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Original Article

Frequency of Congenital Cardiac Malformations in the Neonates with Congenital Hypothyroidism

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ABSTRACT

Background: Congenital hypothyroidism (CH) is a prevalent disorder, which is associated with several other congenital anomalies, especially cardiac diseases. The present study aimed to determine the prevalence of congenital heart disease (CHD) in the neonates with CH.

Methods: This cross-sectional study was conducted on two groups of 79 subjects to compare the type and frequency of congenital cardiac anomalies between the neonates with the confirmed diagnosis of CH (TSH≥10 mlU/ml) and healthy infants. The study was performed in Kowsar Clinic affiliated to Arak University of Medical Sciences, Iran. Level of thyroid-stimulating hormone (TSH) was measured within days 3-7 of birth using the samples collected from the soles of the neonates. In addition, all the subjects were evaluated for the presence of CHD using echocardiography before day 30 of life.

***Results*:** In total, 79 neonates were enrolled in the study. The case group consisted of 34 females (43.04%) and 45 males (53.96%), and the control group consisted of 43 females (54.43%) and 36 males (45.57%). The groups were matched in terms of age and gender. Cardiac involvement was only detected in the case group (CH infants) with the prevalence of 22.7%. Among the non-cyanotic malformations observed in the case group, one infant had ventricular septal defect (1.3%), eight infants had atrial septal defect (10.1%), three infants had patent ductus arteriosus (3.8%), three neonates had endocardial cushion defect (3.8%), two neonates had pulmonary stenosis (2.5%), and one infant had dilated cardiomyopathy (1.3%). Moreover, six neonates were diagnosed with Down syndrome. All the infants with endocardial cushion defect (n=3) had Down syndrome, and no significant association was observed between TSH and thyroxine (T4) in the presence of CHD.

Conclusion: According to the results, the high prevalence of cardiac malformations in the neonates with CH necessitated cardiac examinations using echocardiography.

Keywords: Congenital cardiac abnormalities, Congenital hypothyroidism, Frequency, Neonatal

Introduction

Congenital hypothyroidism (CH) is a prevalent disorder in neonates, affecting one per every 2,500-4,000 infants. CH is of great importance due to its known influence on the physical and mental development of newborns. Therefore, screening for the detection of the abnormalities involving the thyroid gland is widely performed around the world in order to diagnose and prevent the avoidable complications.

The prevalence of congenital heart disease (CHD) has been estimated at approximately 8-12% across the world. CHD is the most frequent malformation associated with CH, and it seems that cardiac disease examinations are critical in all the neonates diagnosed with CH. Studies have demonstrated a strong correlation between CH

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and concomitant congenital defects, especially cardiac diseases (1).

Cardiac and musculoskeletal anomalies are the most common malformations associated with CH (1). According to statistics, the prevalence of CH is higher in Markazi Province (Iran) compared to other countries (2). Furthermore, extrathyroidal congenital anomalies have been detected in the neonates with CH, the incidence of which varies depending on the geographical region and ethnicity.

High prevalence of CH in various geographical regions and involvement of the distant body organ in neonatal CH may raise the suspicion that other factors (e.g., genetics, ethnicity, and environment) may also play a key role in the occurrence of CH and its complications. Therefore, early detection of CHD through noninvasive methods, such as echocardiography, could effectively reduce the mortality and morbidity in these patients, particularly in association with other congenital anomalies.

The present study aimed to evaluate the frequency of congenital cardiac abnormalities associated with primary CH in neonates.

Methods

This cross-sectional study was conducted in Kowsar Clinic affiliated to Arak University of Medical Sciences in Arak, Iran during February 2015-March 2016. Sample population consisted of the neonates with hypothyroidism, who were examined for congenital cardiac malformations. The study protocol was approved by the Ethics Committee of Arak University of Medical Sciences (ID=93-173-4). The only inclusion criterion was the confirmed diagnosis of CH in term neonates based on neonatal screening programs. Infants were selected via convenience sampling from all the neonates with CH referring to the pediatric cardiology clinic for examinations within one year.

All the newborns received hypothyroidism screening by measuring the level of the thyroid-stimulating hormone (TSH) level using the samples collected from their sole within days 3-7 of birth. In the case the TSH level was higher than the recommended value (>10 mlU/L), a confirmatory TSH level by venous samples was requested. Diagnosis was confirmed if the primary and secondary TSH levels were higher than 10 mlU/L. Moreover, the levels of TSH and thyroxine (T4) were measured using the immunoradiometric assay (IRMA) kit and radioimmunoassay (RIA), respectively. For further evaluation, venous blood samples were stored in the laboratory of the clinic for two months to determine the total T4 and TSH. In all the neonates with confirmed CH diagnosis, medical therapy was initiated with appropriate doses of levothyroxine.

In the present study, the hypothyroid patients were classified as the case group, and a similar age group with normal thyroid function test results was assessed as the control group. Parents of the neonates were justified about the objectives and methodology of the research, and written informed consent was obtained. In order to reduce the alteration effects, all the preterm infants (born before 37 weeks of gestation) were excluded from the study. In addition, all the infants who had been conceived through *in-vitro* fertilization were eliminated from further evaluation.

Data on the TSH level, gender, maternal age, mode of delivery (natural vaginal versus cesarean section), place of residence (urban or rural areas), history of previous abortions, and parental consanguinity were collected and recorded in checklists. Afterwards, the subjects were examined thoroughly by a pediatric cardiologist via screening so as to determine the presence or absence of cardiac abnormalities. Finally, echocardiography was performed using a 2-4 MHz pediatric probe (MEDISON-EKO7) in order to detect the presence of congenital cardiac malformations.

All the study procedures, including the detection of hypothyroidism and diagnosis of CHD, were performed during the neonatal period (before day 30 of birth). Additionally, the neonates were studied repeatedly in the case of cyanotic or non-cyanotic cardiac impairment.

Statistical analysis

All the studied variables were expressed as mean ± standard deviation. Data analysis was performed in SPSS version 20 (SPSS, Inc., Chicago, IL, USA) using independent samples and student's t-test. In all the statistical analyses, P-value of less than 0.05 was considered significant.

Results

The presentstudy was conducted during July 2015-2016 on 158 neonates, who were divided into two groups of case and control. The case group consisted of 79 infants with documented hypothyroidism, and the control group included 79 infants. The study groups were matched in

terms of age and gender (77 females versus 81 males). With regard to the distribution of the genders, the case group consisted of 34 females (43.04%) and 45 males (53.96%), and the control group consisted of 43 females (54.43%) and 36 males (45.57%). Furthermore, the sample population was evaluated in terms of age, mean birth weight, and maternal age at childbirth in both groups, as well as the TSH level (mean: 79.44±30.52) and T4 level (mean: 7.39±3.37) in the case group.

According to the findings, weight of the neonates with CH was higher compared to the controls. the study groups were also analyzed in terms of the history of previous abortions (P=0.003), history of cardiac impairment in parents (P=0.001), and parental consanguinity (P=0.51). History of abortions and family history of cardiac diseases were statistically significant between the groups (Table 1). The frequency of congenital cardiac malformations among the neonates is presented in Figure 1 and Table 2.

In total, 18 neonates had cardiac involvement, in which atrial septal defect (ASD) was the most commonly detected malformation. Congenital cardiac malformation was significantly more prevalent in the case group compared to the control group as no congenital cardiac malformations were observed in the control group. Moreover, the subjects were assessed in terms of the classification of cardiac diseases (cyanotic and non-cyanotic). According to the results, there were no cases of cyanotic cardiac

Table 1. Demographic Characteristics of Case and Control Groups

Variables		Mean±SD	P-value
Age(day)	Case	16.37±11.69	0.167
	Control	17.25±10.94	
Weight (g)	Case	3338.40±299.72	0.01
	Control	3269.87±229.91	
Height (cm)	Case	48.25±2.12	0.704
	Control	50.90±3.31	
Maternal Age (year)	Case	27.61±2.98	0.745
	Control	27.48±2.46	

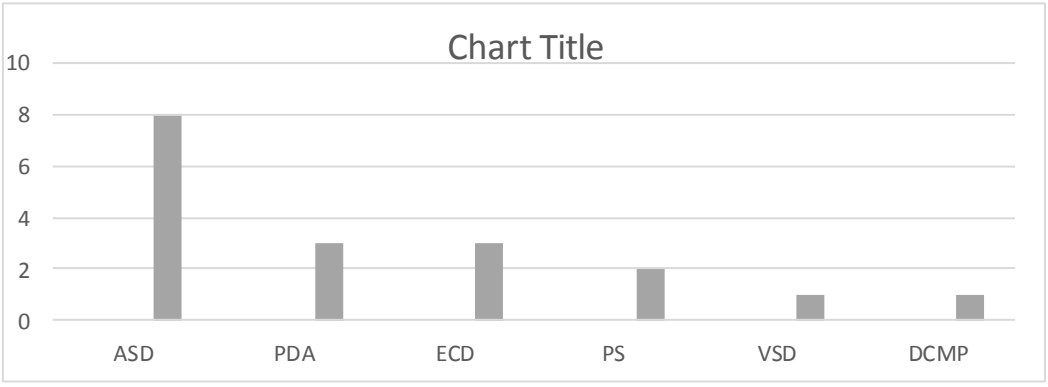

Figure 1. Type and Prevalence of Cardiac Malformations Diagnosed in Study Groups
ASD: atrial septal defect; PDA: patent ductus arteriosus; ECD: endocardial cushion defect; PS: pulmonary stenosis; DCMP: dilated cardiomyopathy

Table 2. Frequency of Congenital Cardiac Abnormalities in Case and Control Groups

Cardiac Abnormality	Patients with CH N (%)	Patients without CH N (%)
VSD	1 (5.55)	0 (0)
ASD	8 (16.66)	0 (0)
PDA	3 (16.66)	0 (0)
Endocardial Cushion Defect	3 (16.66)	0 (0)
PS	2 (11.11)	0 (0)
DCMP	1 (5.55)	0 (0)

VSD: ventricular septal defect; ASD: atrial septal defect; PDA: patent ductus arteriosus; PS: pulmonary stenosis; DCMP: dilated cardiomyopathy

Table 3. Comparison of Mean TSH and T4 Levels between Infants with and without Congenital Cardiac Abnormalities

Laboratory Results	CH with Cardiac Involvement (n=18) Mean ± SD	CH without Cardiac Involvement (n=61) Mean ± SD	P-value
TSH (mlU/L)	68.71±32.94	82.61±28.27	0.11
T4 (µg/dL)	5.67±2.49	7.90±4.49	0.06

TSH: thyroid-stimulating hormone

diseases, and all the cases in this regard were non-cyanotic as detected in the case group. Mean levels of TSH and T4 were also compared between the infants with and without congenital cardiac malformations (Table 3).

Discussion

According to the results of the present study, the prevalence of congenital cardiac anomalies was significantly higher in the neonates with CH(22.7%) compared to those without CH. In a study conducted in Brazil, among 76 patients diagnosed with CH, eight cases had severe cardiac involvement (3). In a retrospective study performed in Italy, congenital cardiac malformations were reported to be the most common co-existing anomaly in the patients with CH (5.5%) (4).

In Isfahan central province (Iran), Sabri et al. carried out a prospective study and estimated the prevalence of congenital cardiac diseases at 6.25% (5), while this rate was reported to be 4.9% in another research by Razavi in Hamadan western province (Iran) (6). In this regard, the findings of other studies across the world (whether performed near or far from the investigation site in our study) are mostly consistent with the results of the present study. For instance, the prevalence of cardiac anomalies in the patients with CH has been estimated at 5.8% in Saudi Arabia (7), 5.8% in France, 3% in Wales, 5.5% in Italy, and 8.9% in Japan (4, 8-10). The higher prevalence rate of CH in the current research compared to the mentioned findings could be attributed to the different geographical regions and other factors (e.g., genetics), while ethnicity and environment may also play a key role in the occurrence of CH and its complications.

In the current research, patent foramen oval was observed as a variation of atrial septal defect and CHD. Therefore, we evaluated all the neonates with CH and not only the neonates with cardiac murmur in the physical examination. According to the information in Table 3, no significant differences were observed in terms of the TSH and T4 levels between the infants with and without cardiac abnormalities. This finding is inconsistent with the results of the previous studies as we denoted no correlations between the occurrence of congenital cardiac malformations and TSH, T4, maternal age, and history of parental consanguinity. Severe CHD and CH in neonates may have affected this finding.

On the other hand,a statistically significant association was observed between the presence of CHD and history of parental cardiac diseases (P=0.001) and positive experience of previous abortions (P=0.003). All the patients diagnosed with endocardial cushion defect (n=3) had Down syndrome simultaneously. This funding may support the correlation between this syndrome and endocardial cushion defect (11).

Differences in the reported prevalence of cardiac involvement in the previous studies performed in the same geographical regions and those with a significant geographical distance propose the assumption that adverse genetic and environmental factors might also affect the occurrence of such disorders. Therefore, the idea of the presence of a significant developmental syndrome that is involved in embryogenesis rather than simple CH seems to be valid.

Among the few studies investigating this proposition, some genes have been noted to be involved in the mentioned process, such as *NKX2.1* and *FOEX.2* (11-13). On the other hand, the fact that in most studies cardiac involvement has been considered to be the most common co-existing abnormality in CH patients raises the suspicion that some common contributing factors may be present in cardiac and thyroid development during the embryonic period. Studies on experimental samples have indicated the effect of the *NKX2.5* gene on thyroidogenesis. Furthermore, some reports have confirmed the effect of this gene on the occurrence of cardiac disorders (14).

In similar studies, a subgroup belonging to the cardiac neural crest has been shown to be involved in cardiac morphogenesis; however, this finding requires further investigation (15, 16). In fact, it seems that cardiac involvement in CH patients is remarkably more complicated

than the common assumptions in this regard considering the involvement of adverse factors.

Conclusion

Based on the findings of the current research, it is recommended that all the patients with CH with or without abnormal physical examinations (e.g. murmur or cyanosis) consult a pediatric cardiologist to receive echocardiography and further evaluation.

Limitations of the study

One of the limitations of the present study was that we did not determine the etiology of CH as dyshormonogenesis or dysgenesis**.** In addition, the patients were not followed-up for cardiac congenital heart defects and assessing the effects of medical treatment on the improvement of cardiac diseases. Therefore, it is suggested that further investigations in this regard be conducted on larger sample sizes.

Acknowledgments

This study was approved by the Ethics Committee of the Medical Research School at Arak University of Medical Sciences, Iran.

Conflicts of interests

None declared.

References

1. Hinton CF, Harris KB, Borgfeld L, Drummond-Borg M, Eaton R, Lorey F, et al. Trends in incidence rates of congenital hypothyroidism related to select demographic factors: data from the United States, California, Massachusetts, New York, and Texas. Pediatrics. 2010; 125: S37-47.
2. Dorreh F, Chaijan PY, Javaheri J, Zeinalzadeh AH. Epidemiology of congenital hypothyroidism in Markazi Province, Iran. J Clin Res Pediatr Endocrinol. 2014; 6(2):105-10.
3. Kreisner E, Neto EC, Gross JL. High prevalence of extrathyroid malformations in a cohort of Brazilian patients with permanent primary congenital hypothyroidism. Thyroid. 2005; 15(2):165-9.
4. Olivieri A, Stazi M, Mastroiacovo P, Fazzini C, Medda E, Spagnolo A, et al. A population-based study on the frequency of additional congenital malformations in infants with congenital hypothyroidism: data from the Italian Registry for Congenital Hypothyroidism (1991-1998). J Clin Endocrinol Metab. 2002; 87(2):557-62.
5. Sabri M, Shahriari H, Hashemipour M. Congenital cardiac malformations in congenital hypothyroid patients Isfahan. J Res Med Sci. 2006; 11(4): 234-9.
6. Razavi Z, Mohammadi L. Permanent and transient congenital hypothyroidism in hamadan west province of Iran. Int J Endocrinol Metab. 2016; 14(4):e38256.
7. Al Jurayyan N, Al Herbish A, El Desouki M, Al Nuaim A, Abo-Bakr A, Husain A. Congenital anomalies in infants with congenital hypothyroidism: is it a coincidental or an associated finding? Hum Hered. 1997; 47(1):33-7.
8. Stoll C, Dott B, Alembik Y, Koehl C. Congenital anomalies associated with congenital hypothyroidism. Ann Genet. 1999; 42(1): 17-20.
9. Law WY, Bradley DM, Lazarus JH, John R, Gregory JW. Congenital hypothyroidism in Wales (1982-1993): demographic features, clinical presentation and effects on early neurodevelopment. Clin Endocrinol (Oxf). 1998; 48(2):201-7.
10. Gu Y, Harada S, Kato T, Inomata H, Aoki K, Hirahara F. Increased incidence of extrathyroidal congenital malformations in Japanese patients with congenital hypothyroidism and their relationship with Down syndrome and other factors. Thyroid. 2009; 19(8):869-79.
11. AL-Biltagi MA. Echocardiography in children with Down syndrome. World J Clin Pediatr. 2013; 2(4):36-45.
12. Macchia PE, De Felice M, Di Lauro R. Molecular genetics of congenital hypothyroidism. Curr Opin Genet Dev. 1999; 9(3):289-94.
13. Castanet M, Polak C, Bonaiti-Pellie S, Lyonnet P, Leger J. Nineteen years of national screening for congenital hypothyroidism: familial cases with thyroid dysgenesis suggest the involvement of genetic factors. J Clin Endocrinol Metab. 2000; 86(5):2009-14.
14. Dentice V, Cordeddu A, Rosica A, Ferrara AM, Santarpia L, Salvatore D, et al. Missense-mutation in the transcription factor NKX2-5: a novel molecular event in the pathogenesis of thyroid dysgenesis. J Clin Endocrinol Metab. 2006; 91(4):1428-33.
15. Hall BK, Horstadius S. The neural crest: including a facsimile reprint of the neural crest by Sven Hörstadius. London: Toronto: Oxford University Press; 1988.
16. Franz T. Persistent truncus arteriosus in the Splotch mutant mouse. Anat Embryol. 1989; 180(5):457-64.