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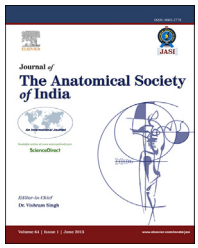

Original Article

Cytogenetic variations in a series of cases of Down Syndrome

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ARTICLE INFO

Article history:
Received 26 March 2015
Accepted 1 April 2015
Available online 2 May 2015

Keywords:
Cytogenetic analysis
Down Syndrome
Karyotype
Trisomy 21
Robertsonian translocation

ABSTRACT

Introduction: Down Syndrome (DS) is generally associated with mental retardation and developmental delay. The occurrence of DS is associated with multiple factors like maternal age, consanguineous marriage, early induced abortion etc. Chances of recurrences of DS in next pregnancy depend on the genetic constitution of the affected individual and the parents. So this study was done to find out the different types of cytogenetic abnormalities in DS patients and also the association of parental age to DS in a population in West Bengal. It is hoped that the present study will emphasize the need for genetic counseling of prospective parents as well as parents of individuals affected with DS, together with cytogenetic screening of pregnancies which are at high risk for DS.

Methods: A cytogenetic analysis was performed using conventional GTG banding on 120 patients with clinical features of DS, referred to the Department of Genetics, Vivekananda Institute of Medical Sciences, Kolkata during the period from October, 2008 to September, 2014.

Results: Cytogenetic analysis confirmed the diagnosis of DS in 117 cases, among them regular trisomy constituted 83.76%, mosaicism recorded in 11.11% and Robertsonian translocation in 5.12% of cases. The mean maternal age was higher in regular trisomy 21 (25.08 yrs) than in translocation (22.50 yrs). No significant difference was noted in mean paternal age among different categories of DS cases.

Discussion: This study documents the types of cytogenetic abnormalities in DS children of West Bengal population of India and thus emphasizes the need for genetic counseling in these cases.

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http://dx.doi.org/10.1016/j.jasi.2015.04.005

1. Introduction

Down Syndrome is the commonest autosomal genetic disorder in human with a prevalence of 1:600 newborn.[1] The prevalence of Down Syndrome (DS) in India is 0.88 per 1000 (1 out of 1139) to 1.09 per 1000 (1 out of 916) and three DS children are reported to be born every hour.[2,3] Patients with DS have a characteristic phenotype along with mental retardation and developmental delay. Although there is a considerable variation in the appearance of individuals with DS, they present a constellation of features that help the clinician to make a diagnosis. The facial features include a low nasal root, upslanting narrow close set palpebral fissures, measurably small and sometimes over-folded ears and a flattened maxillary and malar region with irregularly arranged teeth and large furrowed semi-protruded tongue giving the face a typical appearance. Males have poorly developed genitals and are almost always sterile. In females, ovarian defects and irregular menstruation are the rule, but fertility is possible and over two dozen live births have been recorded. They may also present with heart disease (40–50%) and duodenal atresia, increased risk of acute myeloid leukemia, Hirsprung's disease and Alzheimer's disease (especially after the fourth decade).[4] Diagnosis is evident from typical clinical features but the cytogenetic abnormalities should be studied for determination of the risk of recurrence and thereby helping in genetic counseling.

DS presents mainly in four cytogenetic forms[5,6]:

1. **Regular trisomy 21** is due to meiotic non-disjunction (T21) having karyotype 47,XX,+21 or 47,XY,+21 present in 93–95% of cases.
2. **Robertsonian translocations (RT)** involves the rearrangement of chromosome 21 with another acrocentric chromosomes (Group D or G), 46,XX, or 46,XY,rob(D or G;21)(q10;q10), they present in approximately 4% of cases.

D group includes 13, 14, 15 chromosomes, G group includes 21, 22 chromosomes.

3. In **Mosaicism** there is presence of two or more different cell lines in the same individual. In these cases, one line with T21 with another normal or abnormal line, represented by the formula 47,XX or XY,+21/46, XX or XY & correspond to 1–3% of all cases.
4. **Non-classical forms** like partial trisomy of the region 21q22.3 with karyotype 46,XX or 46,XY,dup(21)(q22.3), trisomy 21 associated with other chromosomal disorder – observed in <1% cases etc.

There are several reports on the increased incidence of DS from the different parts of the world with respect to ethnicity and parental age.[7,8] Prenatal screening is still inaccessible to most families in developing countries like us and almost all patients were diagnosed during postnatal period.

This study was thus conducted to document the prevalence of cytogenetic variants of Down Syndrome in West Bengal population and their relation to parental age.

2. Materials & methods

The study included 120 children in the age range of 4 days–15 yrs with phenotypically suspected Down Syndrome. They were referred to Vivekananda Institute of Medical Sciences (VIMS), Kolkata during the periods of October, 2008 to September, 2014 from different areas of West Bengal. This study was approved by the ethics review board of VIMS.

The blood sample was collected from the patients in a completely sterile heparinized vacutainer tube and mixed well. The cultures were set up with RPMI 1640 (Rosewell Park Memorial Institute) culture medium. Peripherial blood lymphocytes inducted with 2% phytohemagglutinin (PHA) were incubated at 37.5 °C for 72 h. One and a half hours prior to harvest, the cultures were arrested with colchicine and treated with 0.75 M KCl (potassium chloride) for 30 min and fixed in 3:1 ratio of methanol/glacial acetic acid fixative. After air drying, routine Giemsa (GTG) banding technique was performed to identify the chromosomes. After banding, 50 metaphases were scanned under low power for each case on OLYMPUS BX51 microscope and then 10 metaphases were analyzed by automated karyotyping system (CYTOVISION software). In cases of mosaics 30 metaphases were analyzed.

3. Results

Among 120 cases of phenotypically DS three showed normal karyotype. In rest of the 117 cases the chromosomal patterns are presented in Table 1. Free trisomy 21 was found in 98 cases (83.76%) (Fig. 1) and 13 cases (11.11%) showed mosaicism. In mosaicism group three cases of trisomy 21 along with Robertsonian translocation were noted, rest mosaics showed trisomy 21 along with normal cell line. In 6 cases (5.12%) pure translocation was noted (Figs. 2 and 3).

The majority of Down Syndome patients belonged to the age group of 4 days–15 years. The mean age of referral didn't differ in different categories of karyotypic abnormalities. Only few patients were referred from the neonatal ward while the others were referred for delayed development and speech defect.

The mean parental age in different type of DS is shown in Table 2. From the table it is evident that mean maternal age is lower in Robertsonian translocation group than trisomy 21 group. In our study no significant relation was found with the paternal age in the occurrence of DS.

4. Discussion

Aneuploidy is the most common and clinically significant type of human chromosome abnormality, occurring in at least 3–4% of all clinically recognized pregnancies.[4] Down Syndrome or Trisomy 21 is the most common aneuploidy in live born fetuses and is associated with mental retardation and developmental delay.

Essentially, DS consists of three or more copies of the genetic material of chromosome 21. This may occur as 3 copies