Is any Relation between Cytogenetic types of Down's Syndrome and Congenital Heart Disease

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Abstract:

Background: Down's syndrome was the first of the chromosomal trisomy to be reported in 1959, Lejeune et al, with a prevalence of 0.7% live births. Garrod in 1894 who were noted a specific association between this syndrome and heart malformation.

Aim: To find any relation between cytogenetic types of Down's syndrome and congenital heart disease, and early neonatal screening for congenital heart disease since early detection, help to prevent the future complication of pulmonary hypertension in old age.

Patients and methods: A descriptive study done in AL-Yarmouk Teaching Hospital \Neonatatology Department during one year period between January 1996- and 1997. The study involved 9000 live born infants screened for congenital anomaliese, we found 40 Down babies after full clinical examination to check the criteria of Down's syndrome and presence of congenital heart disease, then a blood sample was aspirated in a heparinized tubes and prepared for chromosomal analysis, those with congenital heart disease (CHD) were send for elective cardiograph, chest roentenography, Doppler echocardiography.

Results: Out of the 40 Down's babies studied, 26(65%) were male and 14(35%) were female out of eight cases with CHD (20%) we found 3 (37.5%) had atrio-ventricular septal defect, 3(37.5%) had atrial septal defect,2(25%) had ventricular septal defect. Chromosomal pattern for all cases with CHD was Non disjunction (ND) triosomy 21.

Conclusion: our study revealed no relationship between CHD types and chromosomal pattern. Prenatal screening for CHD in DS fetus and early neonatal screening for CHD as early detection, help to prevents the future complication of pulmonary hypertension in old age ,for whom new therapeutic option are available.

Key words: cytogenetics, congenital heart disease.

Introduction

Since the original description of Down's syndrome (Langdon Down 1866) this disorder has been recognized to be the commonest single cause of mental handicap. Garrod in 1894 noted a specific association between this syndrome and heart malformation.[1]

Down's syndrome was the first of the chromosomal trisomy to be reported in 1959, Lejeune et al[2]) with a prevalence of 0.7% live births[3]. Down syndrome is usually diagnosed clinically at birth by its clinical feature like craino-facial, short neck, short broad hand with simian creases and congenital heart disease CHD (Ventriculoseptal defect VSD, endocardial Cushing) are the most common types of cardiac disease found in DS cases[2,4,5].Studies indicate that CHD in DS infants have direct impact on mortality. Survival in DS patients with out CHD has been 87% at the age of 5y and 79% at the age of 30y but with CHD the survival was reduced to 62% at the age of 5y and only 50% at the age of 30y.[6,7,8]

There is evidence that the risk of early and severe pulmonary hypertension in children with DS could be significantly reduced by performing palliative or correction cardiac surgery. This emphasizes the importance of early diagnosis in this group of children.[9] Current technology allows earlier diagnosis of CHD and this, with the improvement in operative procedure has yielded results in DS infants comparable to those in the general infant population with CHD.

Aim: To find any relation between cytogenetic types of Down's syndrome and congenital heart disease, and early neonatal screening for congenital heart disease since early detection, help to prevent the future complication of pulmonary hypertension in old age.

Patients and methods:

A descriptive study was done in AL-Yarmouk Teaching Hospital\ Neonatatology Department during one year period from January 1996 to January 1997.

The study involved 9000 live born infants screened for congenital anomalies. We found 40 Down's babies after full clinical examination to check the criteria of DS (craino-facial, short neck, short broad hand with simian creases and congenital heart disease) in those babies specifically.[2,4,5]

Then a blood sample was aspirated in a heparinized tubes and prepared for chromosomal analysis send to Iraqi center for medical genetics researches in Baghdad (Ministry for High Education), using standard cytogenetic method (0.3 ml fresh venous blood is added to 5 ml Tc199 media and incubated at 37°C for 72 hours. 0.1 ml colcemid is added for 30 minutes then incubated with hypotonic solution for 20 minutes followed by at least 3 changes of freshly prepared fixative slides were prepared and Giemsa trypsin-G banding is performed at least 25 cell of good quality banding were analyzed).[10]

Patient with congenital heart disease were selected specially to find possible correlation with the result of cytogenetic study of DS and send for

elective cardiograph (ECG), chest roentenography (CXR), Doppler echocardiography (Echo).

Results:

*Out of the 40 Down's babies studied, 26(65%) were male and 14(35%) were female as shown in table 1

Table 1: The sex distribution of Down's babies in the study

Sex	Freq	%
Female	14	35
Male	26	65
TOTAL	40	100

*The percentage of clinical feature and the number of cases was included in table 2.

Table 2: The clinical features of Down's babies

Clinical features	%	No. cases
Hypotonia	85	34
Creases (single)	57.5	23
Up slant eye	100	40
Auricle anomaly	60	24
Flat occiput	90	36
Low set ear	62.5	25
High arch palate	92.5	37
CHD	20	8
Undescended test	17.5	7
***Other features**	27.5	11

* Other features {speckling of the Iris –brush field spots, redundant folds of the skin about the neck ,Little fingers are short and incurved-clinodactyly ,wide gap between the first and second toes, atlantoaxial instability}.[11]
* Out of 40 Down's babies, 8cases had CHD (20%), {2 male, 6 female}.Table2
* Chromosomal study revaled that thirty nine babies were definitely Down's , and one was normal study {Non disjunction- ND 33, Mosaic- M5, Translocation- T 1}. Chromosomal complements were seen with clinical feature of DS. Tab.3

Table 3: Results of cytogenetic chromosomal study.

cytogenetic chromosomal study	No.	%
Non disjunction-ND	33	84.6
Mosaic -M	5	12.8
Translocation-T	1	2.56
Total	39	100

Chromosomal pattern for all cases with CHD was ND triosomy 21.

*From this 8(20%) Down's baby with CHD, we found 3 (37.5%) had atrio-ventricular septal defect, 3(37.5%) had Atrial septal defect,2(25%) had ventricular septal defect. Tab 4

Table 4: Types and percentage of CHD in Down's baby for the 33 non-dysjunction chromosomal type.

Type of lesion	cytogenetic chromosomal study			No.(%)
	Non disjunction	Mosaic	Translocation	
CHD (all)	**8**	**-**	**-**	**8(20.5%)**
AVSD	**3**	**-**	**-**	**3(37.5%)**
ASD	**3**	**-**	**-**	**3(37.5%)**
VSD	**2**	**-**	**-**	**2(25%)**
None	**25**	**5**	**1**	**31(79.5%)**

Discussion:

Down's syndrome is a major and most common chromosomal abnormality detected in approximately 0.7% of live births. Congenital abnormalities, growth deficiency, and mental retardation are finding often present in individuals with chromosome abnormalities.

Rapid progress in human cytogenetic has demonstrated a causal relationship between various chromosomal abnormities and their phenotypic manifestation. In addition, the specific chromosomal etiologies of a wide variety of syndromes have been established.[3]

There are three main types of chromosomal pattern in DS, as in our samples we found (47,+21) trisomy non disjunction in 33 case with mosaic in 5 and translocation in one, and all the 8 CHD cases are of non disjunction, so there is no relationship between the chromosomal pattern and the type of CHD, the same results were found by Wells GL et al[12], who had 47 cases of ND, and 2 cases of unbalanced translocation. Granzotti JA et al [13], found 35 cases of ND, and 3 case of translocation. There are many reports about specific gene locus involved in AVSD; Pierpont ME et al [14] had identified an AVSD susceptibility 5 gene. Robinson SW et al [15]

Identified and characterized the cell adhesion molecule CRELDI (previously known as cirrin) as a candidate gene for the AVSD2 locus mapping to chromosome 3P25.This CRELDI was the first human gene to be implicated in the pathogenesis of

isolated AVSD, on the other hand Sandri C et al [16]reported that heart morphogenesis is not affected by over expression of SH3BGR gene and Wilson L et al [17] also excluded a locus within the trisomy 21 region as a cause of AVSD defect.

It seems that there is no relation between CHD in DS and the chromosomal pattern but it is still too early to be dogmatic about gene abnormalities and CHD in DS.

The demographical pattern of CHD in DS is a changing variable. The frequency of CHD in DS in our sample was 20% while Michci E et al had a prevalence of 72.7% in Turkey.[18]

While in Europe live born CHD association with DS in 0.5 per 1000 births with more than 4 fold variation between countries Dolk H et al [19], while Hartman RJ et al found the most common chromosomal abnormality observed were 21 trisomy in 52%, and one in 8 infant with CHD had a chromosomal abnormality .[20], and Mogra R et al in U.K found structural CHD was found in 34% .[21], while prevalence in Coartia was 48% as by Basic Bozovic I et al[22].

CHD is more common in female DS patient in our study the female\ male ratio was 3\1, while Ban A et al found the majority were males with M\F ratio of 1.5\1. [24] While Pinto FF et al found 54% of his cases to be female[24], while Tandon and Edwards from USA found the ratio was M\F 0.83\1 ,these variations could be explained on the basis of different sampling techniques.

The type of CHD defect in DS varies in different parts of the world, in our study we had AVSD 37.5%,ASD 37.5% and VSD 25%,while Ban A et al found the majority was VSD in 52.5% [23],while Mogra R et al[21] found the majority was AVSD(24%),and Hartman RJ[20] found the majority of his cases were AVSD in67.2% and double outlet right ventricle in 33%, this can be explained by regional differences.

In our study we started screening since birth for DS cases, some studies were started intrauterine by fetal echocardiography early as in Mogra et al[21] and found increased incidence of AVSD in female, and CHD does not appear to increase the chance of spontaneous intrauterine loss in ongoing pregnancies, so use of new technologies that have recently been available(chromosomal microarray) may increase the identified contribution of chromosomal abnormalities even further[21,20].

In conclusion, our study revealed no relationship between CHD types and chromosomal pattern. Prenatal screening for CHD in DS fetus and early neonatal screening for CHD as early detection help to prevent the future complication of pulmonary hypertension in old age, for whom new therapeutic options are available.

Investing in primary prevention and pathogenetic research is essential to reduce this burden as well as continuing to improve cardiac services from in utero to adulthood.

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