Original Article

Clinical Study of Extra Cardiac Malformations Associated with Congenital Heart Disease

Vamshidhar Reddy Vade, Prithvi Yadavelli*

Department of Pediatrics, Dr. Patnam Mahender Reddy Institute of Medical Sciences, Chevella, Ranga Reddy District, Telangana, India.

***Corresponding author's E-mail:** articlegimsr@gmail.com

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ABSTRACT

Objective: The main objectives of the present study are to find the burden of CHDs in the hospital's admission and also to find the prevalence of occurrence of clinically recognizable extracardiac malformations associated with CHDs.

Materials and Methods: This was a cross-sectional observational study done in a tertiary pediatric referral hospital, between the time period September 2016 and September 2018. Patients were included in the study are those who admitted to the pediatric general ward, PICU and NICU, either with a diagnosis of CHD or in whom a diagnosis of CHD was made after admission. The patients were examined clinically in detail for associated ECM. When any malformation present, patients were grouped in to two, one belonging to a clinically recognizable genetic syndrome or as an isolated occurrence of ECM.

Results: The hospital admission rate was found to be 17.6 per 1000 pediatric hospital admissions. 31% of the patients with CHDs were found to have an associated significant ECM. Of this 58.1% of the ECM occurred as a part of a clinically recognizable syndrome and the rest were isolated anomalies. A high rate of hospital admission was found for CHDs in the pediatric setting, underscoring the need for improvement of pediatric cardiology infrastructure in the Indian scenario; which should help in providing better medical and surgical care for the patients with CHD.

Conclusion: A significant proportion of patients with CHD had associated ECM, implicating a genetic background for the etiology of CHD. This also undermines the importance of recognizing these anomalies and associated syndromes for complete evaluation of the patient and adequate counseling of the parents.

Keywords: Heart Defects; Congenital; Congenital Abnormalities; Consanguinity.

INTRODUCTION

Congenital heart diseases (CHD) refer to structural or functional heart diseases, which are present at birth. Some of these may be discovered later. These are primarily seen in neonates, infants and children; although in our country it is not uncommon to see adults with uncorrected CHD. The burden of congenital heart disease in India is likely to be enormous, due to a very high birth rate. This heavy burden emphasizes the importance of this group of heart diseases. The reported incidence of CHD is 8-10/1000 live births according to various series from different parts of the world. It is believed that this incidence has remained constant worldwide. Nearly one third to half of these CHDs is critical, requiring intervention in the first year of life itself. Rapid advances have taken place in the diagnosis and treatment of CHD over the last 6 decades. There are diagnostic tools available today by which an accurate diagnosis of CHD can be made even before birth. With currently available treatment modalities, over 75% of infants born with critical heart disease can survive beyond the first year of life and many can lead near normal lives thereafter. The prevalence of CHD in the Indian subcontinent based on birth statistics and school based studies varies from as low as 0.8 to 5.2/1000 live births depending upon the age group considered[1-4]. The burden of congenital heart disease in the pediatric population in a hospital setting in India including inpatient and outpatient was found to be 26.4/1000patients[5]. 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; two critical elements for disease prevention. The importance of genetic factors in the etiology of CHD is demonstrated by clinical, epidemiological and embryological studies. 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[6]. For the clinician caring for a child with CHD, it is very important to determine whether there is an underlying genetic pattern (eg: deletions, duplications, or mutations), for the following reasons[7] - there may be other important organ system involvement; there may be prognostic information for clinical and surgical outcomes; there may be important genetic reproductive risks the family should know about; there may be other family members for whom genetic testing is appropriate. Indians with their extremely high rate of in-breeding are at a very high risk for perturbations of the human genome and the resultant malformations. In addition to the factors stated above, the burden of multitudes of myths and folklore leads to a concatenation of situations for an Indian parent to have a child with not only a CHD but also external anomalies, that creates an aura of fear, guilt and marital disharmony rather than

sympathy and empathy for the child. Thus, the state of an Indian pediatrician being symbiotically paired with knowledge of malformations that occur in association with CHD is of paramount importance. Furthermore, in a country like ours where the tentacles of poverty reach out to all aspects of life; genetic testing with the exuberant cost involved is not yet in the reach of most of the population. Hence in the current scenario a clinical approach to this problem of genetic aetiology to CHD seems much more appropriate. A clinical approach to a genetic condition necessarily translates into dysmorphology since we are dealing with a malformation i.e. CHD and it's associated extra cardiac defects especially those that can be found on physical examination with minimal investigations. Hence the present study is intended to do a clinical study of extracardiac malformations (ECM) associated with 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 my study an added advantage of increased number of genetically acquired disorders. Since a detailed evaluation may not be possible in the community setting, the study restricted to those children admitted in the hospital; which has also made possible to determine the prevalence of CHD in a children's hospital setting.

MATERIALS AND METHODS

Study design: This is a cross-sectional hospital based study, done on 100 children, who were admitted between September 2016 and September 2018.

Source of data: Children who were admitted to either the pediatric intensive care unit, general ward or to the neonatal intensive care unit of M.N.R hospital, Sangareddy.

Study period: Patients admitted between the period of September 2016 to September 2018.

Sample size: The study sample size was 100 children who were found to have a CHD.

Informed consent: The study was conducted after taking the informed consent from all the ten patients.

Ethics clearance: The study was conducted after obtaining the Ethics clearance from the hospital.

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 (0-18years) has 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 was not structural in nature.
- Those patients who refused to be included in the study.

METHODOLOGY

This is a cross-sectional hospital based observational study. In this child from 0-18 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, ultrasound of the abdomen and genetic studies (Karyotyping & FISH analysis) were done if anomalies were expected based on clinical data. Investigations which were attributable, to there as on for admission, such as complete hemogram and blood culture in cases of infective endocarditis were done. Once the patients were diagnosed with a CHD, a detailed search was done by clinical examination for associated congenital anomalies. If warranted, investigations such as ophthalmological evaluation, hearing assessment, skeletal surveys and ultrasound of the abdomen were done based on the clinical features.

Patients were divided into 2 groups. Group – I which includes Non-Syndromic group), consisted of patients with no ECM or patients with ECM but with no clinically identifiable syndrome and Group – II which include Syndromic group, consisted of patients who fit into clinically recognizable syndrome example like Down syndrome. Syndrome delineation were done according to guidelines set forth by authorities in the field of dysmorphology[7-8]. The ECM, when found in group – I, were subdivided into minor and major malformations. A major anomaly is one that has severe medical or cosmetic consequences. A minor anomaly represents a medically insignificant departure from normal development, such as wide-set eyes or a single palmar crease[7-10].

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.

RESULTS

During the period September 2016 – September 2018, 5674 patients were admitted to the pediatric department of M.N.R hospital, a tertiary referral hospital. It was inclusive of patients admitted to the pediatric intensive care unit, pediatric general ward and the neonatal intensive care unit.

Table 1: Profile of CHD

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

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 17.6 per 1000 admissions. 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 (Table 1).

Out of the total 100 cases of CHD, 18 were admitted in the neonatal period, 29 in their infancy, and 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 (Figure 1). Critical cyanotic CHD such as HLHS, TAT, TAR and TAPVC were more likely to be admitted in the neonatal period. Acyanotic CHD were more likely to present later in childhood (Table 2).

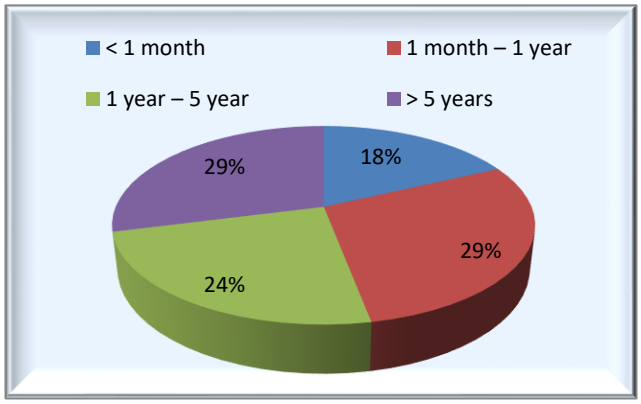

Figure 1: Age distribution of patients admitted with CHD

Table 2: Age at admission for different types of CHD

CHD	<1 month No. (% of the total no. of specific CHD)	1 month – 1 year No. (% of the total no. of specific CHD)	1 year – 5 years No. (% of the total no. of specific CHD)	>5 years No. (% of the total no. of specific CHD)
VSD (n=32)	4(12.5)	10(31.3)	8(25)	10(31.3)
ASD (n=10)	1(10)	2(20)	4(40)	3(30)
PS (n=7)	-	1(14.3)	2(28.6)	4(57.1)
AVSD (n=6)	2(33.3)	3(50)	-	1(16.7)
DX (n=6)	3(50)	1(16.7)	1(16.7)	1(16.7)
PDA (n=4)	-	2(50)	2(50)	-
COA (n=2)	-	-	1(50)	1(50)
AR (n=2)	-	-		2(100)
AS (n=1)	-	-		1(100)
MR (n=1)	-	-		1(100)
MS (n=1)	-	-		1(100)
CT (n=1)	-	-	-	1(100)
EA (n=1)	-	-	-	1(100)
Acyanotic (n=74)	10(13.5)	19(25.7)	18(24.3)	27(36.5)
TOF (n=10)	-	3(30)	5(50)	2(20)
TGA (n=7)	1(14.3)	5(71.4)	1(14.3)	-
TAPVC (n=3)	3(100)	-	-	-
TAR (n=2)	1(50)	-	1(50)	-
TAT (n=2)	1(50)	1(50)	-	-
HLHS (n=2)	2(100)	-	-	-
Cyanotic (n=26)	8(30.8)	9(34.6)	7(26.9)	2(7.7)

Table 3: Sex distribution of patients admitted with CHD

Type of CHD	Acyanotic CHD (n=73)	Cyanotic CHD (n=27)	All CHDs (n=100)
Male	53 (71.6%)	18 (69.2%)	71 (71%)
Female	21 (28.4%)	8 (30.8%)	29 (29%)
X2 = 0.05; P = 0.82 – not significant			

Table 4: Parental consanguinity among patients admitted with CHD

CHD	Total No. of Patients	Non-consanguineous parents (% of the type of CHD)	Consanguineous parents (% of the type of CHD)
Acyanotic CHD	74	43 (58.1)	31(41.9)
Cyanotic CHD	26	10 (38.5)	16(61.5)
All CHDs	100	53 (53)	47 (47)
X2 = 2.98; P = 0.08 – Not significant			

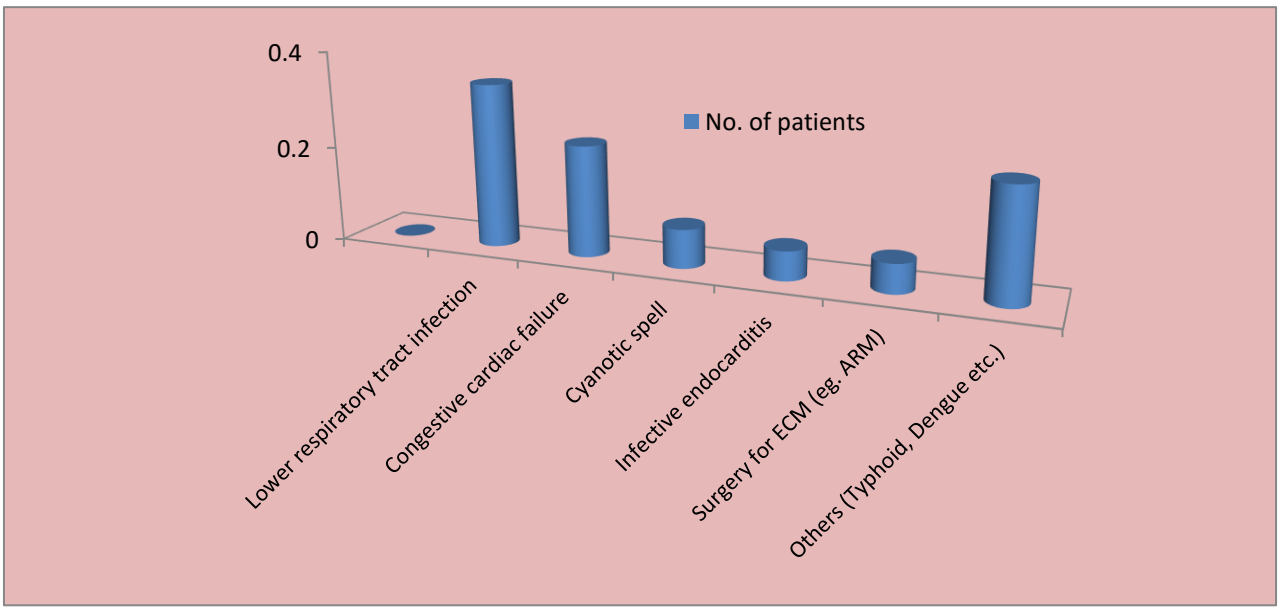

Figure 2: Reason for admission

Table 5: Consanguinity among patients with significant ECM (major ECM and clinically recognizable syndromes)

	No. of patients	Non- consanguineous parents (% of the type of ECM)	Consanguineous parents (% of the type of ECM)
Syndromes	18	13(72.2)	5(27.8)
Major ECM	13	3(23.1)	10(76.9)
Significant ECM (Total)	31	16(51.6)	15(48.4)
X2 = 7.30; P < 0.05 – significant			

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 (Table 3). 8% of the patients were found to have family history of CHD and remaining 92% not having a family history of CHD. Most of the familial occurrence was present in siblings. Out of the total number of patients with CHD, 47% of the patients were offsprings of consanguineous marriage. Parental consanguinity was more common among cyanotic CHD (61.5%) as compared to acyanotic CHD (41.9%); but this difference was not found to be statistically significant (Table 4). The most common reason for admission was for LRTI followed by CCF. 6% of the patients were admitted for surgical conditions such as ARM, which involved ECM. 23% of the patients were admitted incidentally for other medical conditions unrelated to CHD or ECM (Figure 2). Out of the total study group, 31 patients had a significant ECM associated and

69% not have ECM association. Significant ECM referred to either a major ECM (those malformations with significant medical or cosmetic consequences) or a clinically recognizable genetic syndrome. Out of the 31 patients with a significant ECM, 58.1% of the patients had a clinically recognizable genetic syndrome, whereas 41.9% of the patients had a major ECM which was not a part of a syndrome. 48.4% of the patients with significant ECM (major ECM + syndromes), were born to consanguineously married couples. Three fourths of the patients with a major ECM (not as a part of a syndrome) had a history of parental consanguinity. This association of major ECM with consanguinity was found to be statistically significant (Table 5). In order to further delineate the association of ECM among patients without a syndrome, patients were divided into 2 groups. Group I consisted of patients with CHD but no identifiable syndrome; this was found to be 82%. Group II consisted of patients, in whom CHD occurred as a part of a recognizable syndrome; this was found to be 18%. 15.8% of the non-syndromic group was found to have a major ECM (those with 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 (Table 6).

Table 6: Prevalence of ECM in the group – I

Type of ECM	No. (%) of patients with non-syndromic (n=82)
No malformation	33 (40.2%)
Major ECM	13 (15.8%)
Minor ECM	40 (48.8%)
Major + Minor ECM	4 (4.9%)

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 (Table 7).

Table 7: Profile of ECM in group – I

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

Gastrointestinal system was affected in 61.5%, musculoskeletal in 30.8% and genitourinary in 7.7% of the patients with major ECM in group-I. Gastrointestinal system was the most commonly affected (Table 8).

Table 8: System wise frequency of major ECM in group – I

System wise distribution of ECM	No. of patients with major ECM i.e Non syndromic (n=13)
Gastrointestinal	8(61.5%)
Musculokeletal	4(30.8%)
Genitourinary	1 (7.7%)

Out of the 82 children belonging to the non-syndromic group, 52.4% of the patients had no minor ECM, whereas the rest had one or more minor ECM. 29.2% of the patients had 1 minor ECM, 10.9% had 2 minor ECM and 7.3% had 3 or more (Table 9).

Table 9: Minor ECM in group - I

No. Of minor ECM	No. (%) of patients (n=82)
0	43 (52.4)
1	24 (29.2)
2	9(10.9)
≥ 3	6(7.3)

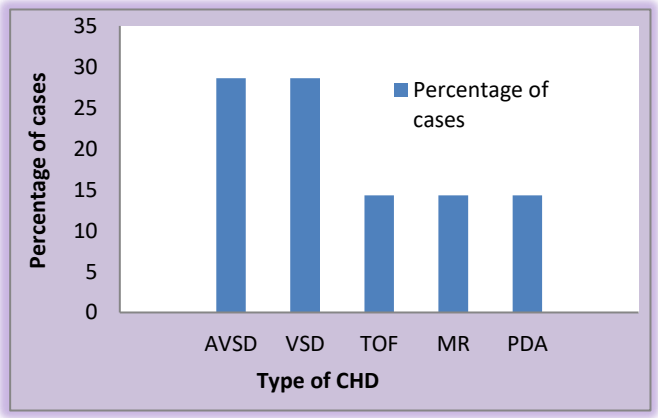

Figure 3: Profile of CHD in Down syndrome

Table 10: Prevalence of specific syndromes in group – II

Specific syndrome in group – II (n=18)	No. of Cases (%) (n=18)
Downs	7 (38.9)
VCF	2 (11.1)
Marfans	2 (11.1)
Adams-Oliver	1 (5.5)
Ellis van crevald	1 (5.5)
Kabuki makeup	1 (5.5)
Noonan	1 (5.5)
Turner	1 (5.5)
Goldenhar	1 (5.5)
Williams	1 (5.5)

Out of the 18 cases belonging to the syndromic group, Down syndrome was the most common accounting for 38.9% of the patients in this group (Table 10).

Out of the total 7 cases of Down syndrome, septal defects such as VSD and AVSD were the most common (Figure 3).

DISCUSSION

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 per1000 live births[11-12]. 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. Furthermore, statistics of live births may miss out on a large number of CHDs, which present later than at birth. Hospital based studies incorporating the entire pediatric age group, may represent the true burden of CHD, dealt by the medical community. These studies bring to lime light those patients who have a significant lesion that may require treatment and would help in getting data which could help in determining how healthcare resources are allotted for pediatric cardiology infrastructure in India, which is currently far from satisfactory. In the present study the hospital admission rate for CHD from birth to 18 years, covering the entire pediatric age group, was found to be 17.6 per 1000 hospital admissions. A similar picture of 16.5 patients with CHD per 1000 hospital admissions was found in a tertiary care center in Bombay[13]. The BWIS, showed that 3-5% of patients with non-syndromic CHD had a familial recurrence pattern[10]. This is almost similar to the present study which reveals that 8% of the patients had familial occurrence of CHD. Hence the present study supports the multifactorial mode of inheritance of CHD. 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[13]. 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 the present study, 47% of the patients were off springs of consanguineous parents. Thus, one can easily see, the present study confirms the previous findings[14] that consanguinity plays an important role in the causation of CHD. Though consanguinity was apparently more common among cyanotic CHD, this was not statistically significant. In the present study the most common CHD was found to be VSD which accounted for 32% of the total number of cases. This is in accordance with previously done studies[13, 15]. VSD was followed 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. 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[16-19]. In the present study more than half of the isolated major ECM, were in the gastrointestinal system and the remainder were in the musculoskeletal and genitourinary system. It is worthy to note that those ECM involving the gastrointestinal system in the present study such as anorectal malformations, biliary atresia, choledochal cyst and Hirsch sprungs disease were surgical conditions. These conditions were the cause for the admission in the 6% of the individual's for surgical reasons. This underlines the importance of proper cardiac evaluation of infant's prior to gastrointestinal surgery, even in cases of emergency for anesthetic and prognosis consideration. Due to the small size of the study group, association of a particular major ECM with a particular CHD could not be made. In the present study the prevalence of minor ECM was found to be 48.8%, this is in accordance with the study done by Kramer et al.[17] In the present study 10.9% of the non-syndromic individuals had 2 minor ECM and 7.3% of the non-syndromic individuals had 3 or more minor ECM. These individuals though were not always associated with a major ECM, their association with CHD, is itself a proof that they are associated with an underlying major malformation. In the present study 58.1% of the patients with CHD and significant ECM, had a clinically recognizable syndrome. Our study results are similar to that done by Grech and Gatt[20] whereas show an increased frequency when compared to studies done by Greenwood et al. [16] and the BWIS. This could be because since in recent times innumerous genetic syndromes have been elucidated and their recognition could not have been possible in the older studies. The most commonly found genetic syndrome in all of the previously published literature on ECM in children with CHD, was Down syndrome. Our study is in accordance with this statement, and Downs syndrome, was identified in 38.9% of all the syndromic cases of the study. The most commonly associated CHD with Down syndrome was AVSD and VSD. Each accounted individually for 28.6% cases with CHD and Downs Syndrome. This is in accordance with previous studies done to find the prevalence of CHD in Downs syndrome, wherein the most common CHD has been invariably found to be AVSD and VSD[21-22].

CONCLUSION

In the present study, Down's syndrome was the most commonly identified syndrome which accounting for 38.9% of the patients. The most common CHD among patients with Down's syndrome were AVSD and VSD. 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.

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