

Original Article**Congenital cardiac malformations in congenital hypothyroid patients in Isfahan***Mohammad Reza Sabri\*, Hossein Shahriari\*\*, Mahin Hashemipour\*\*\****Abstract**

**BACKGROUND:** Congenital hypothyroidism (CH) often seems to be associated with other congenital abnormalities, mostly cardiac in nature. The aim of this study was to determine the prevalence of cardiac malformations in patients with CH diagnosed during CH screening program in Isfahan.

**METHODS:** In this cross-sectional study, cardiac malformations were determined in CH patients were compared to controls using echocardiography. The association between cardiac malformations and mean T4 and TSH concentrations, etiology of CH according to radiologic findings and permanent and transient CH were studied in CH patients.

**RESULTS:** Overall, 96 and 59 subjects were included in the case and control groups, respectively. Cardiac malformations were present in 30.2% (n = 29) and 15.2% (n = 9) of case and control groups, respectively; i.e. a higher prevalence in CH patients than in controls (P = 0.03). The prevalence of cardiac malformations without patent foramen oval was 6.25% (n = 6) in CH patients and 1.7% (n = 1) in control group (P = 0.1). There was no significant association between the presence of cardiac malformations and the aforementioned variables.

**CONCLUSIONS:** High prevalence of cardiac malformations in CH patients strongly suggests the potential involvement of genetic factors in the pathogenesis of CH. This emphasizes on the necessity of genetic studies involving CH patients.

**KEY WORDS:** Congenital hypothyroidism, cardiac malformations, genetics.

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Congenital hypothyroidism (CH) is a common endocrine disorder with a prevalence of 1:3000-4000 at birth. With delay in treatment, CH will result in severe neurodevelopment impairment. Consequently, most countries operate a neonatal screening program to enable early detection of cases and therapeutic interventions <sup>1</sup>.

CH screening was initiated in Iran-Tehran for the first time by Azizi et al in 1997 <sup>2</sup> and thereafter in Fars province in 1990 by Karamizadeh et al who reported a prevalence of 1:1433 for CH <sup>3</sup>. Following elimination of iodine deficiency, CH screening was re-established in Tehran (1998) and Isfahan

(2002), using different screening methods <sup>4,5</sup>. Preliminary findings showed a high prevalence of overall CH both in Tehran (1/914) and Isfahan (1/370) <sup>6,7</sup>. Recently, Ordoorkhani et al have reported a high prevalence of permanent and severe CH (1/1430) in Tehran <sup>6</sup>.

CH often seems to be associated with other congenital abnormalities. During the last decade, a high frequency of other congenital defects mostly cardiac in nature has been reported in infants with CH detected by neonatal screening programs <sup>7-11</sup>. The higher frequency of extrathyroidal congenital malformations in CH infants compared to the general population bears out the role of a genetic component

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in the etiology of CH<sup>12,13</sup>. Some studies have reported that mutations in thyroid developmental control genes are associated with some cardiac congenital malformations<sup>14-19</sup>.

Given the high prevalence of CH in our region and the fact that studying additional extrathyroidal congenital malformations in this group of patients has important implications for understanding the etiology of CH, the aim of this study was to determine the co-existence of cardiac anomalies in CH patients in Isfahan.

## Methods

This cross-sectional study was conducted in 2004-2005. Neonates diagnosed with CH through the screening program in Isfahan, were studied at Isfahan Endocrine & Metabolism Research Center, Isfahan University of Medical Sciences. Neonates with normal screening results were enrolled in the study as control group.

According to our screening protocol, neonates were referred for screening on their 3<sup>rd</sup>-7<sup>th</sup> days of birth. Serum T4 and TSH concentrations were measured through venous sampling (from the cubital vein by trained nurses). The required information including the neonates' sex, height, weight, birth date and maternal age of pregnancy, as well as their physical examination and laboratory data was gathered by the pediatric endocrinologist and a collaborating general practitioner. Then, based on TSH and T4, decision was made as which neonates must be recalled. Neonates who were referred on the 3<sup>rd</sup> to 7<sup>th</sup> days after birth were recalled in the case of having TSH>20 mIU/L or T4<6.5 µg/dl; neonates who were referred after the 7<sup>th</sup> day of birth were recalled in the case of having TSH>10 mIU/L or T4<6.5µg/dl. Among recalled neonates, secondary laboratory tests and treatment were performed simultaneously if TSH in the first measurement exceeded 40mIU/L. Only secondary laboratory tests were performed for cases with TSH concentration between 20 and 39 mIU/L in the first measurement.

Secondary laboratory exams, performed on the 7<sup>th</sup>-28<sup>th</sup> days of birth, included measure-

ments of both TSH and T4 levels. Neonates were considered as hypothyroid if they had a T4<6.5 ±g/dl and TSH>10 mIU/L. Hypothyroid neonates were treated with levothyroxine (10-15 ±g/kg/day) and were followed up according to the scheduled times of our protocol. In order to identify the etiology of CH, families were recommended to have thyroid scintigraphy performed for their neonates with CH, before starting the treatment. In order to determine the permanent and transient cases of CH, treatment was discontinued for 4-6 weeks in children aged three years and higher. After 4-6 weeks, thyroid function tests (T4 and TSH) were evaluated with the same laboratory methods and the same enzymatic kits. Thyroid scintigraphy and/or ultrasonography were performed for all patients. Patients with abnormal thyroid function test results (TSH≥6 mIU/L) were diagnosed as cases with permanent CH and those with normal test results were considered as transient cases<sup>20-24</sup>.

Subjects studied in both case and control groups were matched for covariates of sex and age. Neonates with low birth weight and those with Down syndrome were excluded from the study. Given that some congenital cardiac malformations resolve within the first 28 days of life<sup>25</sup>, we studied subjects aged more than 1 month.

After explaining the aim of the study and obtaining written consents of the neonates' parents, we referred them to the pediatric cardiologist. Echocardiography (Wing Med 750-1999) revealed different cardiac malformations in the studied population.

In CH patients, we studied the relation between cardiac malformations and different etiologies of CH according to the radiologic findings (agenesia, ectopia and normal), permanent and transient CH and mean screening T4 and TSH concentrations. Since patent foramen oval (PFO) could be considered as part of normal variation<sup>26</sup>, we classified the cardiac malformations into two groups; i.e. all malformations including PFO, and malformations other than PFO.

### Laboratory Methods

Using Iran-Kavoshyar Co. kits, TSH and T4 were measured by immunoradiometric assay (IRMA) and radioimmuno-assay (RIA) methods, respectively.

### Statistical Analysis

Data was analyzed using SPSS software version 13.0 (SPSS Inc., Chicago, IL, USA). Differences between mean values of quantitative variables were compared with *t* test. Differences in the proportion of CH infants with and without cardiac malformations were evaluated with Chi square ( $\chi^2$ ) test. The significance level was set at  $P < 0.05$ .

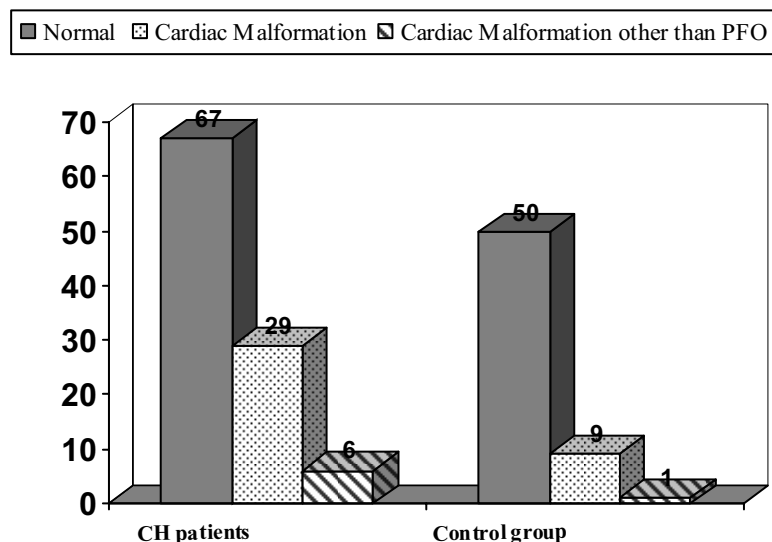
### Results

The study population comprised 96 CH patients and 59 controls who were matched according to age (mean age of  $17.1 \pm 4.7$  months in CH patients vs.  $17.7 \pm 5.6$  months in the control group,  $P > 0.05$ ) and sex (female/male = 45/51 in CH patients vs. 29/30 in the control group,  $P > 0.05$ ). The presence of different cardiac malformations in case and control groups is shown in figure 1. Overall cardiac malforma-

tions were present in 29 (30.2%) of CH patients and 9 (15.2%) of control group. In other words, cardiac malformations were significantly more prevalent among CH patients than in controls ( $P = 0.03$ , OR = 2.4). The prevalence of cardiac malformations without PFO was 6.25% ( $n = 6$ ) among CH patients and 1.7% ( $n = 1$ ) among control group ( $P > 0.05$ ). Different cardiac malformations observed in the case and control groups are presented in detail in table 1.

Overall cardiac malformations in CH patients were significantly more prevalent in boys than girls ( $P = 0.01$ , OR = 0.3). Cardiac malformations without PFO were similar in boys and girls. Mean screening T4 and TSH concentrations in CH patients with and without cardiac malformations (other than PFO) are presented in table 2.

The prevalence of cardiac malformations (other than PFO) was not significantly different between CH patients with agenesis, ectopia and hypoplasia. The presence of cardiac malformations (other than PFO) was not significantly different between permanent and transient cases of CH.



**Figure 1.** Prevalence of cardiac malformations in patients with congenital hypothyroidism (CH) and controls.

**Table 1.** Different cardiac malformations in patients with congenital hypothyroidism (CH) and controls according to echocardiographic findings.

Cardiac malformations	Control group	CH patients
Isolated Patent Foramen Ovale (PFO)	8	23
Atrial Septal Defect (ASD)	-	2
Pulmonary Stenosis	-	1
PFO + Patent Ductus Arteriosus (PDA)	-	2
PFO + Aneurysmal small VSD + minimal AI* + dilated LV* with borderline LV function	-	1
PFO + COA* + MR* + dilated left atrium + + dilated LV with decreased LV function	1	-
Total	9	29

\* AI: Aortic Insufficiency, LV: Left Ventricle, COA: Coarctation Of Aorta, MR: Mitral Regurgitation.

**Table 2.** Mean screening T4 and TSH concentrations in congenital hypothyroid (CH) patients with and without cardiac malformations.

	Mean concentration of T4 ( $\mu\text{g/dl}$ )	Mean concentration of TSH (mIU/L)
CH patients with cardiac malformation	$8.01 \pm 4.2$	$90.8 \pm 79.7^*$
CH patients without cardiac malformation	$6.7 \pm 3.3$	$71.6 \pm 66.1^*$

\* $P > 0.05$

## Discussion

We found a high prevalence of cardiac malformations in infants diagnosed with CH in a CH screening program in Isfahan; this finding is in line with the high prevalence of cardiac malformations previously reported in other studies 7-11. In our study, the prevalence of cardiac malformations other than PFO was 6.25% in CH patients. Cardiac anomalies other than PFO were present in 8.6% of CH patients in Saudi Arabia 11, 5.8% in France 27, 3% in Wales 28 and 5.5% in Italy 29. Our results were similar to those of the mentioned studies except for Wales, where different environmental or genetic factors may account for different findings. In our study the prevalence of cardiac malformations other than PFO was not higher significantly in CH patients than in control ones which could be due to small sample size.

It is reasonable to assume that teratogenic effects acting during organogenesis may affect simultaneously many organs, including the developing thyroid, causing a relatively high percentage of CH infants with congenital extrathyroidal anomalies, mostly of cardiac nature. Different environmental and genetic factors could influence these teratogenic effects which may explain different findings in various regions. Moreover, in our study population, the high prevalence of consanguinity and its effect on CH 30 could explain the higher rate of cardiac malformations which must be investigated in future studies.

Overall cardiac malformations were more frequently observed in males than in females. Cardiac malformations without PFO were similar in boys and girls. There are different reports in this area. Cardiac malformations were more prevalent in females as reported

by a study in Parma 31, whereas the opposite was true in Iceland 32.

In our study, there was no significant association between the presence of cardiac malformations and etiology of CH according to radiologic findings; neither was there a significant association between the permanent and transient cases of CH. A high frequency of co-existing congenital malformations has been reported in infants with transiently elevated TSH than in those with definitive CH 33. Our findings were in accordance with the study of Oliveri et al in Italy 29. In addition, they have reported lower mean T4 concentrations at screening in children with congenital malformations than in those with isolated CH. However, we did not find any relationship between mean T4 and TSH concentrations at screening and cardiac malformations.

According to a study in Brazil, extra thyroidal malformations-mostly cardiac- were observed only in patients with thyroid dysgenesis 34. Whereas Chao et al in Taiwan have reported that neither the type of CH (i.e. agenesis, ectopia or eutopic goiter), nor its severity was different among patients with or without concomitant anomalies 35.

However, for more accurate results especially in the field of the relationship between cardiac malformations and CH etiologies and the permanent and transient forms of CH, further studies with large sample sizes are recommended.

It is recommended that all neonates diagnosed with CH be examined during follow-up for the presence of heart murmurs. In the presence of these cardiac signs the neonates should be referred to a pediatric cardiologist for further investigations.

In conclusion, our findings suggest that many pathophysiological mechanisms may be involved in cardiac malformations in CH patients. Consequently, elucidation of the genetic-environmental networks and mechanisms responsible for CH may help understand the etiology of CH and its related congenital malformations.

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