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Congenital Heart Defects and Genetic Syndromes

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Abstract

Congenital heart defects may be because of genetic and or environmental factors. Genetic could be Mendelian and non-Mendeliandisorders resulting in syndromes. *Aim:* The paper reports the identified Mendelianand non-mendelian syndromes in patients with congenital heart defects. *Material and Method:* 65 patients with heart defectswere referred for karyotyping and counseling. The details were recorded in proforma. Percentage analysis was calculated. *Results:* Genetic syndromes were identified in 11 patients (11/65,16.92%). There were 4 female and 7 male patients. All had normal karyotype: 46,XX or 46,XY. Among them 6 (54.5%) were born to consanguinous parents; out of whom 4 were 1st cousin unions, one each was from uncle-niece and distant relation. 7 had Mendelian and 4 had non-Mendelian disorders. The Mendelian were autosomal dominant (AD) or recessive (AR). AD was in one case of Marfan syndrome (male). AR was in the following 6 syndromes: Acrocallosal (male)/ Bixler (female)/ Diastrophic dysplasia (male)/ Ellis-van Crevald (female)/ Fanconi pancytopenia (male)/ Smith-LemliOpitz (male). Among the 4 non-Mendelian; 2 were sporadic: Beckwith Wiedmann (male) and CHARGE association (female) and the other 2 were ?AD (Brachymelia-Renal syndrome (male) and ?AR (Klippel Fell sequence)(female). *Conclusion:* As per the mode of inheritance, genetic counseling was provided to the family.

Keywords: Heart Defects; Syndromes; Genetic Counseling.

Introduction

The prevalence of congenital heart defects (CHDs) is 3.7 to 7.7 per 1000 (Ferencz et al 1985).live births. Gene defects could cause CHDs or with pleiotropic effects CHDs along with other malformations. Around 3% of CHDs are due to single gene defects (Nora and Nora 1978). The effects of the genes depending on their location may be autosomal dominant (AD) or recessive AR) and X linked dominant (X-LD) or recessive (X-LR) or Y-linked. For example, the following are the syndromes with CHDs resulting from single gene disorders (Jones 1997):Marfan (AD), Fanconi Pancytopenia (AR), Diastrophic dysplasia (AR), Acrocallosal (AR), Bixler (AR), Ellis-van Crevald (AR) and Smith-LemliOpitz (AR). In CHDs, there are microdeletion syndromes; here most of them are 'de novo' in occurrence; in case the parent has the chromosomal abnormality then from counseling point of view they behave like dominant Mendelian disorders. They are: Wolf-Hirschhorn, Williams, 8p deletion, Alagille anddeletion 22q11. CHDs could occur in families in non-traditional modes of inheritance such as mitochondrial, germ line mosaicism, uniparentaldisomy and genomic imprinting.For example, in CHDs, syndrome due to genomic imprinting and uniparentaldisomy is Beckwith-Weidemann. Herein, depending on the parents' chromosomes they behave like Mendelian disorders and they do contribute to the etiology of CHDs. CHDs also occur sporadic with unknown etiology; such as CHARGE association, Brachymesomelia- Renal and Klippel-Fell.

The paper is aimed to estimate the prevalence of both Mendelian and Non-Mendelian syndromes in

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the referred patients with CHDs to Division of Human Genetics, St. John's Medical College, Bangalore.

Material and Method

A total of consecutively referred patients with CHDs were selected for the study. There were 33 male and 32 female patients with the age range from neonate to 16 years. A detailed history was recorded in the proforma (personal/family/clinical history, investigations). The syndromes were diagnosed and accordingly the patients' families were counseled. Percentage analysis was calculated.

Result

Table 1: Genetic syndromes were identified in 11 CHD patients (11/65,16.92%). There were 4 female (36.36%) and 7 male (63.64%) patients. All had normal karyotype:46,XX or 46,XY. Among them 6 (54.5%) were born to consanguinous parents; out of whom 4 were 1st cousin unions, one each was from uncle-niece and distant relations.CHD as single was seen in 4 (2 atrial septal defects (ASD); mitral valve prolapse/ Tetralogy of Fallot/ ventricular septal defects(VSD) 1 each) and as a complex entity in 1 (VSD, pulmonary stenosis, patent foramen ovale) and undifferentiated in 5.

The syndromes and the features observed in the affected probands are listed.

Beckwith –Wiedemann syndrome: Proband 14 days old male baby,2nd child was born to consanguineous parents (1st cousins) and pregnancy was full term and unevenful. Features: large baby/ dolicocephaly/ broad forehead/bilateral conjunctivalchemosis/ slight facial palsy/ macroglossia/ bilateral creased ear lobes/ small low set ears/ cupid bow shaped lips/ murmur/ mild hepatomegaly/ omphalocele/ hypoglycemia/ dilated right kidney. Most cases are sporadic but possible patterns include AD, maternal or paternal imprinting/ contiguous gene duplication. *Family History:* maternal grandparents also had consanguineous marriage(distant relation).

CHARGE Association: One year 2 months old female child, 1st birth order was born to non-consanguinous parents by LSCS following full term pregnancy. Features: frontal prominence/bitemporal narrowing/ convergent squint/ short palpebral fissures/ hypertelorism/ epicanthic folds/ upward slant of the eyes/ small nose/ depressed nasal bridge/antiverted nares/ tethered tip/ small mouth/ tented upper lip/ cleft palate/micrognathia/atrial septal defects (ASD)/ mild left hydronephrosis/hypoplastic female genitalia/ imperforate anus (dilatation done)/ hypotonia. Mode of imheritance is uncertain and probably sporadic.

Fanconi Pancytopenia: 6 year old male child, 2nd birth order was born to non-consanguinous parents following full term uneventful pregnancy. Features: Absent thumb and radius on right/ murmur/ decreased platelet count at 41/2 years/ purpuric spots on face and body at 4 years/ pallor/ bluish black face and neck/ hypocellular bone marrow erythropoiesis/diminished normoblastic megakaryocytes. AR mode of inheritance.

Diastrophic Dysplasia: 4 month old male baby, 2nd birth order was born to consanguineous parents(1st cousins) following uneventful full term pregnancy. Features: did not cry after birth for 30 minutes/ high arched palate/ micrognahia/low set posteriorly rotated ears/ cystic mass like hypertrophic cartilage more on left ear than on right/ obese/ pectuscarinatum/ bilateral absence of creases on 2nd, 3rd, 4th fingers/ bilateral curved 2nd, 3rd, 4th fingers/ bilateral Simian crease/ bilateral clinodactyly/ ventricular septal defects (VSD), pulmonary stenosis,patent foramen ovale/ respiratory distress. AR mode of inheritance. *Family history:* Previously premature born 1st female child died after birth had similar appearance.

Klippel-Fell sequence: One year old female baby, 1st birth order was born to non-consanguinous parents by LSCS following a non-eventful pregnancy. Features: low hairline/ short neck/ torticollis/ X-ray: hemivertebrae, absent odontoid process/ labia majora prominent/ labia minora absent/ murmur. Sporadic occurrence with unkown etiology.Family history: Subsequently, parents had normal male child.

Marfan syndrome: 13 year old male child of 3rd birth order was born to consanguineous parents(1st cousins) after an uneventful full term pregnancy. Features: baby did not cry after birth for 15 minutes/ pectuscarinatum/ slender upper and lower limbs/ slender long fingers/ bilateral over lapping of little toes over 4th toes/ lumbar lordosis/ scoliosis of spine/ mitral valve prolapse. AD mode of inheritance.

Smith-Lemli-Opitz syndrome: One day old male child of 1st birth order was born to non-consanguinous parents after an uneventful full term pregnancy. *Features:* Oligohydramnios/ reduced fetal movements/ respiratory distress/ cyanosis after birth/ prominent occipital/ small forehead/ narrow bifrontal diameter/ left facial palsy/ micropthalmos/ short palpebral fissures/ hypertelorism/ eyebrows

and eyelashes absent/ small nose/broad nasal bridge/ antiverted nares/ small mouth/ cleft palate/ short plain philtrum/ tented upper lip/ low set ears/ periauricular tags on left ear/ narrow chest/ hypoplastic nipples/ bilateral deviation of hands at wrist/ bilateral hypoplasia of nails at index and little fingers and 5th toe/rocker bottom feet/ VSD/ anteriorly placed anus/ hypospadias with chordee/ hypertonia. AR mode of inheritance. *Family history:* Subsequently parents had one more child with same features.

Acrocallosal syndrome: 2 ½ year old male, 2nd birth order was born to consanguineous parents(1st cousins) following non-eventful full term pregnancy. *Features:* Frontal prominence/ prominent glabella/ flat occiput/ macrocepahly/ midfacial hypoplasia/ short palpebral fissures/ antimogoloid slant/ hypertelorism/ medial part of eyebrows not well formed/ depressed broad nasal bridge/ antiverted nares/ depressed tip/ short philtrum/ tented upper lip/ high arched palate/ micrognathia/ posteriorly rotated low set ears/ depressed xiphisternum/ polydactyly (6 fingers; 7 toes)/ syndactyly/ clinodactyly/ increased distance between 1st and 2nd toes/ cryptorchidism/ bilateral undescended gonads/ penile length3 cms/ scrotum with fused rugae/ hypotonia/ systolic murmur. AR mode of inheritance. *Family history:* maternal grandparents were uncle-niece and paternal grandparents were also 1st cousins.

Ellis-van Creveld syndrome: One year old female baby, 1st birth order was born to consanguineous parents (uncle-niece) after an uneventful full term pregnancy. Features: Scanning during pregnancy: short limbed dwarfism, left congenital talipesequinovarus, left hydronephrosis. Scanty hair, microcephaly/ frontal bossing/ bilateral epicanthic folds/ broad depressed nasal bridge/ antiverted nares/ high arched palate/ short neck/ small chest/ short hands and fingers/ left polydactyly/ bilateral Simian crease/ hypoplastic nails/ short hypoplastic toes/ left polydactyly/ bilateral syndactyly of 2nd and 3rd toes/ almost single atrium/ large ASD/ complete atrio ventricular canal. AR mode of inheritance. *Family history:* Maternal grand parents were 1st cousins.

Brachymesomelia-Renal syndrome (Langer-Nisheno-Yamaguchi syndrome: 1st born, 4 month old male baby to consanguineous parents(distant) following an uneventful full term pregnancy. *Features:* Frontal bossing/ slight scaphocephaly/ navevusflammeus over forehead/ epicanthic folds/ bilateral medial squint/ strabismus/ depressed nasal bridge/ high arched palate/ posteriorly rotated low set ears/ short neck/ depressed xiphisternum/ fullness of chest/ bilaterally displaced and laterally deviated short radial head/ bilateral Simian crease/ single crease in right little finger/ short fibula and tibia bone deformity/ contractures at kness/ bilaterally deviated to lateral side in 2nd, 3rd, 4th toes/ cleft between big toe and 2nd toe/ left small toe larger than 4th toe/ pan systolic murmur. Unknown mode of inheritance.

Bixler syndrome (hypertelorism, microtia, clefting syndrome) 1st born 3 week old female child to non-consanguinous parents after full term pregnancy. *Features:* did not cry immediately after birth/ in incubator for 7 days in view of CHD-Tetralogy of fallot, hypoplastic pulmonary artery/ microcephaly/ sloping forehead/ micropthalmos/ epicanthic folds/ short palpebral fissures/ hypertelorism/ depressed nasal bridge/ antiverted nares/ bilateral cleft palate/ narrow high arched palate/ micrognathia/ posteriorly rotated low set ears/ left ear microtia with auricular pit/ short neck. AR mode of inheritance. *Family history:* Maternal grandparents were consanguineous (distant).

Discussion

Table 1: CHDs and Genetic Syndromes: Normal karyotype

Serial No.	Diagnosis	Sex	CHDs	Con	Mode of Inheritance
1	Beckwith –Wiedmann	M	Systolic murmur	1st cousin	UPD /GI
2	CHARGE association	F	ASD	-	Non-mendelian
3	Fanconi Pancytopenia	M	Systolic murmur	-	AR
4	Diastrophic dysplasia	M	VSD,PS,PFO	1st cousin	AR
5	Klippel-Fell sequence	F	Systolic murmur	-	Non-mendelian
6	Marfan	M	MVP	1st cousin	AD
7	Bixler	F	TOF	-	AR
8	Smith-Lemli-Opitz	M	VSD	-	AR
9	Acrocallosal	M	Systolic murmur	1st cousin	AR
10	Ellis-van Creveld	F	ASD	Uncle-niece	AR
11	Brachymesomelia-Renal	M	Murmur	Distant	Non-Mendelian

(M-male;F-female-ASD-atrial septal defects;VSD-ventricular septal defects; PS-pulmonary stenosis; PFO-patent foramen ovale; MVP-mitral vlave prolapsed; TOF-teralogy of fallot;; AD-autosomal dominat; AR-autosomal recessive; UPD/GI-uniparentaldisomy.genomic imprinting)

Table 2: Review: Marfan syndrome

Jones 1997	Present study 2003
Tall stature	+
Arachnodactyly	+
Pectusexcavatum or carinatum	+
Eye anomalies/sub luxation of lens	-
CHD	+ mitral valve propapse

Table 3: Review: Brachymesomelia syndrome

Langer et al 1983	**Present study 2003**
Mesomelic shortness of limbs	+
Abnormal/bowed long bones	+
Unusual facies	+
CHD	+ murmur
Renal dysplasia	?
Neonatal death	?

Table 4: Review: Acrocallosal syndrome

Jones 1997	**Present study 2003**
Hypoplastic/absent corpus callosum	/
Hypotonia	+
Microcephaly/frontal prominence	+
Hypertelorism/antimongoloid slant	+
Broad nasal bridge	+
Malformed ears	+
Upper limb:poly/ syn/ clinodactyly	+
Lower limb: poly/ syndactyly	+/ broad 1st toe
CHD	+ systolic murmur
Genitalia	Cryptorchidism

Table 5: Review: Bixler syndrome

Bixler et al 1969	**Present study 2003**
Cleft lip and palate	+
Striking hypertelorism	+
Microtia	+
Malformed ear	+
CHD (may be coincidental ,but can't be excluded)	+Tetralogy of Fallot, hypoplasia pf pulmonary artery
Microcepahly	+
Bifid nose, broad nasal tip	+
Syndactyly (2/3 toes not remarkable)	-
Renal defects	-

Table 6: Review: Diastrophic dysplasia

Jones 1997	**Present study 2003**
Short tubular bones	+
Joint limitations	?
Scoliosis	?
Talipes	+
Hypertrophied auricular cartilage	+
?CHD	+ ventricular septal defects/ pulmonary stenosis/ patent foramen ovale

Table 7: Review: Ellis-van Crevald syndrome

Jones 1997	**EVS**	**Present study 2003**
Mesomelic dwarfism	+	+
Postaxial polydacytly	+	+
Dystrophy of nails in fingers and toes	+	+
Fusion of hamatic and capitate bones in wrist	+/-	+
Change in upper lip	+/-	-
CHD	+	+ atrial septal defects
Natal teeth	+/-	+
Mental retardation	+/-	+

Table 8: Review: Fanconi Pancytopenia syndrome

Jones 1997	Present study 2003
Short stature	?
Microcephaly	-
Eye anomalies	+
Skeletal anomalies	+
Urogenital anomalies	-
Haematological anomalies	+
Skin	+ purpuric spots
CHD	+systolic murmur

Table 9: Review: Smith-LemliOpitz syndrome

Jones 1997	Present study 2003
Small child	-
Failure to thrive	+
Low set ears	+ ear tags
Ptosis	+
Antiverted nares	+
Simian crease	+
Syndactyly	-
Short fingers	-
Genital abnormalities	+
CHD	+ventricular septal defects
Cleft palate	+
CNS	hypertonia

Table 10: Review: Klippel-Fell sequence

Jones 1997	Present study 2003
Short neck	+
Low hairline	+
Limited head movement	+
Cervical vertebral defect	+
CHD	+ systolic murmur

Table 11: Review: Beckwith –Wiedmann syndrome

Jones 1997	Present study 2003
Mental retardation	?
Macrosomia	+
Macroglossia	+
Prominent eyes	-
NaevusFlammeus	-
Ear creases	+
Enlarge kidneys	+
Adenocorticalcytomegaly	+
Hypoglycemia	+
Diastasis recti	-
Hepatosplenomegaly	+
Cryptorchidism	+
CHD	+ ventricular septal defects

Table 12: Review: charge association

Jones 1997	Present study 2003
Colobomatous formation (80%)	-
Heart defect	+atrial septal defect
Atresia choanae (58%)	-
Retarded growth and development (87%)	+
Genital hypoplasia (75%)	+
Ear anomalies (88%)	+
Cleft palate	+
Anal atresia	+

The patterns of inheritance could be Mendelian or single gene and Non-Mendelian disorders. Included in the Mendelian are the AD or AR and X-LD or X-LR or Y-linked disorders.

In the Present Study, syndromes with sex linked genetic disorders were not observed. Non-Mendelian includes mitochondrial, genomic imprinting, uniparentaldisomy or sporadic. It is stated that 3 to 10% of CHDs may be due to single gene disorders *(Nora 1993).* 1/3rd of CHDs could be due to syndromes *(Greenwood et al 1975). In the present study,* 11 syndromes (11/65,16.92%) were identified; 7 of which were Mendelian (63.6%) and 4 were Non-mendelian (36.4%) syndromes. Among Mendelian one was AD and the remaining 6 were AR disorders. Out of the non-Mendelian 2 were sporadic and 2 were ?either AD or AR; but could be considered as sporadic. AD was in one case of Marfan syndrome (male). AR was in the following 6 syndromes: Acrocallosal (male)/ Bixler (female)/Diastrophic dysplasia (male)/ Ellis-van Crevald (female)/ Fanconi pancytopenia (male)/ Smith-LemliOpitz (male). Among the 4 non-Mendelian; 2 were sporadic: Beckwith Wiedmann (male) and CHARGE association (female) and the other 2 were ?AD (Brachymelia-Renal syndrome(male) and ?AR (Klippel Fell sequence)(female).

Table 2. *AD: Marfan syndrome:* It is an AD syndrome of connective tissue disorder characterized by skeletal, ocular and cardiovascular abnormalities. There could be variations in phenotype. In 61% of cases cardiac anomalies may be present (Phornphutkulet al 1973), the leading cause of mortality. Parents were consanguineous (1st cousins) and normal; even family members are normal. Hence, it appears to be 'de novo mutation'; since it is opined that in 25% of Marfan syndrome could be due to AD but 'de novo' mutation.

Table 3. *AD: Brachymesomelia syndrome:* The syndrome is based on a single case report of mesomelic shortness of limbs with abnormal bowed long bones and unusual facies. Clinical examination and POSSUM search indicated this syndrome as the closest match to the proband. The mode of inheritance is unknown but may be AD. The consanguinity in the parents (distant) may be a coincidental finding.

Table 4. *AR: Acrocallosal syndrome:* Nearly 30 cases are reported.Consanguinity was present in the parents (1st cousins) as well as both in the maternal (uncle-niece) and paternal (1st cousins) grandparents..

Table 5. *AR: Bixler syndrome:* First it was reported as HMC syndrome (hypertelorism, microtia, clefting). Most of the features were exhibited in the proband. Maternal grandparents were consanguineous (distant).

Table 6. *AR: Diastrophic dysplasia:* Phenotype seemed to be variable.CHD in general does not occur in this syndrome; hence its presence in the present study is an unusual feature. Parents were consanguineous (1st cousins)

Table 7. *AR: Ellis-van Crevaldsyndrome (EVS):* A rare AR disorder (short ribs,polydactyly,skeletal dysplasia, morbuscordis). Birth prevalence less than 1 in 200,000 except among Amish (McKusick 1998) and aboriginal population of Australia (Goldblatt et al 1992). 60% may have CHDs. Recently, uniparentaldisomy in this syndrome is reported (Tompson et al 2001) suggesting that the gene may be imprinted.Cardiac defect usually are complete atrio ventricular canal and very large ASD; almost a complete atrium may be observed. 50% may die in early infancy. Survivors may have normal intelligence with stature ranging from 43 to 70". Dental problems are frequent. Proband's parents (uncle-niece) and maternal grandparents were consanguineous (distant).

Table 8. *AR: Fanconi Pancytopenia syndrome:* Chromosomal abnormalities, acquired or constitutional predispose to malignancy. In addition, it is recognized that a small number of Mendelian disorders are characterized by chromosome breaks and gaps as well as increase susceptibility to neoplasia and Fanconi is one among them.The mechanism by which mutation leads to multitude of anomalies in Fanconi is unknown. The Fanconi gene may create a susceptibility to factors, which can alter organogenesis perhaps as early as 4th week (Giampietro et al 1993).

Table 9. A*R: Smith-LemliOpitz syndrome:* Parents had another child with similar features. Some authors have classified a more lethal form, wherein the child dies; which is the case here with the proband and its sibling.

Table 10. *AR: Klippel-Fell sequence:* Etiology is unknown; generally held that it is produced by the disturbance of secondary mesodermal migration at the time when the cervical centersand discs are being formed. Defects in other organ systems developing at the same time of embryogenesis are also reported (Morrison et al 1968). Generally it is considered to be AR in inheritance. In female it is supposed to be prevalent. Subsequently parents had a normal male baby and there was no similar family history. Hence, present study appears to be sporadic in occurrence.

Table 11. *Sporadic: Beckwith –Wiedmann syndrome:* Mode of inheritance is complex; possible modes

include: AD,maternal imprinting, paternal imprinting, contiguous gene duplication.Genomic imprinting suggests the absence of the maternal gene. The case is considered as sporadic.Proband's parents (1st cousins) and maternal grandparents (distant) were consanguinous.

Table 12. *Sporadic: CHARGE association:* The term association indicates that certain malformations occur together more often than would be expected by chance. Yet the non-random occurrence of abnormalities can't be explained on the basis of a sequence or syndrome. The main difference from the syndrome is the lack of consistency of abnormalities from one affected individual to another and the absence of a satisfactory underlying explanation. The names are often acronyms derived from by juggling the 1st letters of the organs or systems most commonly included (CHARGE). This particular way of classifying the defect may not be perfect. Still, it serves as an aid to understand and ensure the correct information.The mode of inheritance is considered to be sporadic.

Consanguinity

The consanguinity observed in the parents and grandparents and its association to the mode of inheritance needs to be described. In the parents, 6 were consanguineous.In grandparents, 3 maternal and in one instant both maternal and paternal grandparents were consanguinous. Among grandparents in one case only they were consanguineous (distant) and parents were non-consanguinous (Bixler syndrome-AR). In one case (Acrocallosal-AR) parents (1st cousins) and the maternal (1st cousins)/ paternal (uncle-niece) grand parents were consanguinous. In 2 cases parents (1st cousins; uncle-niece) and maternal grand parents (distant) were consanguinous (Beckwith Wiedmann-?AD) (Ellis-van Crevald-AR).

In parental consanguinity, AD was associated to 2; AR to 3 and sporadic to one. In one case, ?AD (Beckwih Weidemann) it was parents -1st cousins and maternal grandparents -distant and in the other case (Marfan), it was only the parents -1st cousins. In AR 3 cases: i) Diastrophic dysplasia: parents- 1st cousins; ii) Acrocallosal: parents -1st cousins; maternal grandparents -1st cousins; paternal grandparents -uncle-niece; iii) Ellis-van Crevald: parents -uncle niece; maternal grandparents-distant. Sporadic (Brachymesomelia) parents-distant relation. AD and sporadic conditions; in them, consanguinity may be considered to be coincidental; but in AR the consanguinity might be associated to the homozygosity in the genes in the probands resulting in the syndromes.

Information

The complexity of the heart development requires precise timing and integration to achieve its correct function. Hence, it is hardly surprising that cardiovascular embryology involves a large number of genes. The mode of inheritance of the 11 syndromes were: 1 AD, 6 AR and 4 sporadic.

1. *Marfan syndrome (male): AD:* The fibrillin gene (FBN1) is located in 15q2.11. Fibrillina glycoprotein is a major component of suspensory ligament of eye and substrate for elastin in aorta and other elastic tissues. Mutations result in the defects seen in Marfan syndrome. CHDs could be present in 80% of cases.
2. *Brachymesomelia-Renal syndrome (male): AD/ sporadic:* Etiology is unknown. One of the multiple congenital anomaly disorders with renal dysplasia. The gene is localized to 6p12.3 to12.2.
3. *Acrocalloal (male): AR:* It involves limb defects and CNS disorder such as agenesis of caorpus callosum. The gene is mapped to 12 p13.3 to p11.2. CHDs are reported in 33% of cases.
4. *Bixler syndrome (female): AR:* The syndrome of hypertelorism, microtia and clefting gene is mapped to 1q or 7p.
5. *Diastrophic dysplasia (male): AR:* An abnormal organization of cells to tissues occurs in this condition. Theeffects seen in all parts of the body in which that particular tissue is present. Dysplasia is caused by single gene effects.The gene coding for a novel sulphate transporter is mapped to chromosome 5q. The impaired function of it may have led to the production of undersulphated proteoglycans in the matrix of cartilage. CHDs are reported in 75% of cases.
6. *Ellis –van Crevald syndrome (EVC) (female): AR:* Also known as chondroectodermal dysplasia. The EVC protein gene is mapped to 4p16 region. Frequently it is lethal in new borns with limb defects and bone dysplasia. CHDs are reported in 60% of cases.
7. *Fanconi Pancytopenia syndrome (AR)(male):* Basically AR but also with multiple chromosomal breaks. The defect is in therepair of DNA strand cross-links. 5 (A,B,C,D,E) sub types are there;each by recessive mutations at different loci. The commonest type A is mapped to 16q24 and type C to 9q22.3. The mechanism behind the involvement of Fanconianaemia genes in the integrity of DNA cross-links is not known. 13% of cases may have CHDs.

8. *Smith-Lemli Opitz syndrome (male): AR:* A severe defect in cholesterol biosynthesis leading to abnormally low plasma cholesterol levels and elevated concentrations of the cholesterol precursor 7-dehydrocholesterol. Cholestrol is vital in the normal development through its contribution to cell and mitochondrial membranes as well as its role in steroid, bile acid and vitamin D metabolism and myelination of the nervous system. Deficiency provides the potential for the treatment. The 7-dehydrocholesterol-reductase gene is localized to 11q12-13.
9. *Klippel Fell sequence (female): AR/sporadic:* The most logical and easily understood pattern of multiple abnormalities is the concept of a sequence. Here, the findings occur as a cascade of events initiated by a single primary factor. The reported incidence is 1/42,000 live births. $% of cases may have CHDs. Nearly 65% of patients are female. The particular sequence may be sporadic and in some may be AR or AD. The sequence may be part of a serious problem in early neural tube development. In case of AD the genes GDF3 and GDF6 mapped to chromosomes 8q22.2.
10. *Beckwith-Wiedeman syndrome (male): Sporadic:* it is the common congenital overgrowth syndrome. The syndrome is caused by genetic alterations in 11p15.5, a genomic imprinting area. Here, genes in this region(major fetal growth,IGF-2 –insulin like growth factor type 2) play an important role in enhancing and suppressing growth.Imbalance of these genes and the functions could lead to overgrowth.
11. *CHARGE associations (female):* The genetic etiology in most cases is sporadic. The gene CHD7 is mapped to chromosome 8.

Genetic Counseling

The communication process includes conveying information over sessions on diagnosis, prognosis, medical management/ treatment and recurrence risk.

Recurrence risk is further described. Syndromes with AD Mendelian disorders have 50% chances of transmitting the mutated gene to the offsprings who will be affected with the features of the syndrome. Incase parents are normal; then the condition is considered as 'mutation in the conception as de novo'. That individual behaves like AD for its off springs. AR syndromes have 25% of recurrence risk to have the homozygosity in the mutated gene; provided the parentsare heterozygotes. In case of variation in phenotype, genetic and mutational heterogeneity need to be considered. Those cases with sporadic occurrence, the recurrence risk seemed to be negligible.

There are occasions wherein investigations may not have been completed. In the present study, for example, parents could not submit the reports of ultra sound or X-ray or CT scan for the 3 syndromes: Acrocallosal/ Klippel-Fell/ Smith-Lemli; still they were diagnosed with the presence of the other features.

Conclusion

Genetic syndromes were identified in 11 out of the 65 referred patients with CHDs for karyotyping and genetic counseling. There were 7 male and 4 female patients. All 11 had normal male (46,XY) and female (46,XX) karyotypes. Among them 7 were Mendelian and 4 were non-Mendelian disorders. The Mendelian were grouped into AD and AR. AD was in one case of Marfan syndrome (male). AR was in the following 6 syndromes: Acrocallosal (male)/ Bixler (female)/ Diastrophic dysplasia (male)/ Ellis-van Crevald (female)/ Fanconi pancytopenia (male)/ Smith-Lemli Opitz (male). Among the 4 non-Mendelian 2 were sporadic: Beckwith Wiedmann (male) and CHARGE association (female) and the other 2 were ?AD (Brachymelia-Renal syndrome(male) and AR (Klippel Fell sequence) (female). Genetic counseling was provided to the family.

References

1. Bixler D, Christian JC, Gorlin RJ. Hypertelorism, Microtia and facial clefting: a newly described inherited syndrome. Am J Dis Child 1969; 118;495-500.
2. Ferencz C, Rubin JD, McCarter RJ, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: prevalence at the live birth. The Baltimore – Washigton Infant Study. AmJEpidemiol 1985;121:31-6.
3. Giampietro Pf, Adler-Brechet B, Verlander PC, Pavakis SG, Davis JG, Auerbach AD. The need for more accurate and timely diagnosis in Fanconianaemia: a report from the international FanconianaemiaRgistry. Pediatrics 1993;91:1116-20.
4. Goldblatt J Munitillo C, Pemberton PJ, Hurst J. Ellivan Crevald syndrome in a West Australian Aboriginal community. Postaxial polydactyly as a heterozygous manifestation? Med J Aust1992;157:271-72.
5. Greenwood RD, Rosenthal A, Paris L, Fyler DC,

Nadas AS. Extracardiac abnormalities in infants with congebnital heart disease. Pediatrics 1975;55:485-92.

6. Jones KL 1997. Smith's recognizable patterns of Human malformations. 5th edition. Philadelphia: WB Saunders Company.
7. Langer LO, Nishino R, Yamaguchi A. Brachymeso-melia-renal syndrome. Am J Med Genet 1983;15;57-65.
8. McKusick VA. Mendelian Inheritance in Man. 12th edition.Baltimore: John Hopkins University Press. 1998.
9. Nora JJ. Causes of congenital heart diseases. Old and new modes, mechanism and models. Am Heart J 1993; 125:1409-19.
10. Nora JJ, Nora AH. The evolution of specific genetic and environmental counseling in congenital heart diseases. Circulation 1978;57:205-13.
11. Phomphutkul C, Rosenthal A, Nadas AS. Cardiac manifestations of marfan syndrome in infancy and childhood. Circulation 1973;47:587-96.
12. Tompson SW, Ruiz-Perez VL, Wright MJ, Goodship JA.Ellis-van Crevald syndrome resulting from segmental uniparentaldisomy of chromosome 4. J Med Genet 2001;38:E18.