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Congenital hypothyroidism in the north of Iran

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ABSTRACT

Objective: We studied Congenital hypothyroidism detected by newborn screening programs in the north of Iran.

Methods: In this study, the records of all confirmed neonates with congenital hypothyroidism from April 2018 to March 2019, whose information is available in the registration system of the provincial health center; were reviewed.In addition, the family health records were reviewed for other required variables. In case of lack of information, the necessary information was collected by calling the child's family. Data were analyzed with SPSS ver 18. Mean and standard deviation was used for quantitative data and chi-square or Fisher test was used for qualitative data.

Results: In 2018, 26738children were born in the Guilan province, of which 65 infants were diagnosed with CH. Accordingly, 2.4 per 1000 live births had CH and this situation was 49/22864newborns born in 2019, i.e., 2.1:1000 live births. Preterm history and low birth weight neonates significantly were more prevalent in CH children in comparison to Healthy children (28.9% preterm vs 9.8%; 21.1% LBW vs 6.8%)

Conclusion: This study has shown a higher rate of CH in this area. Differences in the prevalence of CH can be due to maternal, neonatal, geographical, and genetic factors that further studies are recommended.

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INTRODUCTION

Congenital hypothyroidism [CH] affects one in every 2,000–4,000 live births all over the world and is one of the most common treatable causes of growth retardation and delayed cognitive development, resulting in mental deficiency. [1-3]There is evidence of an increase in CH incidence [1: 1400–1: 1700] over the past few decades, possibly related to birth demographic changes and methodological shifts in newborn screening (NBS) with the lowering of the screening TSH cutoff as well as prematurity due to improvements in neonatal medicine. [4, 5, 6, 7] Evidence suggests a female dominance for CH, with a female-to-male ratio of 2: 1 among thyroid dysgenesis, but a 1: 1 ratio has been suggested for patients with eutopic thyroid.[1, 2, 8] It has been described that large variability of the CH incidence in various areas (e.g., Asian populations vs USA populations) can be associated with the adoption of screening procedures for at-risk babies, demographic shift due to migration, and higher exposure to environmental risk factors, e.g., iodine deficiency. [1, 2, 9,10]

It is noteworthy that delayed diagnosis of CH can lead to severe complications, but detection by newborn screening followed by treatment leads to elimination of retardation from this disorder.[11, 12] Regarding the nature of the disease, newborn screening for CH seems to be one of the most important achievements in preventive medicine, as it has been targeted by the health systems of many countries.[11, 13,14]

Despite significant public health successes in newborn screening and CH management programs, there are still challenges such as transient CH and increased thyroid-stimulating hormone [TSH] about 2 weeks after birth, despite having normal NST.[14, 15, 16]Therefore, continuous and repeated monitoring of this system(e.g., the correctness of implementation and adequacy of coverage, etc.), as well as assessment of the incidence and frequency of risk factors for use in health care planning, should be considered to improve health services. Frequent thyroid screening is of great importance for newborns considered to be at high risk for thyroid dysfunction.

The congenital hypothyroid screening program has been implemented in Iran since 2005. According to previous studies, the incidence of this disease in the country has varied from 1:370 -1: 1000. [17, 18] National reports showed the prevalence of CH 1: 670 live Births. A study conducted in 2007 in Guilan showed the incidence of this disease (1: 714). [19] The high incidence of the disease in the country, especially in northern Iran, is multifactorial and needs further investigation. This study was conducted for this purpose.

MATERIAL AND METHODS

Guilan province is located in the north of Iran, the southern boundary of the Caspian Sea, according to the latest census has 16 cities with more than 2400,000 inhabitants.

In this cross-sectional study, the health records of all children who were born from April 2018 to April 2020 and had to confirm the diagnosis of neonatal hypothyroidism in the congenital hypothyroidism registry of Health vice-chancellorship of Guilan University of Medical Sciences were reviewed. This study was approved by the ethics committee of the university under code IR.GUMS.REC.1399.535.

Data were extracted and entered into the checklist. In addition, the family health records of these children were reviewed for family histories (history of thyroid diseases in mother or under treatment for them, family relation between parent) and other required variables such as birth weight, gestational age, history of blood transfusions, Neonatal jaundice, birth, delivery type, weight at birth to 1years of age as an indicator of physical growth. In case of lack of information, the necessary information was collected by calling the child's family. Informed consent was taken from the neonates' parents verbally.

Most of the medical records had been filled based on the Protocol of the Iranian Ministry of Health. The first heel prick test was performed in all infants born alive on their 3rd-5th days after birth. TSH levels were measured from samples collected on filter papers from the heel pricks. Infants with TSH levels ≥5-9.9 mill units per liter ([mU/L) were recalled for a second heel prick test on the 8th-14th days after birth. If the TSH levels were ≥5-19.9 mU/L, they were referred for venous blood sampling to measure the levels of TSH, Triiodothyronine resin uptake (T3RU), and T4/Free T4. Infants with TSH levels ≥20 mU/L, in addition to venous blood sampling, were immediately started on treatment with levothyroxine without waiting for the test results. The TSH cut-off concentration is 5 mU/L in Iran. Therefore, according to the Ministry of Health's guideline on screening in Iran, all infants with venous TSH values above this cutoff were diagnosed with primary hypothyroidism and treated with levothyroxine ([10-15 µg/kg/day) by the focal point physician. The aim was to provide a treatment based on the Iranian neonatal screening program and to normalize T4 and TSH levels within 2 weeks and one month, respectively. Accordingly, the infants were first followed-up two weeks after starting treatment, then every month during the first six months of life, then every two months during the second six months, and finally every three months from one to three years of age. After three years, the drug dosage was reduced by half or discontinued; TSH and T4 tests were performed after 4 weeks in order to differentiate transient and permanent hypothyroidism cases. According to the national protocol, subsequent hormone tests were repeated 2-3 months later and then annually. If the clinical examinations and the serum TSH and T4 levels of these children were normal after discontinuation of the drug, they were diagnosed with transient hypothyroidism and asked to visit the focal point physician at certain intervals for testing and examination of the thyroid status. Otherwise, they were diagnosed with permanent hypothyroidism and were required to undergo lifetime thyroid scanning hormone therapy. [20]

Data were analyzed using Statistical Package for the Social (Sciences SPSS software version 18). Mean and standard deviation were used for quantitative data. Chi-square or Fisher test were used for showing the association of congenital hypothyroidism with maternal and neonatal factors. A P value <0.05 was considered to be significant.

RESULTS

In 2018, 26738children were born in the Guilan province, of which 65 infants were diagnosed with CH. Accordingly, 2.4 per 1000 live births had CH and this situation was49/22864 newborns born in 2019, i.e., 2.1:1000 live births.

Most CH infants were male (58.8%). The mean gestational age of newborns with CH during these two years was 34.10 ±4.51weeks. More than twenty CH infants were preterm (<37 weeks) and 2.1% were post-term (>42 weeks). According to the birth weight of newborns, twenty -one percent of CH infants were low birth weight (less than 2,500 g) and 3.7% were born with a birth weight of more than 4000 g.

The main route of delivery of these infants was cesarean section (86/113). Twenty-five infants (23.1%) out of 108 CH newborns had a history of thyroid diseases in their mothers. Based on the growth and development records of CH infants, nineteen children had developmental problems. Thirty-seven percent of infants (34/90), had a history of jaundice at infancy, two infants underwent blood transfusion. The mean weight of these children at 6 and 12 months was 6956.54±1462.89 g and 8938.41±2996.61 g, respectively (Table1).

Table 1: Baseline Characteristics of Infants with Congenital Hypothyroidism

Variable		No(%)
Gender	Male	67(58.8)
	Female	47(41.2)
Gestational Age	Preterm(<37 weeks)	20(20.6)
	Term (37-42 weeks)	75(77.3)
	Postterm(>42 weeks)	2(2.1)
Birth Weight	Low birth weight(<2500 g)	23(21.1)
	Normal weight(2500-4000 g)	82(75.2)
	Macrosomia(>4000 g)	4(3.7)

Type of Delivery	Normal Vaginal Delivery(NVD)	27(23.9)
	Cesarean section	86(76.1)
Maternal History of Hypothyroidism	yes	25(23.1)
	No	83(76.9)

There were significant differences between gestational age and birth weight between CH infants with normal infants but differences according to gender and type of delivery were not significant. Preterm history and low birth weight neonates significantly were more prevalent in CH children in comparison to Healthy children (28.9% preterm vs 9.8%; 21.1% LBW vs 6.8%) (Table 2).

Table 2: Risk factors for CH among infants

Variable		CH infants No(%)	Healthy infants No (%)	P- value
Gender	Male	67(58.8)	25548(51.8)	0.15
	Female	47(41.2)	23925(48.2)	
Gestational Age(wks)	Preterm(<37 weeks)	20(28.9)	4824(9.8)	0.006
	Term (37-42 weeks)	75(69.1)	43547(88)	
	Postterm(>42 weeks)	2(2.1)	1102(2.2)	
Birth Weight(g)	Low birth weight(<2500 g)	23(21.1)	3379(6.8)	0.000
	Normal weight(2500-4000 g)	82(75.2)	45014(91)	
	Macrosomia(>4000 g)	4(3.7)	1080(2.2)	
Type of Delivery	Normal Vaginal Delivery(NVD)	27(23.9)	15239(30.8)	0.068
	Cesarean section	86(76.1)	34234(69.2)	

DISCUSSION

CH is considered to be the most commonly identified endocrine abnormality in newborns. CH affects one in every 2,000–4,000 live births all over the world [1, 2,3] but recent epidemiological studies have reported that the incidence of CH is increasing over the past few decades in different countries.[4, 5, 6, 7]

Multiple factors may be involved in the large variability of the CH incidence in various areas including the adoption of screening procedures for at-risk babies, demographic shift due to migration (i.e., ethnicity), and higher exposure to environmental risk factors, e.g., iodine deficiency, maternal, neonatal, and genetic factors. [1, 2, 9,10]

Previous studies have shown that the incidence of this disease has varied in different geographic regions in Iran from 1 in 370 to 1 in 1000 live births. The incidence of this disease has been reported from 1: 5,845 live births in Tehran [17], 1:754 live births in Babol [21], 1: 1,114 live births in Isfahan [18], 1: 1608 live births in Yazd[22], 1: 3,151 live births in Fars [23,] 1: 666 live births in East Azerbaijan[24] and 1:1250 infants in Hamedan[25.] The rate of false-negative results has decreased significantly in Iran because of lowering the cutoff point of the TSH level to 5 mU/L. It seems that the incidence of CH disease is lower in the southern provinces of the country with hot climates.[24]

In our study, the incidence of CH was as1: 417 newborns, which is higher than the other studies in Iran. In the present study, 41.2% of patients were girls and 58.8% were boys. There was not any significant difference between healthy newborns with CH infants according to gender but a male to female predominance for CH has been reported, with female-to-male ratios of 0.69: 1 and 0.8: 1 among newborns with CH in two studies conducted in 2013 in Yazd province and in 2018 in northern Iran .[22,24] In other similar studies, this ratio was reported to be 1:1.17 and 1:1.5 respectively. These differences indicate that the number of male births with CH has been increasing in some parts of the country in recent years [19,26] Therefore, further studies on genetic and environmental factors are required.

Our findings indicated that low birth weight infants are at higher risk of CH, this is inconsistent with previous studies.[27,28,29]

In the present study, nearly one-third of infants were born before 37 weeks gestational age, which significantly was higher than the normal population of infants. Many studies did not find any relation between gestational age and risk of Ch[19,26] but other researchers have been reported a high prevalence of CH in preterm infants.[30]

In Italy, 58% of preterm babies with permanent CH was found in the period 1987-1998 compared with period 1999-2008, where were lower screening of TSH cutoff and higher screening of survival rate in a growing number of preterm in increasing CH incidence.[31]

In the present study, 23.1% of the children had a positive maternal history of hypothyroidism. Dalili et al. conducted a study in 2014 on two control groups and infants with hypothyroidism, where a statistically significant difference was found in the family history of thyroid disease (34.3% in patients VS 13.2% in the control group).[19]

In the present study, 76.1% of neonates were born by the cesarean section, is like to Beheshti's study in 2018 in northern Iran, that cesarean section rate was observed in two-thirds of infants diagnosed with CH. [24] McElduff's study suggests a higher level of TSH in neonates born by cesarean section in comparison to vaginal delivery. [32] However, no significant correlation was observed between type of delivery and CH as reported by Ordookhani et al. It seems that cesarean delivery has been performed not only for CH cases but also for healthy infants. Of course, the high rate of cesarean section in our country compared to global reports is also effective in this regard.[24]

In the current study, out of 90 newborns diagnosed with CH, 34 had jaundice. In a study conducted by Karamizadeh et al. in

2012 in Fars province, prolonged jaundice (73%) was found to be the most common clinical manifestation among newborns with CH.[23]

In the present study, 19.6% of the children had growth and developmental disorders. Faizi's study showed that the infants initially had developmental delays and then will be improved with appropriate treatment and care [33], but Dalili reported the growth and developmental status of these children as normal children, indicating the importance of early diagnosis and treatment of these children. [19] Also, woo et al. in Korea, showed that mean weight, height, head circumference, and developmental score in the low-birth-weight group were similar to the control group and were within the normal range. [34]

This study, like other studies, had limitations such as missing data of some records and limitation of follow-up to less than 3 years. Therefore, it is not possible to completely obtain transient and permanent hypothyroidism. One previous study showed that 79.4% of patients with primary CH had transient conjenital hypothyroidism.[35]

CONCLUSION

Finally, this study showed an upward trend in the incidence of the CH in Guilan province, which may have been due to a change in the cutoff point of patient screening in recent years and increasing the diagnosis of previous false negatives or due to maternal, neonatal, geographical and genetic factors. It is recommended to study geographical factors such as iodine deficiency in different regions, especially in cities with a high incidence of the disease, as well as the amount of pesticides in the environment. Maternal factors such as hypothyroidism should also be considered.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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