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title: Congenital Hypothyroidism (CH); thyroid function abnormalities among first-degree relatives of Iranian CH neonates

Short title: thyroid function test among first degree relatives of CH neonates

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Background:

Congenital hypothyroidism (CH) is a relatively common metabolic disease in neonates. Until recent years, the disorder was usually regarded as occurring in a sporadic manner. However, over the past few years, a considerable proportion of familial cases had identified, and possible roles of autoimmune factors have suggested, the aim of this study was to evaluate the abnormality of thyroid function tests in first-degree relatives of CH neonates and compared it to normal population.

Methods:

From 2002 until 2007 thyroid function tests (T4 and TSH) of randomly selected CH and normal neonates (194&350 respectively) and their first-degree relatives were measured. Most mothers of the CH neonates and control groups were also evaluated for TPO antibody.

Results:

Thyroid function test in first-degree relative of neonates with CH (361parents, 136 siblings) compared with control groups (665 parents, 478 siblings). Abnormal thyroid function tests were found in 85 patients in case group vs. 96 patient in control group, hypothyroidism was found in 75 (15.1%) and 57 (5%) person in case and control groups respectively($P<0.05$). The Positive TPO antibody was found in 22 (17.3%) mothers of CH neonates in comparison with 65 (32.5%) mothers of control groups ($P<0.05$), frequency of hyperthyroidism in parents had trend to be higher than cases ($P=0.05$)

Conclusion:

Our study suggested that familial and genetic component have a role in inheritance of CH, but maternal thyroid autoimmunity may not play an important role in the development of CH in our area.

Key words: Congenital Hypothyroidism, Thyroid Function Test, Thyroid Peroxidase Antibodies, Parents, Siblings

Introduction:

Permanent congenital hypothyroidism (CH) is relatively common metabolic disease accounts about 1 of 3000 to 1 of 4000 live births. Thyroid dysgenesia (TD) is the most frequent (85% of cases) cause of CH (1, 2). In many instances, the pathophysiology of TD remains yet doubtful and until recent years the disorder was usually regarded as sporadic (1-3). However, over the past few years, a small but considerable proportion of familial cases had identified and more recent works had revealed an even higher proportion of familial TD in both symptomatic and asymptomatic individuals (4). Thyroid dyshormonogenesis is a genetically heterogeneous group of inherited errors in the enzymatic cascade of thyroid hormone synthesis that account for 10–15% of congenital hypothyroidism (1-3).

This familial component proposed that, at least in a minority of cases, genetic factors might be concerned. Moreover, because in certain families the affected members of the same family have either athyreosis, ectopic or eutopic thyroid gland, it seems possible that a common fundamental mechanism exists for both etiological groups (1, 5). In addition, the higher prevalence of TD in girls and some ethnic groups, and a higher prevalence of extra thyroidal congenital anomalies among infants with CH in comparison to the general population, suggest the presence of genetic factors in the pathogenesis of CH (6-10).

Screening programs for CH, which have been widely put into practice in developed countries, give the ability to investigate the etiology and the pathogenesis of CH (11). Azizi et al. established CH screening in Iran-Tehran for the first time in 1997 and

thereafter in Fars province in 1990 by Karamizadeh et al., which reported a prevalence of 1:1433 for CH. Following elimination of iodine deficiency, CH screening was reestablished in Tehran (1998) and Isfahan (2002), using different screening methods. Preliminary findings showed a high prevalence of overall CH both in Tehran (1/914) and Isfahan (1/370) (12-14).

Evidence suggested a multifactorial origin of CH in which genetic, autoimmune and environmental factors play a role in the development of the disease. All mentioned factors may affect all family members (3).

Considering the high prevalence of CH in our region (13), additional studies in the field of related thyroidal and extra thyroidal congenital malformations among this group of patients and their families has important implications for understanding the etiology of CH specially the genetic basis of the disease. Some studies in Isfahan, which indicated high rate of congenital cardiac malformations in CH patients (15), high rate of thyroid gland abnormalities in first degree relatives of CH patients (16) and also the high prevalence of parental consanguinity among hypothyroid neonates (4), confirm the role of genetic factors for this high prevalence of disease. In another study Ordookhani et al. (17) also have reported the role of parental consanguinity in the etiology of CH in Tehran. However, it seems that more studies are needed in order to elucidate the genetic component of CH, such as thyroid function abnormalities among first-degree relatives of CH patients, as reported by other studies. Emanuela Medda et al. (3) have reported that permanent CH cases were more likely to have parents with hypothyroidism and/or goiter than controls.

Therefore, in line to our previous studies and as a complementary study which could help us to clarify the role of family history and genetics in the etiology of CH, the aim of this study was to evaluate the abnormality of thyroid function tests and autoimmunity in the first degree relatives of CH neonates and compared it to normal population.

Methods:

This was a cross sectional & case control study, from 2002 until 2007. During 3- to 7-of birthday - thyroid screening was performed in neonates that born in all 17 hospitals of Isfahan city, venous blood sample was taken from newborns with abnormal screening results for confirmed CH. The CH neonates were referred for treatment and follow-up to the Isfahan Endocrine & Metabolic Research Center (Isfahan, Iran) (14).

One hundred ninety four CH newborns were selected randomly, then from their first-degree relatives asked to participate in this study. The control groups were consisted of parents and siblings of 350 sex, age, and urban/rural status matched newborns without CH.

Neonates with multiple anomalies and other co morbid disease excluded from study.

The characteristics of studied population in two groups, is presented in Table1.

Serum T4 & TSH concentrations of all subjects were assessed (parents and siblings of all of neonates) and most of the mothers were evaluated for TPO antibody.

Serum T4& TSH concentrations measured with radioimmunoassay (RIA& IRMA respectively) by Iran Kavoshyar kits (Tehran, Iran), and anti TPO was measured by Rapid ELISA (Genesis Diagnosis Co,).

The characteristics of parents and siblings with hyperthyroid and hypothyroid in two studied groups are presented in Table 2.

The normal range of TSH and T4 was between 0.3-5 mIU/L and 4- 12ug/dL. Neonates were considered as hypothyroid if T4<6.5 (g/dL and TSH>10 mIU/L (18-

21) the patients also were considered as hyperthyroid if TSH<0.3 and T4>12. TPO antibody concentrations more than 75 IU/mL were considered positive. All participants of each group were divided into 3 groups; hypothyroidism, euthyroid and hyperthyroidism. Proportions of each group were compared between groups as noted below.

The Urinary Iodine Concentration (UIC) of 68 randomly selected CH newborns as well as UIC and milk iodine concentration (MIC) of their mothers was measured and compared to a control group (n=179).

Lower, mid and upper range of UIC for neonates and lactating mothers was considered to be <150, 150–230 and >230 µg/l and for MIC was considered to be <150, 150-180 and >180µg/l respectively.

The ethics' committee of Thyroid Research Center affiliated to Isfahan endocrine and metabolic research center approved the study. Written permission was taken from the parents for themselves and their children.

Statistical Analysis:

Data were presented as relative frequencies, Median and mean± SD. Chi-square, wilcoxon and pearson correlation tests were used for statistical analysis. P value less than 0.05 was considered statistically significant and All statistical analysis has been performed by SPSS software for windows.

Results:

The number of first-degree relative of CH neonates was 497 persons, 361 parents (170 fathers and 191 mothers) and 136 siblings (67 boys and 69 girls).

The control group was consisted of 350 newborn without CH with their parents (328 fathers and 337 mothers) and their sibling (229 boys, 249 girls).

85 relatives of CH neonates had abnormal thyroid function test (40 mothers and 13 fathers, 32 siblings), they belonged to 62 families (31.9%) of the 194 CH families investigated. This proportion of affected individuals in the families of CH neonates was significantly higher than that seen in the control population (Table 3).

Frequency of hyperthyroidism in parents had a trend to be higher than cases (P=0.05). However, this was not statistically significant in their sibs (Table 3).

A positive TPO antibody in mothers of CH neonates was significantly lower than the control group. Twenty two mothers of affected neonates (17.3% of 127 mothers) had positive anti TPO antibody that it was significantly lower than the control group in which 65 subjects (32.5% of 200 females) had positive anti TPO antibody (P=0.005). Among them eight (36.3%) person in case group vs. 24(34.7%) person in control group respectively had hypothyroidism, that this was not statistically significant (P value >0.05).

The median of UIC in 68 CH neonates and 179 healthy one was 300.50 and 290.50 µg/l, respectively (P>0.05).(table 4)

The median UIC of mothers of CH newborns and mothers of the control group was 150 and 130 µg/l, respectively (P>0.05).(tablae 4)

The median of MIC in case group was higher than control group (210 vs. 170 µg/l, $P<0.05$).(table 5)

According to the Pearson test; there was positive correlation between newborns UIC and MIC and there was not any correlation between newborns UIC and serum TSH. Maternal UIC did not correlate with maternal MIC, newborn UIC and serum TSH.

Discussion:

Our study indicates that thyroid function abnormality, especially hypothyroidism was significantly higher among first degree relatives of congenitally hypothyroid neonates than that seen in the control group. This result is consistent with Emanuela Medda et al. study, in which they have reported both permanent and transient CH cases were more likely to have parents with hypothyroidism and/or goiter than controls,

On the other hand, Dussault et al. (22) has reported that both hypothyroidism and hyperthyroidism was more frequent in mothers of CH patients than the control group but hypothyroidism was more predominant.

Another study reported that hypothyroidism was more prevalent in mothers of permanently CH patients than controls (23), whereas our study contains primarily diagnosed CH patients and their families, which include both transient and permanent ones.

The difference between mentioned studies with our study may be due to different ethnic, environmental, genetic factors or sample size (22, 23).

In our study, the frequency of hyperthyroidism in parents of the control group had a trend to be higher than cases that it was just in contrast of another study in which there were no differences between cases and controls(3).

This high frequency of hyperthyroidism may be due to iodine supplementation, a rise in the number of iodine-induced hyperthyroidism and autoimmune thyroid disorders after iodine supplementation had been reported before (24) even though azizi et al (25-27) showed decrease in TSH level after the salt iodization program in Tehran but no increase in thyroid abnormalities has been reported.

It should be considered that the data of iodine status of all samples was not available so the analysis of hyperthyroidism between two groups was not possible

The findings of our study indicated that the median of UIC in two groups and MIC was in acceptable range for an iodine sufficient area, which was reported earlier also (20). It shows that iodine insufficiency is not an acceptable reason for high frequency of CH in our region, in the other hand iodine excess can be considered as a contributor for the rising of CH in this region, because both the median of mothers MIC in case group and the proportion of mothers with iodine excess according to our classification was higher than control group.

In this study there was not any correlation between neonatal serums TSH concentration and neonatal or maternal UIC or MIC and in spite of that median of MIC was higher significantly in case group and there was positive correlation between MIC and neonatal UIC but the median of neonatal UIC was not different significantly in case and control group

Even as the vast majority of cases are considered sporadic, there have been recent advances in making clear some of the molecular mechanisms behind this common congenital metabolic disorder. Dyshormonogenetic cases are now well known to have an autosomal recessive genetic base (28- 31), and recent analyses reported 0that approximately 2% of cases with thyroid dysgenesis are familial (30). Regarding

these arguments, a possible genetic component is likely to be involved in inheritance of CH (30) Although in this study, we didn't distinguish between TD and dyshormonogenesis types of CH but this high frequency of thyroid function test abnormality had seen in these groups suggested a possible familial and genetic component in inheritance of CH.

Our results indicated that though great proportion of mothers of affected infants had a positive TPO antibody (17.3%) but it was significantly lower than the control group. From these findings, we could conclude that TPO antibody hasn't significant role in CH, but it seems that for more accurate conclusion in this field, more studies in the groups of permanent and transient CH neonates separately is needed and also it is required to consider other autoantibodies such as TgAb and TSH receptor-binding antibodies.

There are different reports in this field, some studies reported that maternal thyroid autoimmunity is not a frequent cause of permanent CH in contrast of transient CH (22, 31, 32), Quinn FA et.al (33) study showed abnormal TPO-Ab are common in pregnant women of the Samara region. However, some other studies showed that TPO antibody in pregnant mothers had no pathogenesis effect on fetal and neonatal hypothyroidism(28, 31-33) .In Ordookhani et al. (19) study conducted in Iran, have reported that positive anti-TPO antibody were not present neither in any six newborn with transient congenital hypothyroidsm nor in their mothers .

In two studies conducted in Tehran, the prevalence of the positive TPO antibody reported 4.0% and 12.5% in 1985 and 1999-2000 respectively (25-26) but this high frequency of thyroid autoantibody was not accompanied by increase in thyroid dysfunction. This great difference in the prevalence of TPOAb (from 4 to 32.5%) cannot simply be ignored because of differences in the measurement methods (25). As noted before UIC not only was in an acceptable range for iodine insufficient area but also there was no statistically significant difference between case and control groups in a part of our sample, neither in neonates nor in their mothers. And the MIC in case group not only was not lower than control group but also it was higher.

There are controversial findings regarding the effect of iodine excess on CH, some studies showed that it cause transient form of CH (34)but others suggest that hyperthyrotropinemia as a consequence of excessive iodine in some cases may not be transient(35)

In our study the studied neonates in case group consist of both persistent and transient CH patients and permanency of the disorder would be determine later. However transient CH patients also need treatment during the first years of life, so the important issue in this study is the effect of iodine status on the etiology of primarily diagnosed CH patient and further studies is need to investigate its role on the permanency of CH.

However our findings indicate that iodine excess could be a possible risk factor for CH, but according to the findings such as lack of correlation between maternal MIC and UIC, the median of neonatal UIC which was similar in two groups and etc. it seems that making conclusion in this field should be done with some caution.

It seems that other factors except iodine concentrations are responsible for high frequency of CH in our region, so familial; genetics and autoimmunity components should be considered as the major risk factors more.

It seems that salt iodization resulted in an increase in TPO antibody level in our population. However, the comparison of frequency of hypothyroidism was not statistically significant, it implies that this high frequency of thyroid autoantibody was not along with an increase in thyroid dysfunction in case or control group and maternal thyroid autoimmunity is not a frequent cause of CH in our area.

In Our study like other studies, prevalence of hypothyroidism is higher among mothers than fathers (2, 3) but the female/ male ratio in their affected offspring was just about 1. Mireille Castanet et.al (2) study has been reported that the ratio of females to males among hereditary cases of CH was approximately 1.0, they also compared familial and isolated cases of CH due to TD , and their results had shown a significantly lesser predominance of females in familial than isolated cases (2).

In sum, this study has shown that abnormal thyroid function tests are significantly more frequent in first-degree relatives of CH infants than normal population. Though we have, a few limitations because up to the present moment did not distinguish between TD and dyshormonogenesis types and the genetic cause of CH, but our study suggested a possible familial and genetic component in inheritance of CH. In addition regarding the evidence that iodine deficiency considered the most common cause of CH worldwide and this problem has been resolved in our region as reported by WHO too (31, 33), it seems that genetic factors are the most predominant cause of high rate of the disease in our region. However, role of auto immunity must be studied too. Considering these facts and the point that ethnic risk factors are important in development of this disease, future genetic studies on genome-wide linkage analyses in families with multiple probands or parental consanguinity and family history of thyroid disease in Iranian population may provide better evidence in reducing the number of affected infants.

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Table1. Characteristics of studied population in two groups

		CH neonates and their relatives			**Control group and their relatives**	
	neonates	Parents	siblings	neonates	Parents	siblings
Age	19.2m+/-6.1	30.2y+/-6.5	9.2y+/-1.0	18.9m+/-6.5	30.4y+/-6.3	9.5y+/-1.03
TSH (g/dL)	128.8+/-199.6	3.3+/-6.04	5.5+/-9.0	32.7+/-23.1	2.5+/-4.07	2.3+/-3.1
T4 (mIU/L)	6.7+/-7.17	8.6+/-12.4	8.28+/-2.5	7.2+/-7.6	8.5+/-1.58	7.02+/-2.26

m: month
y: years old

Table 2: The characteristics of parents and siblings with hyperthyroid and hypothyroid in two studied groups

	Relatives of CH patients				Relatives of control group			
	Hypo		Hyper			Hypo	Hyper	
	parents	siblings	parents	siblings	parents	siblings	parents	siblings
TSH (g/dL)	12.66+/-14.01	15.47+/-15.2	0.11+/-0.05	0.1	11.43+/-11.92	5.7+/-0.42	0.09+/-0.05	0.14+/-0.06-
T4 (mIU/L)	8.5+/-9.4	7.38+/-2.7	34.72+/-74.38	13.5	6.08+/-1.62	9.9+/-8.2	8.6+/-3.6	8.5+/-3.7

Table 3: The comparison of abnormal thyroid function test between first degree relatives of CH neonates & control groups

First degree relatives	Cases (n=497)	Controls(n=1142)	P value	OR
Hypothyroidism				
Parents	44/361(12.2%)	46/665(6.9%)	P=0.004	**OR=1.9**
Siblings	31/136(22.8%)	11/477(2.3%)	P<0.005	**OR=12.7**
Total	75/497(15.1%)	57/1142(5%)	P<0.005	**OR=3.38**
Hyperthyroidism				
Parents	9/361(2.5%)	33/665(5%)	NS*(P=0.05	
Siblings	1/136(0.02%)	6/478(1.25%)	NS*	
Total	10/487(2.05%)	39/1143(3.4%)	NS*	

*non -significant

Table 4. Proportions of different values of urinary iodine in case and control groups.

Urinary Iodine Concentration (µg/l)	Neonates in case group n (%)	Neonates in control group n (%)	Mothers in case group n (%)	Mothers in control group n (%)
<50	1(1.6%)	2(1.2%)	3(4.8%)	2(1.2%)
50-100	1(1.6%)	3(1.8%)	12(19.4%)	32(19.5%)
100-150	8(12.9%)	13(7.9%)	13(21%)[1]	60(36.6%)
150-230	13(21.0%)	41(25%)	23(37.1)	49(29.9%)
>=230	39(62.9%)	105(64%)	11(17.7%)	21(12.8%)
	62(100%)	164(100 %)	62(100%)	164(100%)

1; P=0.02

Table 5. Proportions of different values of breast Milk iodine in case and control groups.

Breast Milk iodine Concentration(µg/l)	**Mothers in case group n (%)**	**Mothers in control group n (%)**
<50	0(0%)	0(0%)
50-150	8(12.9%)[1]	45(27.4%)
150-180	10(16.1%)	41(25%)
>=180	44(71%)[2]	78(47.6%)
	62(100%)	164(100%)

1; P=0.02

2; P=0.001