



Original Research Article

Cytogenetic abnormalities and clinical presentation in down syndrome patients

Aaishwarya Dilip Dhabe¹, Harsha Hemant Jaykar^{1,*}, Ravindra C. Nimbargi¹¹Dept. of Pathology, Bharati Vidyapeeth Deemed to Be University Medical College and Research Centre, Pune, Maharashtra, India

ARTICLE INFO

Article history:

Received 28-11-2019

Accepted 23-12-2019

Available online 29-02-2020

Keywords:

DS Downs syndrome

Robertsonian translocation

TAM Transient abnormal

myelopoiesis

ABSTRACT

Total 60 samples were received for karyotyping from patients of developmental delay, dysmorphism and mental retardation, of which 20 cases showed trisomy 21. There was an equal incidence in males and females. All neonates (20%) showed broad short neck and decreased muscle tone at birth. Most common feature in infants (50%) was depressed nasal bridge and slanting eyes. All children (30%) presented with developmental delay and mental retardation. Low set ears and depressed nasal bridge (80%) was the most common finding across all age groups. Most common CHD was VSD (20%). Robertsonian translocation involving 14q and 21q was seen in 15 % cases. One case presented with transient abnormal myelopoiesis at birth. One case presented with additional balanced t(10;18)

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1. Introduction

Chromosomal abnormalities are an important cause of developmental delay and mental retardation in children seen in upto 28% of all mental retardation cases.¹ Chromosomal abnormalities include numerical and structural chromosome abnormalities. Down Syndrome (DS), also known as trisomy 21 is the most common genetic cause of mental retardation in humans.²

DS was described in humans by Langdon Down in 1866.³ It is seen due to a genedosage effect of the presence of an additional chromosome 21 or a partial trisomy, mainly in the 21q22 region. It is usually more commonly seen in males with a male: female ratio of 1.2:1 with an incidence of about 1 in 700 live births.^{3,4} Different cytogenetic abnormalities like free trisomy, Robertsonian translocation and additional chromosomal abnormalities can be seen on karyotype which helps in proper counseling and guidance of patients and the family for subsequent pregnancies.

DS cases also present with transient abnormal myelopoiesis which differs from non downs patients prognostically as well as therapeutically.

* Corresponding author.

E-mail address: dr.harshahj@gmail.com (H. H. Jaykar).

2. Materials and Methods

2.1. Study design

Retrospective observational study carried out Bharati Vidyapeeth (Deemed To Be University) and Medical College Hospital and Research Centre, Pune

2.2. Inclusion criteria

Patients diagnosed with trisomy 21 on karyotyping

2.3. Exclusion criteria

Patients not willing to undergo testing

2.4. Study Duration

1.6 year. (1 April 2018 to 31 October 2019)

The study was taken clearance from Institutional Ethical Committee.

2.5. Procedure

We describe the clinical features and cytogenetic findings of 20 children with trisomy 21 at a tertiary hospital. Data

on clinical features was obtained from the medical records. Conventional cytogenetic analysis of phytohemagglutinin-stimulated peripheral blood cultures was performed using standard protocols.⁵ For each patient, 20 G-banded metaphases at 400-550 band resolution were studied at ×1000 magnification using a Leica DM 2000 microscope and analysis was performed using CytoVision* System. Results were recorded using the International System for Human Cytogenetic Nomenclature (ISCN).⁶

3. Results

The clinical features are summarized in Table 1, the data of which was obtained from medical records.

The age wise distribution of cases are described in Table 2.

Table 1: Summary of clinical features

Clinical features	Present study (n=20)
Delayed development	6(30%)
Depressed nasal bridge	16(80%)
Hypotonia	11(55%)
Congenital heart diseases	4(20%)
Mongoloid slant	15(75%)



Fig. 2: Neonate of DS showing depressed nasal bridge and low set ears

Table 2: Age wise distribution

Age wise	Present study (n=20)
Neonates	4(20%)
Infants	10(50%)
Children	6(30%)

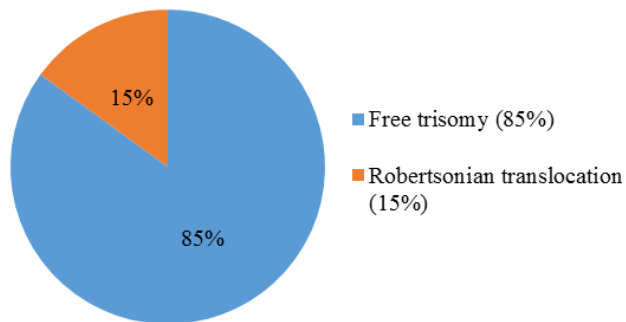


Fig. 1: Cytogenetic abnormalities

4. Discussion

Chromosomal abnormalities are present in nearly 1% of live born children,⁹ and their effects are devastating. Clinical features are important for an early suspicion of DS to reduce morbidity and mortality. These include mental retardation, congenital heart defects, facial features (upward slanting

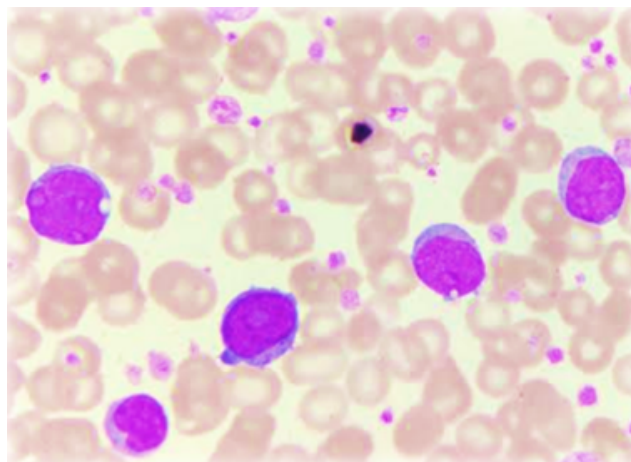


Fig. 3: Peripheral smear of case of TAM showing blasts showing cytoplasmic vacuolations and cytoplasmic blebs

Table 3: Comparison of age distribution with study of Irfan Ahmed et al(10)

Age wise	Present study (n=20)	Irfan Ahmed et al (n=295)
Neonates	4(20%)	49(17%)
Infants	10(50%)	124(42%)
Children	6(30%)	122(41%)

Table 4: Comparison of clinical features with study by Irfan Ahmed et al (10):

Clinical features	Present study (n=20)	Irfan Ahmed et al (n=295)
Delayed development	6(30%)	202(68.5%)
Depressed nasal bridge	16(80%)	180(61%)
Hypotonia	11(55%)	165(55.9%)
Congenital heart diseases	4(20%)	103(34.9%)
Mongoloid slant	15(75%)	245(83%)

Table 5: Comparison of karyotype results with other studies^{7,8}

Karyotype	Present study (n=16)	Abdelrahim A Sadek et al (n=364)	Anila Babameto et al (n=480)
Free trisomy 21	15(85%)	356(97.8%)	436(91%)
Translocations	3(15%)	4(1.1%)	29(6%)
Mosaicism	None	4(1.1%)	10(2%)
Chromosomal aberrations in addition to trisomy 21	1(5%)	None	5(1%)

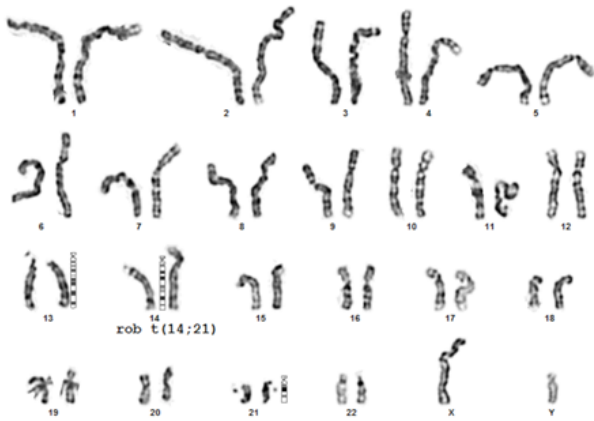


Fig. 4: Karotype showing robertsonian translocation on 14;21, rob(14;21)- Robertsonian translocation between long arm of chromosomes 14 and 21



Fig. 5: Karotype showing free trisomy with t(10;18)(p11;p11)

palpebral fissure, small mouth, thick lips, protruding tongue, flat occiput and small ears) and in 10% cases transient abnormal myelopoiesis is also seen.^{3,10} Confirmation of DS is either done by karyotyping or FISH. Different karyotypes in association with varying phenotypic expression of DS are seen. Trisomy 21 accounts for 95% of all cases of DS, whereas remaining 5% show Robertsonian translocation and mosaicism.³

Down syndrome children have karyotype of free Trisomy 21. This type occurs sporadically de novo due to nondisjunction of homologous chromosomes 21 during gamete formation of parents or during early embryonic development after fertilization.¹¹

Analysis of chromosome heteromorphisms and many other markers of DNA polymorphisms of parents and their children with Down syndrome revealed that chromosome 21 nondisjunction occur more often during the gamete-formation process in females more than in males.^{11,12} This could be due to prolong prophase 1 in Oogenesis. The empirical recurrence risk is around 1% in women under 30years of age. Gonadal mosaicism and Robertsonian translocation in either parent is an important cause of recurrence and should be looked for in families with more than one affected child.³

The diagnosis was established in all 20 children using conventional cytogenetic analysis as part of the workup of developmental delay and dysmorphism.

In the present study free DS was found to be the commonest (85%) (Figure 1). Of these free DS one case was found to have an associated t(10;18). Robertsonian translocation was seen in 15% cases (Figure 1)

Table 3 shows comparable results with the study by Irfan Ahmed et al¹³

Table 4 shows comparison of clinical features of present study with study by Irfan Ahmed et al¹³. Most of the clinical features are comparable, however delayed development was seen only in 30% cases of the present

study as compared to 68.5% in the study by Irfan Ahmed et al. This could be due to the difference in distribution of the age group of studied patients and sample size.

Table 5 shows comparison of karyotype results with other studies done by Sadek and Babameto et al respectively^{7,8}. It shows variation of percentage of cases showing Robertsonian translocation and additional chromosomal abnormalities, this could be explained by the difference in the sample size of present study and their studies. We have not found any case of mosaicism.

One case presented with transient abnormal myelopoiesis. Peripheral smear showed 65% blasts on admission (Figure 3). On flow-cytometry these blasts were positive for CD34, CD33, CD117, CD7 and CD61, moderately positive for CD38 and weakly positive for MPO, CD56, HLA-DR and CD13. Rest all B and T cell markers were negative. In this patient both phytohemagglutinin stimulated and unstimulated overnight cultures were studied, both showed free trisomy 21 as the sole abnormality. On regular follow up the blast count and total count reduced by day 26 without any medication. The associations have been documented between Down syndrome (DS) and various hematopoietic and non-hematopoietic malignancies. Transient abnormal myelopoiesis (TAM) is seen exclusively in Down syndrome and affects approximately 4 to 10% of newborns. The true incidence is not known because many times patients are asymptomatic. The average age of presentation is between 3 to 7 days, but can be diagnosed up to 2 months of age.¹⁰ The pathogenesis of transient abnormal myelopoiesis is complex, which lead to the presence of megakaryocytic lineage blasts in peripheral blood of infants with trisomy 21. The development of TAM require the acquisition of a somatic mutation of the gene encoding the hematopoietic transcription factor GATA-1. The GATA-1 mutations leads to poor megakaryocytic differentiation and uncontrolled proliferation of a blast population.¹⁴ The number of blasts in the peripheral blood is often higher than in the bone marrow, which is why bone marrow studies are usually not required in these patients.¹⁵ These patients usually have hepatosplenomegaly which is the site of fetal hematopoiesis.¹⁶

The characteristic hematological findings include leukocytosis (100000/ microL) in 20%-30% of cases), thrombocytopenia (40% of cases) and a greater number of circulating blasts. The diagnosis of TAM is when there are blasts in the peripheral blood smear and abnormal cell counts.^{15,17} Approximately 10% to 25% of patients are asymptomatic; therefore, diagnosed on an incidental finding during the laboratory investigation as a part of routine checkup, and in such cases the finding of TAM may become the first indication that a patient has trisomy 21^{16,18}. When TAM is clinically suspected, a cytogenetic karyotypic analysis should be performed to establish constitutional

trisomy 21, whereas analysis of the GATA-1 mutation is also recommended. GATA-1 gene mutation or mutations in exon 2 or 3 on the X chromosome proves a diagnosis of TAM, it is also helps in furthure management of the disease in the development of AMKL.^{15,16} In our case GATA-1 mutation analysis was not done due to non- affordability of the patient.

Robertsonian translocations occur during gametogenesis due to non-disjunction at mitosis or meiosis¹⁹. The occurrence of translocations is either sporadic or secondary if one of the parents is carrier of a balanced translocation. The carrier status of both parents must be established to determine the probability of recurrence of Down syndrome in the next child. In our study in both cases parental karyotype was not available. In translocation cases recurrence risk is 1% if neither parent is a carrier. In familial translocation cases the recurrence risk varies from 1-3% for male carriers and upto 10-15% for female carriers, with the exception of rare carriers of t(21;21) for whom the recurrence risk is 100%.²⁰

One case showed the t(10;18)(p11;p11) along with the free trisomy 21. This case highlights the importance of karyotype over FISH for trisomy 21. As in FISH we could have come to know about trisomy 21 only and not about the additional abnormality found in this case. Parental karyotype was not available in this patient. In this case parental karyotype would be of immense use to guide patient about future pregnancy and recurrence risk of chromosomal abnormality.

A correct diagnosis will allow for early intervention which plays a critical role in improving outcome. This is important because Down syndrome is not associated with a shortened life span.

5. Conclusion

Cytogenetic analysis is necessary to establish the diagnosis of DS. Karyotyping helps in assessing associated chromosomal abnormalities along with trisomy 21, which attributes to recurrence of genetic abnormalities in the subsequent pregnancy. FISH can detect presence of trisomy 21, but not associated abnormalities. Parental karyotype is important in cases with robertsonian translocation and associated other structural abnormalities.

An accurate diagnosis will help to counsel families, reduce parental anxiety. It also helps the physician to provide anticipatory guidance about the child's care. Thus, families will be helped to make informed decisions regarding the child's future care and planning on subsequent pregnancies.

6. Limitations

Our study had a small sample size. Parental karyotype was not available in cases with Robertsonian translocation and

one case with balanced t(10;18).

7. Source of funding

None.

8. Conflict of interest

None.

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Author biography

Harsha Hemant Jaykar Assistant Professor

Ravindra C. Nimbargi Professor and Head

Cite this article: Dhabe AD, Jaykar HH, Nimbargi RC. Cytogenetic abnormalities and clinical presentation in down syndrome patients. *IP J Diagn Pathol Oncol* 2020;5(1):35-39.