

FREQUENCY OF CLINICAL FEATURES AND CYTOGENETIC DEFECTS IN DOWN SYNDROME DIAGNOSED AT AFIP

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ABSTRACT

Objective: To determine the frequency of clinical features and cytogenetic abnormalities in patients of down syndrome and correlation of cytogenetic abnormalities with clinical features.

Study Design: Cross sectional study.

Place and Duration of Study: Department of Haematology, Armed Forces Institute of Pathology, Rawalpindi, from Feb 2017 to Feb 2018.

Methodology: Total 163 patients with clinical suspicion of Down syndrome were selected by non-probability convenient sampling and diagnosis was confirmed by conventional cytogenetic analysis using Giemsa trypsin banding technique. Clinical features were assessed and frequency of different cytogenetic abnormalities were noted.

Results: Out of total 163 patients, 96 (59%) were male and 67 (41%) were female. Median age of the patients was 11 months. Trisomy 21 was detected in 158 (96.9%), Robertsonian translocation in 4 (2.4%) and mosaicism in 01 (0.6%) patient. The predominant clinical features observed were slanted with eyes, epicanthic folds, depressed nasal bridge and protruding tongue.

Conclusion: Trisomy 21 is the most common cytogenetic abnormality observed in patients of down syndrome.

Keywords: Down syndrome, Karyotyping, Trisomy 21.

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INTRODUCTION

Down syndrome is the most common autosomal abnormality and an important genetic cause of intellectual disability¹. Its incidence is about 1 in 700 live born infants². Down syndrome is caused by three types of chromosomal abnormalities; trisomy 21, translocation and mosaic trisomy³. Trisomy 21 is observed in over 95% of patients, translocation in 2-4% and mosaicism in 1-2% of patients⁴.

Trisomy 21 occurs due to nondisjunction of chromosome 21 during gametogenesis in one of the parents or during post zygotic mitosis in early embryonic development. Nondisjunction occurs most commonly during gamete formation process in females than in males. Nondisjunction of chromosomes during post zygotic mitosis in early embryonic development occurs in >5% of cases⁵. Exact cause of nondisjunction is not known but

advanced maternal age is an important risk factor for maternal meiotic nondisjunction⁶.

In Robertsonian translocation, extra chromosome 21 is translocated to acrocentric chromosome of G group (chromosome 21, 22) or D group (chromosome 13, 14, 15). The most common type is non homologous Robertsonian translocation between chromosome 14 and 21 and second most common type is homologous Robertsonian translocation between chromosome 21 and 21⁷. It can occur spontaneously de novo during gametogenesis in one of the parents or can be inherited from carrier parents. In the case of Robertsonian translocation created sporadically de novo, the risk to second offspring is small. When one parent is carrier of 21q21q Robertsonian translocation, the risk to second offspring is 100% as all of its produced gametes are unbalanced⁸.

In mosaic trisomy 21 patient has two cell lines, one with 46 Chromosomes having normal karyotype and the other with 47 chromosomes⁹. These individuals may be phenotypically less affected⁷.

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The characteristics features of Down syndrome are facial features (mongoloid face, depressed nasal bridge, hypertelorism), simian crease, brachycephaly, short stature and hypotonia. Patients with Down syndrome have increased risk of congenital heart defects, genitourinary, gastrointestinal, skeletal, haematological and other medical disorders¹⁰.

Cytogenetics is an important technique for diagnosis of Down syndrome¹¹. It is also important for determining recurrent risk and advising genetic counseling¹². In case of Robertsonian translocation; if parent is also carrier of Robertsonian translocation, the risk to next offspring is high. But this technique is only available in few centres in our country. Most of the data regarding the frequency of cytogenetic abnormalities and clinical features of Down syndrome is from Western Studies but limited data is available from our region. So, we conducted this study with the aim to determine the frequency of different cytogenetic abnormalities in Down syndrome to help clinicians to counsel patients regarding the recurrence risk.

METHODOLOGY

This was a cross sectional study conducted in the Department of Haematology, Armed Forces Institute of Pathology Rawalpindi, from Feb 2017 to Feb 2018. All patients with clinical suspicion of Down syndrome irrespective of age and gender were selected by convenient non-probability sampling. Sample size was 163. Patients with haematological malignancy having trisomy 21 were excluded.

Study was conducted after the ethical approval of the institutional review board. All individuals were included in this study after informed consent of their parents. Detailed history was taken and physical examination was carried out and findings were recorded in pre-designed performa.

Cytogenetic analysis was performed to confirm the diagnosis by using conventional G banding technique. 3-5 ml of heparinized blood sample was taken. Samples were cultured in RPMI

1640 medium for 72 hrs. Harvesting was done to obtain metaphases by first adding 1% colchicine followed by incubation, centrifugation and addition of hypotonic solution of 1% KCl. After addition of fixative (3:1 methanol to glacial acetic acid) slides were made and examined under microscope after Leishmann staining to look for presence of at least 20 metaphases which rendered culture successful. Giemsa trypsin banding was performed and slides were analyzed by Cytovision semi-automated image analysis and capture system.

SPSS 24 was used for analysis. Quantitative variables were presented in terms of median while qualitative variables by frequency and percentage.

RESULTS

A total of 163 patients with clinical suspicion of Down syndrome confirmed on Cytogenetic analysis were included in the study. Of these 96 (59%) patients were male and 67 (41%) were female. The median age of the enrolled patients

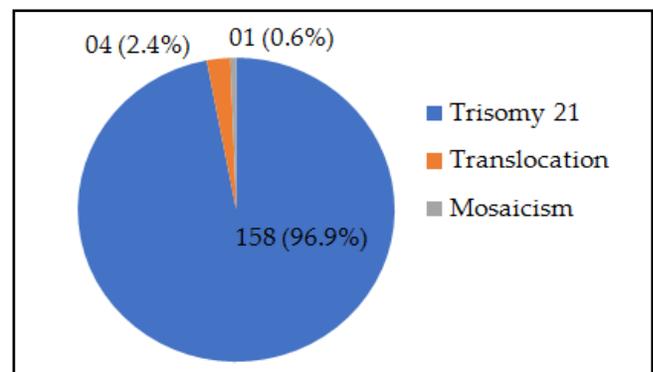


Figure: Different cytogenetic abnormalities in patients of down syndrome.

was 11 months.

The cytogenetic analysis showed that trisomy 21 was the most common abnormality and detected in 158 patients (96.9%), 4 (2.4%) patients had Robertsonian translocation and only 1 (0.6%) patient was shown to have mosaicism. In patients with Robertsonian translocation; chromosome 21 was translocated to chromosome¹⁴.

The clinical features observed in patients of Down syndrome are listed in table.

The predominant clinical features noted were slanted eyes, epicanthic folds and depressed nasal bridge.

Table: Frequency of clinical features in patients of down syndrome (n=163).

Clinical Feature	Frequency n (%)	Free Trisomy 21	Robertsonian translocation	Mosaicism
Slanted eyes	121 (74.2)	118	3	-
Depressed nasal bridge	115 (70.5)	111	3	1
Epicanthic folds	95 (58.2)	92	3	-
Protruding tongue	84 (51.5)	82	2	-
Sandal gap	73 (44.7)	70	3	-
Flat occiput	69 (42.3)	66	2	1
Transverse palmer crease	59 (36.1)	57	2	-
Congenital heart disease	55 (33.7)	54	1	-
Respiratory infections	53 (32.5)	51	1	1
Dysplastic ears	23 (14.1)	23	-	-
Umbilical hernia	14 (8.5)	14	-	-

DISCUSSION

Down syndrome is the most common birth defect and common cause of mental retardation. Though strong clinical suspicion favours the diagnosis but cytogenetic studies are essential to confirm the clinical diagnosis. The particular karyotype has little if, any effect on clinical presentation but it helps in determining recurrence risk. However, facilities for cytogenetic analysis are available only in few centres in Pakistan resulting in delay in diagnosis in some patients.

The median age in our study was 11 months. Male to female ratio was 1.4:1. The predominance of males appears to be universal and reported by many studies and ranged from 1.1:1 to 2.3:1.13 Study conducted by Ahmed *et al* (Pakistan), Jaouad *et al* (Morocco) and Hirak *et al* (India) also

reported male to female ratio of 1.3:1^{14,15,8}. However, study conducted in Iraq by Salih *et al* showed female predominance among Down syndrome patients¹⁶.

Cytogenetic studies in patients with Down syndrome carried out in different countries have shown differences in frequencies of these abnormalities. The cytogenetic abnormalities observed in our study are trisomy 21 (96.9%), translocation (2.4%) and mosaicism (0.6%). Similar results are seen in many other studies like Mokhtar *et al* (Egypt) reported trisomy 21 (95.4%), translocation (2.7%) and mosaicism (0.7%)¹⁷. El Gilany *et al* reported trisomy 21 (96.1%), translocation (3.1%) and mosaicism (0.8%)¹³. Jaouad *et al* from Morocco reported trisomy 21 (96.2%), translocation (3.1%) and mosaicism (0.5%)¹⁵. However study conducted by Salih *et al* in the Iraqi population has reported higher frequency of translocations as being 5.8%¹⁶. Similar results have been reported by Pankaj *et al* in the Indian children¹⁸. Chandra *et al* (India) in a study conducted at Department of Genetics, University of Madras has observed mosaicism in 10.7% of his population which is quite higher than other studies¹⁹.

The predominant clinical features observed in present study are slanted eyes, epicanthic folds, depressed nasal bridge. Study conducted by Ahmed *et al* also reported high frequency of these clinical features¹⁴. The frequency of Simian crease and sandal gap in our study was 36.2% and 44.8% respectively. Similar results were reported by study conducted by Kava *et al*²⁰.

CONCLUSION

Trisomy 21 is the most common cytogenetic abnormality observed in patients of Down syndrome. Patients with mosaic Down syndrome are mildly affected. Identification of specific types of chromosomal abnormalities is important as it can help clinicians to counsel the parents regarding the recurrence risk.

CONFLICT OF INTEREST

This study has no conflict of interest to declare by any author.

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