Original Article

Cytogenetic findings and maternal age in patients with Down Syndrome at a tertiary level hospital in Bangladesh.

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Conflict of Interest: None
Received: 10.09.2024
Accepted: 23.09.2024
www.banglajol.info/index.php/JSSMC

ABSTRACT:

Down syndrome is a common chromosomal disorder, related with multiple congenital anomalies with mental retardation. The cytogenetic profile of Down syndrome includes free trisomy 21, Robertsonian translocations, mosaicism, duplication of the DS critical region and other structural rearrangements involving chromosome 21. Identification of various types of chromosomal abnormalities in Down syndrome is very important. It aids in management of these children and to aware the affected families about recurrence risk and options available. The objective of this study was to describe the cytogenetic alterations of patients with Down syndrome and their relationship with maternal age. In this cross-sectional analytical study, Karyotyping was done in 42 patients out of 103 clinically suspected DS cases. Among them, free trisomy (n=33; 78%) was most common followed by Robertsonian translocation (n=7; 17%) and mosaic trisomy (n=2; 5 %) respectively. Majority of patients were males (n=30; 71.43%) and the male: female ratio was 5:2. Most (n=18; 43%) of patients with Down syndrome were born to mother age below 30 years, suggesting that there are other risk factors than advanced maternal age in this group.

Key Words:
Down syndrome, Trisomy 21, Robertsonian translocations, Mosaicism, Cytogenetic, Karyotyping.

[J Shaheed Suhrawardy Med Coll 2024; 16(2): 83-86]
DOI:https://doi.org/10.3329/jssmc.v16i2.88351

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Introduction:

Down syndrome(DS) is a common chromosomal disorder, related with multiple congenital anomalies with mental retardation. Incidence of Down syndrome varies from 1 in 600 to 1 in 1000 live births1. 12-15% of subjects with learning disabilities in developing countries were of down syndrome2.The cytogenetic profile of down syndrome includes free trisomy 21, Robertsonian translocations(RT), mosaicism, duplication of the DS critical region and other structural rearrangements involving chromosome 213,4. In approximately 95% of cases, Down syndrome is caused by nondisjunction(ND) resulting in an extra chromosome 21 (trisomy 21)1 . Such people have 47 chromosomes instead of the normal 465.

Investigations revealed that an extra chromosome 21 mainly originates from errors in maternal meiosis and associated with maternal age>35 year6. Approximately 4% of Down syndrome cases are due to a translocation7. In Robertsonian translocation chromosome 21 may be translocated to another acrocentric chromosome. Down Syndrome due to translocation can be de novo or inherited from a balanced carrier parent. In a balanced translocation, genetic material is exchanged with material from another non-homologous chromosome, and the chromosome count is maintained at 46. The most common translocation is t(14;21), in which chromosome 21 is attached to chromosome 14.

The next most common translocation is t(21;22). Translocation 21q;21q, which occurs when the extra chromosome 21 is attached to another chromosome 21, is much less common. It is particularly important to determine whether a parent is a carrier of, or a mosaic for, translocation 21q;21q. Each child of a carrier of the translocation will have Down syndrome or monosomy 21. Because monosomy 21 is not typically compatible with life, the risk of having a viable child with Down syndrome is 100%. If the parent is mosaic, that parent has some normal cells and some 45-chromosome cells with 21q;21q, and so the risk of Down syndrome is markedly increased, although these people may also have children with normal chromosomes. Down syndrome mosaicism presumably results from nondisjunction during cell division in the embryo. People with mosaic Down syndrome have two cell lines, one with the normal 46 chromosomes and another with 47 chromosomes, including an extra chromosome 21. Some people with mosaic Down syndrome have very subtle clinical signs and may have normal intelligence; however, even people with no detectable mosaicism can have very variable findings. If a parent has germline mosaicism for trisomy 21, an increased risk, above the maternal age-based risk, exists for a second affected child. Around 3-5% of DS cases occur due to mosaicism8. Confirmation of trisomy syndromes is done by cytogenetic techniques. Cytogenetics is the study of the structure and properties of chromosomes, chromosomal behavior during somatic cell division in growth and development (mitosis) and germ cell division in reproduction (meiosis), chromosomal influence on the phenotype and the factors that cause chromosomal changes. Fluorescent in situ hybridization(FISH) technology permits the detection of specific nucleic acid sequences in morphologically preserved chromosomes, cells, and tissues. Using FISH, cytogeneticists can detect chromosomal abnormalities that involve small segments of DNA if their probe is situated, fortuitously or by design, in the affected chromosomal segment9. The purpose of this study was to carry out a cytogenetic evaluation of suspected cases of Down syndrome in both sexes using classical karyotyping and to report the incidence of Down syndrome and the frequency of the 3 cytogenetic variants of Down syndrome in Bangladesh, as well as to evaluate the association of maternal age on the prevalence of Down syndrome.

Materials and Methods:

This cross-sectional analytical study was done at Down syndrome clinic of a tertiary level hospital in Bangladesh. Study period was one year, during this period clinically suspected 103 cases of Down syndrome were counselled for karyotyping to confirm the diagnosis. These patients showed the clinical features consistent with Down syndrome like epicanthic eye fold, brush field spot, flat nasal bridge, abnormal teeth, furrowed tongue, narrow palate, short neck, short and broad hands, incurved 5th finger, gap between 1st and 2nd toes, murmur, muscular hypotonia, oblique eye fissure, blepharitis, conjunctivitis, nystagmus, mouth permanently open, protruding tongue, high arched palate, folded ear, loose neck of skin, short 5th finger and transverse palmar crease. All of the children had mental retardation. Among these clinically suspected cases 42 underwent chromosome study with the GTG technique (G bands, trypsin digestion, and Giemsa staining) and the cytogenetic findings were described according to the International System for Human Cytogenomic Nomenclature 2016. Cytogenetic analysis was done by classical karyotyping technique. For classical karyotyping technique peripheral venous blood of the patient was collected in BD Vacutainer sodium heparin vial. 0.5 ml of blood sample was taken in 5 ml of culture media (PB MAX) in a test tube, under laminar air flow to maintain sterile condition.

Results:

During the study period clinically, suspected Down syndrome cases were 103. Karyotyping was advised to all of them for confirmation. But 42 cases convinced to do the investigation. All cytogenetic findings consistent

with Down syndrome. Majority of patients were males (n=30; 71.43%). The male: female ratio was 5:2 (Table-1). Among 33 cases with free trisomy, 24 cases were male (47XY, +21) and 9 cases were female (47XX, +21). Out of 7 cases with Robertsonian translocation, 4 cases were male and 3 cases were female. Two cases with mosaicism were male.

Table -1: Distribution of chromosomal abnormalities according to gender (N=42).

Gender	Free trisomy	Robertsonian translocation	Mosaic	Total
Male	24	4	2	30
Female	9	3	0	12
Total	33	7	2	42

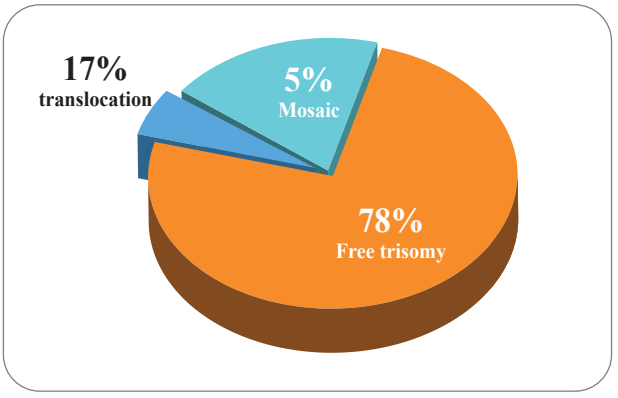

Fig-1: Distribution of chromosomal abnormalities

On classical karyotyping free trisomy (n=33; 78%) was most common followed by Robertsonian translocation (n=7; 17%) and Mosaic trisomy (n=2; 5%) respectively (Fig-1)

Table-2: Genotype of Down syndrome (N=42).

SN	Genotype	No
1.	Free trisomy	
	a) 47XY, +21	24
	b) 47XX, +21	9
2.	Robertsonian translocation	
	a) 46, XY (t 21; 21)	2
	b) 46, XX, (t 21; 21)	1
	c) 46, XY, (t 14; 21)	1
	d) 46, XY, (t 13; 21)	1
	e) 46, XX, (t 13; 21)	1
	f) 47, XX, -21, +t (21;21)	1
3.	Mosaic 47, XY, +21/46XY	2

The most common translocation involved in DS is between 21 and 21 which was followed by translocation between two chromosome 14 and 21 (Table-2).

Table-3: Distribution of chromosomal abnormalities according to maternal age at birth (N=42)

Mother Age during delivery (Y)	Free trisomy Number (%)	Robertsonian translocation Number (%)	Mosaic Number (%)	Total
≤ 30 Y	10	7	1	18(43%)
31-35 Y	12		1	13(31%)
36-40 Y	5			5(12%)
>40 Y	6			6(14%)
Total	33(78%)	7(17%)	2(5%)	42(100%)

Most of (n=18; 43%) patients with DS were born to mother age below 30 year. Among 33 mothers of trisomy 21, maximum (n=12) were born to mother aged between 31-35year followed by below 30year(n=10), more than 40year (n= 6), 36-40year(n=5). Among those showing Robertsonian translocation all were born to mother aged below 30year. In one mosaic case maternal age was below 30year and, in another case, maternal age was between 31-40 year (Table-3).

Discussion:

Several studies in different population worldwide indicate that free trisomy 21 is the most common variant of Down syndrome whose incidence varies between 95.51 to 83.82% 10. Lower percentages were found in Bosnia and Herzegovina with 86.6%11. It is evident through this study that free trisomy is most common (n=33; 78%) that is similar to other study. The difference in percentages could be attributed to the population studied, maternal age, or the number of metaphases analysed, although free trisomy 21 is always predominant in all reports. In this study Robertsonian translocations made the second most frequent variant (16.67%) which was more than previously reported range (2.66-5.1%)12. However findings are similar to those in Mexico, Kosovo, Cuba, Bosnia and Herzegovina, and India, percentages ranging from 4.3 to 15.2% 13. The most common translocation involved in DS is between 14 and 21 which was followed by translocation between two chromosome2114. In another study found 1 case of rob (14; 21) and rea (21; 21)15. Since Down syndrome can be de novo or inherited, it is necessary to perform a karyotype on the parents to detect a possible carrier and assess the risk of recurrence, which is important in genetic counselling. In this study, the information on the karyotypes of the parents was not available, so its origin could not be known. In our study mosaic DS was 4.76% which is within the range reported from different parts of th (1.19-10.78%)10. Advanced maternal age is one of the most important risk factors contributing to the non-disjunction of chromosome.

The risk increases gradually with increasing maternal age. Based on a large study, at 20 years of maternal age, the risk is 1/1466 births; at 35, it is 1/343; and at 40, it is 1/8516. However, it was observed in this study that 42.86% DS children were born to mothers below 30 y of age. This finding is not matched with association between increased maternal age and the risk of having a child with DS as evident in various studies17,18. This dissimilarity indicate that there would be other risk factors beyond maternal age, such as environmental exposure and ethnicity19. In our study among the free trisomy DS maximum patients (n=13; 36.36%) were born to mothers aged 31-35 years. Another study observed that translocation DS was more frequent in the offspring of mothers under 30 years of age, this may be due to child marriage20,22. Pandey et al in their study found that two children belonging to Robertsonian translocation group were born to mothers of age group<30 years and 31-35 years15. This study revealed that all children with Robertsonian translocation born to mothers belonging to age group below 30. Hulten et al. hypothesized that most females might be having low grade trisomy 21 ovarian mosaics with an average of 0.54% trisomy 21 cells and concluded that this ovarian mosaicism may predispose to trisomy 21 conception and conception of a translocation DS foetus in a mother at a younger age as compared to free trisomic Down syndrome21. As in children having RT the peripheral blood lymphocytes from both the parents had normal karyotype so we can conclude that the trisomy 21 due to Robertsonian translocation must have arisen either de novo or due to ovarian mosaicism. This explains the comparatively young maternal age for translocation trisomy children.

Conclusion:

Free trisomy made the most common cytogenetic variant followed by Robertsonian translocation and mosaic trisomy. This study finds a very interesting finding that maximum children with DS were born to mothers below 30 years of age which is may be due to early marital age. Cytogenetic analysis is the most important diagnostic tool for DS. Cytogenetic data also provide a basis for the genetic counselling of families into which DS children are born and further management of children with trisomy 21.

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