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Investigation of Non-cardiac Findings in Conotruncal Heart Diseases in Children

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What is known on this subject?

Conotruncal heart diseases are a group of cardiac malformations heterogeneous from an anatomic standpoint but with a common embryologic origin: abnormal rotation of the outflow tract.

What this study adds?

In children with conotruncal heart defects, routine extracardiac evaluation is beneficial and assists in improving surgical outcomes.

ABSTRACT

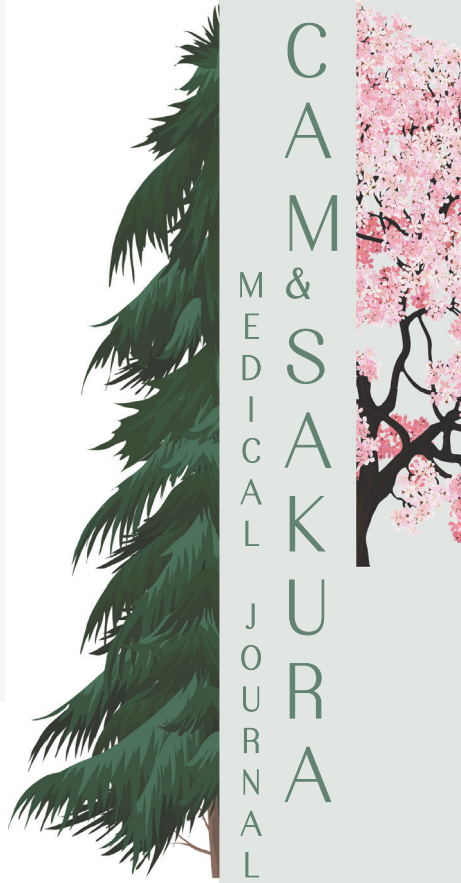
Objective: Individuals with conotruncal heart disease (CHD) often exhibit a range of associated anomalies. Our study aimed to investigate the frequency of non-cardiac comorbidities in patients with CHD.

Material and Methods: Our study was a hospital-based, single-center, retrospective, observational study conducted at our clinic between August 1, 2020, and November 1, 2022. The study included 179 cases, both male and female, aged between 0 day and 6 months, with CHDs diagnosed. Data from each patient, including gender, complete blood count, biochemical and coagulation tests, abdominal ultrasound (USG), cranial USG, and serum immune globulin levels, were evaluated.

Results: In 14.5% of the 179 patients included in the study, abnormal renal function test results were detected. In 18.4% of the cases, abnormal liver function test results were detected. When evaluated according to the diagnosis group, among the 21 patients diagnosed with interrupted aortic arch (IAA), 7 (33.3%) had abnormal liver function test results. In 25.7% of the cases, the leukocyte count was abnormal. In 12.8% of the cases, the platelet count in the complete blood count was abnormal. In 10.6% of the cases, abnormal results were found in the coagulation tests. In 21.2% of the cases, abnormal results were found in the serum immunoglobulin (Ig) and Ig subgroups. When evaluated according to the diagnosis group, among the 21 patients diagnosed with IAA, 10 (47.6%) had abnormal results. In 19% of the cases, abdominal USG results were pathological, and in 9.5% of the cases, cranial USG results were pathological.

Conclusion: CHD in children may be accompanied by non-cardiac problems that cause hemodynamic and systemic problems and affect organ systems. Routine liver function tests, renal function tests, coagulation, complete blood count, immune screening, and abdominal USG evaluation may be useful to improve the quality of life of patients and reduce morbidity and mortality while waiting for necessary surgical interventions.

Keywords: Child, conotruncal heart diseases, extracardiac manifestations



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Introduction

Congenital heart defects are the most common type of birth defect and one of the major causes of perinatal mortality, with a worldwide prevalence of 1 per 100 births (1). Because of the heterogeneity within the group of Conotruncal heart diseases (CHDs), epidemiologic studies often focus on subgroups of conditions, such as conotruncal heart defects (CTDs). Conotruncal defects are a subset of serious and relatively common CHDs, defined as defects of the cardiac outflow tracts of the great arteries.

This class of defects includes transposition of the great arteries (TGA), tetralogy of Fallot (TOF), double outlet right ventricle (DORV), ventricular septal defect with pulmonary atresia (VSD-PA), interrupted aortic arch (IAA), double outlet left ventricle (DOLV), and truncus arteriosus (TA). The manifestations and prognoses of CHD in children vary significantly. In addition to these diseases, non-cardiac problems that cause serious hemodynamic and systemic issues and affect organ systems can also occur (2,3).

Patients with CTDs often require early surgical treatment and have high mortality and morbidity (4).

These findings can impact the diagnosis and treatment processes of patients. Our study aimed to investigate the frequency of extracardiac manifestations in patients with CHD.

Material and Methods

The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital Local Ethics Committee (decision no: 2022.04.130).

Our study was a hospital-based, single-center, retrospective, observational study conducted at the Department of Pediatric Cardiology, Child Health and Diseases Division, University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital, between August 1, 2020, and November 1, 2022. The study included 179 cases, both male and female, aged between 0 day and 6 months, diagnosed with CHD such as TGA, TOF, DORV, VSD-PA, IAA, and TA. Data from each patient, including gender, complete blood count, biochemical and coagulation tests, abdominal ultrasound (USG), cranial USG, and serum immunoglobulin levels (IgA, IgG, IgM, and IgG subclasses: IgG1, IgG2, IgG3, IgG4), were evaluated.

In the blood tests obtained from patients, parameters such as white blood cell count, platelet count, and biochemical factors including renal function tests [urea, creatinine (Cr)] and liver function tests (alanine transaminase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, albumin), as well as coagulation tests (prothrombin time, activated partial thromboplastin time, fibrinogen), and serum immune globulin levels were compared to age-appropriate reference ranges, and values falling outside these ranges were considered abnormal.

The USG results were evaluated by the radiology department of University of Health Sciences Turkey, Başakşehir Çam and Sakura City Hospital.

Statistical Analysis

Statistical analyses were performed using SPSS 25 program (SPSS Inc., Chicago, IL, USA). Frequencies and percentages are presented for categorical data. Median values and interquartile ranges were used for variables with non-normal distributions, whereas those with normal distributions were described using the mean and standard deviation.

Results

The primary diagnosis of patients is shown in Table 1. Extracardiac findings of patients are shown in Table 2. In 14.5% of the 179 patients included in the study, abnormal renal function test results were detected. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 17 (30.9%) had abnormal renal function test results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 21 patients diagnosed with IAA, 2 (9.5%) had abnormal results. Among the 13 patients diagnosed with TA, 1 (7.7%) had abnormal results. Among the 15 patients diagnosed with DORV, 1 (6.1%) had abnormal results. Among the 49 patients diagnosed with TOF,

Table 1. Gender and diagnosis of patients

		n	%
Total		179	100.0
	Female	76	42.5
	Male	103	57.5
TGA		55	30.7
TOF		49	27.4
DORV		15	8.4
VSD-PA		19	10.6
IAA		21	11.7
DOLV		7	3.9
TA		13	7.3

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

3 (6.1%) had abnormal results. No abnormalities were found in the renal function test results of the 19 patients diagnosed with VSD-PA. There was a statistically significant difference among the parameters when evaluating renal function tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.02).

In 18.4% of the cases, abnormal liver function test results were detected. When evaluated according to the diagnosis groups, among the 21 patients diagnosed with IAA, 7 (33.3%) had abnormal liver function test results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 55 patients diagnosed with TGA, 15 (27.3%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had abnormal results. Among the 15 patients diagnosed with DORV, 2 (13.3%) had abnormal results. Among the 13 patients diagnosed with TA, 1 (7.7%) had abnormal results. Among the 49 patients diagnosed with TOF, 2 (4.1%) had abnormal renal function test results. There was a statistically significant difference among the parameters when evaluating liver function tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.025).

Table 2. Evaluation of blood tests in conotruncal diseases

	Normal test result n (%)	Anormal test result n (%)
Renal function test	153 (85.5)	26 (14.5)
Liver function test	146 (81.6)	33 (18.4)
Leukocyte counts	133 (74.3)	46 (25.7)
Platelet counts	156 (87.2)	23 (12.8)
Coagulation test	160 (89.4)	19 (10.6)
Immune function test	141 (78.8)	38 (21.2)

In 25.7% of the cases, the leukocyte count was abnormal. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 26 (47.3%) had abnormal leukocyte counts. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had abnormal results. Among the 15 patients diagnosed with DORV, 3 (20%) had abnormal results. Among the 21 patients diagnosed with IAA, 4 (19%) had abnormal results. Among the 49 patients diagnosed with TOF, 17 (14.3%) had abnormal leukocyte counts. There was a statistically significant difference among the parameters when evaluating leukocyte counts according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.01).

In 12.8% of the cases, the platelet count in the complete blood count was abnormal. In the complete blood count, the platelet count was abnormal in 18.2% of the patients diagnosed with TGA, 14.3% of the patients diagnosed with IAA and DOLV, 10.5% of the patients diagnosed with VSD-PA, 10.2% of the patients diagnosed with TOF, and 7.7% of the patients diagnosed with TA. There was no statistically significant difference among the parameters when evaluating platelet counts according to the diagnoses (p=0.894).

Table 3 summarizes the results of coagulation parameters according to diagnoses. In 10.6% of the cases, abnormal results were found in coagulation tests. When evaluated according to the diagnosis groups, among the 55 patients diagnosed with TGA, 12 (21.8%) had abnormal coagulation test results. Among the 7 patients diagnosed with DOLV, 1 (14.3%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 2 (10.5%) had abnormal results. Among the 21 patients diagnosed with IAA, 2 (9.5%) had abnormal results. Among the 15 patients diagnosed with DORV, 1 (6.7%) had abnormal

Table 3. Evaluation of coagulation tests according to diagnoses in conotruncal heart diseases

Diagnosis	Total number of patients	Normal value			Non-reference value (abnormal)			p value
		Number	Original diagnosis %	Total patient %	Number	Original diagnosis %	Total patient %	
TGA	55	43	78.2	24	12	21.8	6.7	
TOF	49	48	98	26.8	1	2	0.6	
DORV	15	14	93.3	7.8	1	6.7	0.6	
VSD-PA	19	17	89.5	9.5	2	10.5	1.1	**0.043**
IAA	21	19	90.5	10.6	2	9.5	1.1	
DOLV	7	6	85.7	3.4	1	14.3	0.6	
TA	13	13	100	7.3	-	-	-	

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

results. Among the 49 patients diagnosed with TOF, 1 (2%) had abnormal coagulation test results. There was a statistically significant difference among the parameters when evaluating coagulation tests according to the diagnoses, and the likelihood of abnormal results was significantly increased (p=0.043).

In Table 4, Ig levels are shown according to the diagnoses. In 21.2% of the cases, abnormal results were found in the serum Ig and Ig subgroups. When evaluated according to the diagnosis groups, among the 21 patients diagnosed with IAA, 10 (47.6%) had abnormal results. Among the 13 patients diagnosed with TA, 6 (46.2%) had abnormal results. Among the 19 patients diagnosed with VSD-PA, 6 (31.6%) had abnormal results. Among the 7 patients diagnosed with DOLV, 2 (28.6%) had abnormal results. Among the 49 patients diagnosed with TOF, 10 (20.4%) had abnormal results. Among the 15 patients diagnosed with DORV, 3 (20%) had abnormal results. Among the 55 patients diagnosed with TGA, 1 (1.8%) had abnormal results in serum Ig and Ig subgroups, indicating immunodeficiency. There was a statistically significant difference among the parameters when evaluating Ig tests according to the diagnoses, and the likelihood of pathological results was significantly increased (p<0.001).

In 19% of the cases, abdominal USG results were pathological, and in 9.5% of the cases, cranial USG results were pathological. Among abdominal USG pathologies, 70% were related to the kidneys (increased renal parenchymal echogenicity in 10 patients, renal pelvis dilation in 8 patients, horseshoe kidney in 4 patients, and one patient with dysplastic kidney). The remaining 30% involved liver and biliary tract pathology (increased liver echogenicity in 7 patients, increased gallbladder wall thickness, and dilation in 4 patients). When evaluated according to the diagnosis groups, among the 15 patients diagnosed with DORV, 7 (46.7%) had pathological abdominal USG results. Among the 55 patients diagnosed with TOF, 13 (23.6%) had pathological findings. Among the 19 patients diagnosed with VSD-PA, 4 (21.1%) had pathological findings. Among the 21 patients diagnosed with IAA, 4 (19%) had pathological findings. Among the 13 patients diagnosed with TA, 2 (15.4%) had pathological findings. Among the 49 patients diagnosed with TOF, 4 (8.2%) had pathological results in abdominal USG. No pathological abdominal USG results were found in the 7 patients diagnosed with DOLV. There was a statistically significant difference among the parameters when evaluating abdominal USG results (p=0.032). Cranial USG evaluation showed pathological results in 17 (9.5%) of all conotruncal patients. the cranial pathologies detected in USG were as follows: 8 cases of corpus callosum abnormalities, 5 cases of hydrocephalus, 2 cases of cerebellar atrophy, and 2 cases of choroid plexus cyst. Among these patients, 4 had TGA (2.2%), 5 had TOF (2.8%), 3 had PA-VSD (1.7%), 3 had IAA (1.7%), and 2 had DOLV (1.1%). There was no statistically significant difference among the parameters when evaluating cranial USG results according to the diagnoses (p>0.05).

Discussion

In this study, we investigated abnormal laboratory results in children with CHD and explored extracardiac manifestations. The number of studies conducted in this field is limited. Our study suggests the need for better risk classification and improved resource allocation for future patients.

Regarding white blood cell counts, 25.7% of cases had abnormal results. Patients diagnosed with TOF exhibited a higher frequency of abnormal white blood cell counts (47.4%, p=0.01) compared with other diagnoses, whereas TGA cases did not show abnormal counts. Among specific diagnoses, DOLV had a frequency of 28.6%, VSD-PA had 21.1%, DORV had 20%, IAA had 19%, and Fallot tetralogy (FT) had 14.3%

Table 4. Evaluation of immune function tests according to diagnoses in conotruncal heart diseases

Diagnosis	Total number of patients	Normal value			Non-reference value (abnormal)			p value
		Number	Original diagnosis %	Total patient %	Number	Original diagnosis %	Total patient %	
TGA	55	54	98.2	30.2	1	1.8	0.6	
TOF	49	39	79.6	21.8	10	20.4	5.6	
DORV	15	12	80	6.7	3	20	1.7	
VSD-PA	19	13	68.4	7.3	6	31.6	3.4	**<0.001**
IAA	21	11	52.4	6.1	10	47.6	5.6	
DOLV	7	5	71.4	2.8	2	28.6	1.1	
TA	13	7	53.8	3.9	6	46.2	3.4	

TGA: Transposition of the great arteries, TOF: Tetralogy of Fallot, DORV: Double outlet right ventricle, VSD-PA: Ventricular septal defect with pulmonary atresia, IAA: Interrupted aortic arch, DOLV: Double outlet left ventricle, TA: Truncus arteriosus

abnormal white blood cell count frequencies (p=0.01). However, it is worth noting that a limited number of studies have been conducted in this area.

Trombocytopenia is a common finding in patients with 22q11.2 deletion syndrome. Lawrence et al. (5) found that approximately 70% of patients exhibited thrombocytopenia when compared with control subjects. Our study yielded incongruent results with these data. No statistically significant differences were observed in thrombocyte counts between different diagnoses (p>0.05).

In our study, 14.5% of cases had abnormal blood urea nitrogen, Cr, and kidney function test (KFT) results. Among the specific diagnoses, TGA and DOLV cases showed the highest rates of abnormalities (30.9% and 28.6%, respectively). No abnormalities were found in the KFT results of VSD-PA cases. The evaluation of KFT results based on diagnoses revealed statistically significant differences between parameters (p=0.02), indicating the need for close monitoring of KFT tests.

For liver function tests, 18.4% of cases yielded abnormal results. Evaluating results according to diagnoses, 33.3% of IAA cases, 28.6% of DOLV cases, 27.3% of TOF cases, 21.1% of VSD-PA cases, and 13.3% of DORV cases showed abnormalities. The rates were lower in TA and FT cases (7.7% and 4.1% respectively, p=0.025). Close monitoring of LFT tests is recommended in CHDs.

Majiyagbe et al. (6) found a prevalence of 37.1% for coagulation abnormalities in children with congenital heart diseases and 7.1% in control groups. They also reported a significantly higher prevalence of coagulation abnormalities in cyanotic CHD patients compared to acyanotic ones (57.1% vs. 17.1%). They found significant associations between oxygen saturation levels, coagulation abnormalities, and cyanotic CTDs. Detection of coagulation anomalies is crucial for improving the quality of life and reducing morbidity and mortality in cyanotic children with CTDs. Our study identified abnormal coagulation test results in 10.6% of the cases. This prevalence was highest in TGA cases (21.8%). No abnormalities were found in the coagulation tests of TA cases. Despite cyanotic heart defects being the predominant cause, the prevalence of abnormal coagulation tests in FT cases was relatively low. Therefore, routine coagulation screening is recommended to enhance the quality of life and reduce morbidity and mortality while awaiting corrective surgeries.

Diller et al. (7) discovered that 27.5% of cases exhibited immunodeficiency among 54,449 patients with congenital heart diseases. They noted that this condition increased hospitalization rates. In our study, 21.2% of the cases exhibited out-of-range serum Ig and Ig subclasses test results, indicating immunodeficiency (p<0.001). This prevalence was highest in IAA and TA cases (47.6% and 46.2%, respectively). Only 1.8% of the TGA cases had immunodeficiency. The evaluation of immunodeficiency based on diagnoses revealed statistically significant differences between parameters (p<0.001), which could impact hospitalization rates and durations.

In our study, 19% of cases yielded pathological abdominal USG results. Evaluating results based on diagnoses, 46.7% of DORV cases had pathological abdominal USG results, whereas no DOLV cases showed pathological abdominal USG results. Pathological results were observed in 23.6% of TGA cases, 21.1% of VSD-PA cases, and 19% of IAA cases (p=0.0329. In our study, the frequency of pathological results in cranial USG did not exhibit statistically significant differences (p=0.262).

Study Limitations

This study was conducted in a single center with a limited number of patients and was retrospective.

Conclusion

Children with CHD can experience non-cardiac issues that contribute to hemodynamic and systemic challenges, affecting various organ systems. Employing a comprehensive approach that involves regular assessments of liver and renal functions, coagulation profiles, complete blood counts, immune function, and abdominal USG can prove beneficial. These measures aim to enhance patients' quality of life, mitigate morbidity and mortality, and provide essential insights while awaiting crucial surgical interventions.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Başaksehir Çam and Sakura City Hospital Local Ethics Committee (decision no: 2022.04.130).

Informed Consent: An informed consent form was signed by each subject included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.G., Concept: G.G., H.Z.G., İ.C.T., Design: G.G., H.Z.G., İ.C.T., Data Collection or Processing: G.G., İ.C.T., E.Ö., Analysis or Interpretation: G.G., H.Z.G., İ.C.T., E.Ö., Literature Search: G.G., İ.C.T., E.Ö., Writing: G.G., H.Z.G.

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