Research Article
Volume 14:2, 2020
DOI: 10.37421/jmgm.2020.14.444

Journal of Molecular and Genetic Medicine

ISSN: 1747-0862 **Open Access**

Rare Double Aneuploidy in Down Syndrome (Down-Klinefelter Syndrome)

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Abstract

Background: The chromosomal aneuploidy described as Cytogenetic condition characterized by abnormality in numbers of the chromosome. Aneuploid patient either trisomy or monosomy, can occur in both sex chromosomes as well as autosome chromosomes. However, double aneuploidies involving both sex and autosome chromosomes relatively a rare phenomenon. In present study, we reported a double aneuploidy (Down-Klinefelter syndrome) in infant from Saudi Arabia.

Materials and Methods: In the present investigation, chromosomal analysis (standard chromosomal karyotyping) and fluorescence in situ hybridization (FISH) were performed according to the standard protocols.

Results: Here, we report a single affected individual (boy) having Saudi origin, suffering from double chromosomal aneuploidy. The main presenting complaint is the obvious dysmorphic features suggesting Down syndrome. Chromosomal analysis and FISH revealed 48,XXY,+21, show the presence of three copies of chromosome 21, two copies of X chromosome and one copy of Y chromosome chromosomes.

Conclusion: Patients with Down syndrome must be tested for other associated sex chromosome aneuploidies. Hence, proper diagnosis is needed for proper management and the cytogenetic tests should be performed as the first diagnostic approach.

Keywords: Double Aneuploidies • 48 XXY+21 Syndrome • Down-Klinefelter Syndrome

Introduction

The chromosomal aneuploidy described as cytogenetic condition characterized by abnormality in numbers of the chromosomes. Aneuploidy is one of the most common and clinical significant chromosomal disorder, occurring at least 5% of all recognized pregnancies [1].

Aneuploid patient either trisomy (three instead of two copies) or monosomy (one instead of two copies). Double aneuploidy that leads to trisomy of the two different chromosomes occurs due to accidentally meiotic nondisjunction events; both could have a same or different parental origin [1]. The first case of double aneuploidy (48,XXY,+21) was reported in 1959 by Ford et al. [2]. Various combination of double aneuploidy can occur in both sex chromosomes as well as autosome chromosomes. In general it is not inherited disorders and likely results from an error (nondisjunction) during cell division meiosis I or meiosis II. However, the presence of two extra chromosomes more than the normal chromosomal number in the same person is a rare phenomenon [1].

Down syndrome is the most common chromosomal abnormality with an incidence around 1/800 characterized by the presence of all or part of three copies of chromosome 21. Clinically usually presented with dysmorphic features which present since newborn period including broad head , flat face , depressed nasal bridge, up-slanting eyes, large tongue, small chin, low seated ears and broad short hands with single palmar crease associated various degree of mental retardation, decrease muscle tone as well as congenital heart diseases mainly septal defects [3].

Klinefelter syndrome is the most common sex chromosome with approximated incidence around 1/500 characterized by the presence of three sex chromosomes (XXY) instead of two chromosomes [4-6]. Clinically not detected during newborn period, dysmorphic facial feature was clue to diagnosis at infantile period in one case from Saudi Arabia. In general the manifestation usually after puberty or during follow up at infertility clinic with tall stature, large breast, small testicles and penis associated with hypergonadotropic hypogonadism and varying degree of educational and emotional problems.

Down-Klinefelter syndrome it a rare condition affected male in many aspects physically and developmentally. The Incidence of double aneuploidy is less than either syndrome alone, it reach near 1/10000 male birth [5].

In the case presented here, the infant belongs to non-consanguineous couple, the proband referred to genetic clinic with dysmorphic features fitting the diagnosis of Down syndrome with no features of Klinefelter syndrome. However, the cytogenetic studies revealed the diagnosis of 48,XXY,+21.

Materials and Methods

Human subject

In the present study, we clinically investigated a single affected individual (proband) from Saudi origin family. The proband underwent a comprehensive clinical evaluation by a general pediatrician, neonatologist, cardiologist, and clinical geneticist.

Cytogenetic analysis

Karyotyping

Standard chromosomal karyotyping was performed on the lymphocytes from peripheral blood. The Giemsa Banding by trypsin, BPHS 450, 20 cells were counted at the metaphases. Six cells of metaphases were analyzed and karyotyped.

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Received 31 March 2020; **Accepted** 04 April 2020; **Published** 13 April 2020

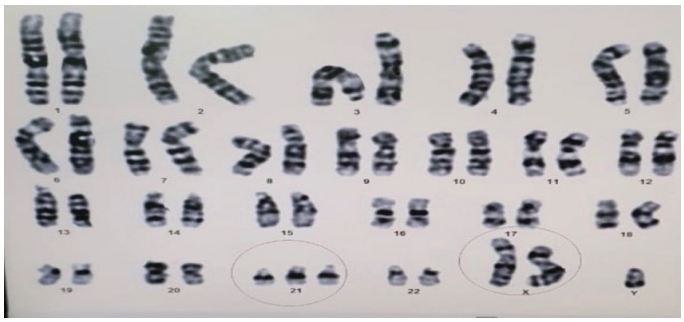

Figure 1A. Chromosomal analysis and karyotyping from peripheral blood lymphocytes revealed 48,XXY,+21.

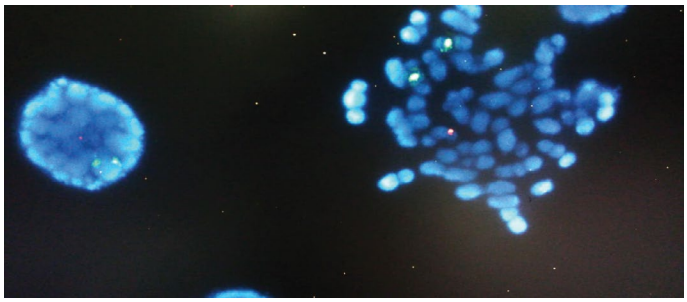

Figure 1B. FISH analysis three copies of sex chromosome (two copies of X chromosome and one copy of Y chromosome and showed three copies of Chromosome 21 respectively).

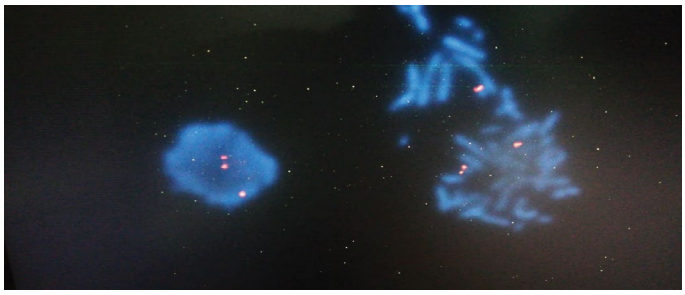

Figure 1C. FISH analysis three copies of sex chromosome (two copies of X chromosome and one copy of Y chromosome and showed three copies of Chromosome 21 respectively).

Fluorescence *in situ* hybridization

The fluorescence in situ hybridization (FISH) study was performed using Probe set: LSI SO DNA probe hyperdizes to 21q22.13-q22.2 for chromosome 21 chromatin studies and LSI CEP X/SRY for sex determination according to standard methods.

Result

Clinical presentation

The proband is an infant 4 months old boy belongs to non-consanguineous couple from saudi origin .He is the first baby for the couple , mother age 38 years old and father age 39 years old with no family history of chromosomal aberration. The proband delivered Full term by normal spontaneous vaginal delivery with APGAR score 8 and 9 at one and five minutes respectively Birth weight 2.4 kg just below 3ed centile. The proband admitted to nursery due to dysmorphism and hypotonia suggesting the diagnosis of Down syndrome. In addition to the normal result of newborn screening for hypothyroidism, Echocardiogram, cranial and abdominal ultrasounds were reported to be normal. The proband discharge home on regular feeding and follow up at Down syndrome clinic where further follow up and management offers the infant. Chromosomal karyotyping for the parent have been done and reported to have normal result.

Cytogenetic analysis

Chromosomal analysis and karyotyping from peripheral blood lymphocytes revealed 48,XXY,+21 (Figure 1A-1C).

Discussion

Double aneuploidies have been reported with various combinations finding have been reported more frequent between sex chromosome and trisomy of autosome chromosomes while double trisomy are less frequent. Different combinations of double aneuploidies have been reported with Down syndrome such as (Down-Trisomy 18 syndrome, Down -Trisomy 13, Down-Turner syndrome and Down-Klinefelter syndrome) [4-6]. Most of these syndromes having combination of physical and developmental features which noticed soon after birth. Moreover, combinations of double aneuploidy between Down syndrome and other trisomy usually having spontaneous abortion or died soon after birth due to multiple congenital anomalies affecting heart and brain while combination between Down syndrome and sex chromosome aneuploidy they reported to survive more.

In present study, we detected Down-Klinefelter syndrome one of the rare syndromic phenomenon who presented with Down syndrome features to family with advanced maternal age which can explain the possibility of nondisjunction errors during cell division. Interestingly, the absence of congenital heart disease in the proband which is reported before to be less than Down syndrome alone.

Conclusion

In the present study, we emphasize a majer problem in chromosomal aneuploidies that involved both autosomes and sex chromosome. Finally, we emphasize the need for longitudinal data, as such information profile encompassing care recommendations and provide proper management of double aneuploidies. Increase awareness, research based on molecular diagnosis is highly recommended in order to elucidate the long-term outcome of these patents and achieving therapeutic goals.

Acknowledgement

We thank all the family members for their invaluablecooperation in this study. Finally, we emphasize the need for longitudinal data, as such information will provide profile encompassing care recommendations and provide proper management of 48,XXY,+21.

Declaration of Conflict of Interest

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Funding

None.

Consent of Publication

Consent for publication was obtained from the parents of the patient.

Ethical Approval

Ethical approval is not required at our institute to publish a case study in a medical journal.

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How to cite this article: Al-Buali Majed J, Al-Sunini Muna M, Al-Faraj Jaffer S and Al Shams Ahmed A, et al. "Rare Double Aneuploidy in Down Syndrome (Down-Klinefelter Syndrome)". J Mol Genet Med 14 (2020): 444 doi: 10.37421/jmgm.2020.14.444