Double aneuploidy in three children

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Introduction

The first case of double aneuploidy (48, XXY, +21) was reported by Ford *et al* in 1959[1]. It is a relatively rare occurrence where two different chromosomal abnormalities coexist in the same individual diverging from the normal (somatic 2n and n in gametes) pattern due to erroneous chromosomal segregation in mitosis or meiosis contributing to 0.21-2.8% of spontaneous abortions[2]. With the advent of newer more sensitive non-invasive prenatal screening methods, such as cell free DNA technique, the past decade has witnessed a reduction in the prevalence of live born multiple aneuploidy cases, yet their survival rates remain unchanged with most succumbing to illness in the neonatal period[3,4]. However, trisomies involving chromosomes such as 8, 13, 18, 21, X and Y have been observed to survive for longer periods of gestation even resulting in a viable fetus as opposed to other autosomal aneuploidies suggesting that lethality of the abnormality depends on which chromosomes are involved[1-4].

An association between advancing maternal age and aneuploidy rates was made in 1933 and it is speculated to increase from 2% in all clinically recognized pregnancies in women less than 25 years of age to 35% in women older than 40 years with no known correlation to race, geography and socioeconomic status[5]. Multiple aneuploidies involving 3 or more chromosomes are rarely reported in the literature[5,6]. The impacts of double aneuploidy are known but its causes are far less understood[6]. Due to the rarity of multiple aneuploidies resulting in a viable pregnancy we report three live born suspected double aneuploidy cases seen at the Human Genetics Unit, Faculty of Medicine, University of Colombo, between 2012 and 2015.

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Case reports

The *first case* was a male baby born at 40 weeks and 2 days of gestation by normal vaginal delivery as the second child of a 40-year-old Sri Lankan female (gravida 2, para 2) and a 40-year-old male of the same ethnicity. The proband was referred to our clinic at 49 days of age. The parents were healthy and unrelated and they had a 9 year old healthy son. Antenatal ultrasound scan revealed intrauterine growth retardation (IUGR). There was no history of antenatal exposure to drugs or alcohol and no known family history of genetic disorders. His birth weight was 2.16 kg and there was microcephaly (head circumference 31 cm) but length was within the normal range (46 cm). There was hypertelorism, elongated head, narrow bifrontal diameter, prominent occiput, low set ears, micrognathia, long thin limbs, overlapping fingers, hypoplastic nails, clinodactyly, bilateral talipes equinovarus (TEV) deformity, rocker bottom feet and bilateral cryptorchidism with normal size phallus. 2D echocardiogram showed a large ventricular septal defect (VSD), a double outlet right ventricle and a moderate size patent ductus arteriosus (PDA) with moderate pulmonary hypertension. The details of this case have been published earlier[7].

The *second case* referred to our clinic was a 17 day old male baby born at term to non-consanguineous parents. He was the first child of an elderly (38 years) primigravida with a history of recurrent pregnancy losses and subfertility. On clinical examination, the child was found to have microcephaly, low set eyes, microphthalmia, cleft lip, cryptorchidism, polydactyly and 'rocker-bottom' feet.

The *third case* was a 1-year-old male born as the first child to non–consanguineous parents whose mother and father were 37 and 38 years of age respectively. There were no antenatal risk factors and no family history of genetic disorders. The child had dysmorphic features similar to Down syndrome, which included a flat nasal bridge, pre-auricular pits, epicanthic folds, clinodactyly and short stature.

Cytogenetic analysis of the proband was performed on 25-40 spreads of metaphase chromosomes from peripheral blood lymphocytes using standard G-banding techniques for each case. This revealed a

karyotype of 48, XXY, +18 after analysing 25 metaphase chromosomes thus confirming the co-existence of Edward and Klinefelter syndrome in the 1st case as shown in Figure 1. In the 2nd case, karyotype revealed a chromosome pattern of 48, XXY, +13 following analysis of 20 metaphase chromosomes confirming the co-existence of Patau and Klinefelter syndrome as shown in Figure 2.

In the 3rd case, karyotype was (47, XY, +21 / 47, XY, +22) revealing a mosaic pattern for both trisomy 21 and 22 by analyzing 40 metaphase chromosomes, 30 spreads showing trisomy 21 and 10 spreads showing trisomy 22 as shown in Figure 3.

All three cases succumbed to illness before the age of 1 year due to medical complications.

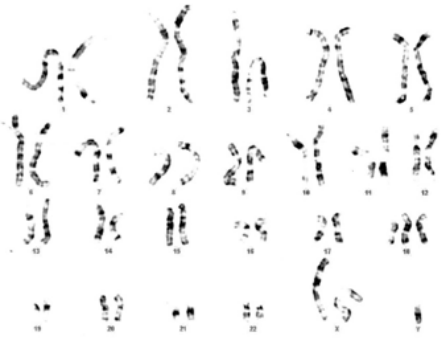


Figure 1: ***G-banded karyotype, 48,XXY, +18.***

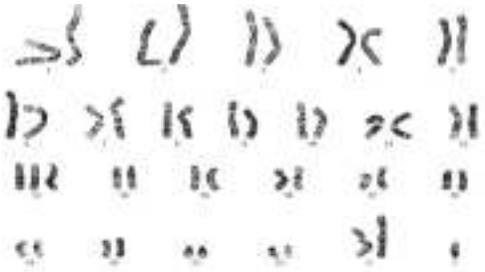
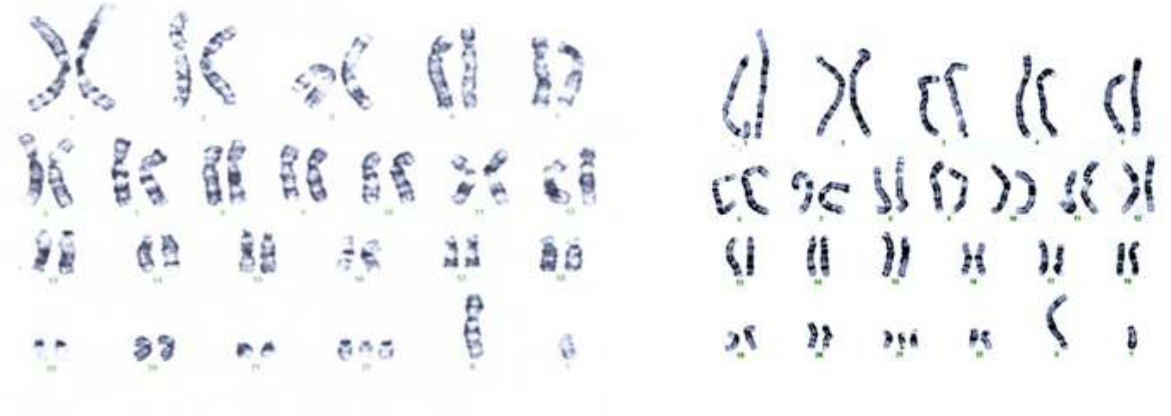


Figure 2: ***G-banded karyotype, 48,XXY, +13.***



A. Spreads with 47, XY, +22 karyotype

B. Spreads with 47, XY, +21 karyotype

Figure 3: ***G- banded karyotype, 47, XY, +21 / 47, XY, +22***

Discussion

Aneuploidy is known to result from errors in chromosome segregation during oogenesis, which increases with advancing maternal age and was observed in all three cases[8,9]. Even though most double aneuploidy fetuses' demise in early gestation, sex chromosome aneuploidies with trisomies involving chromosomes 16, 18 and 21 have been observed to survive for longer periods of gestation[10]. Multiple aneuploidies involving 3 or more chromosomes are rarely reported in the literature. A recent study revealed a percentage of double (4.6%) and multiple aneuploidies involving acrocentric chromosomes 13, 15, 21 and 22 and non-acrocentric chromosomes X, 16 and 18[11,12].

It is reported in the literature that errors in chromosome segregation during oogenesis increase with advancing maternal age due to abnormal mitochondrial function and disturbances in cohesion complex related destabilization of bivalent sister chromatin cohesion, segregation and cell cycle control in aged mammalian oocytes[11]. It is also speculated that there could be lowered sensitivity of the spindle assembly checkpoint (SAC) to certain chromosomes with aging rendering oocytes more susceptible to aneuploidy conditions as they approach menopause[8,9,11]. The third case however needs to be validated with further cytogenetic testing such as Fluorescence *in situ* hybridization (FISH) to differentiate between a partial trisomy of chromosome 22.

Many predisposing factors have been identified in relation to aneuploid conditions such as SAC errors, cohesion complex malfunctions, mitochondrial dysfunctions, altered gene expression and the free radical theory of aging[9,13]. These effects are yet to be demonstrated on human oocytes and it is prudent to delay oocyte aging by a healthy lifestyle and the option of cryopreserving young healthy oocytes in females delaying pregnancy should be taken into consideration[14,15]. Even though most aneuploid conditions result due to meiosis I errors or as a result of an insult that occurred in meiosis I precipitating at meiosis II[12,16], after reviewing the published data we speculate that in double aneuploidy, errors could be occurring at both meiosis I and II in the aged mature female oocyte, although the exact mechanisms may vary depending on the mis-segregated chromosomes.

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