PREDICTORS OF RISK FOR ABNORMAL KARYOTYPE IN DYSMORPHIC CHILDREN

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ABSTRACT

BACKGROUND

Chromosomal anomalies occur in 0.4% of live births. The phenotypic anomalies that result from chromosomal aberrations have multiple minor face- and limb-anomalies. These assume diagnostic significance in combination. Major congenital defects can be defined, rather arbitrarily, as those abnormalities that if uncorrected, impair normal body function or reduce life expectancy. Most babies with two major anomalies or one major and two minor anomalies or three or more minor anomalies have a dysmorphic syndrome. This study aimed at analysing the clinical and karyotypic profile of a section of dysmorphic children presenting in a tertiary care centre and to correlate the dysmorphology with the results of karyotyping.

The aim of the study is to assess the clinical and karyotypic profile of a group of children with congenital anomalies and dysmorphic facies attending OPD and IP of the Department of Paediatrics, SATH, TVM Medical College.

MATERIALS AND METHODS

Children who were enrolled were evaluated using a detailed proforma to analyse the clinical profile. Then 2-4 ml venous blood was collected in sodium heparinised vacutainer with aseptic precautions and sent for karyotyping. 53 children referred with multiple anomalies, failure to thrive, dysmorphic facies, abnormal dermatoglyphics and other major and minor anomalies were included in the study.

RESULTS

Of the 53 dysmorphic children screened, 73.58% had abnormal karyotype. This included numerical autosomal anomalies (50.9%), numerical sex chromosomal anomalies (3.77%), structural autosomal chromosomal anomalies (7.54%) or structural sex chromosomal anomalies (3.77%). There were 3 cases of Fanconi's anaemia and a case of fragile X syndrome in the sample.

CONCLUSION

Among the 53 children, 73.58% had an abnormal karyotype. Those with two major anomalies or one major and two minor anomalies or three minor anomalies were included in the study. One major anomaly may not be indicative of a chromosomal anomaly whereas association of various major and minor anomalies may indicate a chromosomal defect. As karyotyping and further studies to detect chromosomal anomalies are expensive, selection of cases was based on inclusion criteria yields a high positivity rate.

KEYWORDS

Chromosomal Anomalies, Dysmorphology, Karyotype, Risk Predictors.

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BACKGROUND

Dysmorphology is the word coined by David Smith in 1966 to describe the study of human congenital defects. Chromosomal anomalies occur in 0.4% live births. They are supposed to be present in much higher frequencies among spontaneous abortions and stillbirths.[1,2] These occur in any part of the body and most arise in the first trimester of intrauterine life. Some are mild, but about 3% of all children are born with serious structural defects that interfere with normal body function and can lead to lifelong handicap or even early deaths. Congenital anomalies taken together account for a large fraction of morbidity and mortality.[3] In India, congenital malformations account for 8-10% of perinatal deaths and 13-16% of neonatal deaths.[4]

The phenotypic anomalies that result from chromosomal aberrations are mainly due to imbalance of genetic information. Multiple minor face and limb anomalies are usual associations. These anomalies are themselves not unusual, but they assume diagnostic significance in combination.

Major congenital defects can be defined rather arbitrarily as those abnormalities that if uncorrected, significantly impair normal body function or reduce life expectancy.[5] E.g. Down syndrome, pyloric stenosis, cleft lip, some congenital heart diseases. Overall incidence of major defects is 5-6%. Minor anomalies are of primarily cosmetic significance. Found in less than 4% otherwise normal individuals, they are usually isolated and may run in families too, with an autosomal recessive inheritance. A single minor defect may be present in as many as 13% new-born babies

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depending on the observer. Less than 1% have two unrelated minor anomalies and perhaps 1 in 2000 have three. Though usually of no clinical significance to the patient, they may be helpful diagnostic clues, especially when several are present in the same patient. Most babies with two major anomalies or one major and two minor anomalies or three or more minor anomalies have a dysmorphic syndrome.[5]

Structural defects of prenatal onset may represent a single primary defect in development or a multiple malformation syndrome. The aetiology of most of the single primary defects of development are unknown but may are explained on the basis of multifactorial inheritance, where the recurrence risk is between 3-5% for the next child of the unaffected parents with one affected child. Other proposed aetiologies of these are environmental or due to inherited single altered genes which follows mendelian inheritance. Multiple malformations may be due to transcription factor mutations as in Rubinstein-Taybi syndrome, chromosomal abnormalities, teratogens and due to single gene disorders. The recurrence risk varies from 0-100% depending on whether it is a mutation / teratogen or a case as in 21-21 translocation carrier mother in a child with Down syndrome. SAT Hospital witnesses the birth of nearly 16000 deliveries per year. Many of these new-borns are with multiple anomalies which has many genetic and prognostic implications. Many more are attending the OPD, either referred for evaluation of anomalies or for other complaints. This study aims at analysing the risk of association of different dimorphisms and abnormal karyotype.

Cytogenetics is the genetic analysis of cells, a discipline that has flourished since the chromosome-banding techniques introduced in 1969 by Torbjorn Caspersson and Lore Zech first provided a simple and inexpensive way to gauge the number and assess the structural integrity of chromosomes. Chromosome banding is probably the most commonly performed genetic test. Most laboratories use G-banding, named after the German Chemsit Gustav Giemsa.

Aim of the Study

To analyse the dimorphisms in children 0-12 years and predict risk for having abnormal karyotype.

MATERIALS AND METHODS

Design

Descriptive study.

Setting

Dept. of Paediatrics, SATH, Medical College, TVM, Kerala.

Method

Children who were enrolled were evaluated using a detailed proforma. The dimorphisms in the form of major and minor anomalies were assessed and entered. Then 2-4 ml venous blood was collected in sodium heparinised vacutainers with aseptic precautions and sent for karyotyping.

The karyotyping method used was human peripheral blood lymphocyte micro culture method.

The steps are-

Collect 2-4 ml venous blood in sodium heparinised vacutainers with aseptic precautions.

6-10 drops of blood is added to 10 ml RPMI 1640 medium supplemented with 15% foetal bovine serum. Penicillin and streptomycin is added as antibiotics. 0.5 ml phytohemagglutinin is added to proliferate the lymphocytes. The cultures are incubated for 72 hrs at 37^0C.

At the 70^{th} hour, add one drop of colchicine to arrest cell division at metaphase

After two hours, transfer the whole content into a sterile centrifuge at 1000 rpm for 10 minutes. Discard the supernatant. To the cell button, add 0.075 M KCl solution and keep in incubator for 20 minutes.

Fix the contents with methanol: acetic acid mixture in the ratio of 3:1 and keep in refrigerator for at least 30 minutes for proper fixation. Wash the cell pellets with fresh fixative. Repeat the process until we get a clear supernatant. These cell pellets are dropped on to a pre-cleaned, labelled, chilled microscopic slide, air dry and stain with 10% Giemsa staining solution. Stained slides are observed under a research microscope and look for any numerical chromosome abnormalities.

For detecting structural abnormalities and for karyotyping, a GTG banding is done. For this, 2-3 days old slides are treated with 0.05 % trypsin solution and stained with 10% Giemsa containing solution. Good quality metaphases are photographed using camera attached microscope. From the prints, we cut down each chromosome and arrange them according to their size, position of the centromere and the banding pattern called the karyotype.

Statistical Analysis

The data was collected, compiled and analysed using Microsoft Excel percentages. The results were expressed in percentages. Odds Ratios with 95% CI were calculated to assess the predictors of risk for abnormal karyotype in dysmorphic children. Chi square and Fischer's' exact test were used as and where appropriate to check for statistical significance. P value of <0.05 was considered statistically significant.

RESULTS

Numerical Autosomal (50.9%)
47XY, +21 - 12
47 XX, +21 - 07
45XX/47XX, +21 - 02
46XY/47XY, +21 - 05
46XY/47XY, +18 - 01
Numerical sex chromosomal (3.77%)
46XX.47XXX (12%) -01
46XX (80%), 45XO (20%) -01
Structural autosomal (7.54%)
46XY/46XY, 13q+ -01
46XY/46XYdel (15q) -01
46XX/46XX22qdel -01
46XX/46XX, 22Q+ (16%) -01
Structural sex chromosomal (3.77%)
46XX/46XXq+ -01
46XY/46XYq+ (18%) -01
Others (7.54%)
46XY, breaks+++ -0346XY, fraXq (18%) -03 (fig 1)
46XY, fraXq (18%) -01

	Positive Karyotype No (%) n=40	Negative Karyotype No (%) n=13	Total n=53	OR (95% CI)	p-Value
Low Set Ears	22(92)	02(8)	24	6.7(1.3-34.4)	0.023
Epicanthic Folds	23(96)	01(04)	24	16.2 (6.04-44.7)	0.003
Simian Crease	21(95)	1(05)	22	13.3 (4.95-36.6)	0.005
Hypotonia	25(89)	3(11)	28	5.6 (1.2-30)	0.024

Table 1. Profile of Minor Anomalies which were found to be Significant

	Positive Karyotype No (%) n=40	Negative Karyotype No (%) n=13	Total n=53	p-Value
Mental Retardation	23(92)	5(18)	28	0.339
Up Slanting Eyes	20(71)	04(29)	28	0.338
Down Slanting Eyes	06(86)	01(14)	07	0.667
Micrognathia	03(60)	02(40)	05	0.586
Flat Nasal Bridge	18(82)	04(18)	22	0.520
Clinodactyly	14(93)	1(07)	15	0.08
Overriding Toes/Fingers	10(77)	3(23)	13	1.00
Microcephaly	11(73)	4(27)	15	0.489
Hypertelorism	8(67)	4(33)	12	0.459
Cleft Lip	1(33)	2(67)	3	0.145
Cleft Palate	1(33)	2(67)	3	0.145

Table 2. Profile of Minor Anomalies which were found to be Non-Significant

	Positive Karyotype No (%) n=40	Negative Karyotype No (%) n=13	Total N=53	p-Value
CVS Anomaly	20(83)	4(17)	24	0.338
Renal Anomaly	1(100)	0(0)	1	
GIT Anomaly	2(67)	1(33)	3	0.578
Skeletal Anomaly	5(50)	5(50)	10	0.090
Ambiguous Genitalia	1(50)	1(50)	2	0.434

Table 3. Profile of Major Anomalies

	Positive Karyotype No (%) n=40	Negative Karyotype No (%) n=13	Total N=53	p-Value
IUGR	18(82)	4(18)	22	0.520
Malnutrition	8(62)	5(38)	13	0.265
PIH	6(67)	3(33)	9	0.672
GDM	8(67)	4(33)	12	0.459
Fetal Wastage	4(67)	2(33)	6	0.627
Consanguinity	5(56)	4(44)	9	0.271

Table 4. Profile based on Features in Antenatal History

DISCUSSION

53 children belonging to the age group of 0-12 years with suspected chromosomal anomalies were enrolled in the study. Those with two major or one major and two minor anomalies were subjected to karyotyping using peripheral blood micro culture method and Giemsa staining. The major anomalies noted were cardiac defects like VSD, AVSD, GIT anomalies like Hirschsprung's disease etc. Minor anomalies like low set ears, hypotonia, up slant or down slant of eyes, simian crease, inner epicanthic folds were noted.

Majority of the study population (60.3%) were below one year of age, 24.5% were born between one to five years of age and the rest were more than five years of age. 75 % new-born babies and 75% children one month to one year age had an abnormal karyotype. Among the 53 children studied, 73.58% had an abnormal karyotype. Anomalies like Down syndrome, Turner syndrome, Edward syndrome, addition of deletion in chromosome 22, spontaneous breaks in Fanconi anaemia were among the cases studied.

Milia A et al in 1984 reported the results of a karyotype analysis carried out on 282 patients clinically selected for some suspicion of chromosome abnormalities. This population showed a significantly higher incidence of chromosome anomalies (21.6%) than an unselected population (0.5-0.6%).[6] Verma RS et al report in 1980 describes the cytogenetic findings in 357 cases referred for suspected chromosomal abnormalities because of abnormal clinical features. Chromosomal anomalies were found in

27.2% of the cases studied. A significantly high rate of chromosomal abnormalities was found in the population with clinical abnormalities in comparison to an unselected population i.e; 0.48-0.55%.[7,8,9]

The male to female ratio was 28:23 ($p<0.05$). Two children had indeterminate sex. One was an un virilised male and another was a virilised female. Majority of the children with abnormal karyotype were cases of trisomy 21(49%). Of the 901 patients undergoing karyotype analysis in Ghani F et al study in 1995, Down syndrome topped the list in number.[11] A higher incidence of Down syndrome is observed in males. As per our data also, male: female was 2:1. A group of children with a variety of clinical disorders were investigated for the possible presence of chromosomal abnormalities by Navsaria D et al in 1993.[12] Various types of chromosomal anomalies were found which is significantly ($p<0.01$) higher than in a control population (0.48-0.55%). The male:female ratio was 3:2 for the total population. Furthermore, in this survey population, the sex ratio of Down syndrome cases of males: females was 3:2.[10]

The median age of mothers with karyotypically abnormal children was 28 years and the median age of those with normal children was 25 years. Similarly, median age of fathers with karyotypically abnormal children was 32 years and the median age of those with normal children was 30 years. This difference was not statistically significant, One study has showed that the estimated rate of all clinically significant cytogenetic abnormalities rises from about 1 per 500 at the youngest maternal ages to about 1 per 270 at age 30, 1 per 80 at age 35, 1 per 60 at age 40, and 1 per 20 at age 45(8).In the present study, the mean age of mothers of children with Down syndrome was 27. 4 years and that of fathers with Down child was 33.5 years. The age of mothers ranged from 18-40 years and that of fathers ranged from 24-50 years. Previous studies showed that mean maternal age of Down syndrome infants gradually diminished and accumulated between the ages of 31 and 34 years[9] Trimble BK et al opines that maternal age-specific risks of giving birth to a child with Down Syndrome (DS) are given by single-year age intervals. Such data are of value for more precise genetic counselling and in cost-benefit analyses of prenatal diagnostic programs.[10]

According to modified Kuppuswamy scale for assessing socioeconomic status, majority (86.7%) belonged to middle class and the rest to lower class. None of the subjects belonged to upper class.

One study shows that the risk of non-chromosomal anomalies increased with increasing socioeconomic deprivation. They opine that the decreasing risk with increasing deprivation found for all chromosomal malformations and Down syndrome in unadjusted analyses, occurred mainly as a result of differences in the maternal age distribution between social classes.[13]

In this study 9 (16.9%) was born to consanguineous parents. No significant difference was observed among karyotypically abnormal children born to consanguineous and non-consanguineous parents. Consanguinity increases the risk of single gene disorders rather than chromosomal anomalies. 49% of children were first born, 41.5% were second born. More no of chromosomal abnormalities were detected in the first order of birth. Studies have shown an increase in chromosomal abnormalities among higher birth order children.[13] In this study, 60% children were with birth order 3 or 3+ were karyotypically abnormal. However, the number in this group was very low in comparison to that in first and second order of birth. Maternal antenatal events such as history of foetal wastage, symptomatic or asymptomatic bacteriuria, PIH, GDM, history of IUGR were studied, but didn't show any difference. One previous study showed that GDM was not associated with chromosomal anomalies like Down syndrome significantly.[14] The mothers of children in the study population were screened for definite history of exposure to radiation. None gave such a history. Risk of congenital anomaly were assessed in relation to parental exposure to ionising radiation acquired through work within a nuclear generating station of an electric power company previously, but was not associated with an increased risk of congenital anomalies in the offspring of mothers or fathers.[15]

Pedigree tracking of study subjects showed that 5.6% had a suspected chromosomally abnormal blood relative. As karyotyping was relatively new modality at the time of the study, exact details of the anomalies in the previous generations could not be traced.

According to stature, the height of the study subjects belonged to various centiles and there was no trend or significant clustering in any of the centile ranges. Some of the chromosomal anomalies like Turner syndrome are known to have short stature while some others like Klinefelter's syndrome have tall stature.

According to weight for age (IAP classification), varying grades of malnutrition was noted in only 20% of the karyotypically abnormal children. This may probably be a reflection of the better awareness and feeding practices among the mothers of Kerala. In this study, 52% had mental retardation. Of this, 58% had an abnormal karyotype. Out of those without mental retardation, 43% had chromosomal anomaly ($p=0.339$). Mental retardation is characteristically seen in various syndromes like Down syndrome, Edward, Patau, Rubinstein Taybi, Seckel syndrome etc. 5.6 % of the study subjects had cleft lip and cleft palate was seen in same no percentages. Out of these, 2.5% had abnormal karyotype.

Of the chromosomally normal children, 15.3% had above mentioned anomalies p= (0.145). Chromosomal anomalies like Patau and Edward are known to be associated with cleft lip and / or palate. This study didn't have trisomy 13 but had a case of 13q+ syndrome which didn't have cleft lip or palate.

Low set ears were noted in 45.2%. Of this, 55% had abnormal karyotype. Of the chromosomally normal children, 15.3% had low set ears ($p=0.023$ i.e; <0.05; odds ratio = 6.7, 95% confidence intervals 1.3-34.4). The difference was significant.

Low set ears are characteristically seen in Down syndrome, Turner syndrome, trisomies 17, 18, 13, 15,

Smith-Lemli Opitz syndrome, Treacher Collins, Carpenter and Apert syndromes.

Though 7.8% of normal children had epicanthic folds, 57.55% of karyotypically abnormal children had this feature. The difference was significant (p=0.003, odd ratio-16.2, 95% confidence intervals =6.04-44.7). This is seen in many conditions as Down, Zellweger, Edward syndrome.

7.6% of normal children has a simian crease, while 35% of karyotypically abnormal children had this feature. The difference was significant. (p=0.005, odds ratio=13.3, 95% confidence intervals =4.95-36.6) This is seen in many conditions, the classical being Down syndrome. It may be a normal variant too.

While 62.5% of karyotypically abnormal children had hypotonia, 23% of normal children had the same. (p=0.024, odd ratio=5.6, 95% confidence intervals =1.2-30). The difference was significant. Abnormalities of autosomal chromosomes are always associated with infantile hypotonia.[16]

Other anomalies like up slanting eyes, down slanting eyes, micrognathia, flat nasal bridge, microcephaly, hypertelorism were studied (p=0.05). Mongoloid or up slanting eyes are seen in Down syndrome, Prader-Willi syndrome, ectodermal dysplasias. It may be a normal variant too. Antimongoloid slant may be seen in Down, Turner, trisomy 17-18, Apert, Smith Lemli Opitz, Noonan and Treacher Collins syndromes. Micrognathia is characteristically seen in Pierre Robin syndrome, Treacher Collins syndrome, Down, Zellweger, trisomies 13 and 18, Russel Silver syndromes. Flat nasal bridge is seen in Down, Zellweger, Smith Lemli Opitz syndromes. Clinodactyly is seen in Down syndrome. Hypertelorism is increased distance between two eyes and is due to hypertrophy of lesser wing of sphenoid. It is seen in Down, Turner, Noonan, Carpenter, Di George, Rubinstein Taybi syndrome. In Edward syndrome, the index finger characteristically overlaps the third while the fifth finger overlaps the fourth. Microcephaly may be a familial feature or may be part of craniosynostosis syndromes, intrauterine infections as CMV, rubella or as part of trisomies 13 and 21, Smith Lemli Opitz syndromes.

The association of CVS, renal, GIT, skeletal anomalies and ambiguous genitalia to chromosomal anomalies were studied but were found to be significant. One major anomaly may not be indicative of a chromosomal anomaly where as association of various major and minor anomalies may indicate a chromosomal defect.

CONCLUSION

1. Among the 53 children, 73.58% had an abnormal karyotype. Those with two major anomalies or one major and two minor anomalies or three minor anomalies were included in the study. One major anomaly may not be indicative of a chromosomal anomaly whereas association of various major and minor anomalies may indicate a chromosomal defect. As karyotyping and further studies to detect chromosomal anomalies are expensive, selection of cases was based on inclusion criteria which yield a high positivity rate. Proper diagnosis of chromosomal anomalies can lead to prevention of future birth of similarly affected children. This can be achieved by instituting genetic counselling.
2. There was no statistically significant association between paternal ages and incidence of chromosomal anomalies in the study. Even though a causal relationship between chromosomal anomalies and parental ages are present, no such association was observed in this study. This may be because of low sample size.
3. Among the minor anomalies, low set ears, epicanthic folds, simian crease and hypotonia were found to have a statistically significant association with the occurrence of chromosomal anomalies.
4. Among other anomalies, CVS, GIT, renal, skeletal anomalies and mental retardation etc, none were found to be significantly associated with chromosomal anomalies. One major anomaly may not be indicative of a chromosomal anomaly whereas association of various major and minor anomalies may indicate a chromosomal defect.

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