Int J Endocrinol Metab. 2016 October; 14(4):e38256. doi: 10.5812/ijem.38256.

Published online 2016 October 19. **Research Article**

Permanent and Transient Congenital Hypothyroidism in Hamadan West Province of Iran

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Received 2016 April 17; **Revised** 2016 September 25; **Accepted** 2016 October 09.

Abstract

Background: Primary congenital hypothyroidism (CH) is the most common treatable cause of mental retardation and can be classified into permanent and transient types. The purpose of this study was to determine the prevalence of permanent and transient congenital hypothyroidism (CH) in Hamadan, West province of Iran.

Methods: The study population included all cases with primary congenital hypothyroidism, which were confirmed by thyroid function tests (TSH levels $\geq$ 10 mIU/L). All these patients had been followed up at the outpatient pediatric endocrine clinic of Besat hospital (Hamadan, Iran) for a period of time between May 2006 and March 2013. Biochemical findings at diagnosis and detailed medical records were collected. Patients were considered as permanent hypothyroidism if their TSH level was 10 (mIU/l) during 6 - 12 months of treatment. Also three years old patients with TSH level > 10 mU/L during one or three months after discontinuation of levothyroxine treatment were considered as permanent hypothyroidism.

Results: A total of 164 children (49.9% male and 50.6% female) diagnosed with CH completed the study. Female/male ratio was 1.02/1. The incidence of CH was about 1/1250 in Hamadan, West province of Iran. Of the 164 patients, 105 cases (64 %) were diagnosed as permanent CH and other 59 cases (36%) were proven to have transient hypothyroidism. Female to male ratio was 1.14 in patients suffering from permanent CH and 0.8 in patients with transient CH. The initial TSH level was found to be significantly higher in cases with permanent CH compared to the patients with transient CH (P = 0.001). Mean TSH level during the first year of treatment was higher in permanent CH cases compared to transient cases (P = 0.001). Children with transient CH had a lower TSH serum level during the three years of treatment (P = 0.000). A significant statistical difference was not found between the genders and permanent or transient CH (P = 0.352). Co-occurring congenital anomalies and birth order were significantly different between two groups (P = 0.028 and P = 0.024, respectively).

Conclusions: Our regional follow-up data showed that about 40% of newborns with primary CH had transient thyroid dysfunction. Our results further clarify our previous research by providing evidences on the incidence rate of CH. The incidence rates of CH as well as transient type of CH in our region were higher than those reported by other studies which have been conducted in other regions of the world. The initial TSH level was the strongest predictor of treatment cessation. Given the high incidence of transient CH in our region, further studies are needed to confirm the etiology and to provide considerable insight into preventive and/or the treatment strategies.

Keywords: Congenital Hypothyroidism, Permanent Hypothyroidism, Transient Hypothyroidism

1. Background

Congenital hypothyroidism (CH) is defined as lack of thyroid hormones from birth. If it is not detected and treated early, congenital hypothyroidism can lead to irreversible intellectual disability and poor growth. Neonatal screening programs allow early detection and treatment of CH, thus preventing the mental retardation (1).

The incidence of CH detected by screening is about 1 in 4000 births in North America, Europe, and Australia (2, 3). CH has been classified into main categories; permanent and transient. Permanent CH refers to a persistent deficiency of thyroid hormone that requires life-long treatment. Transient CH refers to a temporary deficiency of thyroid hormone which is discovered at birth and can be treated in the first few months or years of life. In most cases, hypothyroidism is permanent due to thyroid maldevelopment (ectopic, hypoplasia and agenesis) or defects in hormone synthesis. Whereas, the transient type of the disease is less likely to be observed, attributed to the trans placental passage of maternal anti-thyroidal medication, Trans placental passage of a maternal thyrotropin receptor blocking antibody (TRB-Ab), gene mutation (heterozygote nonsense DUOX2 mutations), iodine deficiency or excess and immaturity of thyroidal iodine organification (4-6). The very low birth weight (< 1500 gm) and premature (< 37 weeks gestation) infants are especially at risk of hy-

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pothyroidism due to iodine deficiency (7, 8).

According to national data obtained from neonatal thyroid screening programs, the incidence rate of CH is higher (1/1400) in Iran compared to the worldwide neonatal screening (9-12).

2. Objectives

Considering this issue, one important challenge is to know the prevalence of transient cases to avoid long-term unnecessary therapy and financial burden of laboratory follow up posed on families and government.

3. Methods

This prospective study was designed to report the incidence of permanent and transient types of CH. The local ethics and research committee of Hamadan University of medical sciences approved the study (No. p/16/70/2/6855): Data associated with all infants who referred to pediatric endocrinology clinic of Besat hospital Hamadan, Iran and diagnosed with CH were followed up and evaluated in a period of time from May 2006 to March 2013 in a prospective study.

Newborn screening program for CH was established in our region (Hamadan, West province of Iran) in May 2005. Cases were eligible for participation in this study if they had CH diagnosed by a clinical or newborn screening program and confirmed by venous blood samples and also if they had been treated with levothyroxine (L-T4), and were followed up closely in the first three years of life. Serum Free T4 and TSH were assessed by electrochemiluminescence. In accordance with guidelines of American Academy of Pediatrics, T4 < 6.5 μg/dL and thyroid-stimulating hormone (TSH) > 10 mIU/mL after one month of age was considered as CH (13, 14). Variables including gender, place of residence (Urban orrural), age at the time of diagnosis, birth weight, gestational age (full term or premature), mean mother's age at delivery, co-occurring congenital anomalies, maternal history of thyroid disorder, parental consanguinity and birth order were recorded in the questionnaires.

It should be noted that those cases -lacking necessary data for the present study, and cases who were absent for close follow-up for the first three years of life were excluded from the study.

On the basis of observational studies and consensus, in the absence of a firm evidence of permanent congenital hypothyroidism (children with eutopic gland) replacement treatment should be discontinued in children being treated for congenital hypothyroidism at three years of age to determine whether their hypothyroidism was transient (7). For this purpose, in those cases that there was no enough evidences of permanent CH (TSH < 10 after 12 months of age) therapy was discontinued for 30 days after three years of age and Free T4 and TSH were measured. A diagnosis of transient hypothyroidism was defined if the results of TSH was in the reference range (< 10 mIU/L) after therapy withdrawal and during the subsequent follow-up (at least 12 weeks with no long-term requirement for T4 therapy) (13, 14). Permanent CH was defined by serum TSH above 10 mIU/L after 12 months of age (during treatment) or a requirement for levothyroxine beyond 3 years of age (13, 14). Cases with permanent CH were compared to those with transient CH in terms of their age at the time of diagnosis, sex, gestational age, birth weight, birth order, initial TSH serum level, co-occurring congenital anomalies, maternal history of thyroid disorder, and parental consanguinity. The maternal thyroid disease was based solely on the history.

3.1. Statistical Analysis

Statistical analysis was performed using SPSS ver.16.0. Data was summarized using means $\pm$ standard deviations (SD) for quantitative variables. The qualitative data were analyzed using chi square test and expressed as ratio and percentages. The normality of data associated with each variable for all groups of the study was assessed using the Kolmogorov-Smirnov test. The independent two-sample t-test was used to compare the quantitative variables between two groups. Statistical significance was defined as P values equal to or less than 0.05 for all clinical and laboratory data.

4. Results

Between May 2006 and March 2013, CH was diagnosed in 189 infants so that incidence rate was 1/1250. Twenty-five of these infants were absent for close follow-up and excluded from the study. A total 164 subjects with CH were enrolled in this study. Of these, 81 (49.4%) were male and 83 (50.6%) were female, so the female/male ratio was 1.02 /1. Demographic and baseline characteristics of participants are shown in Table 1 and 2. Permanent CH was found in 105 participants (64% of all participants) with a female/male ratio equal to 1.14 /1 and 59 patients (36% of all participants) were diagnosed with transient CH with a female/male ratio equal to 0.84. Out of the 105 cases with permanent CH, 17 cases (16.1%) had a normal TSH level one month after discontinuation of the treatment. Whereas, increased TSH Level above 10 mU/L which results in the need of reintroducing L-T4, was observed during follow-up after three months. The

mean screening TSH values was 52.09 ± 73.4 mIU/mL, median 41.5 (range: 5 - 333 mIU/mL).

Mean mother's age at delivery of patients was 25.56 years (range 17 - 42 years). The mean TSH serum levels at the time of diagnosis were significantly higher in infants with permanent CH compared to those with transient CH (P = 0.001). Mean TSH level during the first and third years of treatment was higher in permanent CH cases compared to transient cases (P = 0.001 and P < 0.001 respectively). TSH levels were significantly higher following treatment discontinuation in patients with persistent hypothyroidism (P < 0.001). Permanent CH was also more common among infants with co-occurring congenital anomalies and those who were not the first child of the family (P = 0.028 and P = 0.024, respectively). No significant differences were observed between groups in terms of their gender, place of residence, age at the time of initiation of the treatment, birth weight, gestational age, and parental consanguinity. Comparison of cases with permanent and transient hypothyroidism is presented in Table 3

Table 1. Baseline Characteristics of Infants With Congenital Hypothyroidism (Qualitative Variables)

Characteristic	States of the Variable	No. (%)
Gender	Female	83 (50.6)
	Male	81 (49.0)
Type of CH	Permanent	105 (64.0)
	Transient	59 (36.0)
Place of residence	Urban	134 (81.7)
	Rural	30 (18.3)
Gestational age	Term	152 (92.7)
	preterm	12 (7.3)
Parental consanguinity	Yes	41 (25.0)
	No	123 (75.0)
Maternal history of thyroid disease	Yes	11 (6.7)
	No	153 (93.3)
Birth order	First child	89 (54.3)
	Second child	75 (46.0)

Table 2. Baseline Characteristics of Infants With Congenital Hypothyroidism (Quantitative Variables)

Characteristic	Mean (Range)
Age at diagnosis, day	28.3 (5 - 90)
Mother's age at delivery, y	25.56 (17 - 42)
Birth weight, gram	3042 (950 - 5700)
Venous TSH level at diagnosis	32 (10 - 152)
TSH during the first year of treatment, mIU/L	4.8 (0.14 - 50.58)
TSH during the three years of treatment, mIUL	4.99 (0.18 - 41.96)
TSH 30 days after withdrawal of L-T4 therapy, mIU/Ll	8.03 (0.3 - 58.25)
TSH 90 days after withdrawal of L-T4 therapy, mIU/L	5.34 (1 - 21.8)

5. Discussion

The purpose of this study was to estimate the incidence of cases with transient and permanent CH in Hamadan, Iran. In our study, the incidence of CH is found to be 1/1250 of live birth. Of the 164 patients 105 cases (64 %) were proven to have permanent CH and 59 cases (36%) had transient hypothyroidism. The frequency of CH as well as transient hypothyroidism was relatively high in our study. Our data confirm the findings of previous studies regarding the high prevalence of hypothyroidism in Iran (15-18). For example, a meta-analysis study by Veisani et al. (18) revealed that the overall incidence of CH in Iran is 2/1000 of live births. Since the most common etiology of CH was dyshormonogenesis as indicated in the studies conducted by Hashemipour et al. (9) and Karamizadeh et al. (19) in Iran, a relatively high rate of parental consanguinity (25%) among infant with congenital hypothyroidism could account for the increased incidence of CH in our region. In support of the previous data, we also propose that the inclusion of infants of transient hypothyroidism increased the reported incidence rate of CH (8, 20). However, the effects of genetic background, autoimmune and environmental factors cannot be omitted.

In the present study, 36% of infants with CH had transient hypothyroidism. Similarly, in a study by Gaudino et al. (21) in France %38 of cases with CH were reported as transient CH. In another study which was conducted in the United States, transient CH was found in 28% of cases with CH (22). Our findings on the high frequency of transient hypothyroidism are also consistent with those of Hashemipour et al., Dorrea and Ordookhani et al. (16, 23, 24). Nevertheless, our findings are not in agreement with the results from other countries which have reported that 10 to 15% of children treated for CH ultimately have transient hypothyroidism (8, 20, 22). In alignment with previous studies carried out in Iran (17, 25-28), we assume that the high frequency of transient CH in Iran may be due to iodine deficiency or overload, although Iran is no longer recognized as an iodine deficient area.

It is noteworthy that 17 out of 105 infants (16.1%) had normal TSH one month after discontinuation of treatment but later developed hypothyroidism. It is reasonable to recommend a longer period follow up for patients who had

Table 3. Comparison of Clinical and Laboratory Characteristics of Permanent and Transient Congenital Hypothyroidism Groups (Qualitative Variables)

Variable	States of the Variable	CH Type		P Value
		Permanent (n = 105)	Transient (n = 59)	
Gender	Female	56	27	0.352
	Male	49	32	
Place of residence	Urban	87	47	0.611
	Rural	18	12	
Gestational age	Term	100	52	0.12
	preterm	5	7	
Parental consanguinity	yes	30	11	0.48
	no	75	48	
Maternal history of thyroid disease	Yes	4	7	0.058
	No	101	52	
Birth order	First child			
	Second child			

Table 4. Comparison of Clinical and Laboratory Characteristics of Permanent and Transient Congenital Hypothyroidism Groups (Quantitative Variables)[a]

Variable	Permanent (n = 105)	Transient (n = 59)	P Value
Age at diagnosis, day	34.70 ± 13.84	41.70 ± 26.27	0.09
Mother's age at delivery, y	25.89 ± 4.91	24.98 ± 3.69	0.221
Birth weight, gram	3112 ± 698	2917 ± 679	0.085
Venous TSH level at diagnosis	37.19 ± 30.40	22.93 ± 19.07	0.001
TSH during the first year of treatment, mIU/L	6.07 ± 8.10	2.50 ± 2.06	0.001
TSH during the three years of treatment, mIU/L	6.10 ± 6.18	2.92 ± 3.50	< 0.001
TSH 30 days after withdrawal of L-T4 therapy, mIUL	12.9 ± 12.8	3.6 ± 1.5	< 0.001
TSH 90 days after withdrawal of L-T4 therapy, mIU/L	10.1 ± 4.6	3.7 ± 1.3	< 0.001

[a]Values are presented as Mean ± SD.

normal results one month after treatment stopped in order to rule out probable permanent hypothyroidism.

The mean TSH serum levels at the time of diagnosis were significantly higher in infants with permanent CH compared to those with transient CH. Contrary to the results of Maruo et al. (5) in Brazil and in line with the results obtained by Dorreh et al. (23) in Iran and Bekhit et al. (8) in Egypt, we believe that the initial TSH level may determine whether hypothyroidism is transient or permanent. Mean TSH level during the first and three years of treatment was higher in permanent CH cases compared to transient cases. A higher TSH value during the first and three years of treatment was related to permanent CH, this finding is similar to that of a study by Hashemipour et al. (24) in Iran and by Nair et al. in India (29).

In accordance with the previous study by Unüvar et al. (30), as we expected TSH levels were significantly higher following one month after stopping treatment in patients with persistent hypothyroidism.

In the present study, significant statistical difference was not found in maternal history of thyroid disease and type of CH. However, given that the results of this study (P = 0.058) are very close to the significant P value, the risks of transient CH with maternal history of thyroid disease should be taken into account. The difference likely would have been meaningful with a larger sample size.

Interestingly, the gender ratio among infants with CH was not striking in our study, whereas females to males ratio reported in the literature in infants affected with CH is typically 2: 1 (16, 31-34). Considering the fact that the female to male ratio (2: 1) mentioned in the literature is relevant to the most common causes of CH (thyroid agenesis

or dysgenesis). A different result observed in the present study may be due to different causes of hypothyroidism in our region in comparison with other countries. Similarly, Hashemipour et al. (9) demonstrated that the most common etiology of CH in Isfahan, Iran, was dyshormonogenesis (different from US and Western countries) (24). We also assume that the inclusion of infants with transient hypothyroidism has changed the expected female/male ratio below the expected value (2: 1) which has also been reported by Parks et al. (20). They concluded that cases with transient hypothyroidism have a much lower female-to-male ratio.

Unlike the results of a study from Taiwan which disclose that the majority of infants with CH were from a first pregnancy (31), it is interesting to observe that birth order in the newborn with permanent CH differ significantly from those of transient CH. Furthermore, second and subsequent children of a family are more likely to have permanent CH than the first child. We have no explanation for this finding and more studies are required to confirm that.

Another feature associated with permanent CH was the co–occurring of congenital anomalies. It could be speculated that the absence or defect in certain genes encoding transcriptional factors and receptors will be associated with the development of permanent congenital hypothyroidism and additional congenital anomalies (35, 36).

Limitations: Thyroid scintigraphy can provide useful information about the etiology and prognosis of CH. However, this technique was not available to be used before treatment in our region. Also the causes of transient and permanent CH have not been determined. Therefore, further studies are needed to investigate the etiology of CH in our patients. Further work is also needed to obtain thyroid imaging for all infants with CH before LT4 replacement therapy in the neonatal period (20, 22). We hope to achieve it in the future studies.

In conclusion, the findings of this study indicate that the incidence rates of CH as well as the transient type of CH are higher than worldwide reports. Major risk factors for permanent CH were higher TSH levels at diagnosis, birth order and extra thyroidal congenital malformations. However, the evolution of CH remains difficult to predict. High incidence of CH in our study could be explained by inclusion of infants of transient hypothyroidism and iodine deficiency. Further researches are needed to confirm the etiology of transient and permanent CH in our region.

Acknowledgments

This paper was extracted from a PhD thesis. We would like to express our gratitude to Dr. Javad Fardmal for his invaluable assistance in the statistical analysis of this study. We would like to thank Mojgan Shahbazi at the Research Center of Hamadan Besat Hospital for her great efforts in conducting this study.

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