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Double aneuploidy 48,XXY,+21 in a fetus with congenital abnormalities

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ABSTRACT

The concurrent occurrence of double aneuploidy in the same individual is a relatively rare phenomenon. Previous studies indicate double trisomies were found in recurrent miscarriages and abortions. Presently, we report on an aborted fetal blood sample of 20 weeks gestation. The fetal summary was given as dilated lateral ventricles, dilated aqueductal stenosis and strong possibility of agenesis of corpus callosum and hydrocephalus. To confirm, whether the abnormality is inherited or de novo, we have done cytogenetic analysis on both parents.Fluorescence in situ hybridization (FISH) technique was used with LSI21 and DYZ3 alpha satellite and CEP X alpha satellite probes to confirm the cytogenetic result and to clarify the non-mosaic status of Down syndrome and the coexistence of Klinefelter syndrome. The XXY constitution may have contributed to the development of normal height and absence of microphthalmia in this patient with trisomy 21.Etiological predisposing factor for 48,XXY,+21 is not known. It is difficult to determine the incidence, phenotypic properties, and recurrence risk of 48,XXY,+21. Upto our knowledge, this is the first case of fetal sample withDown syndrome together with Klinefelter syndrome in India. The literature regarding double aneuploidy, which combines both autosome and sex chromosome aberrations, was also reviewed.

Keywords*:*Double aneuploidy, Down syndrome (trisomy 21), FISH, Klinefelter syndrome (XXY).

INTRODUCTION

Aneuploidies are common structural chromosomal abnormalities. In particular, three of them, trisomy 21, trisomy 18 and trisomy 13 are the most frequently seen autosomal aneuploidies. Other type of aneuploidies which are commonly seen as gonosomal aneuploidies are Turner syndrome, Klinefelter syndrome and their variants.The occurrence of double aneuploidy means existence of two chromosomal abnormalities in the same person, is an uncommon phenomenon[1, 2]. Most reported cases of double aneuploidy are published in the form of recurrent miscarriages[1, 2].The first case with autosomal and sex chromosome anomalies was reported in 1959 by Ford et al[3]. We have reported this case for the extreme rarity and its relation with cephalic and congenital heart defects.

MATERIALS AND METHODS

Case details

The fetus was a male, the first child of young, healthy and non-consanguineous parents, was aborted after 20 weeks of gestation. The family history revealed no specific abnormality. This is only expected, as features characteristic of Klinefelter syndrome are not apparent until the postpubertal stage[4]. The estimated fetal weight was 232 gm (35th percentile). On 4-D ultrasonography, cavum septum pellucidum in brain was not seen. Electroencephalogram showed mildly diffuse cortical dysfunction without abnormal epileptiform discharges.Lateral ventricles are dilated. Only a thin rim of cerebral cortex was present. Choroid plexus and medial wall of ventricle separation was 7.2 mm (normal < 3 mm). All the conditions were suggestive of agenesis of corpus callosum.

Cytogenetic analysis

Chromosome analysis was carried out in fetal sample and parents. Chromosome preparations obtained from PHA-stimulated peripheral blood cultures were subjected to GTG banding as previously described[5].The karyotype was designated according to ISCN (2013)[6]. Fifty metaphases were analysed in the proband and parental sample. To exclude mosaicism, FISH technique was used where the AneuVysion Assay Kit (Abbott-Vysis, U.S.A.) was applied to the blood sample of the fetus. These two set of probes contains chromosomes 13 and 21 (Figure 2A) and another set contains chromosomes 18, X and Y (Figure 2B). 500 interphase cells were counted for the patient.

Chromosome analysis of proband revealed 48,XXY,+21 (Figure 1) double aneuploidy (Down with Klinefelter syndrome), with no evidence of mosaicism with FISH technique (Figure 2) using digoxigenin-labelled probes LSI21 and DYZ3 alpha satellite and CEP X alpha satellite. Parental karyotype was found as normal.

DISCUSSION

A rare case of double chromosome aneuploidy including Down syndrome (trisomy 21) and Klinefelter syndrome (XXY) was described highlighting the fetal demise sample. Most of the cases of double aneuploidies reported so far involve the sex chromosomes with combination of autosomal trisomy 13, 18 and 21. For example, XXX/18, XXX/21, XXY/13, XXY/18, XXY/21, XYY/13, XYY/18 and XYY/21[7-19].

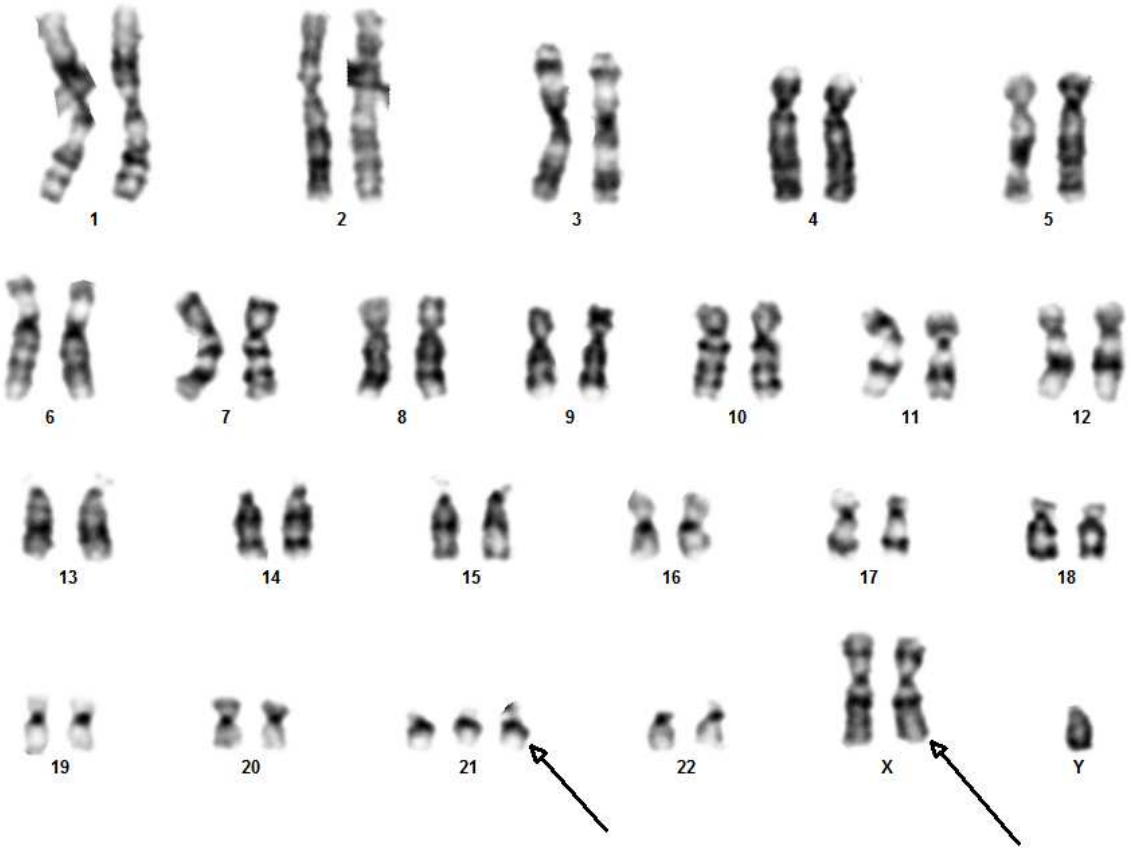

Figure 1: Chromosome complement and karyotype (48,XXY,+21) of the fetus.

Trisomy 21 (Down syndrome) is the most common condition present in the population worldwide with 1 in 1000 to 1 in 1,100 livebirths.However, data suggests that the incidence of Klinefelter and Down syndrome at birth is higher than expected from the incidence of either alone[20]. XXY pattern is recorded in lower values among adult males with Down syndrome suggest that there might be an increased selection against these individuals after birth[21]. Different studies on incidence of Down and Klinefelter syndrome suggest that this double aneuploidy might be more frequent than predicted by multiplying the frequencies of the individual aneuploidies[22].

Several other studies are mentioned in the literature, on described a pair of monozygotic twins[23]. Other types of double aneuploidies are also mentioned in the literature. A reciprocal translocation with combination of double aneuploidy is also mentioned[24]. Zaki and colleagues[25] reported three cases of double aneuploidy involving chromosomes 21 and sex chromosomes; all described as a classical non-disjunction trisomy 21, which was

associated with Turner syndrome in two of the cases and XX in one case, two of these cases were found to be mosaic[25].

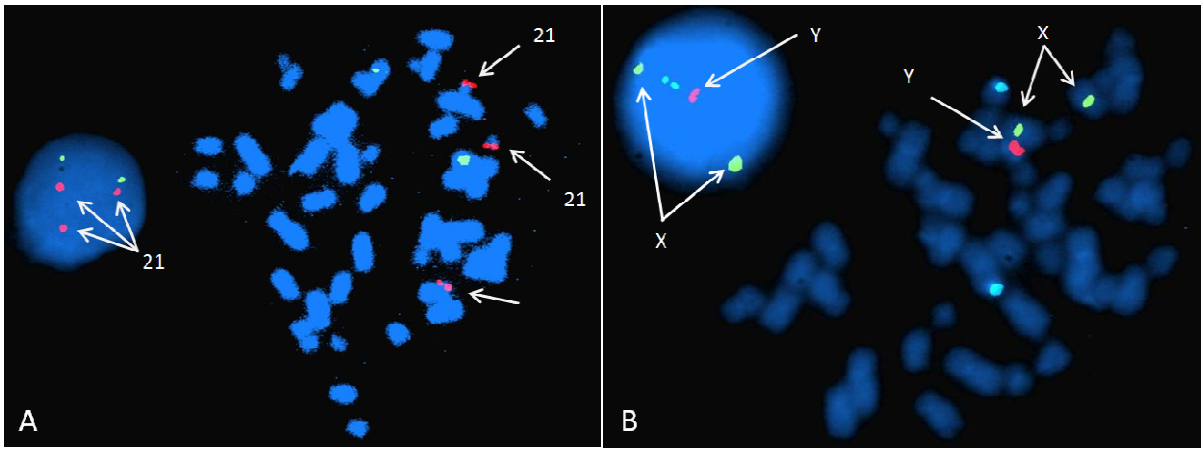

Figure 2: (A) FISH metaphase and interphase showing Down syndrome (three orange signals). Orange signal in this panel indicates chromosome 13.
(B) FISH metaphase and interphase cell showing two green signals represent X chromosome and one green represent Y chromosome indicative of Klinefelter syndrome. Aqua signal is for chromosome 18.

Double aneuploidies occur due to two meiotic non-disjunctional events. Most cases of the double aneuploidies in livebirths involve the sex chromosome along with trisomy 13, 18 and 21[19]. The non-random pattern of such double aneuploidy patterns was considered to be evidence that non-disjunction may be genetically determined[26]. However, an elucidation of the different factors predisposing to non-disjunction would require determination of the parental origin of the supernumerary chromosomes[18]. In present study, parental karyotype was found to be as normal. Maternal age-related factors, rather than genetic predisposition, may play a more important role in the etiology of the most common double aneuploidy, 48,XXY,+21;[27]. Males with Down syndrome are sterile, it would be reasonable to propose that males with 48,XYY,+21 may also be not fertile. Parental karyotype of these patients were normal in previous literature[27].

Prenatal diagnosis can be made by karyotype analysis. When the conventional methods are getting failure, FISH provides a rapid technique for diagnosis. If double aneuploidies have been thought in diagnosis, beside 21st chromosome probe, Y probe must also be used. Otherwise these patients could be diagnosed as Down syndrome and diagnosis of XYY might be missed out.

In conclusion, 48,XYY,+21 syndrome is a very rare disorder. Reporting such double aneuploidies with Klinefelter and Down syndrome highlights the clinical characteristics and will lead to a better understanding of the phenotype-genotype relationship and the incidence of occurrence of such anomalies.

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