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High Incidence and Recall Rate of Congenital Hypothyroidism in Zanjan Province, a Health Problem or a Study Challenge?

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ABSTRACT

Background: In Iran, congenital hypothyroidism (CH) screening programs to prevent mental retardation have been started recently. In this national program, all neonates with thyroid-stimulating hormone (TSH) level ≥ 5mIU/L are required to be recalled for a confirmatory test (venous sampling).

Objectives: This study was designed to investigate the incidence of CH and the patient recall rate on the basis of the above mentioned cutoff value for TSH and to compare the results with those obtained in other studies.

Patients and Methods: According to the screening protocol for CH, we assessed neonates born from February 2007 to January 2008 and registered details on the birth date, sex, birth weight, maternal gestational age, and parental consanguinity. TSH was measured from heel-prick blood samples obtained from neonates aged between 3 and 7 days. Neonates showing a TSH level of ≥ 5mIU/L were recalled for undergoing confirmatory tests.

Results: Among 18008 neonates screened for CH, 730 (4.1%) were recalled (TSH, ≥ 5mIU/L). Out of the recalled neonates, 96% were full-term neonates with a mean age of 5.0 ± 3.2 days and a mean TSH level of 8.6 ± 11.4mIU/L. CH was detected in 20 (2.7%) recalled neonates (incidence ratio of 1 in 895 live births) and subclinical hypothyroidism in 45 (6.1%) recalled neonates (incidence ratio of 1 in 398 live births).

Conclusions: Investigations have shown that Asian and Iranian neonates show a high CH prevalence. The recall rate in our study on the basis of the TSH cutoff value of more than 5mIU/L was higher (4%) than that in other studies. Therefore, in addition to emphasizing the importance of neonatal screening, we suggest that the cutoff level of TSH in the national screening program be reassessed and revised to reduce the recall rate for neonates.

Implication for health policy/practice/research/medical education:
High incidence of congenital hypothyroidism and the recall rate was up to us to arrange a study in our area.While reviewing these data, the possible causes ranging from populaation issues to the sampling and measurment method etc were reviewed once.

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1. Background

Primary congenital hypothyroidism (CH) is one of the commonest treatable endocrine disease and can affect the growth and mental development of neonates (1). The clinical diagnosis of CH is difficult, and since most neonatal cases do not show specific symptoms and signs, the disease is detected in less than 5% of neonatal patients (2). Thus, early diagnosis and treatment of CH by using a screening method are essential to prevent irreversible

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mental retardation. Since the establishment of a pilot CH screening program in Quebec and Pittsburg in 1974 (3), newborn screening has become a routine procedure in all developed countries (4). CH prevalence has been found to differ among races and regions, with a higher prevalence among Asian neonates than among neonates of other regions (5, 6). The incidence of CH in live births varies from 1:3000 to 1:4000 in different parts of the world (7), and the incidence and prevalence of the disease is influenced by multiple environmental, genetic, and autoimmune factors (8-11). According to the American Academy of Pediatrics, the recall rate (percentage of tests where the physician notifies the authorities to contact the infant's family to arrange for another blood test) after primary thyroid stimulating hormone (TSH) screening is approximately 0.05% (1); however, this rate varies between developing and developed countries. In Iran, preliminary screening program for CH was started in Iran in 1997, and subsequent studies conducted in Tehran and Isfahan revealed that CH is more prevalent among Iranian neonates (12-14). According to the screening protocol, neonates with abnormal TSH levels on screening (i.e., TSH level ≥5mIU/L in heel-prick or cord blood samples) are recalled for confirmatory tests to diagnose CH on the basis of the serum levels of TSH and T4.

2. Objectives

We designed a study to estimate the incidence of CH and recall rate in the Zanjan province of Iran. We chose this region because it represented the population of the north-western region of Iran. We also considered the possibility of proposing a new adjusted TSH cutoff value in case the study results revealed a higher incidence and prevalence of CH in this region. Additionally, we showed the influence of parental consanguinity and seasonal variation on the incidence of CH in this region.

3. Patients and Methods

3.1. Study Population and Protocol

This study was conducted among 18008 neonates born in 7 cities of Zanjan province during the 1 year period from February 2007 to January 2008. All neonates were screened according to the CH screening protocol. Demographic information, including data for age, sex, weight, maturity, birth date, parental consanguinity, was recorded in a questionnaire. TSH concentrations were measured from heel-prick blood samples obtained by trained nurses from neonates aged between 3 and 7 days. The blood samples were subjected to enzyme linked immunosorbent assay (ELISA) by using available neonatal TSH kits (Padtan Elm kit, Iran). The minimal detectable concentration of TSH in this assay is estimated to be 0.5μIU/mL. Intra-assay coefficients of variation at TSH concentrations of 17, 78, and 162mIU/L were 8.6%, 9.8%, and 9.1%, respectively. The interassay coefficients of variation for different methods at TSH concentrations of 15, 26, and 54mIU/L were 11.3%, 9%, and 8.8%, respectively. According to the criteria set by the national program, a capillary blood TSH level of 5mIU/L is considered as the cutoff point. Neonates with TSH levels less than 5mIU/L were excluded from further evaluation. However, neonates with TSH levels greater than 5mIU/L in filter-paper blood samples were recalled within 4 weeks for confirmation of CH by radioimmunoassay for TSH and T4 levels from venous serum samples; we excluded neonates with TSH levels more than 20mIU/L, who immediately underwent confirmatory tests and received emergent levothyroxin therapy from an endocrinologist. The results obtained were interpreted according to the normal TSH levels for the respective ages. Primary CH was diagnosed if T4 levels were less than 111.11nmol/L and TSH levels were more than 10mIU/L. Neonates were diagnosed with subclinical hypothyroidism when the serum TSH level was more than 10mIU/L and the T4 level was normal.

3.2. Statistical Analysis

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS, version 16), and the mean (± standard error of the mean [SEM]), median, and range values obtained are provided in the Results section. Descriptive statistical methods were used where appropriate. The inter-relationship between hypothyroidism and sub-clinical hypothyroidism and the neonates' sex, maturity, parental consanguinity, and seasonal distribution were analyzed by Chi-square test. Statistical significance was considered if *P* values were less than 0.05.

4. Results

A total of 18008 neonates were screened for congenital hypothyroidism during the study period of which 730 neonates (TSH, > 5mIU/L) were recalled for confirmatory tests. Thus, the recall rate in our study was estimated as 4.1%. The mean age of the recalled neonates was 5.0 ± 3.2 days (range, 1–31 days). As shown in *Table 1*, 54.7% of the recalled neonates were male. The mean weight of the recalled neonates was 3140.10 ± 484 g (range, 850–5250 g). Of the recalled cases, 95% were full-term births and 17.6% involved parental consanguinity. The mean TSH levels obtained from heel-prick blood samples was 8.6 ± 11.4mIU/L (median, 6.6mIU/L; range, 5–190mIU/L). The distribution of TSH levels in the recalled neonates is shown in *Table 2*.

Twenty (2.7%) recalled neonates were diagnosed with CH on the basis of the serum T4 and TSH levels. The incidence of CH was calculated as 1 in 895 live births. The mean weight of neonates with CH was 2986 ± 521 g (median, 3100 g; range, 2000–3780 g). Eighteen (90%) neonates diagnosed with hypothyroidism were full term. The mean serum TSH and T4 levels of neonates with hypothyroidism were 87.1 80.6 ± mIU/L (median, 59.5mIU/L; range, 10.6–289mIU/L) and 71.7 27.3 ± nmol/L (median, 4.2μg/dL; range, 1.1–6.3μg/dL), respectively. Parental consanguinity was found in 3 (15%) cases of hypothyroidism; however,

Table 1. Demographic Characteristics of Recalled Neonates

	Total Recalled Neonates (n = 731)	Neonates with Hypothyroidism (n = 20)	Neonates with Subclinical Hypothyroidism (n = 45)	*P* value
Sex				
Male	399	11	27	> 0.05
Female	329	9	17	> 0.05
Maturity				
Mature	693	18	40	> 0.05
Immature	37	1	3	> 0.05
Weight				
< 2500	623	16	38	> 0.05
2500–4000	56	3	5	> 0.05
> 4000	21	0	1	> 0.05
Parental consanguinity				
Yes	120	3	2	> 0.05
No	610	16 (1 unknown)	32 (5 unknown)	> 0.05

we could not find a statistical correlation between hypothyroidism and parental consanguinity (*Table 2*).

Forty-five (6.2%) recalled neonates showed subclinical hypothyroidism with an incidence of 1 in 398 live births. The mean weight of neonates with clinical hypothyroidism was 3151 ± 515 g (range, 1800–4370 g) and parental consanguinity was detected in 2.1% of the cases. The proportion of recalled cases was highest during winter (February, 8%) and lowest during summer (May, 2.1%). In addition, we observed a significant difference between the neonate recall rate during the winter and summer seasons ($P = 0.024$) (*Figure 1*).

Table 2. Distribution of Serum TSH Levels in Recalled Neonates

TSH Level (mIU/L)	Number	Percent
5–9.9	631	86.4
10–19.9	83	11.4
> 20	16	2.2
Total	730	100

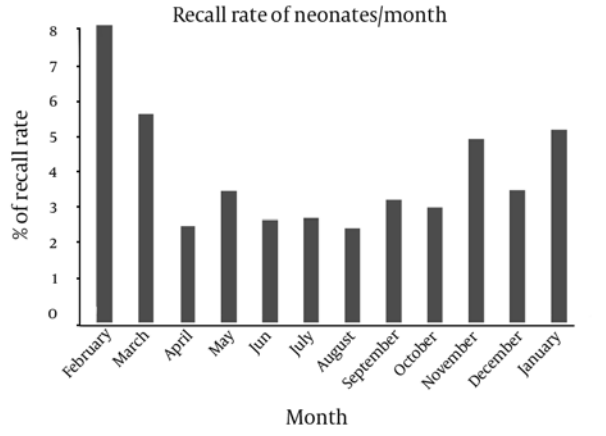

Figure 1. Distribution of Recalled Neonates According to Their Birth Month

At the end of the investigation, we evaluated various cutoff values to define a new one that can ensure greater specificity in screening hypothyroidism and reduce the recall rate. By setting the TSH cutoff level at 10mIU/L for heel-prick blood samples, we observed that 12 neonates whose confirmatory tests had marked them as a clinical hypothyroidism, had heel prick TSH level below new screening cut off value and only 8 of them showed TSH levels above 10mIU/L. It means that by heel-prick TSH value raising from 5 to 10mIU/L, we would miss 12 clinical hypothyroidism neonates. Thus, by setting the TSH cutoff level at 6mIU/L, we would able to reduce the number of recalled neonates from 730 to 504 and decrease the recall rate from 4.1% to 2.7% despite failing to diagnose hypothyroidism in 2 neonates who were later diagnosed after the confirmatory tests.

5. Discussion

In this study, we screened more than 18000 neonates born in 7 cities in Zanjan province; and the study covered 98% of the province. The 1-year incidence of hypothyroidism was estimated to be 1 in 895 live births, whereas the corresponding rates in Tehran and Damavand were about 1 in 950 (15). In Esfahan, a study of 93381 neonates showed that the prevalence of CH was l in 349 live births (16). The worldwide prevalence of CH is reported to be 1 in 3000–4000 live births (17). The results obtained in our study are in-line with those of previous studies (l in 1433, l in 914, and 1 in 370 live births in Fars province, Tehran, and Isfahan, respectively) and were up to 3–4 times higher than the CH prevalence in developed countries (12-14). To clarify the disease characteristics and investigate this high CH incidence rate, researchers will need to conduct a study with 4–5-fold higher population coverage. CH can be definitively diagnosed if the laboratory TSH values are more than 10mIU/L and T4 values are less than 111.11nmol/L (1). Iodine deficiency, which was one of

the risk factors for CH, has been eradicated in our country. Although we did not measure neonatal and maternal urinary iodine levels, a study by Azizi and colleagues in 2002 in the Zanjan province in Iran showed a significant decrease in the number of school-going children with goiter, which is a disease caused by iodine deficiency. Further, they showed that the urinary iodine excretion levels were within the normal range defined by the World Health Organization (18). Considering the high prevalence of CH in Iran, a previous study evaluated the role of iodine in the development of CH by comparing urine and milk iodine concentrations in healthy neonates with those in neonates with CH and their mothers. The results showed that in an iodine-sufficient area, the median urine and milk iodine concentrations were within the acceptable range for both the groups (18, 19).

Recent studies have suggested a relationship between CH and the use of povidone-iodine–containing antiseptic solution, which is used during vaginal and cesarean delivery in the Zanjan province and in Iran (20). However, Ordookhani and colleagues showed that disinfection using povidone-iodine during delivery had no considerable effect on the TSH concentration or the rate of hyperthyrotropinemia in an iodine-replete area of Iran (20) or the contrary results were shown in Europe studies. Further, it has been shown that transient hypothyroidism in premature newborn infants is not a common sequel of routine skin cleansing using iodine in North America (21). However, the results obtained in another study advised against the use of iodine-containing solutions in umbilical cord care of newborns (22). Several studies have shown that CH is more prevalent among Asians than among non-Asians. Rosenthal *et al.* performed a study on the prevalence of CH among different races, nationalities, and minority communities, particularly Muslims and Asians, in the United Kingdom (6). They found that the prevalence rate of CH among Asians was 1 in 918 live births; our results were closer to this value than they were to the prevalence of CH in non-Asians (1 in 3391 live births). They attributed this high prevalence of CH among Asians to increased rates of parental consanguinity (6). Our study showed a recall rate of 4.1% with a TSH cutoff level of more than 5mIU/L for heel-prick blood samples, whereas in the United States, the recall rate after primary TSH screening is approximately 0.05% (1). The recall rates obtained in other studies in Iran with a TSH cutoff level of more than 20mIU/L were one-third or one-fourth of that obtained in our study. For example, in the study conducted by Azizi and colleagues in Tehran and Damavand and using cord blood samples for screening of CH, a recall rate of 1.06% was obtained with a TSH cutoff level of more than 20mIU/L (15), whereas in Esfahan, the recall rate was approximately 2.2% after primary screening for serum TSH levels (23). These varying recall rates for different TSH cutoff levels may be because of several factors, such as the use of T4 or TSH level or both for screening, differences in sample-collection methods and analysis procedures in different laboratories, and differences in recall criteria, which are related to the cultural, regional, and social factors of a country (24-26). The recall rates in other countries, after primary TSH level assessment in neonates aged 3–5 days, may vary from 0.2% to 3.3%. The recall rates were 0.16% in the Philippines, 0.35% in Austria, 0.3% in Greece, 0.28–0.29% in Hungary, 2.3% in Turkey, and 3.3% in Estonia (27-31). In contrast, in some studies conducted in Italy, the recall rate measured on the basis of T4 levels was 2.5%, while that measured on the basis of both T4 and TSH levels was 0.11% (32). In our study, when the TSH cutoff for heel-prick blood samples was increased from more than 5mIU/L to 6mIU/L, the recall rate decreased from 4.1% to 2.7%, although we could not diagnose 2 cases (10%) of clinical CH. Therefore, the laboratory screening methods and TSH cutoff level need to be revised to ensure more specific and sensitive CH screening. We found no significant relationship between CH incidence and sex, weight, maturity of the neonates, or parental consanguinity. This is in line with the results obtained in another study, which also showed no significant relationship between parental consanguinity and CH (33). However, many other studies, such as the study conducted in Isfahan, have shown that parental consanguinity in cases of neonatal CH was 1.5 times than that among neonates without CH (12, 15, 16). Our study also indicated that despite the absence of significant differences in the number of newborns in different months in a year, the neonate recall rates during winter were approximately 3–4-fold higher than those during the summer or spring (*Figure 1*). A similar result was reported by Najafi *et al.* in their study conducted in Mashhad (34). They showed that the aggregated seasonal recall rate was statistically higher in the winter season (January, February, and March) than in other seasons. Aminzadeh *et al.* evaluated the effect of temperature on development of CH and showed a statistically significant difference in the seasonal distribution of the number of neonates with CH, with 32.4% of the cases reported during the warmer months and 67.6% reported during the colder months of the year ($P = 0.001$) (35). Therefore, temperature may be considered as a reverse risk factor for the high incidence of CH in Iran.

Recent studies have shown a high prevalence of CH and high patient recall rate after primary screening, which was in line with the results of previous studies in Iran. Although environmental and genetic variations in addition to the low cutoff TSH level may be responsible for the high recall rate, a nationwide study is necessary to clarify the reasons for the high incidence of CH. Future studies should also be able to clarify why small changes in TSH cutoff levels during screening lead to substantial changes in the number of neonates with undetected CH.

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