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CONGENITAL HEART DEFECTS AND NON-CARDIAC MALFORMATIONS IN PATIENTS WITH A NORMAL KARYOTYPE, ODISHA: A COHORT STUDY.

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ABSTRACT

Background

Congenital heart defects (CHDs) are the most general type of birth defect, frequently associated with non-cardiac malformations, even in patients with normal karyotypes. Understanding these associations can enhance diagnosis, management, and outcomes. The study investigated the prevalence and types of non-cardiac malformations in patients with CHDs and normal karyotypes, and to identify significant associations between these anomalies.

Methods

A retrospective observational study was conducted. The study included 300 patients with CHDs and normal karyotypes. Data were collected from medical records, including demographic information, types of CHDs, and non-cardiac malformations. Statistical analysis was performed, employing chi-square tests and logistic regression.

Results

The participants comprised 160 males (53.3%) and 140 females (46.7%), with a mean age of 3.5 years. The study found that 33.3% of patients had musculoskeletal anomalies, 28.3% had genitourinary anomalies, and 21.7% had gastrointestinal anomalies. Significant associations were observed between VSD and musculoskeletal anomalies (χ^2 = 12.5, p = 0.0004) and ASD and genitourinary anomalies (χ^2 = 5.8, p = 0.02). A family history of anomalies was a significant predictor of multiple congenital anomalies (OR = 3.2, 95% CI: 1.8-5.7, p =0.00002). Surgical interventions led to favorable outcomes in 83.3% of patients.

Conclusion

The study highlights a high prevalence of non-cardiac malformations in patients with CHDs and normal karyotypes, with significant associations between specific CHDs and certain non-cardiac anomalies. These findings underscore the necessity for a multidisciplinary approach to improve diagnosis and management, as well as the importance of considering family history in assessing risks for multiple congenital anomalies.

Recommendations

Future research is needed to explore the genetic and developmental mechanisms underlying these associations. A multidisciplinary approach should be implemented in clinical practice to improve diagnosis and management of patients with CHDs and associated non-cardiac malformations.

Keywords: *Congenital heart defects, non-cardiac malformations, Normal karyotype, Multidisciplinary management, Genetic associations*
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INTRODUCTION

Congenital heart defects (CHDs) are the most general type of birth defect, affecting approximately 1% of live births globally. These structural malformations of the heart present at birth can vary in severity from simple defects with minimal impact to complex malformations requiring immediate intervention. The etiology of CHDs is multifactorial, involving genetic, environmental, and potentially epigenetic factors. Despite advances in prenatal diagnosis and surgical interventions, CHDs remain a leading reason of infant morbidity and mortality worldwide [1].

In addition to CHDs, many affected individuals also present with non-cardiac malformations (NCMs), which can complicate diagnosis, management, and outcomes. Non-cardiac anomalies often involve the musculoskeletal, genitourinary, gastrointestinal, and neurological systems, indicating potential shared developmental pathways or underlying genetic predispositions [2]. The presence of multiple congenital anomalies significantly impacts clinical care, necessitating a comprehensive, multidisciplinary approach to treatment.

While the association between CHDs and chromosomal abnormalities, such as Down syndrome, is well-documented, there is a subset of patients with CHDs and normal karyotypes who also exhibit non-cardiac malformations [3]. The study of this specific population is critical, as it helps to elucidate the genetic and developmental mechanisms that contribute to congenital anomalies in the absence of detectable chromosomal abnormalities [4]. Previous research has often focused on patients with identifiable genetic syndromes, potentially overlooking the unique challenges and characteristics of those with normal karyotypes.

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Recent studies have emphasized the importance of early recognition and intervention in improving outcomes for individuals with CHDs. Advances in genetic testing and imaging technologies have enhanced our ability to diagnose and understand the complexity of congenital anomalies. However, there remains a need for comprehensive data on the prevalence and impact of non-cardiac malformations in patients with normal karyotypes. Such information is essential for developing targeted interventions and optimizing care for this unique patient population.

The aim of the study was to investigate the prevalence and types of non-cardiac malformations in patients with congenital heart defects and normal karyotypes, and to identify significant associations between these anomalies.

METHODOLOGY

Study Design

A retrospective observational cohort study.

Study Setting

The study was carried out at Hi-Tech Medical College and Hospital, Rourkela, Odisha, India, from December 2021 to January 2023.

Participants

A total of 300 patients were included in the study.

Inclusion Criteria

Patients with CHDs and NCMs who had a normal karyotype confirmed through genetic testing.

Exclusion Criteria

Patients with abnormal karyotypes, or with incomplete medical records were excluded.

Sample size

To calculate the sample size for this study, the following formula was used for estimating a proportion in a population:

$$n = \frac{Z^2 \times p \times (1-p)}{E^2}$$

Where:

- n = sample size

- Z = Z-score corresponding to the desired level of confidence

- p = estimated proportion in the population

- E = margin of error

Bias

To minimize bias, a standardized protocol was followed for data collection, and the same criteria were applied uniformly to all participants.

Variables

The primary variables studied were the types and prevalence of congenital heart defects and non-cardiac malformations. Secondary variables included patient demographics such as age, gender, and family history.

Data Collection

Data were collected from patient medical records, including genetic test results, clinical examinations, and diagnostic imaging. Information was recorded using a structured data collection form.

Procedure

Karyotype results were verified to confirm normal karyotypes. Detailed clinical information, including the type and severity of defects, demographic data (age, gender, family history), and relevant medical history, was extracted.

Diagnostic imaging and clinical examination results were reviewed to confirm congenital heart defects and non-cardiac malformations. Data were systematically recorded, with each patient assigned a unique identification code for confidentiality.

Follow-up data, including patient outcomes and long-term prognosis, were collected to assess intervention effectiveness and identify late complications.

Statistical Analysis

The analysis of the gathered data was done with SPSS version 21.0. The data were summarised using descriptive statistics, and the significance of the correlations between the variables was ascertained using inferential statistics. Potential risk factors and the associations between congenital heart abnormalities and non-cardiac malformations were evaluated using logistic regression analyses and chi-square testing.

Ethical considerations

The study protocol was approved by the Ethics Committee and written informed consent was received from all the participants.

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RESULT

The study included 300 patients with congenital heart defects and non-cardiac malformations, all confirmed to have normal karyotypes. The participants comprised 160 males (53.3%) and 140 females (46.7%), with a mean age of 3.5 years (range: 0.1 to 15 years).

The most common CHDs observed were ventricular septal defects (VSD), atrial septal defects (ASD), and patent ductus arteriosus (PDA). The distribution of these defects is detailed in the table 2.

Non-cardiac malformations included musculoskeletal, genitourinary, and gastrointestinal anomalies. The distribution of these malformations is detailed in the table 3.

Table 1: Demographics and Clinical Features

Variable	N	Percentages (%)
Gender		
- Male	160	53.3
- Female	140	46.7
Mean Age (years)	3.5 (± 2.8)	
Family History of Anomalies		
- Yes	45	15.0
- No	255	85.0

Table 2: Types of Congenital Heart Defects

Congenital Heart Defect	N	Percentages (%)
Ventricular Septal Defect (VSD)	90	30.0
Atrial Septal Defect (ASD)	75	25.0
Patent Ductus Arteriosus (PDA)	60	20.0
Tetralogy of Fallot	30	10.0
Coarctation of the Aorta	20	6.7
Other	25	8.3

Table 3: Types of Non-Cardiac Malformations

Non-Cardiac Malformation	N	Percentages (%)
Musculoskeletal Anomalies	100	33.3
Genitourinary Anomalies	85	28.3
Gastrointestinal Anomalies	65	21.7
Neurological Anomalies	30	10.0
Other	20	6.7

Table 4: Significant Associations Between Congenital Heart Defects and Non-Cardiac Malformations

Analysis Type	Results	p-value
Association (Chi-square)		
- VSD and Musculoskeletal Anomalies	$\chi^2 = 12.5$	0.0004
- ASD and Genitourinary Anomalies	$\chi^2 = 5.8$	0.02
- PDA and Gastrointestinal Anomalies	$\chi^2 = 3.2$	0.07
- Tetralogy of Fallot and Neurological Anomalies	$\chi^2 = 4.1$	0.04
- Coarctation of the Aorta and Other Anomalies	$\chi^2 = 2.6$	0.11
Predictive Factor (Logistic Regression)		
- Family History and Multiple Anomalies	OR = 3.2, 95% CI: 1.8-5.7	0.00002
- Age and Favorable Outcomes	OR = 1.1, 95% CI: 0.9-1.3	0.25
- Gender and Complications	OR = 1.5, 95% CI: 0.8-2.7	0.14

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Table 5: Outcomes and Interventions

Outcome	N	Percentages (%)
Favorable	250	83.3
Complications	30	10.0
Unresolved Issues	20	6.7

Chi-square tests were performed to determine the correlation between CHDs and NCMs. A significant association was found between VSD and musculoskeletal anomalies ($\chi^2 = 12.5$, $p = 0.0004$). Logistic regression analysis showed that having a family history of anomalies was a significant predictor for the presence of multiple congenital anomalies (OR = 3.2, 95% CI: 1.8-5.7, $p = 0.00002$).

Among the 300 patients, 180 (60.0%) underwent surgical interventions, 90 (30.0%) required medical management, and 30 (10.0%) were managed conservatively. Follow-up data showed that 250 patients (83.3%) had favorable outcomes, while 30 patients (10.0%) experienced complications, and 20 patients (6.7%) had unresolved issues.

DISCUSSION

The study included 300 patients with CHDs and NCMs, all having normal karyotypes. The demographic distribution showed a slight male predominance, with 53.3% of the participants being male and 46.7% female. The mean age was 3.5 years, ranging from 0.1 to 15 years. Among the CHDs, the most common defects observed were ventricular septal defect (VSD) in 30.0% of the patients, atrial septal defect (ASD) in 25.0%, and patent ductus arteriosus (PDA) in 20.0%. Non-cardiac malformations predominantly included musculoskeletal anomalies (33.3%), genitourinary anomalies (28.3%), and gastrointestinal anomalies (21.7%).

Key findings revealed significant associations between specific CHDs and non-cardiac malformations. A notable association was found between VSD and musculoskeletal anomalies ($\chi^2 = 12.5$, $p = 0.0004$). This suggests that patients with VSD might be more likely to have musculoskeletal anomalies, indicating a potential link between these conditions. Similarly, there was a significant association between ASD and genitourinary anomalies ($\chi^2 = 5.8$, $p = 0.02$), suggesting that patients with ASD might be more likely to have genitourinary anomalies. Tetralogy of Fallot was significantly associated with neurological anomalies ($\chi^2 = 4.1$, $p = 0.04$), indicating that patients with Tetralogy of Fallot might be more likely to have neurological anomalies. However, no substantial associations were observed between PDA and gastrointestinal anomalies ($\chi^2 = 3.2$, $p = 0.07$), or between coarctation of the aorta and other anomalies ($\chi^2 = 2.6$, $p = 0.11$). These associations suggest potential common developmental pathways or genetic predispositions that require further investigation.

The logistic regression analysis identified family history of anomalies as a significant predictor for the presence of multiple congenital anomalies (OR = 3.2, 95% CI: 1.8-5.7, $p = 0.00002$). This finding underscores the importance of detailed family history assessments in clinical practice, as patients with a family history of congenital anomalies are more likely to present with multiple defects. Other factors, such as age and gender, were not significant predictors of outcomes or complications. This suggests that age and gender do not substantially influence the likelihood of complications or outcomes in this patient population.

Regarding patient outcomes, 60.0% of the patients underwent surgical interventions, 30.0% required medical management, and 10.0% were managed conservatively. Follow-up data indicated that 83.3% of patients had favorable outcomes, 10.0% experienced complications, and 6.7% had unresolved issues. These results suggest that timely and appropriate interventions can lead to positive prognoses for the majority of patients.

This study highlights the importance of recognizing the associations between specific CHDs and non-cardiac anomalies, which can aid in early diagnosis and comprehensive management. The significant association between VSD and musculoskeletal anomalies, as well as between ASD and genitourinary anomalies, points to the need for a multidisciplinary approach in managing these patients. By understanding the potential common developmental pathways or genetic predispositions, healthcare providers can ensure holistic care and improved long-term outcomes for patients with congenital heart defects and associated non-cardiac malformations.

In individuals with a normal karyotype, recent research has provided important new understandings of the clinical and genetic features of congenital heart defects (CHDs) and their relationship to non-cardiac abnormalities. De novo and uncommon hereditary copy number variants (CNVs) were found in a sizable percentage of cases in a study of children with syndromic CHDs, emphasising the prevalence of CNVs in particular genomic regions such 1p36, 2q37, and 22q11.2, which were not found by standard approaches [5]. A high frequency of chromosomal abnormalities was discovered in another investigation employing low-depth whole-genome sequencing in foetuses with congenital cardiovascular anomalies, especially in cases with extracardiac findings. This discovery highlights the usefulness of genomic approaches in discovering CNVs [6].

Significant chromosomal abnormalities were found in a Chinese cohort of prenatally diagnosed CHDs;

conotruncal CHDs were shown to have a higher frequency of the 22q11.2 deletion than non-conotruncal CHDs. The significance of invasive testing for karyotyping and 22q11.2 deletion in foetuses with congenital heart defects is highlighted by this observation [7]. Furthermore, the aetiology of congenital heart defects (CHDs) has been linked to specific gene deletions. A study conducted on a family with CHDs caused by chromosome 8p23.1 deletion revealed that the deletion of the GATA4 gene was likely responsible for left ventricular noncompaction (LVNC) and VSD [8].

The clinical approach to CHDs, especially when associated with other malformations or syndromic conditions, necessitates a multidisciplinary approach to diagnosis and management. Genetic testing, including karyotyping and advanced genomic techniques, is crucial for identifying underlying genetic factors and informing personalized treatment plans [9]. Research on Turner syndrome patients with 45,X karyotype found that hidden Y chromosome material was not significantly correlated with congenital cardiovascular malformations, suggesting that other factors may contribute to the cardiac phenotypes observed in these patients [10].

A comprehensive study on fetuses with CHDs demonstrated the utility of karyotyping and chromosomal microarray analysis (CMA) in identifying genetic causes of cardiac anomalies, aiding in the management and genetic counseling of affected pregnancies [11]. Research on germline ABL1-associated CHDs and skeletal malformations syndrome expanded the known phenotypic spectrum to include additional features such as hearing impairment and renal hypoplasia, enhancing the understanding of the clinical variability associated with ABL1 mutations [12].

CONCLUSION

The study revealed a high prevalence of non-cardiac malformations in patients with CHDs and normal karyotypes. Significant associations were found between VSD and musculoskeletal anomalies, ASD and genitourinary anomalies, and Tetralogy of Fallot and neurological anomalies, suggesting common developmental pathways or genetic predispositions. Family history was a significant predictor of multiple congenital anomalies, highlighting the need for detailed assessments in clinical practice. Despite age and gender not being significant predictors, the majority of patients had favorable outcomes with timely interventions. These findings underscore the importance of a multidisciplinary approach for effective diagnosis and management of these patients.

LIMITATIONS

The limitations of this study include a small sample population who were included in this study. Furthermore, the lack of comparison group also poses a limitation for this study's findings.

RECOMMENDATION

Future research is needed to explore the genetic and developmental mechanisms underlying these associations. A multidisciplinary approach should be implemented in clinical practice to improve diagnosis and management of patients with CHDs and associated non-cardiac malformations.

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LIST OF ABBREVIATIONS

CHDs: Congenital Heart Defects
NCMs: Non-Cardiac Malformations
VSD: Ventricular Septal Defect
ASD: Atrial Septal Defect
PDA: Patent Ductus Arteriosus
OR: Odds Ratio
CI: Confidence Interval
CNVs: Copy Number Variants
LVNC: Left Ventricular Noncompaction
CMA: Chromosomal Microarray Analysis

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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