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The Prevalence of Transient and Permanent Congenital Hypothyroidism in Infants of Kurdistan Province, Iran (2006-2014)

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Abstract

Background: Congenital hypothyroidism (CH) is the most common endocrine diseases and one of the major causes of preventable mental retardation. This study was conducted to investigate the prevalence of transient and permanent congenital hypothyroidism in Kurdistan province, Iran.

Materials and Methods: In this cross-sectional study, all registered congenital hypothyroidism neonate of health centers of cities covered by Kurdistan University of Medical Sciences during 2006 to 2014 entered to study. Demographic and laboratory information of CH neonates was collected and entered into the Stata-12 and was analyzed using student t-test and Chi-square statistic and P- value less than 0.05 was considered.

Results: Overall incidence rate during 2006 to 2014 for province was 1.8, 2.3, 3.2, 4.3, 3.3, 4.0, 3.6, 4.6 and 2.7, respectively per 1000 neonates in this period. The number of diagnosed patients was 855 cases including 519 (60.7%) boys and 336 (39.3%) girls who 516 (60.4%) cases were from urban areas. Of the total patients, 202 (22.6%) were permanent. There was no significant difference between gender, location, type of childbirth, and season of birth with transient and permanent types of disease ($P>0.05$); while, there was a significant statistical relationship between consanguineous marriages and congenital hypothyroidism ($P<0.05$).

Conclusion: The prevalence of congenital hypothyroidism in Kurdistan province is significantly higher than the global and country levels that emphasize the continuation and reinforcement of screening program of infants. Therefore, complementary studies are research priorities of the health system in Kurdistan province in order to clarify the environmental and genetic factors related.

Key Words: Congenital hypothyroidism, Hypothyroidism, Neonate, Iran.

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1- INTRODUCTION

Hypothyroidism is the result of decrease in thyroid hormone synthesis or deficiency in activity of thyroid hormone receptors. The most common cause of congenital hypothyroidism is disorder of complete or partial development of the thyroid gland or disorder of inappropriate replacement of thyroid during the fetal period (Entopic Gland) (1). CH is one of the major causes of preventable mental retardation in infants. Hypothalamic-pituitary-thyroid axis starts its activity in the middle of fetal life and evolves until birth of term infant. Existence of hypothyroidism in the fetus leads to some disorders in major organs including the central nervous system and the skeleton (2). Most infants seem quite normal at birth, but children with signs of precocious puberty and short stature and delayed bone age should be sought for hypothyroidism (3). Currently, almost all the industrialized countries of the world carry out the screening program for neonatal hypothyroidism systemically (4).

Developing countries also gradually carry out the screening program for neonatal hypothyroidism at different scales. Its implementation has also started in Iran since 1997 (5). Before beginning screening programs, early diagnosis of the disease is usually conducted with delay due to the low and non-specificity of signs and symptoms in the first days of life, and this issue is associated with the loss of Intelligence Quotient (IQ) to various degrees in patients (6). Congenital hypothyroidism disease can lead to the most important and major problems in patients including failure to weight gain, physical growth slowdown, delay in the overall growth of the body and growth failure of these children that is often remained unknown (7). Congenital hypothyroidism can be referred when Thyroid-Stimulating Hormone (TSH) is greater than 5mu/l of heel sample in infants 3-5 days on filter paper (*S&S 903* paper) and confirmation with venous blood samples TSH is greater than 10mu/l and thyroxine (T4) less than 6.5gr/dl (8). Congenital hypothyroidism is divided into two groups as permanent and transient. The transient type is automatically improving, while; the person has to take medicine for the rest of his life in the permanent type (9). Transient hypothyroidism is thyroid symptoms at the time of birth which are disappeared spontaneously and thoroughly within a few weeks or months (9). The most common cause of transient hypothyroidism has been reported iodine deficiency in the world. Other causes of excessive consumption of iodine are consumption of anti-thyroid medications or presence of antibodies against the thyroid during pregnancy (10).

In general, the incidence rate of disease in the world has been estimated 1 in every 3,000-4,000 live births. According to research conducted, prevalence spectrum of CH in the world varies from 7.14 per 1000 births in Nigeria (2) to 14 per 1000 births in Japan (9). Based on studies conducted in Iran, the incidence of this disorder has been reported about 1 in 400 to 1 in 900 live births which is much higher than the global average (10). Results of studies from other countries have shown that the prevalence of this disease is 1 in 650 in Turkey (12), 1 in 1000 in France (13), 1 in 800 in Greece (14), 1 in 2,372 in America (15), 1 in 2,640 in India (16), and in several studies this amount is about 1 in 400 to 1 in 900 live births (17). National studies had different results in this regard, so that prevalence of this disease was ranged from 1 in 1000 in Tehran, 1 in 370 in Isfahan (18), and 1 in 303 in Kashan (19), to 1 in 1433 live births in Shiraz (20). The incidence of this disease in Kurdistan province which is one of the western provinces of Iran and a mountainous area is higher and about 1 in 400 live births (10).

Given the relatively high prevalence of this disease in Kurdistan province and its importance in the creation of mental retardation in children, we decided to investigate the prevalence of congenital hypothyroidism in Kurdistan province during 2006 to 2014.

2- MATERIALS AND METHODS

2-1. Study Design and Population

This cross-sectional study was conducted on children with neonatal hypothyroidism. In this we used the data collected from the CH screening in Kurdistan Province, Iran, from August 2006 to August 2014. National screening program for early detection of CH was conducted by Iranian Ministry of Health and Medical Education (MOHME) in all provinces in 2005 and has been in progress up to now. Kurdistan is located in west of Iran, and according to National Census, in 2011 population of Kurdistan province was 1,493,645 out of which 66% lived in urban area. The capital of Kurdistan province is the city of Sanandaj and other counties are Marivan, Baneh, Saqqez, Qorveh, Bijar, Kamyaran, Dehgolan, Diwandarreh and Sarvabad.

2-2. Methods

According to the neonatal hypothyroidism screening program, a few drops of blood from the baby's heel is poured onto the filter paper by the Lancet on the third to fifth day of birth, and will be sent to the newborn screening laboratories in the provincial capitals by express post after being dried which usually takes 3 hours. After testing and determining the amount of TSH, if it is less than 5 mu/L, it will be known as a healthy infant otherwise as suspected cases. And if amount of TSH is 5-9.9, the second filter paper is taken and if it is more than 10, it will be referred to the focal point in order to conduct serum tests and approve or reject the disease. Start treatment is ideal about 2 weeks to 3 weeks after birth (21). Treatment of infected infants starts with a dose of 10 to 15 μg / mg levothyroxine medication. After 3 years of treatment, in order to determine whether permanent or transient disease, treatment is discontinued for 2-4 weeks and tests are repeated. If the transient disease is normal, treatment will be discontinued otherwise it is permanent and medication must be consumed until the end of life (22).

In this program, heel prick blood samples have been taken on Whatman filter papers for infants by trained staff, mostly within 3-5 days of birth. They dry and immediately transfer to the reference screening laboratory of the province by express mail service. Thyroid stimulating hormone (TSH) test using the enzyme linked immunosorbent assay (ELISA) method. In this study according National screening program TSH less than 4mu/l and 5mu/l were considered normal for 3-7 day-old and ≥ 8 day- old neonates, respectively. Then, the neonates with TSH more than normal were selected. In order to distinguish between permanent and transient cases of CH, levothyroxine (LT4) therapy was discontinued for 4 weeks in children who were ≥ 3 years old, after which time thyroid function tests (T4 and TSH) were evaluated by the same laboratory methods and the same enzymatic kits. If the thyroid function tests showed a high TSH with low T4, the patient was diagnosed to have permanent CH.

2-3. Measuring tools

We used registered data for each patient which exists in Kurdistan deputy of health. Information including gender (boy/girl), location (rural/urban), county, date of birth, parental consanguinity (present/absent), delivery type (Natural/cesarean section), birth weight, length of infant and TSH and T4 level at first measurement (mIU/L) were extracted from this checklist.

2-4. Eligibility criteria

Eligibility for including in this study were cases had CH diagnosed by a newborn screening program and confirmed by venous blood samples, and also if they had been treated with levothyroxine, and were followed up closely in the first three years of life.

2-5. Ethical considerations

Data were obtained with the consent of the Kurdistan Deputy Health. And data were in possession of researchers without a patient's name.

2-6. Data analyses

Incidence rates were calculated per 1,000 live births by county for each year from 2006 to 2014. The average annual rate of reduction (increase) (AARR [I]) was calculated using a regression analysis to quantify the rate of change of the incidence from 2006 to 2014. In this regression model, the incidence rate for each county was considered as dependent and the year as independent variable. Then, using the coefficient (B) obtained the AARR/I was calculated by the following formula: AARR= 1-exp (B).

By using GIS software, map location of CH cases in the province was drowning. Frequency, mean and standard deviation (SD) for demographic data according CH type (permanent/transient) in neonates were estimated. Qualitative variables were compared using the Chi-square test and quantitative variables were compared by t-test. In this study, P-values less than 0.05 were considered significant. Statistical analyses were performed using the Stata software, version 12.0 (Stata Corp, College Station, TX, USA).

3- RESULTS

According CH register data available in Kurdistan deputy of health, 855 CH patients were registered during 9 years period (March 2006 to March 2014).

Among 855 neonates with CH, 202 (22.6%) of them were permanent CH and 544 (63.6%) were transient CH, 519 (60.7%) were boy and 336 (39.3%) were girls (boy: girl ratio 1.54:1). 516 (60.4%) of them were lived in urban areas. Chi-square test showed no statistically significant relation between gender (P=0.1) and location (P=0.67) with CH type. Neonates with the consanguine parents had the significantly higher proportion of permanent CH (29.7%) compared parents without consanguinity (20.8%) (P=0.03).

608 (71.1%) of neonates were born natural and 247 (28.9%) were born with cesarean section; there was no significance relation between delivery type and CH type (P=0.3). 239 (28%) and 178 (20.8%) of children were born in spring and autumn, respectively. There was no significance relation between season of birth and CH type (P=0.24) (**Table.1**).

The trends of incidence rate (per 1000 live births) for CH cases are shown in **Table.2**. The overall incidence rate for province was 1.8, 2.3, 3.2, 4.3, 3.3, 4.0, 3.6, 4.6 and 2.7, respectively per 1000 neonates in this period. This rate was increasing (1.8 in 2006 to 2.7 in 2014; 6.7% increase per each year in this period). This trend only for Gorveh and Sarvabad were decreasing; but significance trend were shown only for Divandareh with the 26.9% increase per increase in these 9 years (P<0.05).

As shown in **Figure.1**, a geography disparity was observed across Kurdistan province because the spatial distribution of incidence rate of CH varies at county level. Generaly incidence rate of CH was higher in North counties. Higher incidence rate of CH were observed in Divandarreh County in Nnorth and lowest in Qorveh County in Southeast of Kurdistan province, respectively. The mean birth weight of permanent CH and transient CH neonates was 3160 ± 613.7 and 31540 ± 599.5 grams, respectively. The mean TSH levels

at first measurement in permanent were significantly higher than transient CH cases (14.1±17.6 vs. 11.3±16.2 mIU/L) (P=0.04). Also, mean T4 levels at first measurement in permanent CH cases were 8.8 ± 10.8 mIU/L and 11.4 ± 16 mIU/L in transient CH cases. As shown in **Table.3** and there was a significance differences between T4 levels at fist measurement permanent and transient CH patients (P=0.04).

Table-1: Demographic and geographic distribution of CH neonates according CH type

Variables		Total (%)	Permanent CH No (%)	Transient CH No (%)	P-value	Unknown No (%)
Gender	Boy	519(60.7)	133(25.6)	322(64)	0.1	64(12.3)
	Girl	336(39.3)	69(20.5)	222(62.1)		45(13.4)
Residency	Urban	516(60.4)	124(24)	324(62.8)	0.67	68(13.2)
	Rural	339(39.6)	79(23.1)	219(64.8)		41(12.1)
Parental consanguinity	Absent	700(81.9)	146(20.8)	460(65.7)	0.03	94(13.4)
	Present	155(18.3)	46(29.7)	94(60.7)		15(9.7)
Delivery Type	Normal vaginal delivery	608(71.1)	139(22.9)	395(65)	0. 3	74(12.2)
	Cesarean section	247(28.9)	63(25.5)	149(60.3)		35(14.2)
Season of birth	Spring	239(28.0)	47(19.7)	155(64.8)	0.24	37(15.5)
	Summer	203(23.8)	58(28.6)	123(60.1)		22(10.8)
	Autumn	178(20.8)	44(24.9)	112(63.3)		21(11.9)
	Winter	235(27.4)	52(22.2)	153(65.3)		30(12.4)

Table-2: Trend of incidence rate (per 1000 live births) for Congenital Hypothyroidism in Kurdistan province by county (2006-2014)

County		2006	2007	2008	2009	2010	2011	2012	2013	2014	AARR(I)	P-value
Baneh	Fre	6	5	8	5	7	10	10	12	7	+2.2	0.49
	IR	2.4	2.0	2.8	1.8	2.2	3.0	3.0	3.4	1.9		
Bijar	Fre	3	3	4	4	6	9	4	3	3	+2.3	0.7
	IR	2.0	1.5	2.7	2.6	4.2	6.2	2.7	1.9	1.9		
Dehgolan	Fre	2	2	2	1	2	2	3	2	3	+2.42	0.55
	IR	1.9	1.9	1.9	0.9	1.8	1.7	2.5	1.7	2.2		
Diwandarreh	Fre	4	5	5	13	7	18	28	23	3	+26.9	0.003
	IR	2.9	3.3	3.3	8.9	4.9	12.9	19.8	15.5	2.0		
Qorveh	Fre	2	3	2	2	3	2	1	3	2	-3.6	0.44
	IR	0.8	1.2	0.8	0.8	1.2	0.8	0.4	1.1	0.7		
Kamyaran	Fre	5	14	12	5	9	14	12	9	22	+9.25	0.16
	IR	2.7	7.8	6.2	2.6	4.7	7.5	6.3	4.9	11.0		
Marivan	Fre	7	3	8	14	3	19	15	9	17	+11.1	0.23
	IR	2.2	0.9	2.5	4.0	0.9	5.4	4.1	2.3	3.8		
Saqqez	Fre	6	14	19	33	17	13	14	31	11	+4.9	0.5
	IR	1.6	3.4	4.7	8.1	4.4	3.4	3.7	7.6	2.5		
Sanandaj	Fre	10	10	24	38	33	20	13	40	14	+3.1	0.68
	IR	1.5	1.4	3.4	5.0	4.4	2.6	1.6	4.9	1.6		

Sarvabad	Fre	3	2	2	3	2	1	1	2	2	-4.1	0.35
	IR	3.4	2.4	2.5	3.6	2.6	1.6	1.4	2.8	2.7		
Total	Fre	48	61	86	118	89	108	101	134	84	+6.7	0.1
	IR	1.8	2.3	3.2	4.3	3.3	4.0	3.6	4.6	2.7		

Fre: Frequency, IR: Incidence Rate per 1000 birth, AARR (I): average annual rate of reduction (increase). Positive sign for AARR (I) represent increasing trend and negative sign represent decreasing trend.

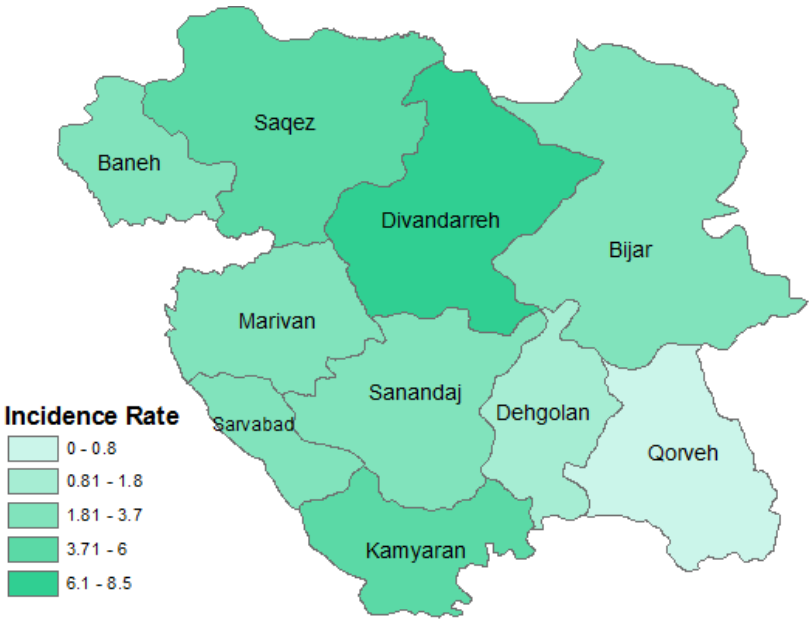

Fig.1: Spatial distribution for CH mean incidence rate according counties in Kurdistan province

Table-3: Biochemical and anthropometric measures of CH neonates according CH type

Variables	Permanent CH (mean± SD)	Transient CH (mean ± SD)	P-value
Birth Weight (gr)	3160.1±613.7	3154.0±599.5	0.9
Length at Birth (cm)	49.5±5.97	48.3±7.6	0.3
TSH level at first measurement (mIU/L)	14.13±17.6	11.3±16.2	0.04
T4 level at first measurement (mIU/L)	8.8±10.8	11.4±16.0	0.04
Age at start of treatment (day)	21.15±13.2	21.44±14.1	0.8

4- DISCUSSION

The results of this study showed that during the years 2006 to 2014, the number of 855 infants were diagnosed with CH, that 519 (60.7%) were boy and 516 patients (60.4%) were lived in urban areas. 202 (22.6%) of them were with permanent hypothyroidism and 519 (63.6%) were transient hypothyroidism. The number of cases with transient hypothyroidism has been more than permanent hypothyroidism cases during the years 2006 to 2014.

The mean age of start of treatment was 21.29 ± 0.328 days in our study that was 21.15 ± 0.027 days in permanent type and 21.44 ± 0.142 days in transient type, and no statistically significant difference was found between age of start of treatment and the type of hypothyroidism (transient and permanent) that was consistent with the study of Hashemipoor in Isfahan (23); while, the mean age of start of treatment was 38 days in the study of Kusdal in Turkey that they have not seen it appropriate and have mentioned delay in conducting and receiving test results as the reason (24).

In this study, the mean of weight and height of infants with congenital hypothyroidism were 3160 ± 0.326 grams and 49.5 ± 0.028 cm, respectively, and there was no statistically significant relationship between weight and height of infants with congenital hypothyroid whereas was not consistent with the study of Abedi et al. in Sanandaj in 2013 (25).

Investigation of annual incidence rate of congenital hypothyroidism showed that Divandareh city had the highest average of annual incidence (+26.9) and this trend has increased during the years 2006 to 2014 (P=0.003). Thus, the need for educational programs in the field of prevention of congenital hypothyroidism in this city should be prioritized.

It seems that initially, doctors of Divandarreh city were identified TSH above 5 (instead of TSH above 10) as patient and treated them which has been lead to the increase in the prevalence of this disease in this city that this criterion has changed in recent years and TSH above 10 has been defined as a patient. The results of study showed that congenital hypothyroidism was higher in boys than girls and a significant relationship between consanguineous marriage and incidence of congenital hypothyroidism disease was obtained.

In the study of Beheshti et al. in 2015 in Mazandaran, the number of cases of transient hypothyroidism was more than permanent type (38.1% vs. 56.7%), which was consistent with the results of our study (11). In the study of Dareh et al. (2013) in Markazi province- Iran, 122 patients were with permanent hypothyroidism (29.5%) and 113 patients were with transient hypothyroidism (27.3%) of the total patients (12). Disease incidence (transient and permanent) in the province Kurdistan is higher than the national average (1 in 300 vs. 1 in 414); of course, disease incidence in the country is also higher than many other countries which genetic and environmental factors can be it causes due to the high percentage of transient hypothyroidism and that iodine deficiency is the most common cause of incidence of the transient type (13).

The prevalence of hypothyroidism is variation in different regions in the world. The difference between contractual criteria which are considered in order to definitive diagnosis of congenital hypothyroidism, iodine deficiency in some areas of the world and racial differences can be mentioned as the causes of variety of the prevalence of hypothyroidism in different parts of the world (14); so that, it is 1 in 67 in Nigeria, and 1 in 781 live births in Pakistan. Several studies in Iran show that the prevalence amount of congenital hypothyroidism was reported 1 in 950 births in Tehran, in Isfahan 1 in 342 live births in 2002 and 1 in 333 live births in 2009, 1 in 1000 in Kerman, 1 in 446 in Qazvin, and 1 in 397 live births in Boroujerd (26). These statistics indicate that the prevalence of congenital hypothyroidism in Kurdistan province compared to the global average (1 in 3,500 to 4,500 live births) is much higher and almost in the average level of Statistics of Iran (1 in 400 to 1 in 900 live births) (9).

The results of our study showed that 519 (60.7%) infants with hypothyroidism were

boy and 336 (39.3%) are girl. In the majority of research conducted, the prevalence of the disease in females are more than males (21), but in the present study, sexual prevalence ratio of female was obtained less than male (1 to 1,41), although this difference was not statistically significant. In the study conducted in Isfahan, the prevalence in females was less than males (1 to 1, 45), which is consistent with the results of our study (27).

In the study of Zitalzadeh et al., the prevalence of congenital hypothyroidism in boys were more than girls, but this difference was not statistically significant (P=0.38) (21). Recent years studies in Iran show that hypothyroidism is slightly more in boys (11, 28).The results of this study showed that hypothyroidism is 516 (60.4%) in urban areas and 339 (39.6%) in rural areas that this difference was not statistically significant. In the study of Mohammadi et al. (2012) in Kerman, the prevalence of congenital hypothyroidism in the village was significantly higher than the city (20) that was not consistent with our study. In the present study, the ratio of consanguineous marriage to non-consanguineous marriage in parents of hypothyroidism infants was 20 to 80 percent. These ratios do not introduce the effect of consanguineous marriage, but this ratio was 70 to 30 percent in the study of Tehran and Damavand. In the study of Siami et al., the ratio of consanguineous marriage to non- consanguineous marriage in parents of hypothyroidism infants was 25 to 75 percent (29).

In the present study, the highest prevalence of congenital hypothyroidism was seen in spring and winter and the lowest in summer and autumn which this difference was not statistically significant (P=0.24). In the study which was conducted in Japan, most cases of congenital hypothyroidism were in spring and winter (30), which was consistent with the results of our study. In another study in Yazd, the highest prevalence of congenital hypothyroidism has been in spring and summer and the lowest in autumn and winter, respectively (25). The seasonal differences in the incidence of congenital hypothyroidism indicate that several factors such as genetic and environmental factors can play a role in creating it (31).

The results of our study showed that TSH range of infants was 11.3 mU/L in transient type and 14.13 mU/L in permanent type, and T4 level was 8.8 mu/L in permanent type and 11.4 mU/L in transient type, and there was a significant relationship between congenital hypothyroidism and level of TSH and T4 (P=0.04). In the study of Beheshti et al., the mean of TSH was 24.19 mU/L (21).

In the study of Siami et al., the mean and standard deviation of TSH and T4 in hypothyroidism infants were 36.05±33.35 and 8.82±9.55, respectively (29). In the present study, 71.7% of childbirth was natural and 28.9% were cesarean, and no significant relationship between the types of childbirth and catching the transient and permanent types of disease was obtained. In the study of Beheshti et al. unlike our study, the ratio of natural childbirth to cesarean was (35.8% vs. 64.2%) (11).

4-1. Limitations of the study

Failure to accurately document existing data in the health centers of cities of the province can be mentioned as the limitation of this study.

5- CONCLUSION

Given the high prevalence of congenital hypothyroidism in Kurdistan and the importance of this disease in creation of mental retardation, informing people and health care personnel in order to encourage parents to participate in the screening program of congenital hypothyroidism is essential to be able to take preventive interventions by a more detailed planning.

Given that the prevalence of this disease has been higher in Divandarreh city and generally has an increasing trend in Kurdistan province counties except Sarvabad and Qorveh during recent years, it emphasizes the need for further trainings and the implementation of measures planned for reducing the disease in the city. Higher incidence rate of CH were observed in Divandarreh county in North and lowest in Qorveh County in Southeast of Kurdistan province, respectively. Complementary studies can provide a clearer picture of the risk factors of this disease in infants of the province for the researchers.

6- CONFLICT OF INTEREST: None.

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