Congenital Heart Defects and Associated Aspects: Parental Age, Birth Order, Consanguinity and Dermatoglyphics

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ABSTRACT: The etiology of the congenital heart defects could be genetic and or environmental factors. In this article is reported whether CHDs could be associated to parental age, consanguinity, birth order and dermatoglyphics. Material consisted of 33 male and 32 female. Their age ranged from new born to 16 years. For the total sample, younger mean parental age (mother 24.26/father 30.61 years) was detected. It is seen that for the mothers in the age group 21 to 25 years and for the fathers in the age group 26 to 35 maximum number of children were born with CHDs. Consanguinity in the parents was present in 14. 34 patients were 1st born. 56 patients' palms were studied and Simian crease was observed in 40/112 of the patients. The younger parental ages, birth order and consanguinity reflected the trends in India: younger age at marriage and child bearing age group.

INTRODUCTION

Congenital heart defects (CHDs) are the most common form of birth defects. The prevalence of CHDs in live births is 3.7 to 7.7 per 1000 (Ferencz *et al.*,'85) The etiology of CHDs could be genetic and or environmental and there seemed to be no significant difference by incidence, race, season of birth, birth order, maternal age or socio-economic status (Newman,'85). There are varying reports on the influence of the parental age on CHDs. A reduction in maternal age may be associated with an increase in the incidence of CHDs (Rothman and Fyler,'76). A study has reported on the relationship of the maternal and paternal ages on CHDs (Tay *et al.*, '82). It is indicated that paternal age over 25 years may increase the chances of CHDs independent of the maternal age (Zhan *et al.*, '91). It is stated that 5% of ventricular septal defects may be due to advanced paternal age over 35 years (Olshan *et al.*,'94).

An analysis on over 2000 children with CHDs indicated positive trends in risk with increasing birth order for some lesions, namely pulmonary stenosis and transposition of great vessels (Rothman and Fyler,'76; Tay *et al.*, '82; Zahn *et al.*,'91). The study indicated a negative trend for patent ductus arteriosus.

Consanguinity is a well known factor in India. An increase in isolated CHDs in the offspring of consanguineous marriages (2.81%) as against the non-consanguinous (1.24%) marriages was reported (Gev *et al.*, '86); when only 1st cousins were considered the percentage of CHD rose to 3.22%. First cousin marriages might be a significant risk factor for specific types of CHDs is also reported (Becker *et al.*, 2001); such as ventricular septal deftec, atrial septal defects, atrio-ventricular septal defects and pulmonary

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stenosis. Relationship was not found between consanguinity and Tetralogy of Fallot, aortic stenosis, Coarctation of Aorta and patent ductus arteriosus. A study on 2000 consanguinous couples showed that the frequency of chromosomal abnormalities was 1.5 times greater than expected. This study also concluded that the influence of consanguinity seemed to be less significant in disorders in which environmental factors played a role (Karimi-Nejad *et al*.,'91).

Dermatoglyphics (DGs) and its association to CHDs was reported (Nair '86). DGs and CHDs; both mostly conform to multifactorial mode of inheritance; thereby a particular DGs feature could be considered as an indicator of CHDs; such as Sydney line and Simian crease.

In view of the above, the present study was aimed to find out the association between CHDs and parental age, birth order, consanguinity and dermatoglyphics in the referred patients to Division of Human Genetics, St John's Medical College, Bangalore.

MATERIALS AND METHODS

A total of 65 patients with CHDs were referred for karyotyping and counseling. There were 33 male and 32 female patients and their age ranged from neonate to 16 years. From the consecutively referred patients' details were recorded in a proforma (personal/family/ clinical/ dermatoglyphics). Percentage analysis was calculated.

RESULTS

The parental age, consanguinity, birth order, congenital heart defects and karyotypes are tabulated (Table 1).

Table 1: It may be noted that for 5 cases the parental age at conception could not be obtained. The inferences from the parental age are listed.

The calculated mean age for the total sample and the other groups (normal karyotype/ abnormal karyotype/ numerical chromosomal abnormality/ structural chromosomal abnormality) are given below.

TABLE 1

Parental age and karyotypes in sample patients

-	Mean mother's age	Mean Father's age	AD
Total sample (n 60)	24.26 +/- 4.75	30.61+/-5.16	6.26+/-2.74
Parental age – normal karyotype (n 33)	23.68+/- 3.01	30.20+/- 3.31	6.40+/- 2.53
Parental age –abnormal karyotype (n 27)	24.92+/- 6.26	31.37+/- 6.80	6.44+/- 3.21
Numerical chromosomal abnormality (n 21)	24.71+/- 6.52	31.95+/- 7.42	7.23+/- 2.79
Structural chromosomal abnormality (n 6)	25.66+/- 5.75	29.33+/- 3.66	3.66+/- 3.26

Younger mean parental age is detected. Mean maternal age was found to be high for the groups with abnormal karyotype, numerical and structural chromosomal abnormality than the total sample and the group with normal karyotype. Paternal age was high for the 2 groups with abnormal karyotype and numerical chromosomal abnormality than the total sample and the groups with normal karyotype and the structural chromosomal abnormality. .Mean age difference was also found to be high for the group with numerical chromosomal abnormality than the rest.

TABLE 2

Parental age grouped into 5 years and then correlated with the karyotype.

Mother's age-group (in years)	Normal karyotype	Abnormal karyotype	Parental age-group (in years)	Normal karyotype	Abnormal karyotype
16-20	4/12	8/12	21-25	3/6	3/6
21-25	21/28	7/28	26-30	16/27	11/27
26-30	8/15	7/15	31-35	13/22	9/22
31-35	—	4/4	36-40	1/3	2/3
41-45	—	1/1	46-50	—	1/1
	—	—	51-55	—	1/1
Total	33	27	—	33	27

Parents in the younger age group have given rise to offsprings with normal karyotype.

TABLE 3

CHDs distributed among different parental age-groups

MA: 5 year interval	CHDs	PA: 5 year interval	CHDs
16-20 years (12)	3 undifferentiated 2 PDA/2 ASD 1 VSD /1 AVSD/1 ASD & PFO/ 1 CoA/ 1 DORV+ VSD+PAH	21-25 years (6)	1 undifferentiated/ 1 ASD/1 VSD/ 1 ASD+PFO/1 VSD+ PAH+DORV/1CoA
21-25 years (28)	6 VSD 4 undifferentiated / 4 ASD 3 MVP 2 Dextrocardia 1 VSD+PS+PFO/ 1 VSD +ASD/ 1 VSD+PAH/ 1 AVSD/1 TOF/ 1 TOF +PAH/ 1 VSD+PS/ 1 PDA/ 1 PDA+VSD+PS+TS	26-30 years (27)	6 undifferentiated 5 ASD 2 VSD/ 2 MVP/ 2 PDA/ 2 AVSD 1 dextrocardia/ 1 TOF/ 1 VSD+PAH/ 1 VSD+PS/ 1 VSD+ASD/ 1 TOF+PAH/ 1 VSD+PDA+PS+TS
26-30 years(15)	3 undifferentiated / 3 ASD 1 VSD/ 1PFO/ 1 dextrocardia/ 1 MVP/ 1 AVSD/ 1VSD/ 1 PA/ 1 TOF/ 1 MS+ AS/ 1 CoA+BAV	31-35 years (22)	6 VSD 3 ASD 2 undifferentiated/ 2 dextrocardia/ 2 MVP 1 VSD+PS+PFO/ 1 AVSD/ 1 TOF/ 1 PDA/ 1 PFO/ 1 MS|AS/ 1 CoA +BAV
31-35 years (4)	2 VSD/ 2 AVSD	36-40 years (3)	1 undifferentiated/ 1 VSD/ 1 AVSD
41-45 years (1)	1 VSD+ cleft MV+mild TR	46-50 years (1)	1 AVSD
—	—	51-55 years (1)	1 VSD+mild TR+cleft MV
Unknown parental ages (5)	3 undifferentiated; 1 TGA+multiple VSD+single CA/ 1 TOF+PDA+PA		

PDA:patent ductus arteriosus; ASD: atrial septal defects; VSD:ventricular septal defects; AVSD: atrio ventricular septal defects; PFO:patent foramen ovale; CoA:coarctation of aorta; DORV:double outlet right ventricle; PAH:pulmonary artery hypoplasia; MVP: mitral valve prolapsed; PS: pulmonary stenosis; TOF: tetralogy of Fallot; TS: tricuspid stenosis; PA: pulmonary atresia; MVS: mitral stenosis; AS: aortic stenosis; BAV: bicuspid aortic valave; TR: tricuspid regurgitation; TGA: transposition of great vessels; CA: coronary artery

It is seen that for the mothers in the age-group 21 to 25 years and for the fathers in the age-group 26 35 maximum number of children were born with CHDs; including the complex CHDs.

Consanguinity: Consanguinity in the parents was present in 14 cases (21.54%). Among them 8 were 1st cousin unions, 3 were uncle –niece unions (21.43%) and the remaining 5 were distant unions (35.71%). In consanguinity, chromosomal abnormalities were observed in 5 (5/14, 21.54%). Out of which 2 had structural chromosomal abnormality and their parents were distantly related. 3 had numerical abnormality; one was Down syndrome whose parents were uncle-niece. 2 were Turner syndrome, one of the parents was 1st cousins and the 2nd parent had distant relationship. Only VSD was observed in 2 offsprings of 1st cousin unions.

Birth order: Majority of the patients were 1st born (34,52.31%) followed by 2nd born in 14 (21.58%). The prevalent CHDs in them were: 10 with VSD; ASD in 9; AVSDa and PDA in 3 each and TOF in 2. Among 2nd born the prevalent CHDs were: VSD in 3 and PFO in 2.

Dermatoglyphics: 56 patients (26 male;30 female) i.e. 112 palms were studied and Simian crease was observed in 35.71% (40/112) of the patients. In 230 controls (150 male; 80 female) its occurrence was 12.83% (59/460 palms). Whether in patients (26/60, 43.3%) or in controls (22/160; 13.75%), it was noticed, that more females had Simian crease. Simian crease was observed in 50% (26/52 palms) of the

patients with abnormal karyotype when compared to the patients with normal karyotype (15/60 palms, 25%).

DISCUSSION

Parental age: Parental age was stratified into single year and 5 years intervals. They were segregated as per the normal and abnormal karyotypes in the offsprings and also as per the presence of the CHDs. In literature, it is reported that autosomal trisomies seemed to be associated to advanced maternal age (Zhen and Byers,'92). On the contrary, in the present study, the mean MA of the mothers with children having numerical chromosomal abnormalities, especially the patients with trisomy 21 Down syndrome was less than 30 years. The reasons could be the younger maternal age at marriage and reproductive life span of the female, the prevailing customs in India. The explanation from literature is that in spite of the younger MA, it may be because of delayed ovulation and or fertilization resulting in trisomy conceptions (Jongbloet,'85) and congenital malformations including CHDs. In the present study, abnormal karyotype in children was observed at the MA group of 16 to 20 years.

Reports are conflicting on the presence or absence of the influence of advanced paternal age or decreased maternal age on CHDs. In the present study, 40 (66.6%) CHD patients were born to mothers less than 25 years and 33 (55%) to fathers less than 30 years. The findings agreed with the report (Rothman and Flyer,'76) that reduction in MA may be associated with increased incidence of CHDs. Even though, it is stated (Zhan *et al*.,'91) that paternal age less than 25 years may be associated with the risk of CHDs; in the present study, paternal age less than 30 years was associated with an increase in CHDs (33, 55%). Neither VSD was associated with advanced paternal age as reported in literature (Pleshan *et al*.,'94; Teller *et al*.,'96).

Consanguinity: Consanguinity is widespread in the world especially in India (5 to 60%); where uncle-niece marriages are prevalent. In consanguinity there seemed to be an increased incidence of congenital malformations and mental retardation. The high mortality and morbidity is attributed to the homozygous condition of the genes. In literature, it is stated that CHDs in consanguinity is 2.8% and 1st cousin unions have 3.22% of CHDs. (Gev *et al*., '86, Becker *et al*., 2001). In the present study, most of the CHDs have occurred in non-consanguinity. In the present study, 5 out of 14 had chromosomal abnormality and both Turner syndrome patients belonged to this group.

Birth order: It was opined that there is a trend for higher birth order with CHD. (Rothman and Flyer,'76; Tay *et al*.,'82; Zheng and Byers,'92)**.** In the present study, the birth order ranged from 1st to 8th born and 34 out of 65 were 1st born.

Dermatoglyphics (DGs): DGs is unique to the individuals and is considered to be multifactorial i.e both genetic and or environmental factors have their influence on DGs. DGs are correlated to chromosomal abnormality and clinical conditions. Hence, DGs are considered to be a diagnostic tool for the diseases by using its qualitative and quantitative analysis. However , authors have differed from the view that DGs could be an useful diagnostic tool in CHDs (David,'81).The present study showed an incidence of 35.7% of Simian crease among the patient group, which corresponded to a previous study with CHD. The study group did not show any Sydney line; where as in literature, it is reported that a significant increase in the incidence of Sydney line than Simian crease may be associated to CHDs (Nair,'86). In spite of the modest sample size, the presence of Simian crease suggested that the involved chromosomes and in them some common genes may have a role in the formation of it as well as CHDs.

CONCLUSION

The present study attempted to find out the association between CHDs and parental age, birth order, consanguinity and dermatoglyphics.

For the total sample, younger mean parental age (mother 24.26 years; father 30.61 years) was detected. It is seen that for the mothers in the age group 21 to 25 years and for the fathers both in the age group 26 35 maximum number of children with CHDs were born. Consanguinity in the parents was present in 14 cases. Among them 8 were 1st cousin unions, 3 were uncle –niece unions and the remaining 5 were distant unions. Majority of the patients were 1st born (34). 56 patients' palms (26 male;30 female) were studied

TABLE 1

Congenital heart defects (CHDs), parental age, birth order, consanguinity and karyotype

Serial Nos	MA	PA	AD	BO	Con	CHDs	Karyotype
1	24	27	3	2	1st cou	Systolic Murmur	46,XY
2	42	52	10	6	NC	Ventricular septal defects (VSD), mild tricuspid regurgitation, cleft mitral valve	47,XX,+21
3	25	29	4	1	NC	ASD	46,XX
4	21	29	8	1	NC	Systolic Murmur	46,XY
5	19	27	8	1	NC	Murmur	47,XX,+21
6	28	31	3	4	NC	VSD	47,XX,+21
7	23	34	9	2	1st cou	VSD, pulmonary stenosis, patent foramen ovale	46,XY
8	22	32	10	3	NC	VSD	46,XY
9	26	33	7	1	NC	Mitral & aortic valve stenosis	46,XY
10	23	32	9	1	NC	Sub aortic VSD	47,XY,+21
11	29	34	5	2	NC	Systolic murmur	46,XX
12	29	34	5	2	NC	Patent foramen ovale	47,XY,+21
13	25	28	3	1	NC	Pulmonary systolic murmur	46,XX
14	28	34	6	2	NC	Dextrocardia	46,XX
15	18	26	8	1	NC	Patent ductus arteriosus	47,XX,+21
16	18	27	9	1	NC	Atrio ventricular septal defects	46,XY,t(14;21)(q10;q10)+21
17	23	28	5	3	1st cou	Mitral valve prolapsed	46,XY
18	30	33	3	1	NC	Systolic Murmur	47,XY,+21
19	22	25	3	3	NC	VSD	47,XX,+21
20	18	24	6	1	NC	Atrial septal defects(ASD), patent foramen ovale	46,XY
21	30	32	2	1	distant	ASD	46,XY,del(11)(q23)
22	26	35	8	1	1st cou	Coarctation of aorta, bicuspid aortic valve	45,X
23	35	48	13	3	NC	AVSD	47,XX,+21
24	22	28	6	1	distant	TOF with hypoplastic pulmonary artery	46,XX
25	20	26	6	1	Distant	Patent ductus arteriosus	46,XX,der(9),t(2;9)p22;p23)pat
26	26	26	0	3	NC	ASD	46,XX,r(18)/46,XX
27	21	30	9	1	NC	Systolic Murmur	47,XX+21
28	21	29	8	1	NC	AVSD	47,XY,+21
29	28	37	9	2	NC	Systolic Murmur	46,XY
30	24	32	8	1	NC	VSD	46,XX
31	24	29	5	3	NC	Dextrocardia	47,XX+13
32	23	28	5	2	U-N	ASD	47,XX+21
33	33	35	2	3	NC	VSD	46,XX,der(14)t(3;14)(q24;p10)pat
34	24	29	5	1	NC	ASD	46,XY
35	24	29	5	1	NC	VSD	46,XY
36	27	30	3	1	NC	ASD	46,XX,-21,+der(9)t(9;21)(q22;q22)
37	24	32	8	1	NC	VSD	47,XY+21
38	20	32	12	1	NC	ASD	47,XX+21
39	31	37	6	2	NC	AVSD	47,XX,+21
40	16	21	5	3	distant	Coarctation of aorta	45,X
41	18	27	9	1	NC	VSD	47,XX,+21
42	—	—	—	8	NC	Murmur	46,XY
43	—	—	—	4	NC	Murmur	46,XY
44	22	29	7	1	NC	VSD,ASD	46,XX

contd. table 1

45	—	—	—	2	NC	Murmur	46,XX
46	28	29	1	3	NC	MVP	46,XY
47	22	32	10	1	NC	Dextrocardia	46,XX
48	22	27	5	2	NC	VSD, pulmonary artey hypoplasia	46,XX
49	31	39	8	2	NC	VSD	47,Y,+21
50	19	24	5	2	1st cou	Systolic Murmur	46,XY
51	18	24	6	1	NC	ASD	47,XY,+21
52	25	32	7	2	NC	Mitral valve prolapse with mitral regurgitation	46,XX
53	24	33	9	1	U-N	ASD	46,XX
54	16	23	7	1	NC	Double outlet right ventricle, VSD, pulmonary artey hypoplasia	46,XY
55	23	28	5	3	1st cou	Pulmonary valve stenosis, VSD	46,XY
56	24	35	9	4	U-N	Mitral valve prolapsed	46,XX
57	24	28	4	2	NC	Tetralogy of Fallot	46,XY
58	—	—	—	1	NC	Transposition of great arteries, multiple VSD, single coronary artery	46,XY
59	—	—	—	1	NC	Tetralogy of Fallot, patent ductus arteriosus, pulmonary atresia	46,XY
60	25	33	8	5	NC	Patent ductus arteriosus	46,XY
61	27	31	4	1	NC	Atrio ventricular canal defect	46,XY
62	23	29	6	1	NC	Pulmonary tricuspid stenosis, VSD, patent ductus arteriosus	46,XY
63	26	28	2	1	NC	Pulmonary atresia,VSD	46,XY
64	28	33	5	5	NC	Tetralogy of Fallot	46,XX
65	19	29	10	1	distant	Pan systolic murmur	46,XY

(MA:maternal age; PA: paternal age; AD: age difference between parents,Con:consanguinity; COU: cousin; NC: non-consanguinity/)

and Simian crease was observed in (40/112) of the patients. In 230 controls (150 male; 80 female) its occurrence was 12.83% (59/460) palms. Younger parental age, 1st birth order, 1st cousin union and Simian crease were associated to CHDs. The younger parental ages, birth order and consanguinity reflected the trends in India: i.e. younger age at marriage, consanguinity and the child bearing age group. The association of dermatoglyphics also highlighted that many factors are involved in the formation of congenital heart defects.

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