Turkish Archives of Pediatrics

ORIGINAL ARTICLE
DOI: 10.5152/TurkArchPediatr.2023.22277

Thyroid Function in Children with Cyanotic and Non-Cyanotic Congenital Heart Disease

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What is already known on this topic?

- *Adults with congenital heart disease have a higher prevalence of thyroid dysfunction due to genetic and embryonic coexistence.*
- *Subclinical hypothyroidism is a common finding in adult patients with cyanotic congenital heart disease.*

What this study adds on this topic?

- *Subclinical hypothyroidism is a common finding in cyanotic congenital heart disease patients during childhood.*
- *It is crucial to note that there is no correlation between subclinical hypothyroidism and increased levels of oxygen saturation or severity of cyanosis with age.*

ABSTRACT

Objective: Congenital heart disease (CHD) is one of the common diseases of childhood, which is classified into non-cyanotic and cyanotic types. It can affect thyroid function and lead to disruptions in thyroid hormone secretion and hypofunction. This study aimed to evaluate thyroid function in patients younger than 2 years old with cyanotic and non-cyanotic CHD.

Materials and Methods: In our study, 101 patients (female/male: 50/51) were included. The thyroid-stimulating hormone and thyroid hormones such as thyroxine (T4) and triiodothyronine (T3) were measured using the electrochemiluminescence method, and thyroid peroxidase antibodies were measured by an enzyme-linked immunosorbent assay. Subclinical hypothyroidism referred to normal levels of T4, with elevated levels of thyroid-stimulating hormone in the serum.

Results: The frequency of subclinical hypothyroidism and hypothyroidism in patients with cyanotic CHD was estimated at 27.5% and 10%, respectively, and 1 patient had hyperthyroidism. The majority of cyanotic and non-cyanotic CHD cases were diagnosed with tetralogy of Fallot (30%) and patent ductus arteriosus (32.79%). There were no significant differences between cyanotic and non-cyanotic groups regarding T3, T4, free T3, free T4, and anti-thyroid peroxidase antibody levels (0.389, 0.142, 0.354, 0.248, and 0.333, respectively).

Conclusion: Based on the present findings, subclinical hypothyroidism is a common finding in cyanotic CHD patients during childhood, which is associated with increased levels of oxygen saturation, severity of cyanosis, and age.

Keywords: Congenital heart disease, hypothyroidism, thyroid-stimulating hormone

INTRODUCTION

Today, congenital heart disease (CHD) is the superlative customary congenital malformation worldwide.[1] It is estimated that 88% of children born with CHD survive to adulthood, although it can be very costly for the healthcare system.[2] A prevalence of 0.8%-1.2% has been estimated for CHD around the world. This disease may affect multiple organs in the body and is regarded as one of the most prevalent malformations linked to congenital hypothyroidism (CH).[3]

CHD is a common disorder in newborns, observed in 1 case of every 2500 to 4000 newborns. It is the most common etiology of avoidable mental retardation during infancy, which can be diagnosed at an early stage via newborn screening; it is also a popular etiology of transient thyroid dysfunction among premature infants. Generally, thyroid hormone is essential to the normal development of the nervous system in children, and even transient hypothyroidism can induce negative effects on the development of the nervous system.[3]

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Received: December 13, 2022
Accepted: August 7, 2023
Publication Date: September 22, 2023

Cite this article as: Sadegh Fakhari M, Dorreh F, Ahangar Davoodi M, Ghandi Y. Thyroid function in children with cyanotic and non-cyanotic congenital heart disease. *Turk Arch Pediatr.* 2023;58(6):594-599.

Neonates with CH have a higher prevalence of congenital cardiac abnormalities (22.7%) in comparison to cases without CH. Therefore, evaluation of all patients with CH by a pediatric cardiologist, regardless of physical examinations, can be effective in better earlier diagnosis.[4] Despite the lack of an accepted guideline to screen thyroid dysfunctions in infants with CHD, CHD can be introduced as a risk factor for non-autoimmune hypothyroidism in children.[5] In a population of infants with CHD who are exposed to a high risk of long-term growth retardation, detection of hypothyroidism, even of a transient nature, is important, and routine periodic function of thyroid monitoring may be essential to diminish neurological complications and examine the growth and development of the child.[3]

CHD can be divided into cyanotic and non-cyanotic types, with different pathophysiological characteristics and, consequently, distinct clinical manifestations. Non-cyanotic CHD is associated with increased pulmonary blood flow and heart failure, while cyanotic CHD is associated with reduced pulmonary blood flow and prolonged hypoxia.[6] Emphasis on the differences between these 2 types of CHD can provide more detailed information about this disease, and more specific and precise evaluations should be conducted for each patient. In this regard, a small cohort study of cyanotic CHD reported a high prevalence of subclinical hypothyroidism (SCH) in these patients.[7]

Although SCH is typically asymptomatic, it significantly impacts the cardiovascular system and lipid profiles and causes an increase in the risk of progression into overt hypothyroidism.[8,9] Thyroid-stimulating hormone (TSH) screening should be considered for adult patients with cyanotic CHD, owing to the described relationship between cyanotic CHD and SCH.[10] Overall, SCH is a relatively rare disease in children and adolescents (1.7%-2.9%), which is commonly characterized by a self-limiting process and a spontaneous improvement in TSH in 88% of cases.[11]

The guidelines of the European Society of Pediatric Endocrinology recommend a second screening of thyroid function test (TFT) in pediatric cases with high risk factors for hypothyroidism. Previous studies have not assessed the distinction between cyanotic and non-cyanotic cases in relation to TFT. So to have a better knowledge of the relationship between the type of CHD and thyroid function, the present study aimed to appraise and compare thyroid function parameters in patients, aged below 2 years, with cyanotic and non-cyanotic CHD.

MATERIALS AND METHODS

Study Setting and Population

This cross-sectional, descriptive study was conducted on 101 pediatric cases between 2 months and 2 years of age at Amin Kabir Hospital, Arak, Iran. The study population included 40 cyanotic CHD patients who did not undergo surgery and 61 non-cyanotic CHD patients (without surgery).

The study protocol was approved by the ethics committee of Arak University of Medical Sciences (IR.ARAKMU.REC.1399.021). This study was conducted according to the most recent amendments to the Declaration of Helsinki and also in compliance with good clinical practice. Either children or their tutors signed informed consent forms for participation in this study and analytical tests.

Data were gathered from the medical records of patients with a diagnosis of CHD who were successively admitted from January 2014 to January 2020. Inclusion and exclusion criteria are as follows:

Inclusion criteria: (1) Aged between 2 months and 2 years, (2) diagnosed with either cyanotic or non-cyanotic CHD, and (3) normal hemoglobin (Hb) levels.

Exclusion criteria: (1) Use of thyroid medications, (2) confirmed diagnosis of down syndrome, (3) having an active inflammatory disease, (4) undergoing cardiac surgery, and (5) lack of consent for data extraction.

Measurements

CHD was confirmed by echocardiography, which was carried out using a 3-7 MHz transducer (GE Vivid 6S, Vingmed Ultrasound, Diagnostx, LLC, 5735 Benjamin Center Dr., Tampa, FL 33634, USA). The patients were classified into 2 diagnostic groups according to the underlying cardiac involvement. They were divided into 2 groups: cyanotic and non-cyanotic CHD. Patients with a Hb oxygen saturation level below 90% were identified and included in the cyanotic CHD group; otherwise, they were included in the non-cyanotic group. The oxygen saturation was measured by a digital oximeter (Model: CHOICEMMED C21C).

After recruiting participants, demographic data, including sex, age, and ethnicity, were recorded, and then, the presence of CHD was assessed. The patients' blood pressure and heart rate (HR) were also assessed in a physical examination by a pediatric cardiologist.

Blood samples were collected after at least 10 hours of nocturnal fasting from the antecubital vein and kept in specific tubes for each test. The tests included the measurement of TSH (UIU/mL), triiodothyronine (T3) (ng/dL), thyroxine (T4) (mcg/dL), free T3 (pmol/L), free T4 (pmol/L), thyroid peroxidase antibodies (anti-TPO, IU/mL), Hb (g/dL), and hematocrit (HCT, %). All tests were performed by the electrogenerated chemiluminescence method using a Cobas e-411 device and a Hitachi/Roche kit, except for anti-TPO measurements, which were carried out by the enzyme-linked immunosorbent assay (ELISA) method.

The level of TSH is commonly measured in micro-international units per milliliter (uIU/mL), which is equivalent to milli-international units per liter (mIU/L). The normal range is 0.4-4.5 mIU/mL (lower normal and upper normal). Subclinical hypothyroidism was established as a serum TSH level ≥5.5 mIU/L in the setting of normal free T4 levels. A TSH level below 0.4 mIU/L represents an overactive thyroid, also known as hyperthyroidism. In data analysis, biochemical parameters were compared between patients with a serum TSH level of 5.5 mIU/L or lower and patients with a serum TSH level exceeding 5.6 mIU/L (upper normal TSH level).[12]

Statistical Analysis

Quantitative variables are expressed as mean ± standard deviation (SD) and qualitative data as frequency and percentages. Kolmogorov–Smirnov test was used to evaluate the normality of variables. Possible associations between categorical variables were assessed by Pearson's chi-square test, and the comparison mean of variables between 2 groups was assessed

by Mann–Whitney test. Additionally, a linear regression analysis was conducted in order to ascertain the relationship between oxygen saturation and thyroid function parameters, with the aim of discerning the association between these variables. The serum levels of TSH in different age subgroups were evaluated using a univariate general linear model, adjusted for a *P* value of .05. Data analysis was performed using Statistical Package for the Social Sciences version 16.0 (SPSS Inc., Chicago, Ill, USA).

RESULTS

Demographic Characteristics of Evaluated Cases

Of 101 evaluated cases, the mean and SD of age in cyanotic cases were 8.83 ± 7.01 and in non-cyanotic cases was 11.08 ± 6.12 years (*P* = .051). In addition, female/male ratio in cyanotic cases was 28/33 and in non-cyanotic cases was 22/18 (*P* = .371) (Table 1).

Frequently Distribution of Cyanotic and Non-Cyanotic Types of Congenital Heart Disease

A total of 101 children with CHD who met the inclusion criteria were included in this study (cyanotic CHD, 60.4%; non-cyanotic CHD, 39.6%). Overall, 27.5% of patients with cyanotic CHD also had SCH, 10% had hypothyroidism, and 1 patient had

Table 1. Demographic Characteristics of Evaluated Cases

Variables	Non-Cyanotic (n = 61)	Cyanotic (n = 40)	*P*
Age (month)			
Mean ± SD	11.08 ± 6.12	8.83 ± 7.01	.062
Min/max	2.5/24	2/23	
Median	9	8.5	
Gender			
Female/male	28/33	22/18	.371

Table 2. Frequency Distribution of Cyanotic and Non-Cyanotic Types of CHD

Type	Frequency	Percent	95% CI
Non-cyanotic			
PDA	20	32.79	21.3-46.0
VSD	16	26.23	15.8-39.1
ASD	17	27.87	17.14-40.8
COA	5	8.2	2.71-18.1
PS	3	4.92	1.02-13.7
Cyanotic			
TOF	12	30.0	16.56-46.53
TGA	4	10.0	2.79-23.66
DORV	2	5.0	0.6-16.91
AVSD	11	27.5	14.6-43.88
SV	5	12.5	4.18-26.8
TA	2	5.0	0.6-16.91
TrA	2	5.0	0.6-16.91
EBA	1	2.5	0.06-13.15
TAPVC	1	2.5	0.06-13.15

ASD, atrial septal defect; AVSD, atrioventricular septal defect; COA, coarctation of the aorta; CHD, congenital heart disease; DORV, double outlet right ventricle; EBA, Ebstein anomaly; PDA, persistent ductus arteriosus; PS, pulmonary stenosis; SV, single ventricle; TA, truncus arteriosus; TAPVC, total anomalous pulmonary venous connection; TGA, transposition of the great arteries; TOF, tetralogy of Fallot; TrA, tricuspid atresia; VSD, ventricular septal defect.

Table 3. Comparing Laboratory Results Between Cyanotic and Non-Cyanotic CHD patients

Variables	Non-Cyanotic (n = 61)	Cyanotic (n = 40)	*P*
Oxygen saturation			
Mean ± SD	95.13 ± 1.29	76.97 ± 4.44	<.001
Min/max	92/97	68/94	
Median	94	75.5	
HR			
Mean ± SD	118.62 ± 9.51	131.95 ± 14.66	<.001
Min/max	100/140	107/166	
Median	115	129.5	
SBP			
Mean ± SD	86.80 ± 11.73	66.22 ± 7.98	<.001
Min/max	60/105	52/95	
Median	84	64	
DBP			
Mean ± SD	58.85 ± 7.81	47.27 ± 7.62	<.001
Min/max	40/70	32/62	
Median	58	46.5	
Hb			
Mean ± SD	10.8 ± 1.33	17.05 ± 2.82	.08
Median	10.6	16.54	
HCT			
Mean ± SD	32.31 ± 3.92	36.53 ± 6.72	<.001
Median	31.15	35.45	
Albumin			
Mean ± SD	4.48 ± 0.57	4.43 ± 0.57	.298
Min/max	3.5/6.5	3.4/5.5	
Median	4.35	4.15	
T3			
Mean ± SD	2.67 ± 0.73	2.61 ± 1.25	.485
Min/max	1.43/4.12	0.59/7.97	
Median	2.5	2.49	
T4			
Mean ± SD	10.23 ± 2.90	9.47 ± 4.18	.311
Min/max	5.69/15.96	1.93/20.32	
Median	10	9.1	
TSH			
Mean ± SD	3.38 ± 1.92	8.79 ± 6.48	<.01
Min/max	0.75/8.12	0.62/20.71	
Median	3.11	8.54	
FT3			
Mean ± SD	5.78 ± 1.38	5.65 ± 2.06	.325
Min/max	3.56/8.63	2.59/13.15	
Median	5.69	5.5	
FT4			
Mean ± SD	17.19 ± 4.0	16.63 ± 4.18	.198
Min/max	11.9/25.61	8.52/26.3	
Median	17	16.5	
Anti-TPO			
Mean ± SD	21.21 ± 8.41	20.54 ± 6.04	.289
Min/max	5.2/39.1	2.17/31.73	
Median	19.8	19.5	

CHD, congenital heart disease; DBP, diastolic blood pressure; FT3, free triiodothyronine; FT4, free thyroxine; Hb, hemoglobin; HCT, hematocrit; HR, heart rate; SBP, systolic blood pressure; SO_2, saturated oxygen; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.
P value was calculated Mann–Whitney test at 95% levels of CI.

Table 4. Linear Regression for Correlation Between Oxygen Saturation and Thyroid Function Criteria

	Non-Cyanotic (n = 61)				Cyanotic (n = 40)			
	Crude		Adjust*		Crude		Adjust*	
Variables	Beta	*P*	Beta	*P*	Beta	*P*	Beta	*P*
T3	−0.103	.430	−0.109	.385	0.152	.346	0.171	.303
T4	0.060	.648	0.012	.926	0.251	.117	0.262	.112
TSH	0.065	.620	0.031	.805	−0.242	.132	0.233	.194
FT3	0.106	.417	0.117	.368	0.114	.481	0.115	.489
FT4	0.014	.912	−0.033	.796	0.176	.277	0.185	.270
Anti TPO	0.257	.049	0.244	.053	-0.086	.594	-0.088	.594

FT3, free triiodothyronine; FT4, free thyroxine; T3, triiodothyronine; T4, thyroxine; TPO, thyroid peroxidase; TSH, thyroid-stimulating hormone.

hyperthyroidism. All patients with non-cyanotic CHD had normal thyroid function. According to the results, 45.9% of non-cyanotic and 55% of cyanotic patients were female. There were significant differences in the mean values of variables. The results indicated the frequency of cyanotic and non-cyanotic CHD. Most of the patients with cyanotic CHD (30%) had tetralogy of Fallot, and the majority of patients with non-cyanotic CHD (32.79%) had patent ductus arteriosus (Table 2).

Comparing Laboratory Results Between Cyanotic and Non-Cyanotic Congenital Heart Disease

Table 3 compares the results of the laboratory data between the 2 groups of cyanotic and non-cyanotic CHD. There were significant differences between the means of HR, SBP, DBP, Hb, HCT, and TSH in the 2 groups.

Linear Regression Analysis for the Correlation Between Oxygen Saturation and Thyroid Function Parameters

Table 4 shows linear regression for the correlation between oxygen saturation and thyroid function criteria. Although there was a considerable and positive correlation between oxygen saturation and anti-TPO in the crude results, the adjusted model revealed no considerable correlation among thyroid hormone criteria and oxygen saturation.

DISCUSSION

Thyroid hormones have significant effects on the cardiovascular system. These hormones increase the contractility of the heart by exerting direct effects and also by increasing the amount of oxygen consumption. Therefore, it is important to pay attention to the interactions of these 2 organs. Among thyroid hormones, T3 is clinically the most effective hormone in causing low cardiac output, decreasing systemic vascular resistance, and improving myocardial oxygen expenditure.

Thyroid dysfunction can be classified from mild to severe types. The term "subclinical hypothyroidism" is employed to describe a condition in which individuals exhibit normal levels of T4, but have moderately elevated levels of TSH in their serum. SCH is often asymptomatic and identified in routine TSH screening. This disorder is associated with various poor clinical outcomes, such as prognostic cardiac surgery and poor ventricular function. The prevalence of SCH in patients with cyanotic CHD is higher than that of the general population, as acknowledged in the present study. In our study, a high prevalence of autoimmunity was reported, and no relationship was found between the degree of cyanosis and age.

Since SCH can lead to overt hypothyroidism, frequent monitoring of thyroid function in patients with cyanotic CHD needs to be considered. Although some studies have emphasized the relationship between SCH and CHD, the impact of clinical SCH on CHD remains unknown, and further studies are needed. Careful clinical and hemodynamic assessments should be carried out in a timely manner to diagnose any life-threatening deteriorations in the cardiac status of patients with CHD; such information can help us design follow-ups for patients with cyanosis who may have a concurrent cardiac or thyroid disease. Although it is difficult to conclude about cyanotic CHD, the results of this study present a proper framework for future research.

Bak et al,[13] in a study on SCH in adult patients with cyanotic CHD, found that SCH is a common condition in the setting of cyanotic CHD. In the present study, thyroid function was evaluated in children with CHD, and SCH was confirmed despite their younger age. In another study, Kaushik and Agrawal[14] investigated the serum levels of thyroid hormones in a pediatric population with CHD following cardiopulmonary bypass surgery. The results showed that pediatric patients who underwent this surgery were at risk of a significant decline in thyroid hormone levels; therefore, prophylaxis to increase hormone levels and accelerate recovery is crucial for these patients. Similarly, the present results have highlighted the importance of thyroid dysfunctions in patients with cardiac disease.

Additionally, Martínez-Quintana et al,[10] in a study on SCH in adult patients with CHD, found that SCH was associated with a higher risk of cardiovascular complications. Therefore, the thyroid function of these patients should be assessed in periodic evaluations. In another study, Benjamin et al[15] evaluated CHD during infancy and assessed progressive thyroid dysfunction over 100 days. They found thyroid dysfunction in two-thirds of infants; it was transient in 53.7% of cases. However, it could be persistent in 13.0% of cases with risk factors who underwent TFT screening over 100 days, despite normal newborn screening test results. These results are inconsistent with the present findings in terms of prevalence, which can be related to the use of different methods in these 2 studies. Overall, previous findings are contradictory, which suggests the importance of further research to obtain more accurate results.

The thyroid gland of cyanotic CHD patients may be subjected to a large amount of iodine from different origins. One of the most common sources of iodine exposure is angiography or cardiac catheterization; also, computed tomography angiography relies on iodinated contrast media. In a study by Kubicki

et al,[16] the prevalence of acquired hypothyroidism following overplus of iodine was 15.4%, although most patients only developed transient hypothyroidism. Systemic iodine disposal seems to be clinically and metabolically well tolerated in long-time follow-ups.

Thyroid hormone regulation directly affects the myocardium. It is known that insufficient thyroid hormones can lead to a decrease in myocardial contracture, ventricular arrhythmias, and heart failure. These cardiac abnormalities are commonly reversible with the treatment of an underlying thyroid condition.[17] In this regard, Mohamed et al[18] reported that thyroid function may be altered in pediatric heart failure; this change in thyroid function can be related to the severity of heart failure and poor outcomes.

There are many etiologies for thyroid dysfunction in patients with cardiac diseases, such as genetic predisposition, Down syndrome, CH, transient hypothyroidism due to preterm birth, and exposure to iodine or cardiac bypass. Misdiagnosis is possible, as there are often no typical signs or symptoms of hypothyroidism. One of the symptoms of hypothyroidism in infants is neurodevelopmental delay. This complication often deteriorates the patient's condition, and a hypothyroidism diagnosis may be even more consequential.

Based on the present findings, serial thyroid function monitoring should be routinely performed for infants with cyanotic CHD. Therapeutic decisions should be made for individual patients while considering the signs and symptoms of thyroid dysfunction. It seems that there is no clear relationship between the severity of cyanosis and hypothyroidism; also, clinicians should do more than just wait for thyroid dysfunction to occur with advancing age. These findings can help us design follow-up plans for patients with cyanosis who may have concurrent thyroid diseases.

Present research was limited based on its descriptive method, which necessitated a nonuniform follow-up duration. Because many of the cases in the present study were critically ill at the time of the detection of hypothyroidism, ultrasound examination of the thyroid was not conducted. So, it is possible that some infants could have morphologically abnormal thyroid glands. Congenital hypothyroidism is highly observed in cases with CHD;[1,3] however, we excluded pediatric cases with the use of thyroid medications, a confirmed diagnosis of Down syndrome,having an active inflammatory disease, undergoing cardiac surgery, and lack of consent for data extraction.

CONCLUSION

Based on our results and in comparison to other studies in this field, SCH is a very common condition in patients with cyanotic CHD during childhood. It is not related to increased levels of oxygen saturation or severity of cyanosis and age. Since the clinical effects of SCH on cardiac function and surgical prognosis are uncertain, further research is essential. As SCH cannot develop into overt hypothyroidism, timely thyroid assessment is suggested for cyanotic CHD patients. Based on these results, our studies have a message that pediatric cases with CHD should be evaluated and considered for TFT.

Ethics Committee Approval: This study was approved by Ethics Committee of Arak University of Medical Sciences (Approval No: IR.ARAKMU.REC.1399.021, Date: 2020/04/19).

Informed Consent: Either children or their tutors signed informed consent forms for participation in this study and analytical tests.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – Y.Gh.; Design – Y.Gh., A.H.M., M.S.F., F.D.; Data Collection and/or Processing – F.D.; Analysis and/or Interpretation – A.H.M.; Writing Manuscript – A.H.M., M.S.F., F.D., M.A.D.; Critical Review – Y.Gh.

Acknowledgments: This study was performed in partial fulfillment of the requirements for an MD degree, Arak University of Medical Sciences Faculty of Medicine, Arak, Iran ("Assessment of thyroid function in patients aged two months to two years with congenital heart disease"; IR.ARAKMU.REC.1399.021). This study was approved by the research deputy of Arak University of Medical Sciences. The authors would like to thank all the participants for their sincere cooperation in this study.

Declaration of Interests: The authors have no conflict of interest to declare.

Funding: This study was supported by Arak University of Medical Sciences, Arak, Iran (No.: 6031).

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