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Original Research Article

Prevalence of extracardiac malformations associated with congenital heart disease

Sailen Kumar Bana[1], Asok Kumar Mandal[1], Niranjan Nagaraj[2], Sameer Saraswat[2]*, Ankush Shukla[3]

[1]Department of Pediatrics, Dr. B. C. Roy Postgraduate Institute of Pediatric Sciences, Kolkata, India
[2]Department of Pediatrics, PGIMER, Dr. RML Hospital, New Delhi, India
[3]Department of Pediatrics, Dr. BLK Hospital, New Delhi, India

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***Correspondence:**
Dr. Sameer Saraswat,
E-mail: drsameersaraswat86@gmail.com

ABSTRACT

Background: Congenital heart disease is defined as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance. This study aims to know the prevalence of occurrence of extra cardiac malformations in patients with CHD, based on clinical features and necessary investigations when required and to study whether these extracardiac malformations occur as a part of a known syndrome or they occur in isolation.
Methods: This study is a cross sectional hospital based observational study, carried out in the Department of Paediatrics, Dr. B. C. Roy Postgraduate Institute of Paediatric Sciences, Kolkata over two years from July 2014 to June 2016. A thorough general physical examination, vitals, anthropometry was undertaken. Systemic examination was done in all cases according to the study proforma. CHD was confirmed by X-ray chest, Electrocardiography, Echocardiography.
Results: Twenty-three percentages (23%) of the patients were found to have an associated major ECM. Down syndrome was the most commonly identified syndrome in the present study accounting for 50% of the patients of CHD with an associated syndrome. The most common CHD among patients with Down syndrome were multiple CHD and VSD.
Conclusions: Whenever more than 1 minor anomalies are found, a careful search for an underling major malformation such as CHD should be made. In all cases of congenital heart diseases with associated extracardiac malformations, effort should be made by the treating pediatrician to rule out an associated syndrome; so that parents can be counselled about prognosis, recurrence in the subsequent pregnancies.

Keywords: Congenital heart disease, Extra cardiac malformation, Kolkata, Syndrome

INTRODUCTION

Congenital heart disease is defined as "a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance".[1] It also excludes electrophysiological disturbances (long QT and the Wolf- Parkinson-White syndromes) and lesions such as hypertrophic or dilated cardiomyopathy. The worldwide prevalence of CHD at birth ranges from 3.7-17.5 per 1000 live births. In Indian studies this has been found to be 3.9 per 1000 live births by Khalil et al and the value is 13.29 per 1000 live births in the study performed by Sawant et al.[2,3] The results of the Indian study might not represent the true burden of CHD in live births, since

these were hospital based studies. Since a large number of births in our country take place at home, mostly unsupervised by a qualified doctor, hospital statistics are unlikely to be truly representative.[4]

Apart from that, statistics of live births may miss out a large number of CHDs, which present later in life. The hospital admission rate from birth to 14 years for CHD between 2003-2004, in the NHS hospitals of England was found to be 1.8 per 1000 hospital admissions.[5] This is in contrast to the figure of 26.4 per 1000 hospital visits and admissions quoted by Kapoor et al, 8.58 per 1000 hospital admissions by Bhat et al, 8.55 per 1000 hospital admissions by Rajendra et al from India and to the figure of 5.8 per 1000 hospital admissions quoted by Shah et al, from Kathmandu.[6-9] High admission rate of CHD quoted by Kapoor et al, may be because of the inclusion of hospital OPD visits. It still reveals the magnitude of the problem. Recent investigations have clearly demonstrated a much higher incidence of inherited CHDs than previously thought, and it appears more likely that genetic variation can play a role in predisposition to the majority of heart defects.[10]

Hence authors intended to do a clinical study of extra cardiac malformations (ECM) associated with congenital heart disease (CHD); taking into account both their occurrence in isolation or as a part of a well-defined syndrome in a place which incidentally also has a high incidence of consanguineous marriage; thus, giving this study an added advantage of increased number of genetically acquired disorders. Since a detailed evaluation may not be possible in the community setting, this study was restricted to those children admitted in the hospital; which has also made possible to determine the prevalence of CHD in a hospital setting.

METHODS

This study is a cross sectional hospital based Observational study, carried out in the Department of Paediatrics, Dr. B. C. Roy Postgraduate Institute of Paediatric Sciences, Kolkata over two years from July 2014 to June 2016. Our institutional ethical committee approved this study. All children between 0 to 12 years of age; who were admitted in Paediatric ward. Written informed consents were taken from the parents or legal guardian after explaining them about the study in their local language. The number of subjects for this study was 100.8 ~ 100 with power 85%. (From the different studies done, expected proportion of the patients, amongst the cases has been assumed to be 60%).

Inclusion criteria

- All patients, old or new of the age group 0 to 12 years, who were admitted to this hospital with a diagnosis of congenital heart disease (CHD) or were found to have CHD on subsequent work up;
- The patients whose parents gave consent to include their child in this study.

Exclusion criteria

- Patients with CHD that require invasive procedures like angiography for confirmation
- Patients with CHD those were not structural.
- Patients, whose parents didn't give consent to include their children in the study.

A detailed history of the patient was taken from the parents in their local language on the day of admission. A predesigned proforma was used to interview the informant in which the necessary information was recorded in detail giving importance to the followings:

- Patients name
- Age
- Sex
- Religion
- Reason for admission
- Any family history of congenital heart disease
- History of consanguinity
- Past history of medical and surgical illness.

A thorough general physical examination, vitals, anthropometry was undertaken. Systemic examination was done in all cases according to the study proforma. Once the patient was diagnosed with a congenital heart disease, a detailed search was done by clinical examination for associated extra cardiac malformations. Findings were confirmed by the guide. If warranted, investigations such as ophthalmological evaluation, hearing assessment, skeletal surveys and ultra-sonogram of the abdomen were done based on the clinical features. The following investigations were done after obtaining informed consent from the parents: X-ray chest, Electrocardiography, Echocardiography. Pathological, microbiological and biochemical investigations were carried out as per disease profile of the patient.

Statistical analysis

For statistical analysis, data were entered into a Microsoft excel spreadsheet and then analyzed by SPSS 20.0.1 and Graph Pad Prism version 5. Data have been summarized as mean and standard deviation for numerical variables and count and percentages for categorical variables. The median and the interquartile range have been stated for numerical variables that are not normally distributed. Student's independent sample's t-test was applied to compare normally distributed numerical variables between groups; unpaired proportions were compared by Chi-square test or Fischer's exact test, as appropriate. Z-test (Standard Normal Deviate) was used to test the significant difference between two proportions. If the calculated *p*-value is below the threshold chosen for statistical significance (usually the 0.10, the 0.05, or 0.01

level), then the null hypothesis is rejected in favour of the alternative hypothesis. P-value ≤0.05 was considered for statistically significant.

The result of the study was then tabulated; different variables like age, sex, history of consanguinity, type of CHD was diagrammatically represented in pie or bar diagrams. Final outcome was then expressed in percentage and finally the results of the study were discussed in comparison to the previous similar studies and summarized.

RESULTS

A cross-sectional hospital based study was done in a tertiary paediatric referral hospital, between July 2014 and June 2016. During this time period, 100 cases were admitted either with a diagnosis of CHD, or a diagnosis of CHD was made after admission. The hospital admission rate for CHD was found to be 7.12 per 1000 paediatric hospital admissions. This study revealed that the admission rate for CHD, is higher in India when compared to developed countries. This study hence points to the need for better paediatric cardiology infrastructure in the present Indian scenario. The present study revealed that 10% of the patients had familial occurrence of CHD, which is similar to previous studies, and hence valuable for counselling of parents.

The most common age of admission was in the infancy and pre-school age group. This data has strong implications for the age group to be targeted for screening purposes. School based studies may not be ideal for the Indian situation, since the majority of the cases of CHD presented even earlier. History of consanguinity was elicited in in 17% cases of CHD which implicates the deleterious effect of consanguineous marriage and hence the need of social awareness in this aspect twenty-three percentages (23%) of the patients were found to have an associated major ECM. This huge number highlights the importance of the role played by genetics in CHD.

Table 1: Prevalence of specific syndromes.

Syndromes	No. of cases	Percentage
Down Syndrome	9	50.0%
Congenital Rubella syndrome	3	16.7%
Ellis-Van-Crevald syndrome	1	5.6%
Goldenhar syndrome	1	5.6%
Holt-Oram syndrome	1	5.6%
Sturge- weber syndrome	1	5.6%
Turner syndrome	1	5.6%
Velocardiofacial syndrome	1	5.6%
Total	18	100.0%

More than one third of these patients had an associated recognizable syndrome and hence paediatricians should be able to identify at least those commonly occurring syndromes, for the proper evaluation and counselling.

Table 2: Prevalence of ECM in acyanotic and cyanotic CHD.

Type of malformations	Number and percentage of cases of Acyanotic CHD	Number and percentage of cases of Cyanotic CHD	Total number and percentage of cases
Major	12	4	16
Row %	75.0	25.0	100.0
Col %	17.1	13.3	16.0
Major + Minor	5	2	7
Row %	71.4	28.6	100.0
Col %	7.1	6.7	7.0
Minor	16	5	21
Row %	76.2	23.8	100.0
Col %	22.9	16.7	21.0
NO ECM	37	19	56
Row %	66.1	33.9	100.0
Col %	52.9	63.3	56.0
TOTAL	70	30	100
Row %	70.0	30.0	100.0
Col %	100.0	100.0	100.0

8% of the patients were admitted mainly for surgical conditions related to these ECM, and hence this study highlights the importance of proper cardiac evaluation of surgical patients. The present study is a step forward towards further research into the genetic basis of CHD.

Down syndrome was the most commonly identified syndrome in the present study accounting for 50% of the patients of CHD with an associated syndrome. The most common CHD among patients with Down syndrome were multiple CHD and VSD. Only after proper

evaluation of the genotype phenotype correlation, future research be directed towards novel therapies for CHDs such as gene therapy. In this post-genomic era, future studies will be able to help us fully understand the genetic basis of CHD and treating them even in in-utero, by non-surgical techniques.

Table 3: System wise frequency of major ECM.

System-wise distribution of ECM	No. of cases With major ECM	Percentage of cases with major ECM
CNS	7	30.4%
Gastro-intestinal	7	30.4%
Musculoskeletal	4	17.4%
Renal	2	8.7%
Multiple major ECM	2	8.6%
EYE	1	4.3%
Total	23	100.0%

DISCUSSION

In the BWIS, study of 2102 neonates with CHD, significant ECM was found in 26.8%; 18.5% of the neonates had a clinically recognizable syndrome whereas the rest 8.3% of the neonates had an isolated ECM. [11] Similarly, Greenwood et al, found ECM in 25.2% of the neonates with CHD, two thirds of whom belonged to recognizable syndrome.[12] In the present study, major extracardiac malformation was noted in 23 % of patients. This finding is in accordance with the previous studies.

Out of these 23% of patients with major ECM, isolated major ECM was noted in 14% of cases and in rest 8% of cases with major ECM, a clinically recognisable syndrome was identified. The above mentioned finding of this study might have following implications: the association with ECM in more than one third of the cases means there is a genetic etiology behind CHD. As has been discussed in the review of literature, several genes and their signalling molecules play a role in the development of heart, and in the causation of CHD; knowledge of this association of CHD with ECM implies that the paediatrician should search for associated anomalies and if possible should try to fit the condition into a recognizable syndrome. This will help in further counselling of the parents and for proper medical and surgical care.

Profile of major ECM

According to various studies, the most commonly affected system in patients of CHD with ECM, are the musculoskeletal and gastrointestinal.[12,13] In the present study, 60.8% of major ECM, were noted in the central nervous system and gastrointestinal system and the remainder were in the musculoskeletal, genitourinary system, eye. It is worthy to note that that ECM involving the gastrointestinal system in the present study such as biliary atresia, choledochal cyst and hirschprung's disease were surgical conditions. These conditions were the cause for the admission in the 30.4% of the patients of CHD with major ECM. This underlines the importance of proper cardiac evaluation of infants prior to gastrointestinal surgery, even in cases of emergency for anaesthetic and prognostic consideration. Due to the small size of the study population, association of a particular major ECM with a particular CHD could not be made.

Minor ECM

The prevalence of minor anomalies in the general population varies from 7.26% to 40.7%. The prevalence of minor ECM in children with CHD, was found to be 41.9% by Kramer et al.[14] Occurrence of more than 3 minor anomalies has been associated with a major anomaly in 90% of the individuals. In the present study, minor ECM was found in 28% of the study group. Single minor anomaly was noticed in 13% of cases whereas more than 3 anomalies were noticed in 11% of cases. It is noteworthy that 25% of cases, who had minor ECM, also had one underlying major ECM. Since there is no prevalence studies for the different numbers of minor malformations found in the general population, this particular data is not comparable. However, the implication of this finding is that whenever more than 1 minor anomaly is found, a careful search for an underling major malformation such as CHD should be made.

Prevalence of specific syndromes and associated CHD

Genetic syndromes, including chromosomal disorders, are commonly associated with CHD. In the BWIS, 18.5% of the patients with CHD with associated ECM were found to have a genetic syndrome.[10] In recent times, Grech and Gatt, found that 65% of the individuals with CHD and associated ECM had a recognizable genetic syndrome.[15]

In the present study, 34.8% of the patients with CHD and extarcardiac malformations had a clinically recognizable syndrome. Present study results are similar to that found in BWIS. The most commonly found genetic syndrome in all of the previously published literature on ECM in children with CHD was Down syndrome. This study is in accordance with this statement, and Down syndrome, was identified in 50% of all the syndromic cases of the study. The most commonly associated CHD with Down syndrome was multiple CHD which occurred in 44.4% of cases of Down syndrome. It was followed by VSD which occurred in 22.2% of cases. The results of this study indicate that, there is a high association of CHD with clinically recognizable syndrome, and effort should be made by the treating paediatrician to rule out an associated syndrome; so that parents can be counselled about prognosis, recurrence in the subsequent pregnancies.

Due to the small size of the study population, association of a particular major ECM with a particular CHD could not be made. The current study is a clinical study. In this postgenomic era, a large multicentre genetic approach is required to study the genetic etiology of different congenital heart disease.

CONCLUSION

Whenever more than 1 minor anomalies are found, a careful search for an underling major malformation such as CHD should be made. In all cases of congenital heart diseases with associated extracardiac malformations, effort should be made by the treating paediatrician to rule out an associated syndrome; so that parents can be counselled about prognosis, recurrence in the subsequent pregnancies. An equal importance should be given in training of the surgical professional regarding the surgical management of commonly encountered congenital heart diseases. More research work is needed in this field; particularly a multi-centric study encompassing populations both from community and hospitals, so as to derive the genetic etiology of different types of congenital heart diseases.

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