

Phenotypes and Congenital Anomalies of Down Syndrome In Manipur

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Abstract:

Aims: To study physical expression (phenotype), congenital anomalies, elicit the degree of mental retardation and cytogenetic profile of Down syndrome patients in Manipur.

Methods: The study was carried out in the Department of Anatomy on 50 suspected cases of Down Syndrome selected from mental homes of Manipur and Regional Institute of Medical Sciences hospital with due permission from the concerned authorities. All the cases were physically examined for their phenotype and karyotyping studies was carried out from peripheral blood.

Results: 19(38%) cases under the purview of the study were males and 31(62%) cases were female. 90% had moderate mental retardation and 10% had mild mental retardation. The highest incidence of affected babies are in the maternal age group of >40 years, 19 cases (38%), while the lowest incidence 2 cases (4%) is in the age group <25 years. Chromosomal analysis showed 34(68%) free trisomy, 2 (4%) were cases of Robertsonian translocation, 2(4%) balanced translocation, 2(4%) pericentric inversion and 10(20%) were of the normal karyotype. Flat facial profile, flat nasal bridge, epicanthic folds and upslant palpebral fissure were that most common phenotypic presentation in the study population. As in the studies conducted by various authors in different study populations, phenotypic presentations of Down syndrome seem to vary amongst races.

Keywords- phenotypes, chromosome, karyotyping

I. Introduction

Down syndrome or trisomy 21 is one of the commonest chromosomal abnormalities associated with mental retardation and developmental delay. It was first described by John Langdon Down in 1866.⁽¹⁾ Formerly it was known as Mongolism because of the observed similarities in the descriptions of the Mongols to the anthropometric parameters of these patients with Down syndrome.

The clinical diagnosis of Down syndrome presents with no particular difficulty. The diagnostic accuracy of Down syndrome on the basis of clinical features is reported to be 73% to 100%. Occasionally, even an experienced physician might find it difficult to give a confirmatory diagnosis in an infant with subtle clinical features. Karyotyping is essential for confirmation of the clinical diagnosis, determination of recurrent risk and to provide a basis for genetic counselling. Although the particular karyotype responsible for Down syndrome has little, if any, effect on the phenotype of the patient, it is essential for determining the risk of recurrence.

The present study attempted to find out the following:

1. The physical expression (phenotype) and congenital anomalies in Down syndrome cases in Manipur.
2. The degree of mental retardation and functional disabilities associated with Down syndrome
3. Diagnosis and establishment of the suspected clinical cases of Down syndrome by chromosomal analysis and karyotyping.

II. Materials And Methods

The study was carried out in the Department of Anatomy, Regional Institute of Medical Sciences, Imphal on 50 (21 males and 29 females) suspected cases of Down Syndrome selected from the Mental Homes of Manipur and RIMS Hospital, Imphal, Manipur with due permission from the concerned authorities including permission from the institutional ethics Committee, Regional Institute of Medical Sciences, Imphal. Informed consent from the parents / guardians of the patients was taken.

Karyotyping of 50 of the suspected cases of Down syndrome was done by culturing peripheral blood lymphocytes to determine the type of chromosomal abnormalities.

III. Results And Observations

The results of the present study showed that, females have a higher incidence over males in the study population contrary to other findings which show male predominance. As in the findings of studies by other authors, maternal age has a positive correlation with the incidence of Down syndrome in the study as shown in fig 3. Parity or the order of birth showed no statistical significant relationship with the incidence of Down syndrome in the studied population. Phenotypic expressions varied from race to race and the findings in the present study validate the same. The karyotyping results showed patterns and trends similar to studies conducted by other authors. 19(38%) cases under the purview of the study were males and 31(62%) cases were female. 90% had moderate mental retardation and 10% had mild mental retardation as shown in fig 2. The highest incidence of affected babies are in the maternal age group of >40 years, 19 cases (38%), while the lowest incidence 2 cases (4%) is in the age group <25 years as shown in fig 3.

Chromosomal analysis of the patients whose care takers consented for it showed 34(68%) free trisomy as shown in fig 4 and fig 5, 2 (4%) were cases of Robertsonian translocation as shown in fig 4 and 7, 2(4%) balanced translocation as shown in fig 4 and fig 7, 2(4%) pericentric inversion as shown in fig 4 and 6 and 10(20%) were of the normal karyotype.

Flat facial profile, flat nasal bridge, epicanthic folds and upslant palpebral fissure were the most common phenotypic presentation in the study population. As in the studies conducted by various authors in different study populations, phenotypic presentations of Down syndrome seem to vary amongst races.

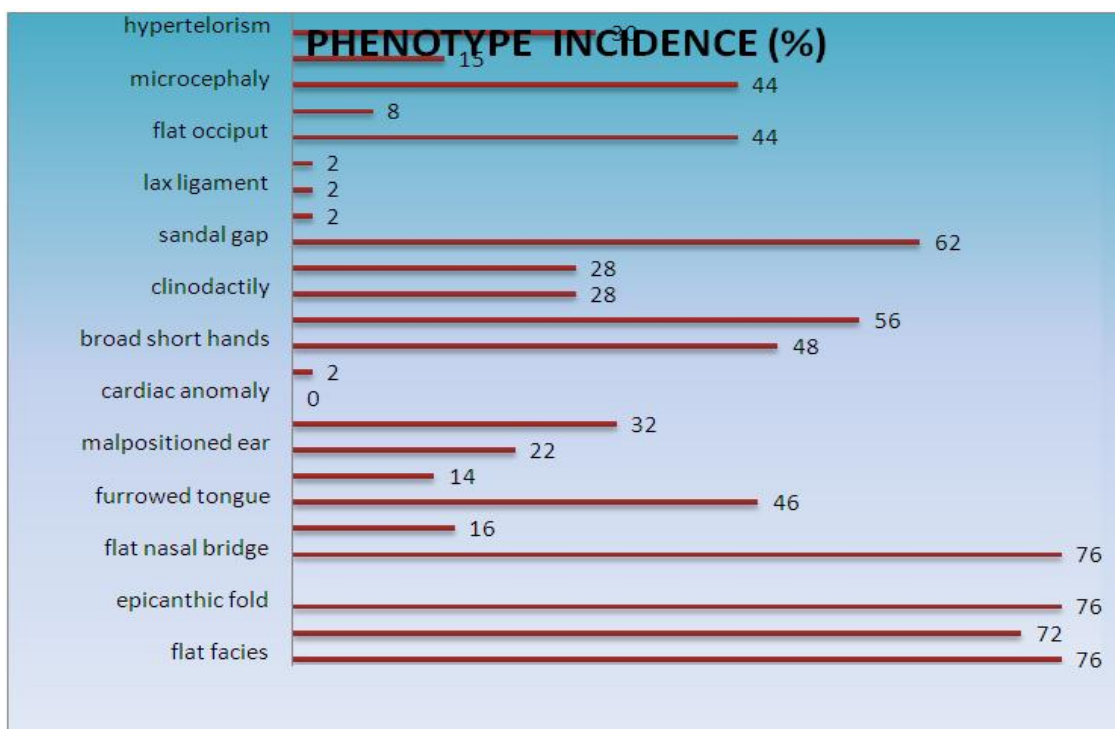


Fig-1 bar chart showing phenotypic incidence.

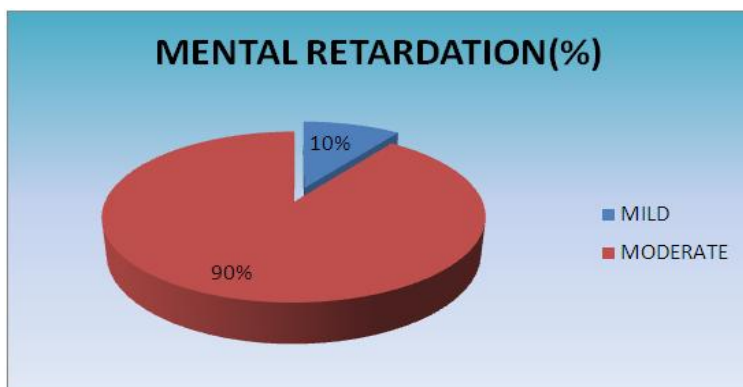


Fig 2: Pie chart showing 10% mild mental retardation (I.Q. 50 – 70) and 90% (I.Q 35-49) moderate mental retardation.

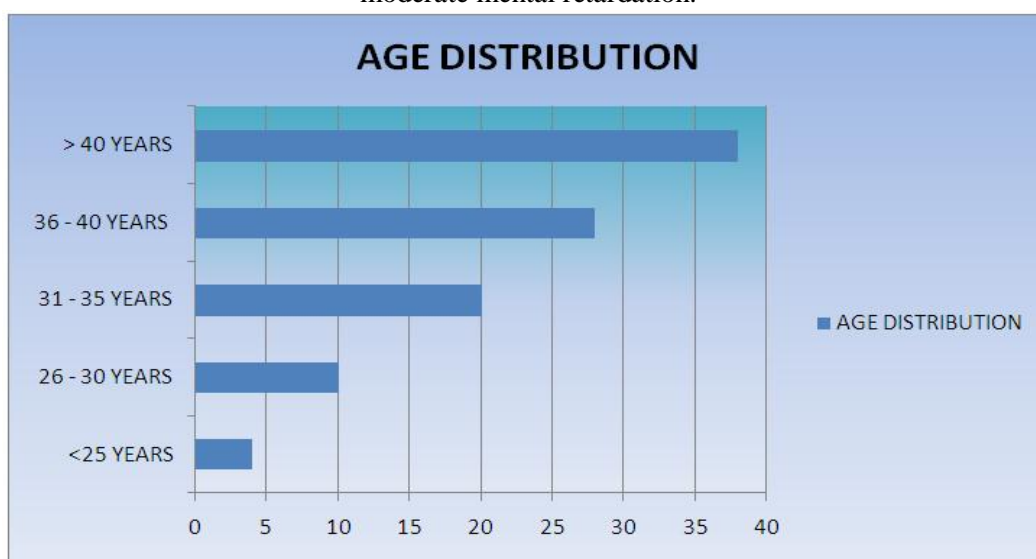


Fig-3 maternal age distribution bar chart.

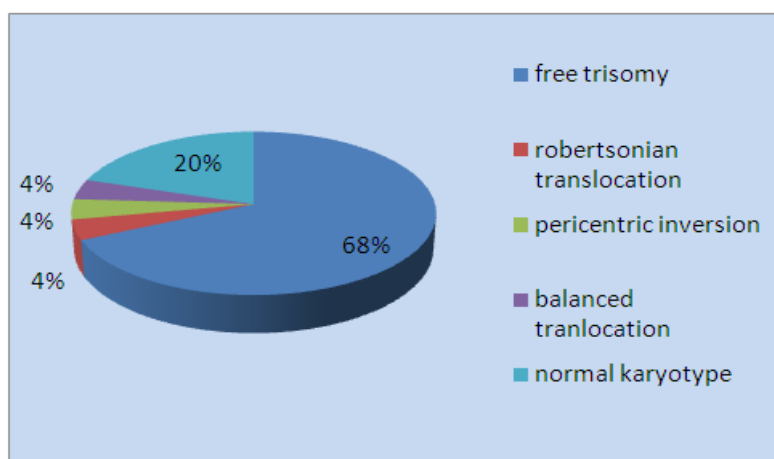


Fig-4 Pie chart showing karyotyping results

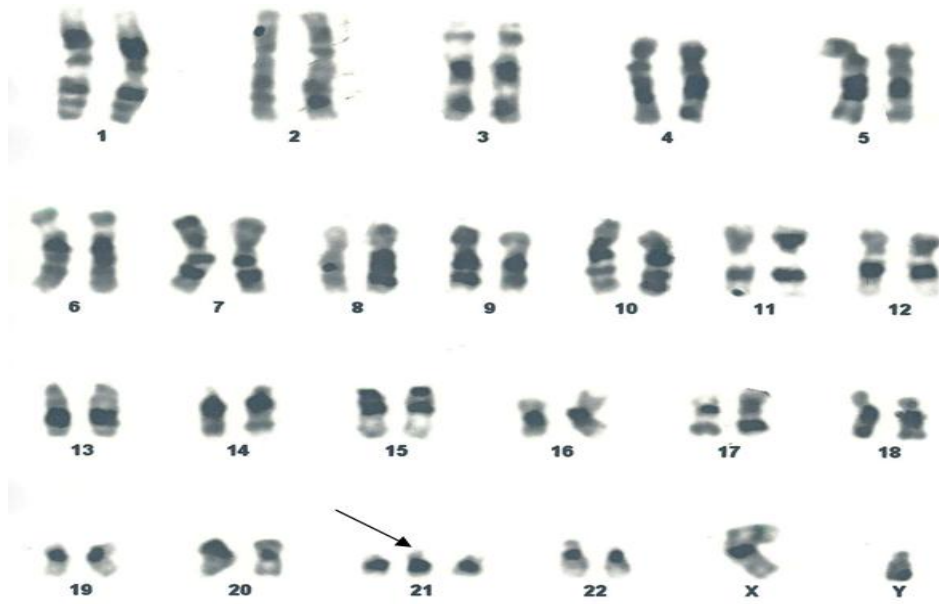


Fig-5- 47,XY,+21

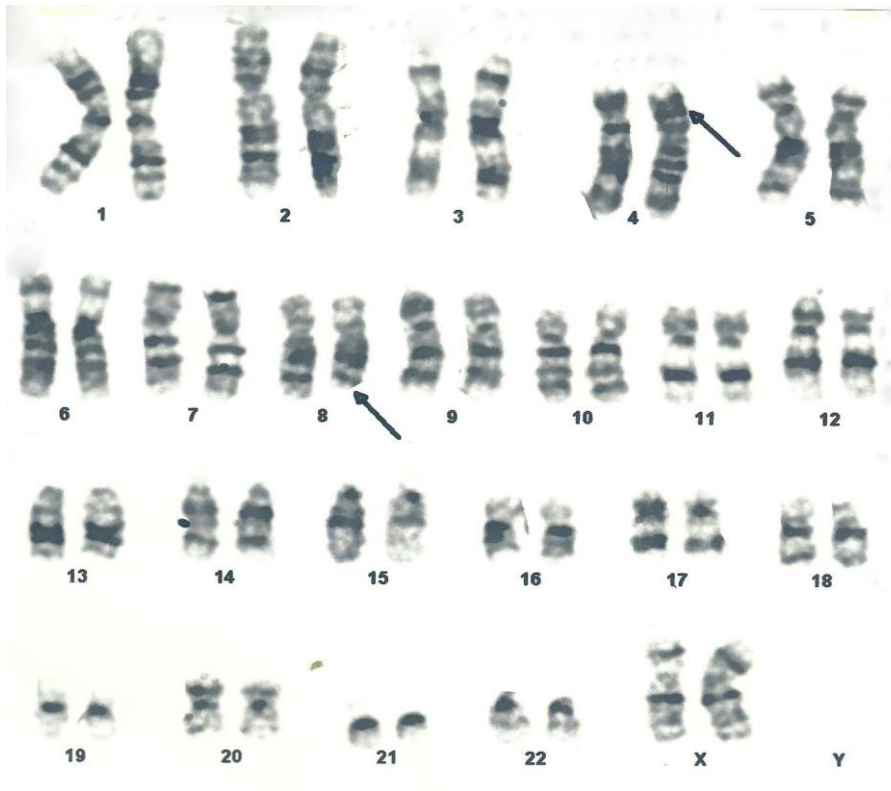


Fig 6. 46,XX,inv(4)(p15.2q21),del(8)(q24)

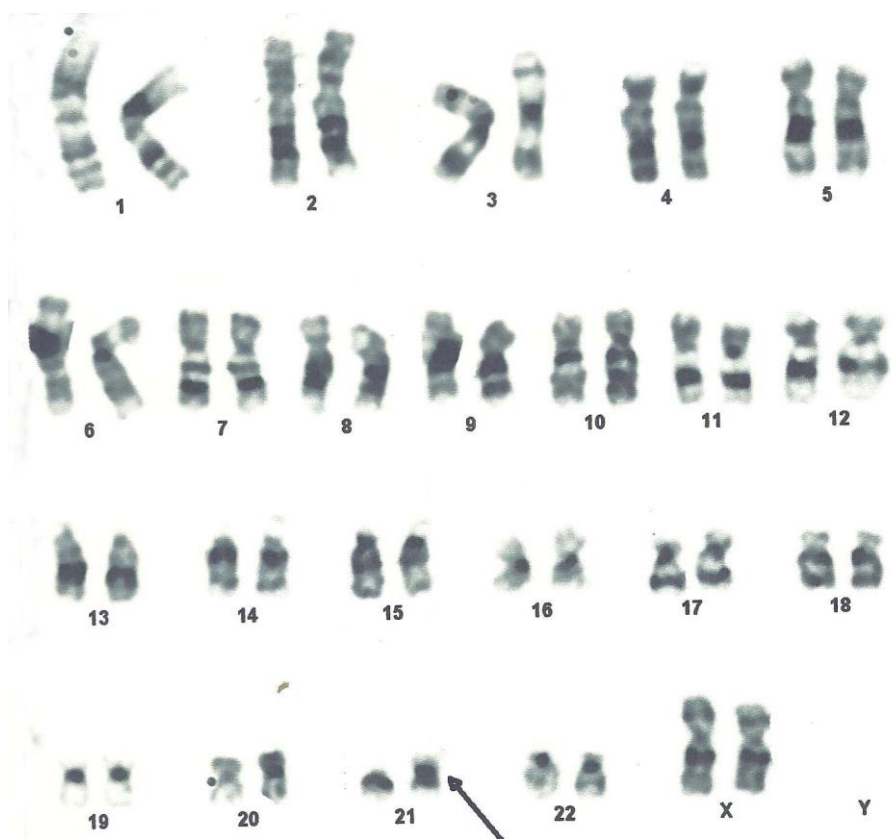


Fig-7. 46,XX,rob(21;21)(q10;q10),+21

IV. Discussion

There are many available literatures on the phenotype and findings of karyotyping of Down syndrome. Here, the findings of the present study are elaborately compared and discussed with the findings of other authors. For convenient purpose the present study is discussed under the following sub-headings:

Phenotypes

Craniofacial features have always been the hallmark of Down syndrome. Flat facial profile, flat nasal bridge and epicanthic fold were the most frequently found characteristics in 76% of the cases. A tabulated form of the phenotypes in order of frequency is presented below.

Dysmorphic feature	Azman BZ 2007(Malay)	Kava et al 2005(Ind)	Kumar et al 2001(Ind)	Jones 1997(U K)	Fryns 1990(US)	Current study2012(I nd)
Upslanting palpebral fissure	89.3	83.9	-	80	80	72
Flat facial profile	64.9	50.9	-	90	90	76
Ears abnormality	56.1	66.9	-	60	50	2
Hypotonia	52.6	76.3	80	80	21-77	2
Simian crease	36.8	33.2	40	45	48	28
Sandle gap	33.3	46.2	-	-	45	62
Hypertelorism	33.3	33.9	-	-	-	30

Short stubby fingers	24.5	-	-	-	-	62
Protruding tongue	19.2	29.9	-	-	-	14
Clinodactyly	19.2	36.1	50	50	62	28
Epicanthic folds	17.5	56.9	60	-	40	76

A comparison of the dysmorphic features of down syndrome by other authors is presented below (%).

Thus there are discrepancies in the phenotypic manifestations among different races. Significant differences include hypotonia present in 2% of the cases under the present study is seen in 76.3% in studies conducted by Kava et al⁽²⁾. Epicanthic fold is seen in 76% of the cases in the study whereas it is seen in 17.5% of the Malaysian Down syndrome study by Azman et al,⁽³⁾ 60% in study by Kumar et al, 56.9% in the study by kava et al, 40% in the study by Fryns⁽⁴⁾; in the north Indian, Russian and the English population respectively. Short stature is seen in only 2% of the cases, which is on the contrary to findings in the other races. Other studies quoted to demonstrate the difference in variations of phenotypes amongst different populations are as under.

Jackson et al,⁽⁵⁾ 1976 stated that in children under two years of age, the 10 most discriminating clinical signs of Trisomy 21 are brachycephaly, oblique palpebral fissure, nystagmus, flat nasal bridge or root, narrow palate, folded ear, short broad neck, incurved 5th finger, sandle gap between great toe and second toe, and hypotonia. Adult with Down Syndrome illustrated with the most obvious signs such as palpebral fissure, brushfield spots on the iris, thickened everted and cracked lips, a fissured tongue, small rounded ears with underdeveloped lobes, short broad neck, short stature and obesity. Phenotypic dysmorphism varied according to the chromosomal basis.

Dumaret et al,⁽⁶⁾ 1996 determined that facial recognition typically precedes systemic examination. The rounded head, a third fontanelle, the appearance of the eye especially on crying, and apparently large tongue in a small mouth, a short neck and single palmar creases may all be appreciated at birth. Primary care physicians need to be trained to recognize the most prevalent subtle signs of Down syndrome in their population, for an early diagnosis. Azman et al,⁽³⁾ studied down syndrome in the Malaysian population and found Ophthalmological abnormalities, such as hypertelorism were observed in 33.3% of cases. The cardiac anomalies were patent foramen ovale (22.8%), ventricular septal defect (20%), atrioventricular septal defect (20%), atrial septal defect (17.1%), patent ductus arteriosus (11.4%) and tetralogy of Fallot (8.5%). Gastrointestinal anomalies were present 22.7%. Imperforated anus was seen in (22.2%), and there were (16.6%) of Hirschsprung's disease and (5.5%) each with anorectal malformation and morgagni hernia. Hypothyroidism was encountered in (8.9%). Lahiri KR et al,⁽⁷⁾ found that the most common cause for referral was dysmorphic features; followed by congenital heart-disease and delayed milestones. Hypotonia, mongoloid slant, flat face and epicanthal fold were the most common minor malformations. Non-disjunction was the most common (93%) cytogenetic abnormality. Most common major malformation was congenital heart disease (59%), followed by thyroid dysfunction (14.9%) and Gastro intestinal anomalies (3.5%). Endocardial cushion defect was seen as most common congenital heart disease followed by VSD and PDA. All physical features may not be present in all cases although hypotonia, mongoloid slant, epicanthal fold, flat face are seen in >50% cases. As many cases may be asymptomatic; all infants with Down syndrome should undergo 2 D-echo/color doppler study. Regular thyroid function tests should be done in cases of all age groups.

Recurrent respiratory tract infections and congenital heart disease constitute the most debilitating disease from birth to 12 years of age. As children with down syndrome grow, their progress should be plotted on a growth chart to detect deviations from expected growth. Special growth charts are available so that children with Down syndrome can be compared with other children of Down syndrome. Thyroid function testing should be performed at 6 months and 12 months of age and yearly thereafter. Evaluation of the ears for infection as well as objective hearing test should be performed at every visit. Formal evaluation for refractive errors, refractive errors requiring glasses should be performed every two years. After the age of 3 the child is advised an x-ray of the neck to screen for atlanto axial instability. The average life expectancy for people with Down syndrome has

risen from 25 years in the 1980 to 49 years in 2002 with considerable variations between different ethnic and socioeconomic groups. Baird and Sadovnick 1989; Bell et al, 1989; Mikkelsen et al,⁽⁸⁾ 1990- Trisomy 21 survival data indicates that over 85% of infant survive to 1 year of age, 80% survive to age 10 years and more than 50% can expect to live longer than 50 years. In Down syndrome, congenital heart disease often in combination with respiratory tract infections has been a major cause of mortality in early childhood. In our study duodenal stenosis was found in 2% of the cases. There were no cases of cardiac anomaly in our study population. A sample size representative of the population is required to generalize the finding to extrapolate to the population as a whole.

Karyotype

Chromosomal analysis of the patients whose caretakers gave consent showed 34(68%) free trisomy, 2(4%) were cases of Robertsonian translocation, 2(4%) balanced translocation, 2(4%) pericentric inversion and 10(20%) were of the normal karyotype. In the free trisomy group, out of a total of 34, 12 were females and 22 were males. Normal karyotype, Robertsonian translocation, pericentric inversion and balanced translocation constituted the rest of the karyotypes, which were all females in this study. The normal karyotype cases had the typical cranio facial dysmorphism and mental retardation at presentation. Microdeletions and cryptic chromosome deletions can't be detected by the method used for chromosomal analysis which could be reason behind the normal karyotype of the cases. Fluorescent in situ hybridization has been suggested to detect such types. Also the possibility of other chromosomal anomalies presenting with mental retardation and phenotypes similar to Down syndrome needs to be ruled out. Abdel-Hady El-Gilany, et al,⁽⁹⁾ performed a retrospective analysis on the case records of 712 cytogenetically diagnosed cases of Down syndrome at the Genetic Unit of Mansoura University Children's Hospital, Egypt, during a 10-year period. They found that Non-disjunction was the most common type of abnormality, followed by translocation and lastly mosaic: 96.1, 3.1, and 0.8%, respectively. Joice B et al,⁽¹⁰⁾ studied the chromosomal defect in the Brazilian population. The results show 387 Down syndrome cases confirmed by karyotypic examinations. Of these, 357 (92.2%) patients had free trisomy of chromosome 21, 24 (6.2%) had translocation involving chromosome 21 and 6 (1.5%) had mosaicism. Non-disjunction was the main cause of Down syndrome, as the majority of the patients have free trisomy of chromosome 21. The cytogenetic pattern of Down syndrome is variable among different studies.

Mokhtar MM et al,⁽¹¹⁾ studied 673 Down syndrome patients were referred to the cases; Robertsonian translocation 2.7%; and mosaicism 0.7%. In 8 cases, regular trisomy 21 was associated with structural or numerical chromosome anomalies. Translocation was parentally inherited for 33.3% of cases and maternal transmission was twice as common as paternal. Two translocated Down syndrome fetuses were diagnosed prenatally in a t(14;21) carrier mother.

Verma IC et al,⁽¹²⁾ conducted Cytogenetic studies in the north Indian population in 645 patients with Down syndrome. Free trisomy of chromosome 21 was present in 600 cases (93%). Translocation karyotypes were observed in 26 cases (4%). Seventeen patients (2.6%) had mosaicism. Two (0.3%) patients had additional karyotypic abnormalities along with trisomy 21. Similar patterns were reported by Jaouad IC⁽¹³⁾. Free trisomy 21 was present in 96.24 %, 3% patients had translocation and 0.05% cases were mosaics. The median maternal age of the Moroccan mothers at the birth of the affected child was 35.39 years. Balkan M et al,⁽¹⁴⁾ reported the genetic basis of chromosomal anomalies syndrome in the Turkish population. The highest frequencies of abnormal karyotypes were found among cases that were referred due to suspicion of Down syndrome (84.8%). Among the chromosomal abnormalities, sexual chromosomal abnormalities were found in 239 cases (17.6%), and Klinefelter syndrome was the most frequent sex chromosomal abnormality. Autosomal abnormalities were found in 1119 cases (82.4%), and Down syndrome was the most frequent autosomal chromosomal abnormality.

Chandra N et al,⁽¹⁵⁾ made an observation of free trisomy in 83.82% Robertsonian translocation in 5% and mosaicism in 10.78% of cases in the study on 1020 cases which was in accordance with earlier report from India. In another study, Sheth F et al,⁽¹⁶⁾ 382 cases clinically suspected for Down syndrome were investigated for cytogenetic study. Free trisomy 21 constituted 84.8% of cases, translocation 8.9%, mosaicism 3.9% and in 2.4% cases regular T21 was associated with structural or numerical changes.

Thus in the present study the chromosomal patterns were in line with the results of other authors, though free trisomy 21 is a little less in incidence than expected. The normal karyotype cases had the typical craniofacial dysmorphism and mental retardation. Microdeletions and cryptic deletions can't be detected by the routine cytogenetic method used for chromosomal analysis which could be the reason behind the normal karyotype of the cases. Fluorescent in situ hybridization can be used to detect such small deletions. Also the possibility of other chromosomal anomalies presenting with mental retardation and phenotypes similar to those of Down syndrome needs to be ruled out.

Maternal age

In the present study 38% of the affected individuals were born to mothers whose age was greater than 40 at the time of birth. 4% of the affected individuals were born to mothers who were <25 years at the time of birth. The average maternal age at birth of the affected child was 32.3 years, the youngest was 18 years and the oldest 43 years of age. Statistical analysis shows a Pearson correlation coefficient of 0.997 between the two variables. A cross sectional examination of Down syndrome in all age groups reveals an age incidence of 10 ± 6.81 (fig.1). Lamb NE et al,⁽¹⁷⁾ investigated into the probable cause of this correlation and found that environmental and age-related insults accumulate in the ovary as a woman ages, leading to malsegregation of oocytes with stable exchange patterns. It is this risk, due to recombination-independent factors, that would be most influenced by increasing age. According to Jorde LB et al,⁽¹⁸⁾ among mothers younger than 30 years of age, the risk is <1/1000, it increases to approximately 1/400 at age 35 years, 1/100 at age 40 and approximately 1/25 after age 45.

Maternal age seems to affect the trisomy 21 type of chromosomal anomaly more than the other types as shown in the studies of [Mutton D et al](#)⁽¹⁹⁾ who reported the overall sex ratio of (male to female: 1.23 to 1) in the England and Wales population. 95% percent had regular trisomy 21, 4% there was a translocation, mostly Robertsonian t(14;21) or t(21;21) and 1% was mosaics with one normal cell line. Mean maternal age was raised in free trisomy 21, but not in translocations. However, in mosaics with one normal cell line the male to female ratio was 0.8 to 1, and in twins discordant for trisomy 21 there was also a female excess. [Wyrobek AJ et al](#),⁽²⁰⁾ reported variation in maternal-age-effect curves, viz. linear increase in chromosome 16 and exponential increase chromosome 21. The paternal-age effect is considerably smaller than the maternal and is more likely to involve meiotic II errors of the sex chromosomes, whereas the maternal-age effect is more likely to arise from meiotic I errors producing autosomal trisomy. [Mulcahy MT](#)⁽²¹⁾ in his report of Down's syndrome in Western Australian subjects confirmed that 95% of cases were trisomic due to nondisjunction, 4% were trisomic due to translocation, and 1% were mosaic, the ratio of inherited/sporadic translocations differed from that usually reported simultaneously. It could be due to age-dependent decay in the spindle fibres or their components, a failure in nucleolar breakdown or an accumulation of the effects of radiation, hormonal imbalances and infection. On the other hand, clinical and experimental studies have shown that age-independent DNA hypomethylation is associated with chromosomal instability and abnormal segregation.

Gender distribution

The gender distribution of Down syndrome as studied in various populations around the world reported a male preponderance, with a ratio ranging from 1.1:1 to 2.3:1. 19 (38%) cases under the purview of the present study were males and 31(62%) cases were female. In the present study, females exceeded males in the ratio of 1.63:1. [Kovaleva NV](#)⁽²²⁾ reported a sex ratio in the former Soviet Republic, the ratio was skewed toward an excess of males in the majority of studied populations.

This discordance with previous studies might be true to the local population from where the sample is taken. However genetic basis of male preponderance has been explained by Kovaleva wherein free trisomy and translocation has been assigned male dominance. Models of joint segregation of chromosome No.21 and chromosome Y in spermatogenesis and chromosome nondisjunction during second meiotic division of oogenesis caused by Y chromosome bearing spermatozoa has been hypothesized to be the cause.

Free trisomy constituted 34(68%) of the cases in the present study and 64% of them were males. Chromosome nondisjunction during second meiotic division of oogenesis caused by Y chromosome bearing spermatozoa is thought to be the basis of the most common genetic basis of free trisomy which constitutes 95% of Down syndrome.⁽²²⁾

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