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Double Aneuploidy - A Rare Condition : Report of Two Cases

S HABIB[a], SG BANU[b], SMS ISLAM[c], CA KAWSER[d]

Summary:

The chance of two chromosome abnormalities occurring in one conceptus is rare. Here we report two cases of double aneuploidy with karyotype 48,XYY,+21 and 48,XXY,+21.The diagnosis was confirmed by cytogenetic analysis using peripheral blood followed by Giemsa banding technique. Clinically both the children had most of the phenotypic features of Trisomy 21. However phenotypic features of XYY were not present but the child with XXY had undescended right testis .The purpose of this communication is to report such rare disorders discovered as the result of the evaluation for Trisomy 21.

Key words: Cytogenetics, double aneuploidy, Trisomy 21, sex chromosomes.

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Introduction:

Chromosomal disorders are of two types: numerical and structural. Numerical disorders include aneupolidy in which the addition or loss of one, or rarely two chromosomes occur. The most common autosomal aneuploidy trisomy21(Down syndrome) is compatible with survival.[1] The incidence of Trisomy 21 is 1 in 700 births in the Western population and 1 in 920 births in the Indian population.[2] Other commonly seen sex chromosomal aneuploidies are Turner syndrome, Klinefelter syndrome and its variants, poly X syndromes and poly Y syndromes. Incidence of 47, XYY was reported to be 1/840 live births.[3] The incidence of Klinefelter syndrome (47,XXY) is 1 per 1000 live male births.[1]

The co-occurrence of two numerical chromosomal abnormalities in same individual (double aneuploidy) is relatively rare with 3% to 7% of fetuses with cytogenetic abnormalities having double aneuploidy.[4,5,6] The incidence of 48,XXY,+21 in the general population is 0.4 to 0.9 per 10,000 male births. [7,8] In 1959, the first case with autosomal and sex chromosomal anomalies, 48,XXY,+21, was presented by Ford et al. [9] The case of 48,XYY,+21's are rare with clinical data limited to only 29 reported cases. [9, 10] To our knowledge these are the first two reported cases of double aneuploidy in Bangladeshi patients.

a. Dr. Saequa Habib, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University

b. Dr. Sultana Gulshana Banu, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University

c. S M Shahedul Islam, Scientific Officer, Department of Pathology, Bangabandhu Sheikh Mujib Medical University

d. Professor Choudhury Ali Kawser, Chairman, Department of Paediatrics, Bangabandhu Sheikh Mujib Medical University

Address of Correspondence: Dr. Sultana Gulshana Banu, Associate Professor, Department of Pathology, Bangabandhu Sheikh Mujib Medical University, Mobile: 01552493970, Email:risalat_march@yahoo.com

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Case Report:

Case 1:

A 23-month old male child was evaluated for recurrent infections like respiratory tract infection, dental caries, angular stomatitis and skin rashes .There was also developmental delay. He was the third child of his family. He had one brother and one sister who were healthy. His weight was 11kg.The features of Trisomy 21 were obvious, that included flat facial profile, depressed nasal bridge, and upward slant of eyes and protruded tongue. The genitalia were those of a normal, immature male. Echocardiography showed atrial septal defect (ASD).

Cytogenetic study was performed on peripheral blood leucocytes culture using Giemsa banding technique in the department of Pathology, Bangabandhu Sheikh Mujib Medical University. Thirty metaphase spreads were analyzed at 400 band level of bands for chromosomal analysis and was report-ed according to ISCN nomenclature 1995. The karyo-type of the case was determined as 48, XYY, +21 (Fig. 1). The diagnosis of double aneuploidy involving chromosome 21 and Y was made. Parental chromosomal analyses could not be carried out.

Case 2:

A 9-month old boy, product of a nonconsanguinous marriage born to a 40- years-old mother was the third offspring delivered without any complication. His weight and head circumference were 7600gm and 41cm respectively. He had history of repeated convulsion. Chromosomal analysis performed because of facial dysmorphic features and developmental delay. At physical examination the patient was hy-potonic with flat facial profile, flat nose, bilateral epicanthal folds, enlarged tongue

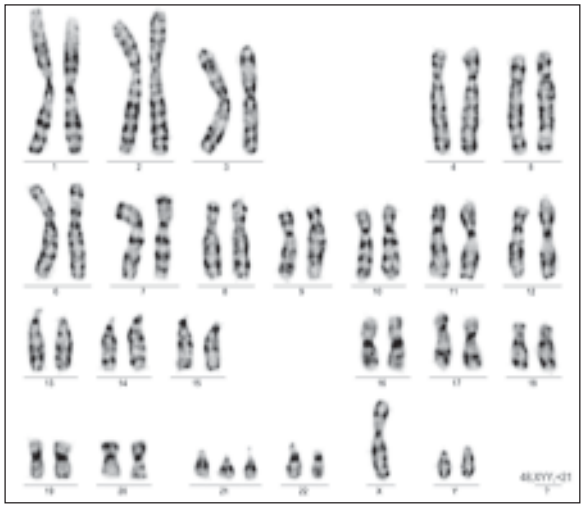

Fig-1: *Photomicrograph of a karyotype of a child having Trisomy 21 and XYY syndrome (Giemsa stain x 100)*

and short neck. Simian crease was also observed. He had also right sided undescended testis. Electroencephalogram suggested epileptic encephalopathy. Ultrasonogram of brain showed dilated lateral ventricle with a 0.8cm cyst in caudothalamic groove.

Cytogenetic study was performed on peripheral blood leucocytes culture using Giemsa banding showed trisomy 21 with XXY. In each of the 30 metaphases 48, XXY, +21 was found. Based on this, diagnosis of double aneuploidy involving chromosome 21 and X was made (Fig 2). Parental chromosomal analyses could not be carried out. on peripheral blood

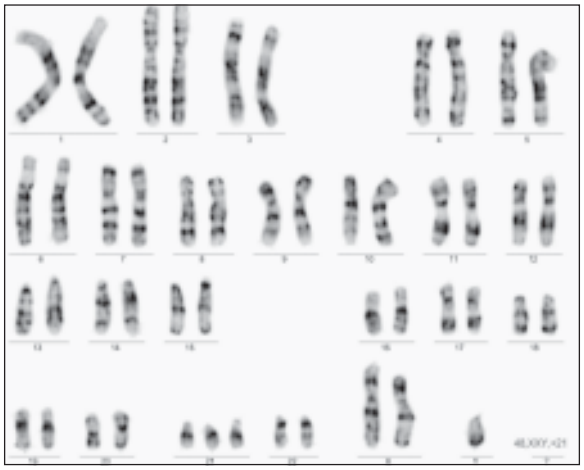

Fig-2: *Photomicrograph of a karyotype of a child having Trisomy 21 and Klinefelter (XXY) syndrome (Giemsa stain x 100)*

Discussion:

Aneuploidy is defined as an abnormal number of chromosomes. Double aneuploidy, the existence of two numerical chromosomal abnormalities in the same individual, is relatively rare. It can involve both autosomal (chromosome 13, 18 or 21) and sex chromosomes and each may manifest either as a monosomy or trisomy or even tetra- or pentasomy. Data collected from the National Down syndrome Cytogenetic Register (NDSCR) in England and Wales and from the literature indicate that the frequencies of all nonmosaic double aneuploidies, except for 48,XXY,+21, are lower than expected, probably because of strong intrauterine selection against such pregnancies.[10] Furthermore, double aneuploidy involving both autosomal and sex chromosomes is seldom described.

The clinical presentations of double aneuploidy are variable depending on the predominating aneuploidy or a combination effect of both. In patients with double aneu-plodies phenotype is more commonly determined by autosomal aneuplodies. Compatible with the litera-ture; the clinical phenotype of Trisomy 21 in our patients was dominant as expected .[11, 12, 13] In our first case the phenotypic features of XYY were not present. An XYY sex chromosome complement, without any abnormal phenotypical effect, may be found in the general population.[14] But patients may characteristically have long stature, large teeth, prominent glabella, asymmetric and long ears and fingers, dull mentality, relative weakness, poor fine coordination and learning disabilities. Behavioral prob-lems like hyperactivity and anger onset may be promi-nent at childhood or adolescence which may be found at a later age.[11] In patients with Klinefelter syndrome, the diagnosis is often made later in life, and they have a tall stature, absent or decreased facial and pubic hair, small hyalinized testes, a small penis, and feminine distribution of adipose tissue, including gynecomastia .[15] Signs that are sometimes noted in infants with Klinefelter syndrome are an underdeveloped phallus and scrotum, valviform hypospadia, hyperpigmentation of scrotal raphe, and small or ectopic testis .[7] In our second case patient with Trisomy21-Klinefelter syndrome, the Trisomy 21syndrome phenotype predominates, with Klinefelter syndrome manifesting as undescended testis. According to the Trisomy 21-Klinefelter case reports neonates and

infants younger than 10 months show few or no signs of Klinefelter syndrome.[7] These characteristics begin developing as the child ages.

Trisomy 21 and numeric sex chromosomal anomalies are common chromosomal disorders caused by parental nondisjunction during gametogenesis. Classical trisomy 21 results from maternal meiotic nondisjunction. Y chromosome of XYY is always paternal and it occurs by nondisjunction at meiosis II or mitosis after fertil-ization. [10, 11, 13] Nondisjunction in cases of double trisomy has been found to be entirely maternal in origin, entirely paternal in origin, and both maternal and paternal in origin. [7] In such cases in which the additional chromosomes originate from different parents, the two errors may be coincidental and unrelated to a genetically determined nondisjunction.

Abnormal separation of chromosomes may occur in older individuals because of dysfunction of structures related to chromosome separation, such as the spindle apparatus and kinetochore. [7] Caron et al[16] found 1 case of 48, XXY, +21 in 24,901 amniocenteses performed for advanced maternal age (e"35 years), which is a 3.8-fold increase over the expected rate. Among 28 reports of 48, XXY, +21, which include 36 cases with known parental ages, Kovaleva and Mutton[10] found that the risk for 48,XXY,+21 was age dependent, with a mean maternal age of 33 years and a mean paternal age of 38 years. This finding is supported by the older parental ages in our second case.

If routine chromosomal study is not done in patients with classical features of Trisomy 21 then cases with double aneuploidy remain largely undiagnosed. Conventional chromosomal study is sufficient for detection of double aneuploidy.

Conclusion:

The occurrence of double trisomy is exceptional. Due to rarity and scanty published data the incidence, phenotype and recurrence risk are difficult to determine.

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