AN UNUSUAL CASE OF DOUBLE ANEUPLOIDY OF DOWN SYNDROME ASSOCIATED WITH TRIPLE X SYNDROME: 48,XXX,+21

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ABSTRACT

Down syndrome is the most common chromosomal abnormality in humans with an estimated incidence of one case in 770 live births. However, the occurrence of double aneuploidy involving autosome and or sex chromosome is a very rare phenomenon in lives born and the majority of reported cases are presented in form of spontaneous abortions. Here, we are reporting a case of a Rwandan patient with combination of trisomy 21 and triple X syndrome. The proband was 8-month-old female with typical features of Down syndrome. In additional to Down syndrome features, the child presented with minor features of triple X syndrome characterized by hypotonia and seizures.

Keywords: Double aneuploidy - Down syndrome - Triple X syndrome - 48, XXX,+21

RESUME

La trisomie 21 ou syndrome de Down est la plus fréquente anomalie chromosomique chez l'homme avec une incidence estimée à 770 cas de nouveau-nés vivants dans le monde. Cependant, la survenue d'une double anomalie chromosomique aneuploide intéressant les chromosomes autosomes ou chromosomes sexuels est un événement très rare et la majorité des cas rapportés sont liés à des formes de fausses couches spontanées. Nous rapportons ici un cas d'un patient Rwandais portant une double aneuploidie de trisomie 21 et le syndrome de Triple X; (48,XXX,+21). Le proband était un sujet de sexe féminin âgé de 8 mois présentant des symptômes typiques du syndrome de Down. En plus de ces symptômes, elle avait aussi des signes mineurs du syndrome de Triple X caracterisés par hypotonie and crises convulsives.

Mots clés: Double aneuploide - Syndrome de Down - Syndrome de Triple X - 48, XXX,+21

INTRODUCTION

Down syndrome is the most common chromosomal abnormality in humans with an estimated incidence of one case in 770 livebirths. However, the occurrence of double aneuploidy involving autosome and or sex chromosome is a very rare phenomenon in liveborn and the majority of reported cases are presented in form of spontaneous abortions with an incidence ranging from 0.21% to 2.8% [1,2, 3].

Reported cases of multiple aneuploidies have been described in liveborns exhibiting two viable aneuploidies, usually aneuploidy of sex chromosomes combined with either trisomy 13,18, or 21 [4-6].

Cases with double aneuploidy may present manifestations of both chromosomal abnormalities. Usually, the cause of these chromosomal abnormalities may arise from two meiotic non-disjunctional events, but up to date the mechanisms by which double aneuploidies arise have not been well studied [2,4]. Here, we report an unusual case of Rwandan patient with double aneuploidy showing trisomy 21 and triple X syndrome.

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MATERIALS AND METHODS

CASE PRESENTATION

The patient consulted our clinical genetic department at Kigali University Teaching Hospital at 8 months of age. The chief complaint was hypotonia with difficulty for feeding. The infant was a third and last born from non-consanguineous parents aged 42 years for the father and 35 years for the mother at the time of her birth. Her two elder sisters are normal and healthy. On physical examination, the patient presents typical features for Down syndrome with upslanted palperal fissures, epicanthal folds, relative hypertelorism and round face, small nose and flat nasal bridge, uncurled hair, relatively low set ears, short neck, hyperlaxity of joints and was unable to sit down alone without support (Figure 1). In addition, she had hypotonia and seizures. A cardiac murmur on auscultation was found and the patient sent to a cardiologist to rule out congenital heart defects. The exam of other systems was unremarkable. We performed karyotype analyses to confirm the diagnosis of Down syndrome (trisomy 21).

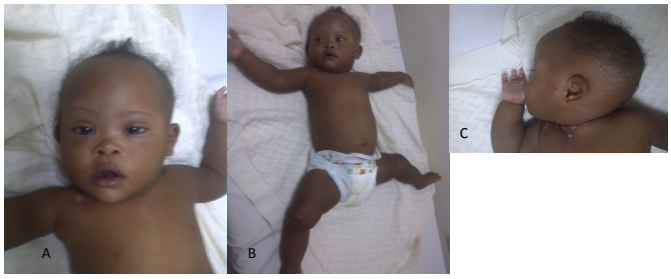

Figure 1: pictures of the proband: characteristic facies with low set ears and short neck (A, B & C); note also hyperlaxity of joints (B)

CYTOGENETIC STUDY AND RESULTS

Blood sample was collected from the patient for cytogenetic studies. Chromosome preparations were made from 72-h peripheral blood lymphocyte cultures and routinely stained with Quinacrin. The karyotype showed trisomy 21 and trisomy X in all 20 cells examined. The chromosomal constitution of the proband showed free trisomy 21 associated with three copies of chromosome X in all cells with a total of 48 chromosomes i.e. 48, XXX, +21 (Figure 2).

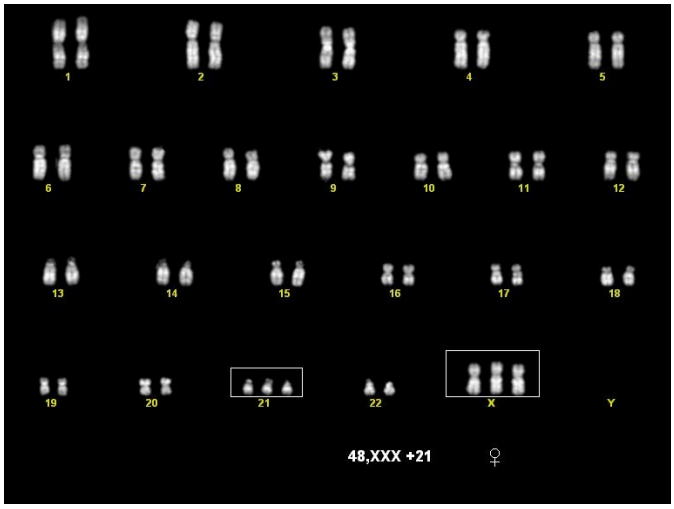

Figure 2: karyotype of the proband showing three copies of both chromosomes 21 and X; 48, XXX, +21.

DISCUSSION

We report a rare case of double aneuploidy consisting of trisomy 21 and Triple X. The patient presented typical features of Down syndrome; this is what is consistent with other published cases[1, 5, 6-8].
Even though the causes of aneuploidies are not well studied, meiotic non-disjunction has been suggested as the most frequent cause of chromosomal abnormalities.
This refers to the failure of a pair of chromosomes to disjoin properly during one of the two meiotic divisions, usually during meiosis I. The consequences of non-disjunction (NDJ) during meiosis I and meiosis II are different. If the error occurs during meiosis I, the gamete with 24 chromosomes contains both the paternal and maternal members of the pair. If it occurs during meiosis II, the gamete with the extra chromosome contains both copies of either the paternal or the maternal chromosome [7]. Both of these aneuploidies could have the same or different parental origin [5]. Most cases reported in literature were a result of nondisjunction in maternal meiosis II [4,9,10].

The chances of two chromosomal anomalies occurring in a single conceptus are a rare event and the reported incidence varies from 0.21% to 2.8% in spontaneous miscarriages subjected to cytogenetic study [11].
Advanced maternal age has always been considered an important risk factor for trisomy 21 and despite few studies on parental origin of double aneuploidies, some of them have shown that both NDJ events may take place in either or both parents [2, 3]. The maternal age for our proband is still a relative risk factor but the parental origin of observed anomalies in our patient could not be determined using a standard karyotype. Up to date, few cases of double aneuploidy showing trisomy 21 and Triple X have been reported in the literature [1,2,4,11,12].

Triple X syndrome is a chromosomal abnormality that affects approximately 1 in every 1,000 females. A healthy female has two X chromosomes, one from her father and one from her mother. A female with Triple-X syndrome has three X chromosomes. A female with Triple-X syndrome does not inherit it from her parents. The syndrome generally results from a mistake in the formation of the father's sperm cell or the mother's egg. In some cases triple-X syndrome may be the result of something that went wrong in the development of the embryo. A girl with triple X syndrome may either have no symptoms, just mild ones, or more severe ones with developmental delays. Developmental delays may include learning disabilities, delayed development of speech and language skills, as well as motor skills. There may be behavioral and emotional difficulties. Approximately 10% of affected females have seizures or kidney abnormalities. Among those who do have symptoms, they will vary widely from person-to-person. Unlike the majority of other chromosomal conditions, there is usually no clear visual difference between a female with triple X syndrome and other females. Some females with triple X syndrome may be taller than average. Most individuals with the syndrome have normal sexual development and can conceive children.
Thus, despite double aneuploidy abnormalities observed in our patient, the clinical manifestations are of trisomy 21 alone like in many other cases reported despite.

REFERENCES

1. Balwan WK, Kumar P, Raina TR, Gupta S (2008) Double trisomy with 48, XXX+21 karyotype in a Down's syndrome child from Jammu and Kashmir, India. J Genet 87: 257-259.

2. Kovaleva NV, Mutton DE (2005) Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. Am J Med Genet A 134A: 24-32.

3. Guzel A. I. et al. (2009) Detection of Parental Origin and Cell Stage Errors of a Double Nondisjunction in a Fetus by QF-PCR. Genetic testing and molecular biomarkers 13(1): 73-77

4. Park VM, Bravo RR, Shulman LP (1995) Double non-disjunction in maternal meiosis II giving rise to a fetus with 48,XXX,+21. J Med Genet 32: 650-653.

5. Shen Z, Zou CC, Shang SQ, Jiang KW (2012) Down-Klinefelter syndrome (48,XXY,+21) in a child with congenital heart disease: case report and literature review. Intern Med 51: 1371-1374.

6. Gerretsen MF, Peelen W, Rammeloo LA, Koolbergen DR, Hruda J (2009) Double aortic arch with double aneuploidy--rare anomaly in combined Down and Klinefelter syndrome. Eur J Pediatr 168: 1479-1481.

7. Karaman A, Kabalar E (2008) Double aneuploidy in a Turkish child: Down-Klinefelter syndrome. Congenit Anom (Kyoto) 48: 45-47.

8. Iliopoulos D, Poultsides G, Peristeri V, Kouri G, Andreou A, et al. (2004) Double trisomy (48,XXY,+21) in monozygotic twins: case report and review of the literature. Ann Genet 47: 95-98.

9. Chen CP, Chern SR, Chen CY, Wu PC, Chen LF, et al. (2011) Double aneuploidy with Edwards-Klinefelter syndromes (48,XXY,+18) of maternal origin: prenatal diagnosis and molecular cytogenetic characterization in a fetus with arthrogryposis of the left wrist and aplasia of the left thumb. Taiwan J Obstet Gynecol 50: 479-484.

10. Biselli JM, Machado FB, Zampieri BL, Alves da Silva AF, Goloni-Bertollo EM, et al. (2009) Double aneuploidy (48,XXY,+21) of maternal origin in a child born to a 13-year-old mother: evaluation of the maternal folate metabolism. Genet Couns 20: 225-234.

12. Guzel AI, Demirhan O, Pazarbasi A, Ozgunen FT, et al. (2009) Detection of parental origin and cell stage errors of a double non-disjunction in a fetus by QF-PCR. Genet Test Mol Biomakers. 13(1): 73-77.

13. Sheth HJ, Munoz A, Sergi C, Pani J, Blouin JL, Sheth JJ, Sheth FJ. et al. (2011) Triple-X syndrome in a Trisomic Down syndrome child: both aneuploidy originated from the mother. Int J Hum Genet, 11(1): 51-53.