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Neonatal Screening for Congenital Hypothyroidism and Its Other Benefits

Yenidoğanlarda Konjenital Hipotiroidi Taraması ve Diğer Yararları

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Abstract

Aim: We aimed to evaluate the prevalence of congenital hypothyroidism and analyze neonatal thyroid stimulating hormone (TSH) levels to estimate iodine status in our province indirectly

Material and Method: This study was conducted in the pediatric clinics of a government hospital in middle-northern Turkey. The data of national neonatal screening program (NNSP) for congenital hypothyroidism and thyroid function tests (free tetraiodothyronine (fT4), TSH) through hospital records were presented. The rate and severity of iodine deficiency was assessed by using the WHO epidemiologic criteria

Results: In this retrospectively designed cross-sectional study 1324 newborns were evaluated. Most of the participants had normal thyroid functions, 15.4% had transient hyperthyrotropinemia of the newborn, 2.7% had subclinical hypothyroidism 1.5% had congenital hypothyroidism (CH). The prevalence of hyperthyrotropinemia was high (26.1%), revealing moderate iodine deficiency indirectly.

Conclusion: Hyperthyrotropinemia is a significant problem in our province. The clinical follow up of the patients can be managed by general pediatricians. Evaluating TSH and fT4 levels seems to be the only way of diagnosing thyroid disorders of the newborn and provides indirect epidemiologic clues for iodine status of the local population. A preventable nutritional public health problem can be solved with a single step by interpreting the data of NNSP.

Keywords: Neonatal screening, thyroid functions, hypertyhrotropinemia, iodine, congenital hypotyhroidism

Öz

Amaç: Bu çalışmada ilimizde konjenital hipotiroidi sıklığı ve yenidoğanlarda tiroid hormonu uyarıcı hormon (tiroid stimülan hormon (TSH)) düzeyleri üzerinden iyot eksikliği durumunun saptanması amaçlandı.

Gereç ve Yöntem: Çalışma Orta Karadeniz'de bir devlet hastanesinin Pediatri bölümünde yürütüldü. Ulusal tarama programı ile hastane kayıtlarından elde edilen tiroid işlev testlerinin sonuçları sunuldu. İyot eksikliği durumu Dünya Sağlık Örgütü (DSÖ) tarafından belirlenen epidemiyolojik kriterlere göre dolaylı olarak tanımlandı.

Bulgular: Bin üç yüz yirmi dört term, sağlıklı yenidoğanın değerlendirildiği bu retrospektif, kesitsel çalışmada katılımcılarının çoğunda tiroid işlevleri normal sınırlarda idi. Katılımcıların %15,4'ünde yenidoğanın geçici tirotropinemisi, %2,7'sinde subklinik hipotiroidi, %1,5'inde konjenital hipotiroidi saptandı. Hipertiritropinemi sıklığı %26,1 idi, bu durum DSÖ'ne göre "orta düzeyde iyot eksikliği bölgesi" kriterleri ile uyumluydu.

Sonuç: İlimiz için konjenital hipotirioidi ve iyot eksikliği önemli bir halk sağlığı sorunudur. Bu hastaların klinik takibi ve tedavisi çocuk sağlığı ve hastalıkları uzmanları tarafından yürütülebilir. Tiroid işlev testlerinin değerlendirilmesi yenidoğan dönemi tiroid bozukluklarının tanısında tek araç olarak görünmektedir. Bu sayede saptanan dolaylı epidemiyolojik veriler, yaşanılan bölgenin iyot eksikliği sıklığı hakkında da bilgi sağlar. Yenidoğan tarama programı sonuçlarının doğru yorumlanması önlenebilir bir besinsel eksiklik sorununun da çözülmesine yardımcı olur.

Anahtar Kelimeler: Yenidoğan tarama programı, tiroid işlev testleri, hipertirotropinemi, iyot, konjenital hipotiroidi

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INTRODUCTION

Congenital hypothyroidism (CH) is the most common endocrinological disorder of the newborn and the reason of preventable mental retardation. Recently, the incidence of CH has increased as the cut–off levels of thyroid– stimulating hormone (TSH) have been lowered. The incidence was reported as 1/3000–1/4000 live births throughout the world and 1/650 in Turkey.[1-3] Because thyroid hormones are essential for neurodevelopment and healthy growth, hypothyroidism results in psychomotor retardation and failure to thrive.[4] The treatment is easy, inexpensive and effective when the patients are diagnosed early; thus screening programmes during the neonatal period have been established in several countries.[5] Unfortunately only 5% of the patients can be clinically diagnosed during the early infancy, but the response to treatment is insufficient to prevent neurologic sequela when L-thyroxine is initiated late.[6,7] Thus, CH satisfies all the criteria of neonatal screening along with effective treatment.[8] National neonatal screening program (NNSP) was initiated in Turkey in 2006 through heel prick blood spot tests under the supervision of the Turkish Ministry of Health.[9] NNSP is based on capillary TSH levels.[10] Suspected cases are referred to hospitals for further evaluation based on venous blood free tetraiodothyronine (fT4) and TSH levels.[11]

Iodine is an essential nutrient for the thyroid gland and the neurological development and thyroid functions are related to the iodine status. Assessing the neonatal TSH level is one of the recommended monitoring methods to detect the iodine status of the target population as well as the results of iodine supplementation programmes.[12,13] The rate and severity of iodine deficiency (ID) may be assessed using the World Health Organization (WHO) epidemiologic criteria.[12] These criteria are based on the proportion of newborns with serum TSH levels of >5 mIU/ ml in venous blood samples so that this nutritional problem of the local population may be detected indirectly.[14] Since 1998, the salt iodization notification obliged the manufacturers to enrich table salt with 25–40 mg/ kg iodine compounds.[15] Consequently, the iodine uptake has improved and the median urinary iodine concentration in school-aged children has increased from 25.5 mcg/ L to 130 mcg/ L in 2007. Nonetheless, ID was reported to be an ongoing common public health problem.[16,17] We aimed to evaluate thyroid dysfunctions in the newborn population of our region a decade after the initiation of NNSP and interpret the neonatal TSH levels to contribute the estimation of iodine status in our province.

MATERIAL AND METHOD

This study was conducted in the pediatric clinics of a secondary health care center from 1 January 2016 to 31 December 2017. The study center is situated in a small city in the West Black Sea Region of Turkey, according to the Turkish Statistical Institute's grouping.[18] During the study period, 7514 babies were born, and 7638 capillary blood samples were sent to the central laboratories from our province. Blood specimens were collected from the third to fifth day after birth or at discharge from the hospital if it was planned earlier. In this study, specimens taken after 48 hours were considered. The standard procedure of obtaining capillary blood samples for neonatal screening is as follows: The heel is warmed for 3 minutes before the process. The blood specimen is obtained by puncturing the heel, and taken onto the standard filter paper cards provided by the Ministry of Health. Circles on the card are appropriately saturated by blood until the drop of blood appears behind. The cards are air-dried at room temperature in the horizontal position for 3 hours, avoiding heat and light, and then sent to the central laboratories of the Public Health Institution (PHI) for testing. These cards contain information regarding the registration number, surname of the newborn, identity information of the mother, residence, date, time and place of birth, gender, gestational week, type of delivery, birth weight, contact address, phone number and date of sampling along with the name and signature of the healthcare worker who obtained the sample and filled the card. The samples are tested within three working days after being received. NNSP in Turkey is based on capillary TSH level, and the cut-off level is determined to be 5.5 mIU/ml (1 mIU/ml= 1 IU/L). Values <5.5 mIU/ml are defined as "normal". Infants having TSH levels between 5.5–20 mIU/ml are recalled for control screening tests. If the second sample measurement is above 5.5 mIU/ ml or the TSH level is higher than 20 mIU/ml even in the first heel prick test, the newborn must be examined further with venous fT4 and TSH (11,19). Overall 660 babies (49.8%) needed venous fT4 and TSH evaluation, and 33 (4.6%) of them were identified as "possible CH" according to the local PHI data. The remaining babies were tested because of family concerns (n= 203; 15.3%) and clinical necessity [jaundice (n=19; 1.4%), constipation (n= 28; 2.1%), family history (n=83; 6.3%) and sleep disturbances (n=12; 0.9%)]. The medical records of all term, healthy, appropriate in weight for gestational age (AGA) newborns, who were evaluated for thyroid functions were investigated through the hospital information system.

Details such as the age on the date of examination and blood sampling for thyroid functions, gender, and the follow up diagnosis of patients were recorded.

TSH and fT4 were analyzed using Electrochemiluminescence Immunoassay "ECLIA" method by using Siemens Advia Centaur XP® device (Siemens Healthcare GmBH, Erlangen, Germany). TSH levels under 6.5 mIU/ml and fT4 levels of 0.82–2.00 ng/dl were defined as"normal"(20,21). Patients were classified as "primary overt CH" with elevated serum TSH and decreased fT4 (<0.9 ng/dl) levels. The localization, volume and parenchymal patterns of the thyroid gland were evaluated by using ultrasonography. Total thyroid volume was calculated using the following formula: height×width×length×0.479 ml for each lobe. Infants with normal fT4 and elevated TSH were followed-up without treatment and rechecked at 2 week intervals. Infants who had elevated serum TSH concentration with low fT4 levels at one month of age were also diagnosed as"overt CH". Infants whose TSH levels returned to normal with sufficient fT4 levels without any intervention were considered to have "transient hyperthyrotropinemia of the newborn" (TNH). The age of normothyrotropinaemia was also noted. Subclinical hypothyroidism (SCH) was diagnosed when TSH was >6.5 mIU/ml and fT4 was ≥0.9 ng/dl without clinical signs of hypothyroidism at age 6 weeks or older.[22,23]

The rate and severity of ID was assessed by using WHO epidemiologic criteria.[12] One of these criteria is based on the proportion of newborns with serum TSH levels of >5 mIU/ml in venous blood samples. The rate of high TSH levels are supposed to be <3% in iodine-sufficient areas, 3–19.9% in mild deficiency areas, 20–39.9% in moderate and >40% in severe deficiency areas.[12]

Ethics

This study was approved by the local ethical committee of the Amasya Education and Research Hospital with the decision number: 62949364-000-6223. Because this was a retrospective and laboratory data based study, informed consent from parents was not required.

Statistical analyses

The data were analyzed using the Statistical Package for the Social Sciences Programme (SPSS; IBM Inc., Chicago, IL., USA, version 15). Descriptive statistics.[mean, standard deviation, median, interquartile range (IQR)] were used to present the study. Compatibility to normal distribution was tested using both analytical (Kolmogorov-Smirnov, tests of normality) and visual methods. In addition, cross-tabulation analyses, chisquare tests, Pearson or Fisher's exact tests were employed to compare the qualitative variables in different groups.

Mann -Whitney U test was performed to test the significance of pairwise differences using Bonferroni corrections to adjust multiple comparisons of non-normally distributed variables. A p value of <0.05 was considered statistically significant.

RESULTS

This retrospective, cross-sectional study evaluated 1324 healthy newborns. Of these, 713 (53.9%) were males and 611 (46.1%) were females with a mean age 11.68±4.00 days old (range: 7–30 days). The median serum concentration of fT4 was 0.9 ng/dl (IQR= 0.31) and median TSH level was 6.71 mIU/ml (range: 0.5–153 mIU/ml; IQR= 3.41). During the study period, 7514 babies were born in our province and the overall heel pricks (>48 hours) were 7638. Overall 660 newborns went through a second NNSP evaluation of by assessing serum TSH and fT4 levels based on PHI records. Most patients (69.3%; n=917) had normal thyroid functions. All results are summarized in the **Table 1**.

CH was detected in 20 newborns (1.5%) with a mean age of 15.5±1.4 days and 70% (n=14) being males. The serum concentrations of fT4 and TSH were 0.88±0.33 ng/dl and 68.46±9.45 mIU/ ml respectively. None of the patients had clinical signs of hypothyroidism, but one of them had maternal history of thyroid dysfunction. Thyroid ultrasonography was performed for patients with CH, and three patients had results compatible with thyroid gland hypoplasia. Thyroid scintigraphy could not be performed because of technical problems. All patients with CH were referred to pediatric endocrinology department of a tertiary healthcare center for aetiological investigations and further consultation because we were unable to measure thyroglobulin levels, TSH receptor antibodies or urinary iodine concentrations. Central hypothyroidism was detected in one patient of our study group. This patient had jaundice with constipation with fT4 level < 0.7ng/dl and TSH level 3.06-7.31 mIU/ml.

Tablo 1. Summary of the results

	Congenital hypothyroidism	Transient hyperthyrotropinemia of the newborn	Subclinical hypothyroidism	P
Mean age (days)	15.5±1.4	9.9±0.4	14.2±1.5	
Gender (n; %)				
Male	14; 70%	106; 52%	20; 55.6%	0.060
Female	6; 30%	98; 48%	16; 44.6%	
fT4 (ng/dl)	0.88±0.33	1.38±0.3	1.38±0.04	0.020
TSH (mIU/ml)	68.46±9.45	10.65±0.45	13.55±1.51	0.054

Subsequently, he was referred to the pediatric endocrinology clinic for further evaluation, and the diagnosis was confirmed. Treatment with Lthyroxine was commenced in all cases of CH during the neonatal period. Even though the CH group had higher TSH levels with a male preponderance, no statistically significant effects were observed regarding TSH levels, symptoms or gender among CH, SCH and TNH groups (p= 0.054, p=0.08, and p=0.06, respectively).

TNH was detected in 204 patients (15.4%). Of these 98 (48%) were girls, and 106 (52%) were boys with a mean age of 9.9±0.4 days. The average TSH level of this group was 10.65±0.45 mIU/ml and normalized within 30.16±15.26 days. The mean serum concentration of fT4 was 1.38±0.38 ng/dl.

Overall 36 patients (2.7%) were diagnosed with SCH because they had high TSH levels even 6 weeks after birth. The mean age of these patients was 14.2±1.5 days at the first evaluation with 55.6% (n=20) being boys and 44.6% (n=16) girls. The mean serum concentrations of fT4 and TSH were 1.38±0.04 ng/dl and 13.55±1.51 mIU/ml, respectively. Among these patients, 16 had normal thyroid functions during the first year of life and L-thyroxine treatment was commenced in one infant because of increasing TSH in repeating measurements (6.84-9.10mIU/ml) in the fourth month of age, but there were no clinical signs of hypothyroidism.

Overall, 87 newborns with high TSH levels were lost to followup during the study because of unavailable records after the first evaluation.

The rate of hyperthyrotropinaemia in the study population, ignoring the diagnosis, was 26.1% (n=347). When compared with the total newborn population, the rate was 4.6% and prevalence was 1:376. This data revealed the iodine status of our province indirectly. The prevalence of high TSH levels was compatible with moderate ID area according to the WHO criteria.

DISCUSSION

This study evaluated 1324 healthy, term newborns for thyroid functions. Approximately 70% of participants had normal thyroid functions, whereas 15.4% had TNH, 2.7% SCH, and 1.5% overt CH. The prevalence of hyperthyrotropinemia was high in our study population (26.1%). The prevalence of patients diagnosed as "possible CH" was 4.6% based on the PHI data. This inconsistency between the hospital records and the PHI data could probably be due to patients with TNH whose TSH levels decreased at the second examination.

CH, TNH and SCH are expected to be high when there is ID or excess iodine status in the community. The recall rate of NNSP in ID areas is expected to be high, like the present study (8.78%). Furthermore, the rate of neonatal thyroid disorders was high in our study group because the data reflected the results of the referral hospital of our province. The prevalence of high TSH levels was compatible with moderate ID area according to the WHO criteria, although our region was reported to be in a mild ID area previously. Iodine nutrition status in Turkey was reported to be "adequate" per WHO reports which presented the data based on the median urinary iodine concentrations in school children.[24,25]

CH is a common endocrinological problem in neonates. Notably, several studies have been conducted to determine its local and global prevalence. According to the NNSP of Turkey the rate of possible CH cases was 0.15% with an incidence of 1:650 in 2008–2010. The recall rate was reported to be 2.6% in this study.[3] Moreover, the researchers have reported the possible incidence of CH to be 1:418 in the West Black Sea Region of Turkey.[3] The incidence of CH was 1:376 in our study with a rate of 0.26% which is higher than the Turkish data. This finding may be related to the technical and population differences between the two studies. Our hospital was the referral center for further evaluation of the suspected cases; therefore our data reflected the results of a disadvantaged population. CH could be transient or permanent, but substantial followup is required to ascertain this. Transient CH is considered when thyroid functions remain within normal ranges without clinical features of hypothyroidism or hyperthyroidism or the clinician does not need to increase the dosage of L-thyroxine. The treatment can be stopped at approximately at age 3 if the neurodevelopment and growth compatible with age are provided. Nevertheless, the patient's clinical followup and laboratory examinations are continued periodically to detect hypothyroidism. If retreatment is needed, the diagnosis is confirmed as "permanent CH". However, if re-initiation of therapy is not required, the case can be assessed as "transient CH". The results of this study do not reflect the follow-up data, thereby rendering us unable to differentiate the CH cases as permanent or transient, which is one of the limitations of the present study.

"TNH" is the elevation of TSH levels with normal fT4 levels and the absence of clinical signs of hypothyroidism. This situation resolves without any intervention within 4–6 weeks. In the present study, the rate was 15.4%. Notably, TNH is a common clinical problem in ID areas and the aetiology is usually related with iodine exposure. Here, as some of the limitations of the study, we did not mention the iodine status, salt consumption habits, types of delivery, iodine exposure during or after delivery or the thyroid functions of the mothers.

Therefore, it was just a clinical observation that salt consumption habits would have been changed because of speculative dietary rules and popular information regarding unrefined salt forms to be considered healthier. Even though populationbased health studies in 2008 reported an increase in iodized salt consumption, no investigations have been reported recently.[26] Another reason for this could be the usage of iodine-containing antiseptics for skin cleaning during obstetrical procedures.[17] Iodine can be transferred to the baby through the placenta and breast milk, which can hinder organification during thyroid hormone synthesis because of the Wolff-Chaikoff effect in early postnatal life.[27] The prevalence of TNH was reported to be 12% in another study from the middle Black Sea Region.[28] When this laboratory situation lasts more than 4–6 weeks this is called SCH. The prevalence of SCH was reported to be 2% in pediatric age group.[29] SCH must be followed periodically because hypothyroidism could become overt with clinical signs or lowered fT4 levels, like in one of our cases or thyroid functions may normalize, as in 16 cases of our study. Because thyroid hormones are necessary for brain development, authors recommend initiating L-thyroxine for TSH levels above10 mIU/ml. When TSH is 6–10 mIU/ml, the treatment decision depends on clinical signs of hypothyroidism or continued TSH elevation, as in our study case.

Study limitations:

This study had several limitations. The study was based on hospital records and the follow-up duration was short. The results of thyroid scintigragphy, thyroglobulin, TSH receptor antibodies and other tests were not presented. Clinical information regarding iodine nutrition, maternal thyroid functions, salt consumption, consanguinity, familial history of thyroid disease and iodine exposure were not mentioned. In addition, our data regarding iodine status reflected a limited region Nonetheless, in this study, we focused on the outcomes of the cooperation between primary and secondary health care centers for the provision of preventive medicine. Even though the results are not novel, we would like to draw attention to the prevalence of hyperthyrotropinemia in neonates and the role of general paediatricians in clinical followup through the outcomes of a well-organized NNSP.

CONCLUSION

This study established that CH and ID are significant public health concerns in our province. NNSP was implemented successfully with adequate cooperation between the local PHI and pediatric clinics of the local referral hospital. Notably, clinical follow-up of patients can be managed by general pediatricians. Whenever pediatric endocrinology consultation is needed, the general pediatrician can consult the patient for further examination. This approach prevents waste of time and money owing to unnecessary consultations. Screening newborn babies for CH is the most efficient and cost-effective way of preventing CH which is the most common reason for preventable mental retardation. The followup of clinical signs and TSH levels seem to be the only way of ascertaining CH, TNH, SCH because we could not detect any statistically significant factors for predicting the followup diagnosis. Moreover, this process provides indirect epidemiologic clues for regarding the iodine status of the local population, thereby enabling the detection of the effects of salt iodization programmes and the prevention of ID related disorders. Therefore, a preventable nutritional public health problem can be solved in a single step by interpreting the NNSP data.

ETHICAL DECLARATIONS

Ethics Comittee Approval: This study was approved by the local ethical committee of the Amasya Education and Research Hospital with the decision number: 62949364-000-6223.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Status of Peer-review: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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