Original Paper

HORMONE RESEARCH

Horm Res 2004;62:79–83
DOI: 10.1159/000079392

Received: September 27, 2003
Accepted: April 20, 2004
Published online: June 24, 2004

Prevalence of Congenital Hypothyroidism in Isfahan, Iran: Results of a Survey on 20,000 Neonates

Mahin Hashemipour[a,b] Massoud Amini[a,b] Ramin Iranpour[b]
Gholam Hossein Sadri[c] Narges Javaheri[a] Sassan Haghighi[a]
Silva Hovsepian[a] Abbas Ali Javadi[d] Mahdi Nematbakhsh[e]
Goshtasb Sattari[a]

[a]Isfahan Endocrine & Metabolism Research Center, [b]Department of Pediatrics, School of Medicine, [c]Department of Social Medicine, School of Medicine, [d]Department of Infectious Diseases, School of Medicine, and [e]Department of Physiology, School of Medicine, Isfahan University of Medical Sciences & Health Services, Isfahan, Iran

Key Words
Congenital hypothyroidism · Thyroxine · Thyroid-stimulating hormone · Neonatal screening · Iran

Abstract
Aims: To evaluate the prevalence of congenital hypothyroidism (CH) in a screening program performed for the first time in Isfahan, Iran. ***Methods:*** From May 2002 to December 2002, T_4 and TSH serum concentrations of 20,000 3- to 7-day-old newborns, born in all 17 hospitals of the city, were measured by radioimmunoassay and immunoradiometric assay, respectively. The newborns with abnormal screening results (TSH >20 mIU/l, T_4 <6.5 μg/dl and based on the weight) were re-examined. ***Results:*** Of 531 recalled subjects (recall rate 2.6%), 54 were confirmed to be hypothyroid, showing a prevalence of 1:370 for CH. ***Conclusion:*** Considering the high frequency of CH, the necessity of implementing a routine screening program in the healthcare system of Isfahan Province is emphasized.

Introduction

Congenital hypothyroidism (CH) is one of the most common preventable causes of mental retardation throughout the world, which can appropriately be prevented by early diagnosis and treatment [1]. Hypothyroid newborns mostly have normal gross appearance. Their clinical signs, early in the neonatal period, are non-specific and as a result, the diagnosis made only on the basis of clinical findings will result in irreversible complications such as mental retardation and deafness [2–4].

Screening programs for CH were first established in North America in 1972. Such programs are now performed routinely in most developed countries, showing a prevalence of 1/3,000–1/4,000 for CH [5]. In Iran, screening programs for CH were first carried out in 1987 by Azizi et al. [6]. During the program of salt iodination in Iran, the same programs were performed in Fars Province (1990) by Amir Hakimi et al. [7], who reported the prevalence of CH to be 1/1,433. In 1997, screening for CH was performed in Tehran and the prevalence of the disorder was again reported to be 1/914 live births [8].

KARGER
Fax + 41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0301–0163/04/0622–0079$21.00/0

Accessible online at:
www.karger.com/hre

Mahin Hashemipour, MD, Isfahan Endocrine & Metabolism Research Center
Sedigheh Tahereh Medical Research Complex
Khorram Street, Isfahan 8187698191 (Iran)
Tel. +98 311 3359933, Fax +98 311 3373733
E-Mail emrc@mui.ac.ir and emrc@medscape.com

The aim of this article is to present our description of the results obtained from a 7-month screening program for CH, performed in 17 hospitals in the city of Isfahan, Iran.

Material and Methods

In accordance with the deans of all 17 hospitals in Isfahan and the heads of their neonatal sections, all 3- to 7-day-old neonates were referred to the Endocrine and Metabolism Research Center of Isfahan University of Medical Sciences. The project's coverage percent was achieved by calculating the ratio of referred neonates to total livebirths. Using a questionnaire, the neonates' sex, weight, height, head circumferences, maternal age, and parents' consanguinity were recorded. Venous blood samples were obtained on the day of referral (3rd–7th day of birth), by trained nurses, from the cubital vein, and serum T_4 and TSH were measured.

A pediatric endocrinologist and collaborating general practitioner evaluated the laboratory results and the questionnaire, and after physical examination, the neonates who need to be recalled were determined. Recall was implemented based on the level of T_4 and TSH. In the case of TSH >20 mIU/l or T_4 <6.5 μg/dl on the 3rd–7th days after birth, and TSH >10 mIU/l or T_4 <6.5 μg/dl after the 7th day of birth, the neonates were recalled. Immature neonates with low levels of T_4 for their weight or high TSH levels for their age were recalled.

Considering the first TSH values, the proper approach was selected. If the TSH level was between 20 and 39 mIU/l, T_4 and TSH measurements were repeated, but if the TSH level was >40 mIU/l, then treatment would be initiated as well as repeating laboratory examinations. If the results of the second set of tests were within normal limits, the neonate was considered as a case of transient TSH elevation, in which the treatment was halted and the subject was excluded from the study. Otherwise, the treatment was continued.

All recalled neonates were examined clinically by a pediatric endocrinologist. According to the results of the secondary measurements (on 7th–28th days of birth), neonates were considered as hypothyroid if T_4 was <6.5 μg/dl and TSH was >10 mIU/l [9–13]. In both premature and full-term neonates whose T_4 measurements were low according to their weight [14], complementary tests including T_3 resin uptake (T_3RU) and free T_4 index (FTI) were performed and treatment was started if the results were abnormal. In a few neonates whose TSH levels were slightly more than normal upper limits (5<TSH<10), thyrotropin-releasing hormone (TRH) test was also performed [15, 16].

Neonates with confirmed hypothyroidism underwent a treatment with a single dose of levothyroxine (10–15 μg/kg/day). Before treatment, it was recommended to perform thyroid scintigraphy in neonates with CH in order to identify the etiology of the hypothyroidism.

Laboratory Methods

TSH was measured with the aid of Iran Kavoshyar Co. Kits with a immunoradiometric assay method. T_4 and T_3RU tests were performed using a radioimmunoassay method. The sensitivity of the T_4 and TSH tests were 0.38 μg/dl and 0.05 mIU/l respectively, which were controlled with a Berthold LB 2111-12 gamma counter. Quality control of the tests was performed in two ways: (1) The first was by intrinsic quality control including four parts: (a) pre-analytical control; (b) analytical control; (c) post-analytical control, and (d) inter-laboratory comparison and utilization of definite controlled samples. All of the laboratory examinations were performed by an expert technician in the same laboratory using standard procedures. (2) The second way was by external quality assessment.

Statistical Analysis

Frequency, mean and standard deviation for demographic data, T_4 and TSH levels in neonates were estimated. Statistical analysis was performed by SPSS software (Version 10).

Table 1. Distribution of serum TSH level among the screened neonates (n = 19,992)

Distribution of TSH levels, mIU/l	n	%
0–4.9	17,187	85.97
5–9.9	2,309	11.55
10–19.9	421	2.1
20–29.9	51	0.26
30–39.9	5	0.025
40–49.9	2	0.01
50–99.9	10	0.05
≥100	7	0.035
Total	19,992	100

Results

Demographic Results. Among all newborns studied, 3.4% were premature. The nationality of 97.5% of all cases was Iranian, 2.4% were of Afghani nationality and 0.1% had other nationalities. The rate of parental consanguinity was 29.7%. The coverage percent of the screening program for CH (i.e. the ratio of the referred neonate to all newborns in all hospitals throughout the city) was 89.3%.

Screening Results. The distribution of serum TSH values among the screened neonates is shown in table 1. The mean TSH level in all measured samples was 3.02 ± 5.92 mIU/l. The distribution of T_4 levels in all screened neonates is presented in table 2. The mean T_4 level in the whole population was 10.9 ± 2.51 mg/dl.

Recalled Neonates. Overall, 531 neonates (2.65%) were recalled. After being tested for T_3RU and FT_4I, 421 (79.9%) were categorized as healthy neonates and 54 (10.2%) were diagnosed and treated as hypothyroid cases. The prevalence of CH among all subjects studied was 2.7/1,000 (1:370).

Table 2. Distribution of serum T_4 values in all screened neonates (n = 19,992)

Distribution of T_4 level, μg/dl	n	%
0–6.5	666	3.3
6.6–9.9	6,572	32.9
10–14.9	11,633	58.19
15–19.9	1,114	5.6
≥20	7	0.01
Total	19,992	100

Table 3. Distribution of TSH levels among hypothyroid neonates, on their first measurement

Distribution of TSH, mIU/l	n	%
0–9.9	6	11.1
10–19.9	13	24.1
20–49.9	16	29.6
50–99.9	9	16.7
≥100	10	18.5
Total	54	100

Hypothyroid Neonates. Among hypothyroid neonates, 32 (59.25%) were male and 22 (40.75%) were female leading to a male:female ratio of 1.45:1. There was no parental consanguinity among 33 (61.1%) hypothyroid neonates, whereas the parents of 16 (29.6%) had first-cousin consanguinity and in 4 (7.4%), second-degree consanguinity between parents had been recorded. One patient had secondary hypothyroidism. Tables 3 and 4 demonstrate the distribution of TSH and T_4 values among hypothyroid neonates respectively. Thyroid scintigraphy was performed in 22 (40.7%) hypothyroid neonates and according to the results, 12 (54.5%) had thyroid dygenesia and in 10 the thyroid scan was normal.

Table 4. Distribution of T_4 levels among hypothyroid neonates on their first measurement

Distribution of T_4, μg/dl	n	%
0–6.5	25	46.3
6.6–9.9	18	33.3
10–14.9	11	20.4
>15	0	0
Total	54	100

Discussion

In the present study, 20,000 neonates referred from all hospitals and delivery departments throughout Isfahan city were studied. The prevalence of CH was estimated to be 1:370. This prevalence was approximately 8.2- to 10.7-fold of that reported from developed countries. The prevalence of CH is different in different parts of the world. It has been reported to be 1:67 in Nigeria [17], 1:781 in Pakistan [18], 1:918 in some Asian families [19] and 1:10,000 in African Americans [20]. The results of one study which was performed in Tehran between 1997 and 2001 by Ordookhani et al. [8] showed that CH had a prevalence of 1:914, although it was reported to be 1:1,433 in the study of Amir Hakimi et al. [7] in Shiraz city in 1991.

The different prevalence rates of CH reported from different parts of the world are suggested to be due to several factors: (1) The use of T_4 or TSH levels as the only tool for screening [10]. (2) The established criteria for the diagnosis of CH being different among different studies [21]. (3) Iodine deficiency has been known to be one of the causes of neonatal hypothyroidism [21–23]; however, this problem has been solved in Iran [24] and one study in Isfahan has shown that urinary iodine excretion was in the optimal range in neonates and their mothers [25]. (4) Ethnic varieties: the prevalence of CH has been reported to be 1:2,943 in Turkey [26], 1:2,759 in Saudi Arabia [27], and 1:7,000 in Japan [28]. The prevalence among Arab neonates residing in Israel was reported to be 1:1,447, which is higher than among Jewish neonates in that country (1:2,070) [22, 29]. (5) Frequent application of iodinated antiseptics is one of the causes of transient neonatal hypothyroidism, especially in premature neonates [26, 30]. In the present study the heads of the neonatal departments were asked not to use povidone iodine if possible. Of course, it cannot be ascertained that this recommendation was accepted and implemented. (6) Environmental, genetic and familial factors are involved in increased prevalence rates in some populations [31–33].

The recall rate has been different among different populations, ranging from 0.16% in the Philippines [34], 2.3% in Turkey [35] to 3.3% in Estonia [36], where the screening programs were performed as usual between 3 and 5 days after birth. In the present study, the recall rate was 2.65% which was within the acceptable ranges. The difference between our rate and that of the Philippine study can be due to the sampling method and a different way of performing laboratory tests.

The female:male ratio in Saudi Arabia assessment was reported to be 1.8:1 [23], 4:1 in Estonia [36] and 3:2 in China [37]. In the present study, this ratio was 1:1.45. The difference may be due to the high prevalence of consanguineous marriages in our region, which may itself result in a higher proportion of CH cases caused by thyroid dysgenesis. According to the results of the study by Castanet et al. [32], a significantly higher proportion of boys was discovered in familial cases of CH caused by thyroid dysgenesis, perhaps due to possible involvement of sex-modified etiologic factors.

The prevalence of secondary hypothyroidism was 1/20,000 in our study, whereas the prevalence of secondary and tertiary hypothyroidism was 1/68,200 in one study performed in the USA [38]. The observed difference is probably due to our small sample size.

In some studies, the prevalence of CH in premature neonates has been twice as much as that in full-term ones [39]. In the present study, the frequency of prematurity was 3.3% for all neonates and 4 of all 54 hypothyroid patients were premature, showing that 0.6% of premature neonates had hypothyroidism. The observed difference can be due to our small sample size.

Maternal thyroid function affects fetal and neonatal thyroid functions [40]. Accordingly, the prevalence of thyroid dysfunction in neonates whose mothers had Grave's disease was more than others [41, 42] and reported to be 2–13% [43]. In our study, hypo- and hyperthyroidism were observed in 2 (3.7%) and 2 (3.7%) of the mothers of hypothyroid neonates, respectively.

In comparison to usual screening programs for CH, we used both T_4 and TSH measurements in our survey. Some countries use primary T_4 with backup TSH measurements. This approach will detect infants with primary hypothyroidism, as well as infants with thyroxine-binding globulin (TBG) deficiency or hypothalamic-pituitary hypothyroidism. Such programs also have the potential to identify infants with hyperthyroxinemia [44]. The major disadvantage of this approach is the higher recall rate and the resultant psychological harm and economic burden.

The majority of CH screening programs use primary TSH measurements, supplemented by T_4 determinations for infants with elevated TSH values. With this approach, it is probable to miss infants with TBG deficiency, hypothalamic-pituitary hypothyroidism and hypothyroxinemia with delayed TSH elevation [44], that are considered disorders with a relatively low frequency. Instead, the screening results obtained by TSH measurement can be used to monitor the iodine supply in the newborn population, especially in iodine-deficient countries [45]. In the present study, we applied combined primary T_4 and TSH measurements in order to obtain more precise results concerning the prevalence of CH in our region. The survey was a centralized program and we used trained nurses to draw blood samples. Of course, the future screening program in the region should favor more practical methods of screening for CH, including filter paper blood spot TSH measurement.

In conclusion, considering the high prevalence of CH in Isfahan, it is recommended to integrate proper screening programs for CH in the routine healthcare system of Isfahan Province. Further studies of longer duration are recommended to determine the distribution of CH subtypes and their relation with consanguinity.

Acknowledgements

This project was funded by the Research Bureau, Isfahan University of Medical Sciences & Health Services. The authors are grateful to the IRIB Center of Isfahan, Isfahan Province Post Company, Isfahan Notary Registration Organization and the Office for Public Relations of Isfahan University of Medical Sciences & Health Services for their close collaboration.

The excellent assistance of Mrs. Kiani, Mrs. Zahmatkesh, Mrs. Nekooei, Miss Aliabadi, Miss Baghoolizadeh, Mrs. Forooghifar, Mr. Abyar and laboratory technician Mr. Ali Parvaresh is gratefully acknowledged.

References

1 Cao XY, Jiang XM, Dou ZH, Rakeman MA, Zhang ML, O'Donnell F, et al: Timing of vulnerability of the brain to iodine deficiency in endemic cretinism. N Engl J Med 1994;331: 1739–1744.
2 Rovet J, Walker W, Bliss B, Buchanan L, Ehrlich R: Long-term sequel of hearing impairment in congenital hypothyroidism. J Pediatr 1996;128:776–783.
3 Bellman SC, Davies A, Fuggle PW, Grant DB, Smith I: Mild impairment of neuro-otological function in early treated congenital hypothyroidism. Arch Dis Child 1996;74:215–218.
4 Foley TP Jr, Klein AH, Agustin AV: Adaptation of TSH filter paper method for regionalized screening for congenital hypothyroidism. J Lab Clin Med 1977;90:11–17.
5 Klett M: Epidemiology of congenital hypothyroidism. Exp Clin Endocrinol Diabetes 1997; 105(suppl 4):19–23.
6 Azzizi F, Oladi B, Nafarabadi MT, Hajipoor R: Screening for congenital hypothyroidism in Tehran: Effect of iodine deficiency on transient elevation of neonatal TSH. J Shaheed Beheshti School Med 1994;18:34–38.
7 Karamizadeh Z, Amir Hakimi GH: Incidence of congenital hypothyroidism in Fars Province, Iran. Iran J Med Sci 1992;17:78–80.
8 Ordookhani A, Mirmiran P, Hedayati M, Hajipour R, Azizi F: Screening for congenital hypothyroidism in Tehran and Damavand: An interim report on descriptive and etiologic findings, 1998–2001. IJEM 2002;4:153–160.
9 Fisher DA: Disorders of the thyroid in the newborn and infant; in Sperling MA (ed): Pediatric Endocrinology, ed 1. Philadelphia, Saunders, 1996, pp 51–70.
10 Editorial: Screening for congenital hypothyroidism. Thyroid 2003;13:87–94.
11 Hung W: Thyroid disorders of infancy and childhood; in Becker KL (ed): Principles and Practice of Endocrinology and Metabolism, ed 3. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 463–471.
12 Klein RZ, Mitchell MH: Hypothyroidism in infants and children; in Braverman LE, Utiger RD (eds): The Thyroid, ed 8. Philadelphia, Lippincott Williams & Wilkins, 000, pp 973–988.
13 Fisher DA: Physiological variations in thyroid hormones: Physiological and pathophysiological considerations. Clin Chem 1996;42:135–139.
14 Frank JE, Faix JE, Hermos RJ, Mullaney DA, Mitchell MI, et al: Low birth weight infant: Effects on neonatal hypothyroidism screening. J Pediatr 1996;128:548–554.
15 Spencer CA, Schwarzbein D, Guttler RB, et al: Thyrotropin (TSH)-releasing hormone stimulation test responses employing third and fourth generation TSH assays. J Clin Endocrinal Metab 1993;76:494.
16 Spencer CA, Lopresti JS, Patel A, Guttler RB, Eigen A, Shen D, et al: Application of a new chemiluminometric thyrotropin assay to subnormal measurement. J Clin Endocrinol Metab 1990;70:435–460.
17 Ojule AC, Osotimehin BO: Maternal and neonatal thyroid status in Saki, Nigeria. Afr J Med Med Sci 1998;27:57–61.
18 Hall SK, Hutchesson AC, Kirk JM: Congenital hypothyroidism, seasonality and consanguinity in the West Midlands, England. Acta Paediatr 1999;88:212–215.
19 Rosenthal M, Addison GM, Price DA: Congenital hypothyroidism: Increased incidence in Asian families. Arch Dis Child 1988;63:790–793.
20 Roberts HE, Moore CA, Fernhoff PM, Brown AL, Khoury MJ: Population study of congenital hypothyroidism and associated birth defects, Atlanta, 1979–1992. Am J Med Genet 1997;71:29–32.
21 Olivieri A, Fazzini C, Grandolfo ME, Medda E, Stazi MA, D'Archivio M, et al: Congenital forms of hypothyroidism: study of risk factors and preventive interventions (in Italian). Ann Ist Super Sanita 1999;35:273–282.
22 Kaiserman I, Siebner R, Sack J: Regional and temporal fluctuations in the incidence of congenital hypothyroidism in Israel. J Endocrinol Invest 1995;18:595–601.
23 Sander J, Niehaus C: Congenital hypothyroidism: Results of screening 30,000 neonates in Lower Saxony (in German). MMW Munch Med Wochenschr 1980;122:309–312.
24 Azizi F, Sheikholeslam R, Hedayati M, Mirmiran P, Malekafzali H, Kimiagar M, et al: Sustainable control of iodine deficiency in Iran: Beneficial result of the implementation of the mandatory law on salt iodization. J Endocrinol Invest 2002;23:409–413.
25 Hashemipoor M, Amini M, Gheisari A, Slaarifei S, Iranpour R, Aminoroaya A: Comparison of urinary iodine excretion in neonates and their mothers in Isfahan, Iran. Endocr Pract 2002;8:347–350.
26 Toublanc JE: Comparison of epidemiological data on congenital hypothyroidism in Europe with those of other parts in world. Horm Res 1992;38:230–235.
27 Henry G, Sobki SH, Othman JM: Screening for congenital hypothyroidism. Saudi Med J 2002; 23:529–535.
28 Delange F: Neonatal hypothyroidism: Recent developments. Baillières Clin Endocrinol Metab 1988;2:637–652.
29 Sack J, Feldman I, Kaiserman I: Congenital hypothyroidism screening in the West Bank: A test case for screening in developing regions. Horm Res 1998;50:151–154.
30 Smerdely P, Lim A, Boyages SC, Waite K, Wu D, Roberts V, et al: Topical iodine-containing antiseptics and neonatal hypothyroidism in very-low-birthweight infants. Lancet 1989;ii: 661–664.
31 Leger J, Marinovic D, Garel C, Bonaiti-Pellie C, Polak M, Czernicho P: Thyroid developmental anomalies in first-degree relatives of children with congenital hypothyroidism. J Clin Endocrinol Metab 2002;87:575–580.
32 Castanet M, Polak M, Bonaiti-Pellie C, Lyonnet S, Czernichow P, Le J, on behalf of AFDPHE (l'Association française pour le dépistage et la prévention des handicaps de l'enfant). Nineteen years of national screening for congenital hypothyroidism: Familial cases with thyroid dysgenesis suggest the involvement of genetic factors. J Clin Endocrinol Metab 2001; 86:2009–2014.
33 Kaiserman I, Maytal A, Siebner R, Sack J: Effects of immigration on the incidence of congenital hypothyroidism. Eur J Endocrinol 1997;137:356–359.
34 Fagela-Domingo C, Padilla CD, Cutiongco EM: Screening for congenital hypothyroidism among Philippine newborn infants. Philippine Newborn Screening Study Group. Southeast Asian J Trop Med Public Health 1999;30(suppl 2):20–22.
35 Yordam N, Calikoglu AS, Hatun S, Kandemir N, Oguz H, Tezie T, et al: Screening for congenital hypothyroidism in Turkey. Eur J Pediatr 1995;154:614–616.
36 Mikelsaar RV, Zordania R, Viikmaa M, Kudrjavtseva G: Neonatal screening for congenital hypothyroidism in Estonia. J Med Screen 1998;5:20–21.
37 Zhang YQ, Cao QX: Experience in neonatal screening for congenital hypothyroidism. Chin Med J 1993;106:216–219.
38 Fisher DA, Dussault JH, Foley TP Jr, Klein AH, Lafranchi S, Larsen PR, et al: Screening for congenital hypothyroidism: Results of screening one million North American infants. J Pediatr 1979;94:700–705.
39 Waller DK, Anderson JL, Lorey F, Cunningham GC: Risk factors for congenital hypothyroidism: An investigation of infant's birth weight, ethnicity, and gender in California, 1990–1998. Teratology 2000;62:36–41.
40 Brown RS, Bellisario RL, Botero D, Fournier L, Abrams CA, Cowger ML, et al: Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over on million babies. J Clin Endocrinol Metab 1996;81:1147–1151.
41 Wada K, Kazukawa I, Someya T, Watanabe T, Minamitani K, Minagawa M: Maternal hypothyroidism in autoimmune thyroiditis and the prognosis of infants. Endocr J 2000;47(suppl): 133–135.
42 Matsuura N, Harada S, Ohyama Y, Shibayama K, Fukushi M, Ishikawa N, et al: The mechanisms of transient hypothyroxinemia in infants born to mothers with Graves' disease. Pediatr Res 1997;42:214–218.
43 Friedland DR, Rothschild MA: Rapid resolution of fetal goiter associated with maternal Grave's disease: A case report. Int J Pediatr Otorhinolaryngol 2000;54:59–62.
44 American Academy of Pediatrics: Newborn screening for congenital hypothyroidism: Recommended guidelines (RE9316). Pediatrics 1993;91:1203–1209.
45 Toublanc JE: Guidelines for neonatal screening programs for congenital hypothyroidism. Acta Paediatr 1999;88(suppl 432):13–14.