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Original Article

# Thyroid function abnormalities among first-degree relatives of Iranian congenital hypothyroidism neonates

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**Abstract** ***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. Over the past few years, however, a considerable proportion of familial cases have been identified, and possible roles of autoimmune factors suggested. The aim of the present study was to evaluate abnormality of thyroid function tests in first-degree relatives of CH neonates and compared this to the normal population.

***Methods***: From 2002 until 2007 thyroid function tests (T4 and thyroid-stimulating hormone [TSH]) were done in randomly selected CH and normal neonates ($n$ = 194 and $n$ = 350, respectively) and their first-degree relatives. Most mothers of the CH neonates and control groups were also evaluated for thyroid peroxidase antibody (TPOAb).

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

***Conclusion***: Familial and genetic components play a role in inheritance of CH, but maternal thyroid autoimmunity may not play an important role in the development of CH in Iran.

**Key words** congenital hypothyroidism, parents, siblings, thyroid function test, thyroid peroxidase antibodies.

Permanent congenital hypothyroidism (CH) is a relatively common metabolic disease accounting for approximately 1 in 3000–1 in 4000 live births. Thyroid dysgenesis (TD) is the most frequent cause of CH (85% of cases).[1,2] In many instances, the pathophysiology of TD remains doubtful and until recently the disorder was usually regarded as sporadic.[1–3] During the past few years, however, a small but considerable proportion of familial cases have been identified and more recent work has identified 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]

It was 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 put into practice widely in developed countries, facilitate investigation of the etiology and the pathogenesis of CH.[14] Azizi *et al.* established CH screening in Iran-Tehran for the first time in 1997.[11] It was established thereafter in Fars province in 1990 by Karamizadeh *et al.*, who reported a prevalence of 1:1433 for CH.[12] Following elimination of iodine deficiency, CH screening was reestablished in Tehran (1998) and Isfahan (2002), using different screening methods. Preliminary findings indicated 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]

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**Table 1** Characteristics of studied subjects in case and control groups

| | CH neonates and their relatives | | | Control group and their relatives | | |
|---|---|---|---|---|---|---|
| | Neonates | Parents | Siblings | Neonates | Parents | Siblings |
| Age | 19.2 ± 6.1 months | 30.2 ± 6.5 years | 9.2 ± 1.0 years | 18.9 ± 6.5 months | 30.4 ± 6.3 years | 9.5 ± 1.03 years |
| TSH (mIU/L) | 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 (μg/dL) | 6.7 ± 7.17 | 8.6 ± 12.4 | 8.28 ± 2.5 | 7.2 ± 7.6 | 8.5 ± 1.58 | 7.02 ± 2.26 |

CH, congenital hypothyroidism; TSH, thyroid stimulating hormone.

Considering the high prevalence of CH in Iran,[13] additional studies in the field of related thyroidal and extra thyroidal congenital malformations among this group of patients and their families have important implications for understanding the etiology of CH, especially the genetic basis of the disease. Some studies in Isfahan, which indicated a high rate of congenital cardiac malformations in CH patients,[15] a 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.* also reported on the role of parental consanguinity in the etiology of CH in Tehran.[17] It seems, however, that more studies are needed in order to identify the genetic component of CH, such as by studying thyroid function abnormalities among first-degree relatives of CH patients, as reported in other studies. Medda *et al.* reported that permanent CH patients were more likely to have parents with hypothyroidism and/or goiter than controls.[3]

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

## Methods

This was a cross-sectional and case–control study, carried out from 2002 until 2007. During 3rd to 7th day of birth, thyroid screening was performed in neonates born in any of the 17 hospitals of Isfahan city, and 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 and Metabolic Research Center (Isfahan, Iran).[14]

One hundred and ninety-four CH newborns were selected randomly, and their first-degree relatives asked to participate in this study. The control groups consisted of parents and siblings of 350 sex-, age-, and urban/rural status-matched newborns without CH. Neonates with multiple anomalies and other comorbid disease were excluded from study. The subject characteristics are given in Table 1.

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

Serum T4 and TSH concentrations were measured on radioimmunoassay (RIA and IRMA, respectively) using Iran Kavoshyar kits (Tehran, Iran), and anti-TPO was measured on Rapid ELISA (Genesis Diagnostic Products Corp., Cambridgeshire, UK).

The characteristics of parents and siblings with hyperthyroidism and hypothyroidism in the two groups are presented in Table 2.

The normal range of TSH and T4 was 0.3–5 mIU/L and 4–12 μg/dL. Neonates were considered as having hypothyroidism for T4 < 6.5 μg/dL and TSH > 10 mIU/L.[18–21] The patients were also considered as having hyperthyroidism for TSH < 0.3 mIU/L and T4 > 12 μg/dL. TPO antibody concentrations >75 IU/mL were considered positive. All participants of each group were divided into three groups: hypothyroid, euthyroid and hyperthyroid, and the proportions compared.

The urinary iodine concentration (IC) of 68 randomly selected CH newborns, and the urinary IC and milk IC of their mothers was measured and compared to a control group ($n = 179$).

The lower, mid and upper range of urinary IC for neonates and lactating mothers was considered to be <150, 150–230 and >230 μg/L and for milk IC this was considered to be <150, 150–180 and >180 μg/L, respectively.

The Ethics Committee of Thyroid Research Center affiliated to Isfahan Endocrine and Metabolic Research Center approved the study. Written permission was obtained from the parents for themselves and their children.

**Table 2** Characteristics of parents and siblings of CH neonates and control group with hyperthyroidism and hypothyroidism

| | Relatives of CH patients | | | | Relatives of control group | | | |
|---|---|---|---|---|---|---|---|---|
| | Hypothyroid | | Hyperthyroid | | Hypothyroid | | Hyperthyroid | |
| | Parents | Siblings | Parents | Siblings | Parents | Siblings | Parents | Siblings |
| TSH (mIU/L) | 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 (μg/dL) | 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 |

CH, congenital hypothyroidism; TSH, thyroid stimulating hormone.

**Table 3** Prevalence of hypothyroidism and hyperthyroidism in parents and siblings of CH neonates and control group

| First-degree relatives | CH group ($n$ = 497) | Control group ($n$ = 1142) | $P$ | OR |
|---|---|---|---|---|
| Hypothyroidism | | | | |
| Parents | 44/361 (12.2) | 46/665 (6.9) | 0.004 | 1.9 |
| Siblings | 31/136 (22.8) | 11/477 (2.3) | <0.005 | 12.7 |
| Total | 75/497 (15.1) | 57/1142 (5) | <0.005 | 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 | |

CH, congenital hypothyroidism; OR, odds ratio.

### *Statistical analysis*

Data are presented as relative frequencies, median and mean ± SD. $\chi^2$, Wilcoxon and Pearson correlation tests were used for statistical analysis. $P < 0.05$ was considered statistically significant and all statistical analysis was been performed using SPSS for Windows (SPSS, Chicago, IL, USA).

## Results

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

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

A total of 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).

The frequency of hyperthyroidism in parents of control group had trend to be higher than parents of CH neonates ($P = 0.05$), but this was not statistically significant in their sibs (Table 3).

The number of mothers of CH neonates with positive TPO antibody was significantly lower than in the control group. Twenty-two mothers of affected neonates (17.3% of 127 mothers) had positive anti-TPO antibody, which was significantly lower than in the control group, in which 65 subjects (32.5% of 200 women) had positive anti-TPO antibody ($P = 0.005$). Among them eight mothers (36.3%) of CH neonates vs 24 mothers (34.7%) of control group, respectively, had hypothyroidism, but this was not statistically significant ($P > 0.05$).

The median urinary IC in 68 CH neonates and 179 healthy neonates was 300.50 μg/L and 290.50 μg/L, respectively ($P > 0.05$). The median urinary IC of mothers of CH newborns and mothers in the control group was 150 and 130 μg/L, respectively ($P > 0.05$). The proportions of lower, mid and upper range of urinary IC in neonates and lactating mothers of case and control groups was not different significantly ($P > 0.05$).

The median milk IC in mothers of CH neonates was higher than mothers of control group (210 μg/L vs 170 μg/L, $P < 0.05$). The proportions of lower range of milk IC was higher in mothers of control group than mothers of CH neonates (27.4% vs 12.9%, $P = 0.02$). The proportions of upper range of milk IC was higher in mothers of CH neonates than mothers of control group (71% vs 47.6%, $P = 0.001$).

According to the Pearson test, there was a positive correlation between newborn urinary IC and milk IC, and there was no correlation between newborn urinary IC and serum TSH. Maternal urinary IC did not correlate with maternal milk IC, newborn urinary IC or serum TSH.

## Discussion

The present study indicates that thyroid function abnormality, especially hypothyroidism, was significantly higher among first-degree relatives of CH neonates than in the control group. This result is consistent with the Medda *et al.* study, in which both permanent and transient CH patients were reported as being more likely to have parents with hypothyroidism and/or goiter than controls.[3]

In contrast, Dussault and Fisher reported that both hypothyroidism and hyperthyroidism were more frequent in mothers of CH patients than in the control group, but that hypothyroidism was more predominant.[22]

Another study reported that hypothyroidism was more prevalent in mothers of permanent CH patients than controls,[23] whereas the present study consisted primarily of diagnosed CH patients and their families, which includes both transient and permanent CH.

The difference between the aforementioned studies and the present one may be due to different ethnic, environmental, genetic factors or sample size.[22,23]

In the present study the frequency of hyperthyroidism in parents of the control group tended to be higher than in parents of CH neonates, in contrast to another study in which there were no differences between parents of CH neonates and those of control neonates.[3]

This high frequency of hyperthyroidism may be due to iodine supplementation. A rise in the number of cases of iodine-induced hyperthyroidism and autoimmune thyroid disorders after iodine supplementation has been previously reported,[24] even though Azizi *et al.* reported a decrease in TSH level after the salt iodization program in Tehran,[25–27] but no increase in thyroid abnormalities has been reported.

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

The present findings indicate that the median urinary IC and milk IC in the two groups was in an acceptable range for an-iodine sufficient area, which has been reported earlier.[20] It shows that iodine insufficiency is not an acceptable reason for the high frequency of CH in Iran; in contrast iodine excess can be considered as a contributor to the increase in CH in this region, because both the median maternal milk IC in the CH neonates group and the proportion of mothers with iodine excess according to our classification was higher than in the control group.

In the present study there was no correlation between neonatal serum TSH concentration and neonatal or maternal urinary IC or milk IC, and in spite of that the median milk IC was significantly higher in mothers of CH neonates, and there was a positive correlation between milk IC and neonatal urinary IC but the median of neonatal urinary IC did not differ significantly between the two groups.

Even though the vast majority of cases are considered sporadic, there have been recent advances in identification of some of the molecular mechanisms behind this common congenital metabolic disorder. Dyshormonogenesis is now well known to have an autosomal recessive genetic base,[28–31] and recent analyses reported that approximately 2% of cases of TD are familial.[30] Regarding these arguments, a possible genetic component is likely to be involved in inheritance of CH.[30] In the present study we did not distinguish between TD and dyshormonogenesis types of CH, but the high frequency of this thyroid function test abnormality seen in these groups suggested a possible familial and genetic component in inheritance of CH.

The present results indicated that although a great proportion of mothers of affected infants had a positive TPO antibody (17.3%), it was significantly lower than in the control group. From these findings we could conclude that TPO antibody does not play a significant role in CH, but it seems that for more accurate conclusions in this field, more studies in permanent and transient CH neonates separately are needed, and also other autoantibodies such as TgAb and TSH receptor-binding antibodies should be considered.

Reports differ in this field; some studies reported that maternal thyroid autoimmunity is not a frequent cause of permanent CH, in contrast to transient CH.[22,31,32] Quinn *et al.* found that abnormal TPO antibody is common in pregnant women of the Samara region.[33] Other studies, however, found that TPO antibody in pregnant mothers had no pathogenic effect on fetal and neonatal hypothyroidism.[28,31–33]In the Ordookhani *et al.* study conducted in Iran, positive anti-TPO antibody was not present in any of six newborn with transient CH nor in their mothers.[19]

In two studies conducted in Tehran, the prevalence of the positive TPO antibody was reported to be 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 TPO antibody (from 4% to 32.5%) cannot simply be ignored because of differences in the measurement methods.[25] As noted before, the median of urinary IC was in an acceptable range for an iodine sufficient area, but there was not statistically significant difference between the median of urinary IC of CH and control groups and their mothers. But the median of milk IC was higher in mothers of CH neonates than mothers of control group.

The effect of iodine excess on CH is controversial; some studies showed that it caused a transient form of CH,[34] but others suggested that hyperthyrotropinemia as a consequence of excessive iodine in some cases may not be transient[35]

In the present study the CH neonate group consisted of both persistent and transient CH patients, and the permanency of the disorder would be determined later. Transient CH patients, however, also need treatment during the first years of life, so the important issue in the present study was the effect of iodine status on the etiology of primarily diagnosed CH, and further studies are needed to investigate its role in the permanency of CH.

The present findings, however, indicate that iodine excess could be a possible risk factor for CH, but the lack of correlation between maternal milk IC and urinary IC, the similar median neonatal urinary IC in the two groups and so on, suggest that conclusions in this field should be reached with some caution.

It seems that other factors apart from iodine concentrations are responsible for the high frequency of CH in Iran, genetics and autoimmunity components should be considered as the major risk factors.

It seems that salt iodization resulted in an increase in TPO antibody level in the present subjects. The comparison of frequency of hypothyroidism, however, was not statistically significant; this implies that this high frequency of thyroid autoantibody was not associated with an increase in thyroid dysfunction in the CH or control group, and maternal thyroid autoimmunity is not a frequent cause of CH in Iran.

In the present study, as in other studies, the prevalence of hypothyroidism was higher among mothers than fathers,[2,3] but the female : male ratio in their affected offspring was approximately 1. Castanet *et al.* reported that the ratio of female to male hereditary CH patients was approximately 1.0; they also compared familial and isolated CH due to TD, and found a significantly lower predominance of female gender in familial than isolated CH.[2]

In conclusion, this study has shown that abnormal thyroid function tests are significantly more frequent in first-degree relatives of CH infants than in the normal population. Although the present study did not distinguish between TD and dyshormonogenesis types and the genetic cause of CH, it has suggested a possible familial and genetic component in the inheritance of CH. In addition, given iodine deficiency is considered the most common cause of CH worldwide and that this problem has been resolved in Iran as reported by the World Health Organization,[31,33] it seems that genetic factors are the most predominant cause of the high rate of the disease in this region. The role of autoimmunity, however, must be studied also. Considering these

facts and the point that ethnic risk factors are important in the development of this disease, genome-wide linkage analyses in families with multiple probands or parental consanguinity and family history of thyroid disease in the Iranian population may provide better evidence for reducing the number of affected infants.

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