CLINICAL STUDY OF EXTRACARDIAC MALFORMATIONS ASSOCIATED WITH CONGENITAL HEART DISEASE

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ABSTRACT

BACKGROUND AND OBJECTIVES

In this post genomic era, congenital heart diseases (CHD) are still the most common and most lethal of all birth defects in children. The genetic basis is expressed in the form of concomitant occurrence of extracardiac malformations (ECM) which may occur alone or as a part of a syndrome. The present study was undertaken with the main objectives as to find the burden of CHDs in the hospital's admission and to find the prevalence of occurrence of clinically recognizable extracardiac malformations associated with CHDs.

METHODS

This was a cross-sectional hospital based observational study, done in a tertiary pediatric referral hospital, between the time period August 2013 and September 2014. Patients admitted to the pediatric general wards, PICU and NICU, either with a diagnosis of CHD or in whom a diagnosis of CHD was made after admission, were included in the study. The patients were clinically examined in detail for associated ECM, when present patients were grouped as either belonging to a clinically recognizable genetic syndrome or as an isolated occurrence of ECM.

RESULTS

The hospital admission rate was found to be 16.7 per 1000 pediatric hospital admissions. 31% of the patients with CHDs were found to have an associated significant ECM.

INTERPRETATION AND CONCLUSION

A high rate of hospital admission were found for CHDs in the pediatric setting, underscoring the need for improvement of pediatric cardiology infrastructure in the Indian scenario; This also undermines the importance of recognizing these anomalies and associated syndromes for complete evaluation of the patient

KEYWORDS

Heart Defects; Congenital; Congenital Abnormalities.

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INTRODUCTION: Congenital heart diseases (CHD) refer to structural or functional heart diseases, which are present at birth. There are diagnostic tools available today by which an accurate diagnosis of CHD can be made even before birth. Although there have been tremendous advances in diagnosis and treatment of CHD, our knowledge of the causes of CHD has been limited but has advanced in recent years. Improved understanding of possible causes will permit insight into the pathobiological basis of the congenital heart problem and allow definition of disease risk. 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.[1] i.e. CHD and it's associated extra cardiac defects especially those that can be found on physical examination with minimal investigations. Since a detailed evaluation may not be possible in the community setting, we have restricted our study to those children admitted in the hospital; which has also made possible to determine the prevalence of CHD in a children's hospital setting.

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OBJECTIVES: The objectives of the present study includes. To identify the prevalence of CHD in a children's hospital setting. To study the prevalence of occurrence of ECM in CHD based on clinical features. To classify these ECM in 2 groups; one, when they occur as a part of a known syndrome; the other, when they occur in isolation.

METHODOLOGY: This is a cross-sectional hospital based study, done on 100 children, who were admitted between August 2013 and September 2014.

Source of Data: Children who were admitted to either the pediatric intensive care unit, general ward or to the neonatal intensive care unit of Kakatiya Medical College/MGM Hospital, Warangal.

Sample Size: Patients admitted between the periods August 2013 to September 2014, who were found to have a CHD; which amounted to 100, were studied.

Inclusion Criteria: All patients, old or new, who were admitted to the above said hospital, either with a diagnosis of CHD, or who were found to have CHD.

All cases in the pediatric age group (0-12 years) have been included irrespective of sex. Informed consent from all the patients was taken before undergoing the study.

Exclusion Criteria: Patients who do not have echocardiographic confirmation of the CHD. Patients with Patent Ductus Arteriosus who were less than 6 months of age. Patients with CHD that required angiogram for confirmation of diagnosis. Patients with CHD that were not structural in nature. Those patients who refused to be included in the study.

Study Design: This is a cross-sectional hospital based observational study. In this children from 0-12 years, who were admitted with a diagnosis or who were found to have CHD were studied.

Detailed note was made regarding, the rationale behind admission, family history of CHD, consanguinity among parents and prior investigations if any, as per the proforma designed for the study.

Investigations that were done included the following;

- Echocardiography; If not done previously.
- Electrocardiogram and chest X-ray as a part of work up of CHD.
- Other investigations, such as ophthalmological evaluation, hearing assessment, skeletal surveys, ultra-sonogram of the abdomen and genetic studies (Karyotyping & FISH analysis); were done if anomalies were expected based on clinical data.
- Investigations which were attributable, to the reason for admission, such as complete hemogram and blood culture in cases of infective endocarditis.

Once the patients were diagnosed with a CHD, a detailed search was done by clinical examination for associated congenital anomalies. Findings were confirmed by a senior genetist. If warranted, investigations such as ophthalmological evaluation, hearing assessment, skeletal surveys and ultra-sonogram of the abdomen were done based on the clinical features.

Patients were then divided into 2 group. Group – I (Non-Syndromic group), consisted of patients with no ECM or patients with ECM but with no clinically identifiable syndrome. Group – II (Syndromic group), consisted of patients who fit into clinically recognizable syndrome (e.g. Down syndrome). Syndrome delineation were done according to guidelines set forth by authorities in the field of dysmorphology.[2,3,4,5]

Statistical Analysis: Comparative analysis was done by test of proportions and chi-square test. 95% confidence interval was found for the prevalence of ECM among patients with CHD.

RESULT:

Total no. of patients admitted during the study period	**5984**
No. of patients with CHD	100
Hospital admission rate	16.7/1000 admissions

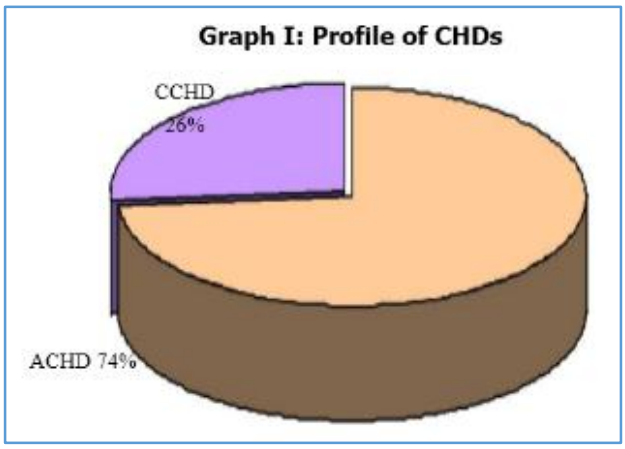
Table 1: Hospital admission rate

During the period August 2013 – September 2014, 5984 patients were admitted to the pediatric department of MGM hospital, Warangal a tertiary referral hospital. This figure was inclusive of patients admitted to the pediatric intensive care unit, pediatric general ward and the neonatal intensive care unit. Of these 100 patients were either admitted with a diagnosis of CHD or a diagnosis of CHD was made after admission. This gives a hospital admission rate for CHD, as 16.7 per 1000 admissions.

Acyanotic CHD	**No. of cases**	**Cyanotic CHD**	**No. of cases**
VSD	32	TOF	10
ASD	10	TGA	7
PS	7	TAPVC	3
AVSD	6	TAT	2
DX	6	TAR	2
PDA	4	HLHS	2
CA	2		
AR	2		
AS	1		
MR	1		
MS	1		
CT	1		
EA	1		
Acyanotic Total	**74**	**Cyanotic Total**	**26**

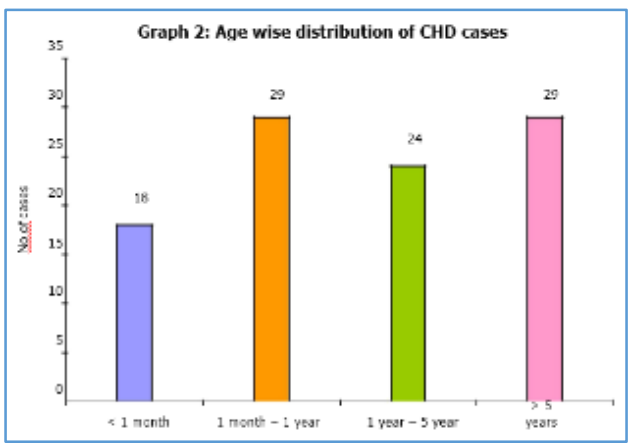
Table 2: Profile of CHD

Out of a total of 100 cases of CHD, 74 of the cases were acyanotic, whereas 26 were cyanotic. The predominant acyanotic CHD was found to be VSD and the predominant cyanotic CHD was found to be TOF.



Age at admission	No. of patients
< 1 month	18
1 month – 1 year	29
1 year – 5 year	24
> 5 years	29
0 – 12 years (Total)	**100**

Table 3: Age distribution of patients admitted with CHD

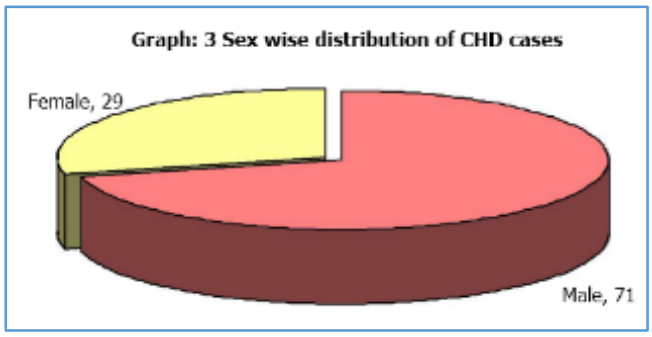


Out of the total 100 cases of CHD, 18 were admitted in the neonatal period, 29 in their infancy, 24 during the preschool period and 29 in later childhood. More than 50% of the patients were admitted in the infancy and preschool age group.

Type of CHD	Acyanotic CHD (n=74)	Cyanotic CHD (n=26)	All CHDs (n=100)
Male	53 (71.6%)	18 (69.2%)	71 (71%)
Female	21 (28.4%)	8 (30.8%)	29 (29%)

Table 4: Sex distribution of patients admitted with CHD

Males formed the major share of the patients, accounting for 71% of the total study group. This finding was consistent in both acyanotic and cyanotic type of CHD and no statistical difference was found.



Presence of significant ECM	Patients with CHD (n=100)
Yes	31
No	69

Table 5: Prevalence of significant ECM (ECM and clinically recognizable Syndromes) in patients with CHD.

Prevalence of significant ECM in CHD=31%.
95% Confidence Interval=22-40%.

Out of the total study group, 31 patients had a significant ECM associated. Significant ECM referred to either a major ECM (those malformations with a significant medical or cosmetic consequences) or a clinically recognizable genetic syndrome.

Type of ECM	No. (%) of patients with non-syndromic (n=82)
No malformation	33 (- 40.20%)
Major ECM	13 (- 15.80%)
Minor ECM	40 (- 48.80%)
Major + Minor ECM	4 (- 4.90%)

Table 6: Prevalence of ECM in the group – I

15.8% of the non-syndromic group were found to have a major ECM (those with a significant medical or cosmetic consequences). 48.8% of the patients in this group were found to have minor malformations. 4.9% of the patients belonging to this group were found to have both minor and major ECM.

Type of ECM	Types of CHD in each case (n=13)
Anorectal malformations	TOF
	DX
	DX
Biliary atresia	TGA
Joint contractures with camptodactyly	TAT
Choledochal cyst with polysyndactyly	ASD
Cleft palate	TGA
Situs inversus	DX
	DX

CTEV	VSD
Facial cleft	VSD
PUJ obstruction	VSD
Hirschprung's disease	VSD

Table 7: Profile of ECM in group – I

The different types of major ECM encountered in group-I is listed, along with the particular type of CHD that they were found associated with. Total of 13 cases were found with major ECM. Dextrocardia and VSD were the most common acyanotic CHD, whereas TAT and TGA were the cyanotic CHD associated with ECM.

DISCUSSION: HOSPITAL ADMISSION RATE FOR CHD: The worldwide prevalence of CHD at birth ranges from 3.7-17.5 per 1000 live births; in India based on a single study this has been found to be 3.9 per 1000 live births.[6.7] The results of the Indian study might not represent the true burden of CHD in live births, since it was a hospital based study. 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.[8] Furthermore statistics of live births may miss out on a large number of CHDs, which present later than at birth. Community based prevalence of CHD, such as those done in school based studies have revealed a prevalence of 0.8 to 5.2 of CHD per 1000 children in India.[9.10,7.11 12]

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.[13] This is in stark contrast to the figure of 26.4 per 1000 hospital visits and admissions quoted by Kapoor et al., from India and to the figure of 5.8 per 1000 hospital admissions quoted by Shah et al., from Kathmandu.[14,15] Though the huge admission rate of CHD quoted by Kapoor et al., maybe because of the inclusion of hospital OPD visits, it still reveals the magnitude of the problem. Another bias in the comparison of the studies from Kathmandu and India to that of the one done in England, might be because the studies done in England incorporated all levels of hospitals, whereas those done elsewhere included only admissions to tertiary care centre.

In the present study the hospital admission rate for CHD from birth to 12 years, covering the entire pediatric age group, was found to be 16.7 per 1000 hospital admissions. A similar picture of 16.5 patients with CHD per 1000 hospital admissions was found in a tertiary care centre in Bombay.[16] Compared to the study done by Kapoor et al., we found a lower prevalence, which may be because the present study did not include OPD patients and was solely restricted to IPD patients. Compared to the study done in England and Kathmandu, the present study reveals a huge case load.

AGE DISTRIBUTION OF PATIENTS: CHDs may be diagnosed at virtually any age. Some conditions always are discovered in neonates; others rarely are identified during infancy.[17] Nearly one third to half of the CHDs are critical, requiring intervention in the first year of life itself.[8]

53% of the admitted children in the present study were less than 5 years of age; which is in concordance with the above statement. The age profile of CHD in the present study is similar to other studies reported from India which were based on hospital admissions.[14,16]

VSD, ASD and TOF were more likely to present after the neonatal period, whereas serious CHDs such as TAT, TAR and TAPVC usually present in the neonatal period. In view of the small study group, data cannot be extrapolated to the general population. But the data does help one to envisage the importance of a thorough cardiovascular examination in the infant and preschooler. A hospital based screening program for CHD, should target this particular age group for maximum efficiency.

SEX DISTRIBUTION OF PATIENTS ADMITTED WITH CHD: Gender difference in the incidence of childhood diseases has long been recognized, usually being unfavorable to the male sex. These can be due to the following reasons.[18]

The first explanation is that during childhood the extra X-chromosome or the absence of the Y-chromosome confers an inherent survival advantage and these admission differentials reflect inherent differences in susceptibility to a wide range of diseases – Sex limitation.

The second is that of the possibility of X-linked disorders, wherein females tend to remain as carriers and males are affected – Sex linkage.

The third explanation would be a social one. Parents, favoring the male offspring, may visit healthcare facilities more readily than they would with their female offspring – Social.

The fourth explanation, maybe simply due to more of male individuals in the population.

In the BWIS, there was no major gender disparity in the prevalence of CHD in live births except, in case of TGA, wherein a male predominance was found.[19] This statement also holds true in the Indian study done by Khalil et al., who found no significant gender disparity in the incidence of CHD in live births.[7] Furthermore there was no gender disparity found by Vashishta et al., in the their study done to find the prevalence of CHD in school going children.[10]

PROFILE OF CHD: In a global perspective, the BWIS; the largest and most comprehensive case control study of CHD to date; showed a wide spectrum of specific types of CVM with a considerable range of prevalence[19]. VSD was by far the most frequently reported anomaly (9.87 per 10,000 live births), two to three times as common as the next most frequently reported anomalies, pulmonic valve stenosis (3.78 per 10,000). In the Indian context, the profile of CHD is similar with VSD topping the list, followed by ASD and TOF in studies done in community basis and in live born.[10,11.12,20,21]

Hospital setting also reveals a similar clinical picture in India, with the majority being attributed to VSD, ASD and TOF.[14.15,16]

In the present study the most common CHD was found to be VSD which accounted for 32% of the total no. Of cases. This is in accordance with previously done studies. VSD was followed by ASD and PS in frequency of occurrence. The most common cyanotic CHD was TOF, which is also in accordance with other studies done in India. Thus one can see, whether done in live births, community basis or in hospital admissions the profile of CHD remains relatively stable, with VSD, ASD, PS and TOF being the most common. This has implications for the training of surgical professionals and also for interventional cardiologists.

PREVALENCE OF SIGNIFICANT ECM (MAJOR ECM AND CLINICALLY RECOGNIZABLE SYNDROME) IN PATIENTS WITH CHD: Congenital cardiac malformations are frequently associated with other non-cardiac congenital malformations and chromosomal anomalies. Such patients may require intervention of a surgical or medical nature independently from the cardiac problem. 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[20] Similarly Greenwood[22] et al., found ECM in 25.2% of the neonates with CHD, two thirds of whom belonged to recognizable syndrome.[23] The prevalence varies from 13%-66% based on various studies, being highest in necropsy studies and in those studies done in the fetal period.[24-31] In the Indian scenario there has been one prior similar study done in 1975, in which 4.75% of the patients with CHD were found to be associated with syndromes.

In the present study 31% of the patients with CHD, had an associated significant ECM. Significant ECM refers to either an associated syndrome or a major ECM. 95% confidence interval was found to be 22–40%. Of this 31% of patients with significant ECM, 58.1% were found to have a clinically recognizable syndrome and in the remaining 41.9% ECM was found to occur in isolation. The results of this present study are in accordance with the previously done studies. The stark contrast found with the previously done Indian study, could be secondary to the fact that the study done by Rao and Reddi, was based on only clinically diagnosed CHDs and they mentioned only those cases that had syndromes, and not isolated ECM.[27]

Though this was not a comparative study with a control group. A study done in normal neonates by Kulkarni[28] et al., found the prevalence of congenital malformations to be 3.9%[28] worldwide prevalence of major anomalies ranges from 1.6–6.9%.[29.3,3,4] Thus one can see that the finding in the present study of 31% of patients with CHD, is significant.

This finding has many strong implications, firstly the association with ECM in more than one third of the cases, means there is a strong genetic etiology behind several genes and their signaling molecules play a role in the development of heart, and in the causation of CHD. The genetic basis of several of the syndromes has also been clearly elucidated. But what causes these defects in these widely separate body regions, is but an enigma and further research is required. One positive step in understanding this is the concept of "evolutionary module" proposed by Kirby.[31] Modules are semi-autonomous units that can take the form of morphological fields, gene regulation networks, signaling, cell types, and so forth. This broad concept of modular development provides a substrate for understanding how gradual changes can take place in evolution by affecting these semi-autonomous units without compromising the viability of the organism as a whole. This same concept of modules is useful in understanding how certain sequences of malformations might occur.

Secondly knowledge of this association of CHD with ECM, allows the pediatrician to diligently search for associated anomalies and if possible to fit the condition into a recognizable syndrome. This will help in further counselling of the parents and for proper medical and surgical care.

CONCLUSION: The hospital admission rate for CHD was found to be 16.7 per 1000 pediatric hospital admissions. This study revealed that the admission rate for CHD, is higher in India when compared to developed countries such as the UK. This study hence points to the need for better pediatric cardiology infrastructure in the present Indian scenario.

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. A strong gender bias was found in this study, with more males being admitted with a diagnosis of CHD.

31% of the patients were found to have an associated significant ECM, this huge number highlights the importance of the role played by genetics in CHD. More than half of these patients had an associated recognizable syndrome and hence pediatricians should be able to identify atleast those commonly occurring syndromes, for the proper evaluation and counseling.

The present study is a step forward towards further research into the genetic basis of CHD. Only after proper elucidation of the genotype phenotype correlation, can future research be directed towards novel therapies for CHDs such as gene therapy. In this post-genomic era, with the vast amount of information that we have acquired about the human genome, future studies will be able to help us fully understand the enigma of CHD and treating them even in in-utero, by non-surgical techniques.

ABBREVIATIONS:

1. ACF-> Asymmetrical crying facies.
2. AR -> Aortic regurgitation.
3. ARM-> Anorectal malformation.
4. AS-> Aortic stenosis.
5. ASD-> Atrial septal defect.
6. AVSD-> Atrio-Ventricular septal defect.
7. BMP -> Bone morphogenetic protein.
8. BWIS -> Baltimore Washington infant study.
9. CATCH ->22 Cardiac abnormality, abnormal facies, thymic aplasia, cleft.
10. CCF-> Congestive cardiac failure.

11. CHD -> Congenital heart disease.
12. COA -> Coarctation of aorta.
13. CS -> Cyanotic spell.
14. CT -> Cor-Triatriatum.
15. CTEV -> Congenital talipes equino varus.
16. DNA -> Deoxyribonucleic acid.
17. DORV -> Double outlet right ventricle.
18. DX-> Dextrocardia.
19. EA -> Ebstein's anomaly.
20. ECM-> Extra cardiac malformation.
21. EVC-> Ellis Van Crevald syndrome.
22. FGFs -> Fibroblast growth factors.
23. FISH -> Fluorescent in situ hybridization.
24. GH-> Growth hormone.
25. HLHS -> Hypoplastic left heart syndrome.
26. IE-> Infective endocarditis.
27. LEOPARD -> syndrome Lentigines, electrocardiographic conduction abnormalities,
28. LRTI-> Lower respiratory tract infection
29. MR-> Mitral regurgitation.
30. MRI-> Magnetic resonance imaging.
31. MS-> Mitral stenosis.
32. NHS-> National health services.
33. NS-> Noonan syndrome.
34. PA-> Pulmonary atresia.
35. PDA->Patent ductus arteriosus.
36. PS ->Peripheral pulmonary artery stenosis.
37. PS-> pulmonary stenosis.
38. SVAS-> Supravalvular aortic stenosis.
39. TA ->Tricuspid atresia.
40. TAPVC-> Total anomalous pulmonary venous connection.
41. TAT ->Truncus arteriosus.
42. TGA ->Transposition of great arteries.
43. TGFBR ->Transforming growth factor beta receptor.
44. TOF-> Tetralogy of Fallot.
45. VCFS-> Velocardiofacial syndrome.
46. VSD-> Ventricular septal defect.
47. WBS ->Williams Beuren Syndrome.

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