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A Novel Case of Live Born with 49, XXXY, + 10 Karyotype: Implications of Autosomal Trisomies Other Than 13, 18 and 21

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KEYWORDS Trisomy; phenotypic abnormalities; non-disjunction; sex chromatin

ABSTRACT Trisomy occurs in at least 4% of pregnancies and is the most common chromosomal abnormality seen in humans. Double trisomies are extremely rare, and most of them involve the sex chromosomes combined with either trisomy 13, 18 or 21. We have identified a novel case with 49, XXXY, +10 karyotype. A ten-month-old boy, with delayed developmental milestones was referred for cytogenetic evaluation. The child was 3rd in birth order delivered vaginally to a consanguineous couple at full term. At birth the only phenotypic abnormalities noticed were low set ears and wide spaced eyes. A suspicion of some abnormality arose when the child failed to attain head holding by 5 months. On detailed evaluation at presentation features observed included short stature, bilateral undescended testis with phallic length of 12mm, the respiratory system had bilateral crepts with wheeze, hepatosplenomegaly was present and D/Q assessment gave a developmental age of 5 months. There was no evidence of mosaicism as all the metaphases analyzed had 49 chromosomes and the buccal epithelium showed cells with a double sex chromatin body. Parental karyotypes were normal and the age of the father and mother were 30 and 25 years respectively, ruling out advanced maternal age as a cause for non-disjunction. No other identifiable factor responsible for inducing double trisomy could be identified, hence the origin of this karyotype is an enigma. The mild phenotypic dysmorphisms seen in this child is surprising and he represents a novel case of a survivor with double trisomy involving sex chromosomes and chromosome 10.

INTRODUCTION

Aneuploidy occurs in 5% of all pregnancies that survive long enough to be clinically recognized, these include both monosomies and trisomies (Hunt et al. 2002). The majority of trisomies have a single additional chromosome and the presence of an extra sex chromosome is often associated with physical, behavioral, and intellectual impairment. While, the presence of additional autosomes is even more serious, as it causes severe mental and physical retardation resulting with death in infancy. The incidence of trisomy varies widely among different chromosomes. This variation appears to reflect a real difference in the frequency of the primary event leading to trisomy as well as in differential selection

Double trisomies are extremely rare and most of them have been identified during prenatal analysis.They usually involve the sex chromosomes (XXX, XXY or XYY) combined with either trisomy 13, 18 or 21 (Reddy et al. 1999).A recent publication in American journal of medical genetics showed a double trisomy in liveborn involving X and 18th chromosome which survived for 14days (Li et al. 2003). However, we have identified an interesting case with double trisomy involving the sex chromosomes and chromosome 10 in a liveborn.

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CASE DETAILS

A male child, with delayed developmental milestones was referred to our department for cytogenetic evaluation. The child was 3rd in birth order delivered vaginally to a consanguineous couple at full term (Fig 1). At birth the only phenotypic abnormalities noticed were low set ears and wide spaced eyes. A suspicion of some abnormality arose at 5 months when the child failed to attain head holding. There was H/o recurrent respiratory tract infections with failure to thrive. On detailed evaluation at 10 months

when the child was presented to our unit he appeared conscious, irritable, moderate pallor, no cyanosis/icterus, no general lymphadenopathy or Pedal oedema. He weighed 5.5kgs (<50th percentile), length 67cm, arm span 58cms, US/LS 48/37 (1:1.3), anthropometry suggest chronic malnutrition with short stature. Normal hair line, anterior fontanel 3/4cms, PF closed, hypertelorism with interpupillary distance of 4cm (>95th percentile), depressed nasal bridge, high arched palate, normal philtrum, low set ears, short stubby fingers with normal dermatoglyphics (Fig 2). Bilateral undescended testis with phallic length of 12mm. Respiratory system showed bilateral crepts with wheeze. Hepatosplenomegaly was observed and D/Q assessment gave a developmental age of 5 months.

Family and antenatal history were unremarkable apart from the fact that an earlier male sibling who had multiple skeletal deformities had died at the age of 5months (medical reports not available).

Lymphocyte culture revealed a karyotype of 49, XXXY, + 10 (Fig 3). There was no evidence of mosaicism as all the metaphases analyzed had 49 chromosomes. Buccal epithelium showed 16% cells with a double sex chromatin body (Fig 4). Parental karyotypes were normal (46, XY and 46, XX) and the ages of the father and mother were 30 years and 25 years, respectively.

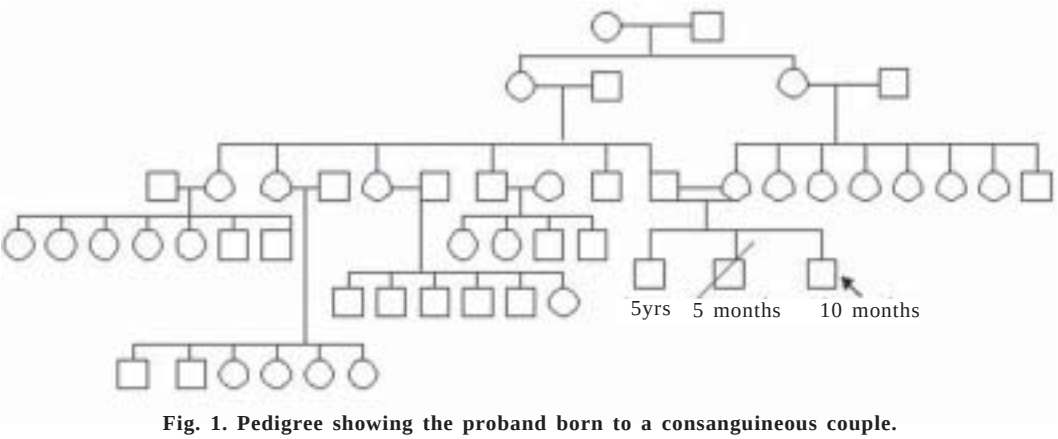

Fig. 1. Pedigree showing the proband born to a consanguineous couple.

Fig. 2. Photograph showing proband with low set ears, wide spaced eyes, depressed nasal bridge.

Fig. 3. Karyotype of the proband showing 49, XXXY + Trisomy 10.

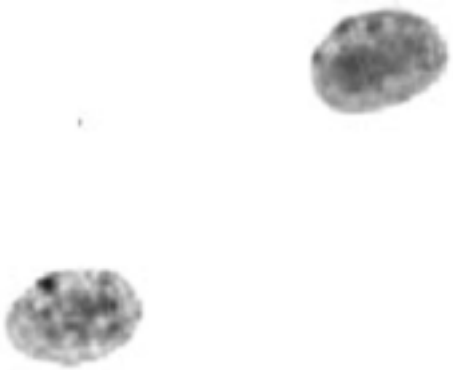

Fig. 4. Buccal epithelial cells showing two bar bodies and one bar body

DISCUSSION

Trisomy is the leading known cause of pregnancy loss, congenital anomalies and mental retardation. The XXY chromosome arrangement appears to be one of the most common genetic abnormalities known, occurring as frequently as 1 in 500 to 1 in 1,000 male births and usually designated as Klinefelters syndrome.Trisomy for X chromosome is associated with abnormal phenotype including facial anomalies such as hypertelorism, epicanthic folds, simplified ears, and mild prognathism (projection of the jaw beyond the forehead) .Generally, there is mild to moderate mental retardation (IQ= 40-60) ,behavior is usually passive and cooperative, genitalia may be small, and gynecomastia is frequently reported some of these features were also observed in the case presented here.

In a recent European study, prenatal karyotyping was carried out on 7,758 cases with congenital anomalies detected prenatally by ultrasound. A number of these cases revealed chromosomal abnormalities including trisomies of chromosomes 8, 9, 10, 14, 15, and 16 (Baena et al, 2003). However, extensive search in publications and Internet by us didn't provide any information on live borns with trisomy10. It has been reported that complete trisomy 10 is a lethal condition and has been detected in approximately 1.8% of miscarriages (Knoblauch 1999).

There are at least five reported cases of trisomy 10 mosaicism in liveborn children, in all cases there were congenital anomalies (Knoblauch 1999). Partial trisomy of the long arm of chromosome 10 is a well-defined but rare syndrome with characteristic features (Moreno-Fuenmayor 1975). Some of these are also seen in the proband discussed in this paper, these include hypertelorism, small nose, depressed nasal bridge, arched wide-spaced eyebrows, low-set ears, bow-shaped mouth with prominent upper lip, micrognathia, palate anomalies (high-arched cleft or agenesis), developmental delay, growth retardation, (Varda et al 2003). Therefore to the best of our knowledge this is the first report of trisomy 10 in a liveborn.

Mosaicism is a relatively common finding in prenatal cytogenetics, accounting for approximately 5% of all prenatal cases, which fail to complete term but this figure drops to 1:3500 in livebirths (Wolstenholme 1994). Mosaicism is defined as the presence in an individual tissue of two or more genetically distinct cell lines derived from a single zygote. All the metaphases analyzed had 49 chromosomes and all the 10 G-banded karyotypes showed 49,XXXY, +10 chromosome compliment. The buccal epithelium showed cells with a double sex chromatin body. Our results do not indicate mosaicism since the lymphocytes, originating from the mesodermal lineage and the buccal epithelial cells,originating from the ectodermal lineage both exhibited evidence of trisomy. In view of these observations there is very little possibility that the endodermal lineage may have a normal chromosomal compliment, however that possibility has not been ruled out.

Although the magnitude of risk due to trisomies varies among chromosomes, increased maternal age has been reported to be an important risk factor in trisomies. The best-studied trisomy is that of chromosome 21, the incidence of this trisomy increases from .05% of livebirths at maternal age 20 years, to over 3% of all livebirths at age 45 years (Hassold 1984). The effect of maternal age is considered to be more pronounced in double trisomies. In our case, we can rule out this possibility as the age of the mother was only 25 years.

Epidemiological studies suggest that maternal irradiation exposure and usage of oral contraceptives, spermicides, or fertility drugs may also lead to trisomies. The probands mother was not exposed to any of these risk factors being a housewife, inhabiting a non-hazardous area, who had not used any hormones or fertility treatment. The father also had no evidence of any harmful exposure occupationally or otherwise and hence, the origin of the extra chromosomes is an enigma.

Over the past decade, molecular studies have demonstrated that most human trisomies originate from errors at maternal meiosis I (Wolstenholme et al. 2000). However, Klinefelter syndrome is a notable exception, as nearly one-half of all cases are derived from paternal non-disjunction (Zaragoza et al. 1994). A recent review by Thomas and Hassold (Thomas NS et al 2003) discusses the possiblites that trisomies arise due to errors in meiosis I, meiosis II or at an early mitotic division in the developing zygote. The role of aberrant recombination as a contributor to human trisomies has also been discussed. Genetic mapping studies led to the identification of the first molecular correlate of autosomal and sex chromosomal non- disjunction (Thomas et al. 2003). Both absent and decreased recombination has been reported for 15, 18, 21 chromosomes (Robinson et al.1998). However, non-disjunction appears to be different for every chromosome and currently there is no data available to hypothesize the origin of trisomy10.

The probands hematological reports did not show any myelodysplastic syndrome and/or hematological malignancies, which are usually associated with such a high chromosome compliment. The child is being conservatively managed at present and is on close follow up. The mild phenotypic dysmorphism seen in this child is surprising and he represents a novel case of a survivor with double trisomy, other than trisomies involving 13, 18, 21 and sex chromosomes.

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