from 0.01% to 13.3% (14). This may result from different screening strategies (use of T4 or TSH or both), different days of sampling, laboratory techniques or different recall criteria (14-16). Our recall rate of 0.67% is higher than AAP recommended rate, but close to most reported recall rates worldwide (14). The recorded false positive rate of 0.58% was close to the lower limits of the worldwide reported false positive rates ranging from 0.5 to 6% (14). The average incidence of CH was higher than in previous studies done in BiH, which corresponds to a worldwide trend of increasing incidence of CH and environmental, ethnic, and genetic factors should be considered. A study of

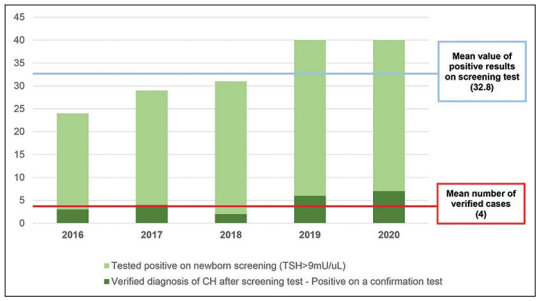

FIGURE 1. Suspect and confirmed cases of congenital hypothyroidism in newborns from Sarajevo region over 5-year period

TABLE 2. Results of NBS and confirmation tests

Year	Screened newborns	Positive screening result (TSH>9μU/mL)	Recall Rate (%)	Verified diagnosis of CH	False positive rate (%)	Incidence per 1,000 newborns	Incidence, expressed as 1 in n
2016	5025	24	0.48%	3	0.42%	0.60	1 in 1.675
2017	5173	29	0.56%	4	0.48%	0.77	1 in 1.293
2018	4954	31	0.63%	2	0.59%	0.40	1 in 2.477
2019	4714	40	0.85%	6	0.72%	1.27	1 in 786
2020	4485	40	0.89%	7	0.74%	1.56	1 in 641

TABLE 3. Mean age at confirmation test and diagnosis of CH

Year	Mean age at confirmation test (days)	Mean age at CH diagnosis (days)
2016	12.0	18.6
2017	11.2	16.8
2018	11.9	17
2019	10.8	13.8
2020	11.1	16.4
Total	11.4	16.5

much longer duration is needed to make a definite conclusion if this phenomenon was a reflection of a real change in the incidence of CH or just a statistical deviation.

CONCLUSION

The main goal of NBS on CH is ensuring high sensitivity which guarantees early diagnosis and early treatment. The sensitivity rises by lowering of TSH cutoff level, but at the same time the recall and false positive rate could be expected to raise. The false positive results cause unnecessary stress to the parents and increase costs of the NBS and are often an argument against lowering TSH cutoff level. Our analysis demonstrated the well selected TSH cutoff value despite the difficulties caused by early discharge and early sampling.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

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