CASE REPORT

MJPCH Vol. 30 (1) April 2024

OFFICIAL JOURNAL

DOUBLE AUTOSOMAL ANEUPLOIDY: A CASE OF TRISOMY 18 AND 21 MOSAICISM IN A NEONATE WITH CLINICAL DOWN SYNDROME

Aliyyah Mohammad Khuzaini[1,2], Adilah W. Ab Rahim[1], Lim Yee Shan[2], Foong Eva[3], Halimah Abdul Halim[1,2]*

Abstract

Background: Double aneuploidy is the phenomenon where two aneuploidies co-exist in the same individual, usually involving one autosomal chromosome and one sex chromosome. Double autosomal aneuploidy is rare and usually results in spontaneous abortions. There are only six published case reports of liveborn with trisomy 18 and trisomy 21 and all of which involve mosaicism. **Case Presentation:** This case report documents an infant born at 35 weeks with phenotypic features of Down Syndrome. However, cytogenetic analysis showed a mosaic of both trisomy 18 and 21. The patient initially had patent ductus arteriosus requiring operative closure and has congenital hypothyroidism. **Conclusion:** We describe five possible pathways leading to this phenomenon, including error during meiosis, meiotic nondisjunction, mitotic nondisjunction, sequential mitotic segregation and chimerism. This case report reiterates the significance of traditional cytogenetic analysis in children with features of Down Syndrome to detect any further abnormalities.

Keywords: Double aneuploidy, clinical genetics, trisomy 18, trisomy 21, pediatric genetics
DOI: 10.51407/mjpch.v30i1.273

Received: 13 December 2023; **Accepted revised manuscript:** 10 March 2024; **Published online:** 29 April 2024

Introduction

Aneuploidy is a common structural chromosomal abnormality, where trisomy 21 is the most prevalent aneuploidy with incidence of 1 in 800 live births [1]. In contrast, double aneuploidy is a rare phenomenon where two aneuploidies co-exist in the same individual [2]. Ford et. al. [3] reported the first double aneuploidy case involving Trisomy 21 and Klinefelter Syndrome (48,XXY,+21) in 1959, and ever since more cases of double aneuploidies were reported amongst children with Trisomy 21. Most of these double aneuploidies involved sex chromosomes (i.e., XXY/XYY/XXX) with incidence of 1 in 626 of live born infants with Trisomy 21 [4].

Double aneuploidies involving chromosome 21 with other autosomal chromosomes are rarer and mostly resulted in early miscarriages in comparison to single trisomy cases [5, 6]. However, there are live cases of double autosomal trisomies reported - involving chromosome +8/+14 [7], +8/+21 [8, 9],' +13/+18 [10] and notably five cases of double trisomies +18/+21 [11, 12, 13, 14, 15] We present the sixth reported live case of +18/+21 trisomies.

Case Presentation

A baby girl was born at 35 weeks' gestation with a birth weight of 2.31kg. Her mother was a 32-year-old primigravid who antenatally had well-controlled gestational diabetes mellitus on oral medication. The patient's father was 33 years old and had no medical illness. During antenatal checkup throughout the pregnancy, no congenital abnormality was seen. There was no family history of aneuploidy or congenital anomalies.

On physical examination after birth, the patient had generalized hypotonia, increased medial epicanthal folds, hypertelorism, low set ears, flattened nasal bridge, short digits, and widened sandal gap, suggestive of Down Syndrome. Features of Edward Syndrome such as clenched fists, overlapping fingers, rocker-bottom feet and micrognathia were absent.

[1]*Paediatric Unit, Universiti Sains Islam Malaysia, Nilai, Malaysia*
[2]*Paediatric Department, Hospital Ampang, Ampang, Malaysia*
[3]*Hospital Tunku Azizah Kuala Lumpur*
***Corresponding Author:**
Adilah W. Ab Rahim, Paediatric Unit, Universiti Sains Islam Malaysia (USIM), Fakulti Perubatan dan Sains Kesihatan, Persiaran Ilmu, Putra Nilai, 71800, Nilai, Negeri Sembilan, Malaysia.
Email: adilahrahim@usim.edu.my

Her height, weight and head circumference were on the 50th centile of the growth chart.

She had a hemodynamically significant patent ductus arteriosus which eventually required operative closure at 4 weeks of age. Screening ultrasound kidney showed mild hydronephrosis with no horseshoe-shaped kidney seen whilst cranial ultrasound showed ventriculomegaly which was confirmed by magnetic resonance imaging (MRI) brain. Chromosomal analysis from peripheral blood was performed on G-banded metaphases at 400 and 550 band resolution and showed 47,XX,+21[19]/ 47,XX,+18[4] karyotype (Fig. 1 and Fig. 2).

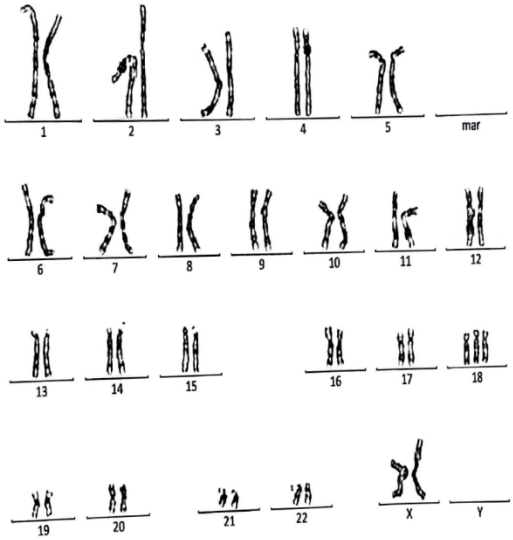

Figure 1. Trisomy 18 karyotype, seen in 18% analyzed metaphases.

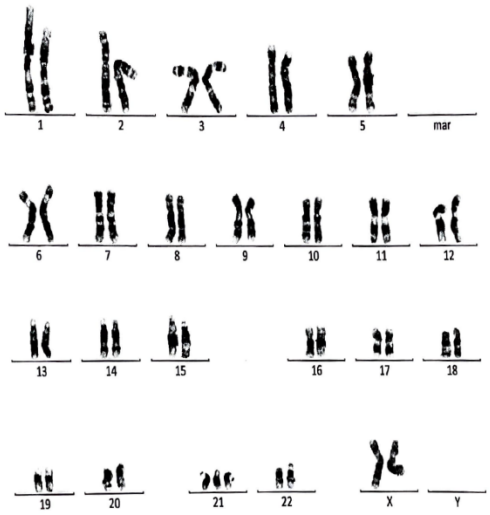

Figure 2. Trisomy 21 karyotype, seen in 82% analyzed metaphases.

During her stay in the neonatal care intensive unit (NICU), she had multiple episodes of infection requiring respiratory support and multiple courses of antibiotics. She also has congenital hypothyroidism and was treated with levothyroxine. The patient was discharged at 3 months of age with nasogastric tube feeding and no respiratory support. At the point of discharge, she was growing at the 50th centile but development was only up to 6 weeks of age. She is currently under a multidisciplinary team follow-up with regular Down Syndrome surveillance. The clinical genetic team has offered genetic testing for both parents; however, they refused further investigations with no further plan to conceive.

Discussion

To our current knowledge, only five cases of double trisomy 18 and 21 have been reported [11, 12, 13, 14, 15]. Yu-Feng Hsu et. al. [15] reported a case of mosaic trisomy 18, trisomy 21 and a normal cell line. It has been postulated that in double aneuploidy of 18 and 21, there may be variable expression of the chromosomes in the tissues, resulting in a predominantly Down's Syndrome phenotype with a better survival rate [13]. This is supported by a recent case report by Mendiola et. al. [14] in which the proband exhibited phenotypic features of both Trisomy 18 and 21 with predominant Trisomy 18 cell lines on cytogenetic testing.

Table 1 demonstrates a comparison of the five cases of double aneuploidy 18 and 21. Although patients showed variable clinical manifestations, it appears that classical features of Down Syndrome were more prominent in these cases. Long term prognosis of these patients is unknown, and it remains elusive whether their clinical manifestations correlate proportionately to their genetic makeup. From these case reports, it may be inferred that double autosomal aneuploidy is only compatible with life when there is mosaicism, consistent with findings from Reddy [5] and Micale et. al. [6] who postulated that most double aneuploidies result in spontaneous abortions.

Table 1. Comparison of Reported Cases of Double Aneuploidy Trisomy 18 and Trisomy 21

Authors	Antenatal and Family History	Birth and Neonatal History	Clinical Features	Cytogenetic Results
Mendiola et. al. (2022)	Mother was 41 years old, para 3 at time of birth. No significant family history. Fetal ultrasound at 29 weeks: ● Atrial septal defect ● Pericardial effusion ● Small bowel dilatation ● Double bubble sign	Born at 36 weeks 4 days. Good APGAR score. No dysmorphic features. Physical examination normal. Systemic issues: ● Jejunal atresia ● Inguinal hernia ● Peter's anomaly with left cataract. ● Complete common AVSD, biventricular hypertrophy, mild AVVR.	Examination at 8 months: ● AVSD ● Hypotonia ● Low set posteriorly rotated ears ● High arched palate ● Micrognathia	Quad screening and non-invasive prenatal test: Trisomy 21 RCA at birth: 47,XX,+18[15]/47,XX,+21[8]/48,XX,+21,+mar[7] RCA at 1 year of age (peripheral blood lymphocytes): 47,XX,+18[76]/47,XX,+21[4]
Thomas et. al. (1994)	Mother was 35 years old, primiparous at time of birth. Father was 38 years old at the time of birth. No significant family history.	Presented at 2.5 years old. No birth history available.	Examination at 2.5 years old: ● Muscular hypotonia. ● Joint laxity. ● Flat occiput. ● Upward slanting palpebral fissures. ● Hypertelorism. ● High arched palate. ● Bilateral 5th finger clinodactyly ● Wide sandal gap. ● Flat feet. ● Prominent heel, but no rocker bottom feet. ● Poor sucking reflex. ● Bilateral simian crease.	Performed at 2.5 years old. A total of 100 metaphase spreads was analyzed: ● 84 cells showed 47,XY+18. ● 16 cells showed 47,XY+21.
Marks et. al. (1967)	Mother was 23 years old at the time of birth. No other history available.	Born at term. No neonatal issues. Examination at point of discharge revealed a cardiac murmur.	Presented at 17 months old with global developmental delay. ● Mongoloid facies and fingers ● Simian crease in right palm ● Grade 2 blowing systolic murmur at the LLSE. ● Umbilical hernia.	Performed at 5 years old. ● Total of 40 cells were karyotyped ● 33 cells with trisomy 21. ● 7 cells with trisomy 18. Both parents' karyotype were normal.
Jenkins et. al. (1978)	Mother was 45 years old, para 3 at time of birth. Father was 52 years old at the time of birth.	Not available. Patient was referred for assessment at 20 years old.	Examination at 20 years old: ● Flat nasal bridge ● Oblique palpebral fissures ● Epicanthal folds ● High arch palate ● Furrowed tongue ● Broad and short hands	Performed at 20 years old. ● 100 cultured lymphocytes. ● 82 cells showed 47,XX+21 ● 18 cells showed 47,XX+18

	No significant family history.		• Bilateral simian lines. • Laterally displaced axial triradii. • Generalized hypotonia.	• Examination of 100 cultured skin fibroblasts showed trisomy 21.
Yu-Feng Hsu et. al. (1965)	Mother was 44 years old, para 5 at time of child's birth. Father was 48 years old at the time of the child's birth. No significant family history. Antenatally uneventful. .	Born with difficulty initiating respiration, requiring resuscitation. Subsequently, appeared weak with poor sucking and frequent episodes of apnoea and cyanosis. Diagnosed with unilateral choanal atresia at two days of age and dilatation was performed. Discharged at two weeks of age.	Readmitted at 5 weeks of age due to progressive symptoms (difficulty feeding, apnoea and cyanosis) and treated for congestive cardiac failure. Examination at 5 weeks old. • Failure to thrive. • Feeble cry, poor sucking. • Infrequent movement. • Prominent occiput, narrow and small cranium. • Low set ears with peculiarly formed auricles. • Receded chin, small mouth and high arch palate. • Bilateral ptosis and poor ocular motility. • Widened nasal bridge and inner epicanthal folds. • Hypoplastic nails. • Bilateral simian crease with distal axial triradii. • Relatively long fingers. • Equinovarus and rocker-bottom feet. • Small umbilical hernia. • Hepatomegaly. • Harsh grade 3/6 systolic murmur at the LLSE	Performed at 8 weeks of age. • 51 peripheral blood leukocytes were analyzed. • 19 cells had 48 chromosomes XX - Karyotypes on 5 metaphase cells showed trisomy 18 and trisomy 21 • 24 cells had 46 chromosomes XX. • 6 cells had 47 chromosomes XX. • 2 cells had 45 chromosomes Both parents' karyotypes were normal.

Abbreviations. AVSD: atrioventricular septal defect; AVVR: atrioventricular valve regurgitation; RCA: Routine chromosome analysis; LLSE: lower left sternal edge.

It is suggested that several mechanisms may trigger double trisomy mosaicism, including non-disjunction of both chromosomes 18 and 21, anaphase lag of both chromosomes, and a combination of these mechanisms [13]. Based on the available investigations, there are five possible pathways that could have led to the double mosaic aneuploidy in the present case. These pathways are summarized in Figure 3.

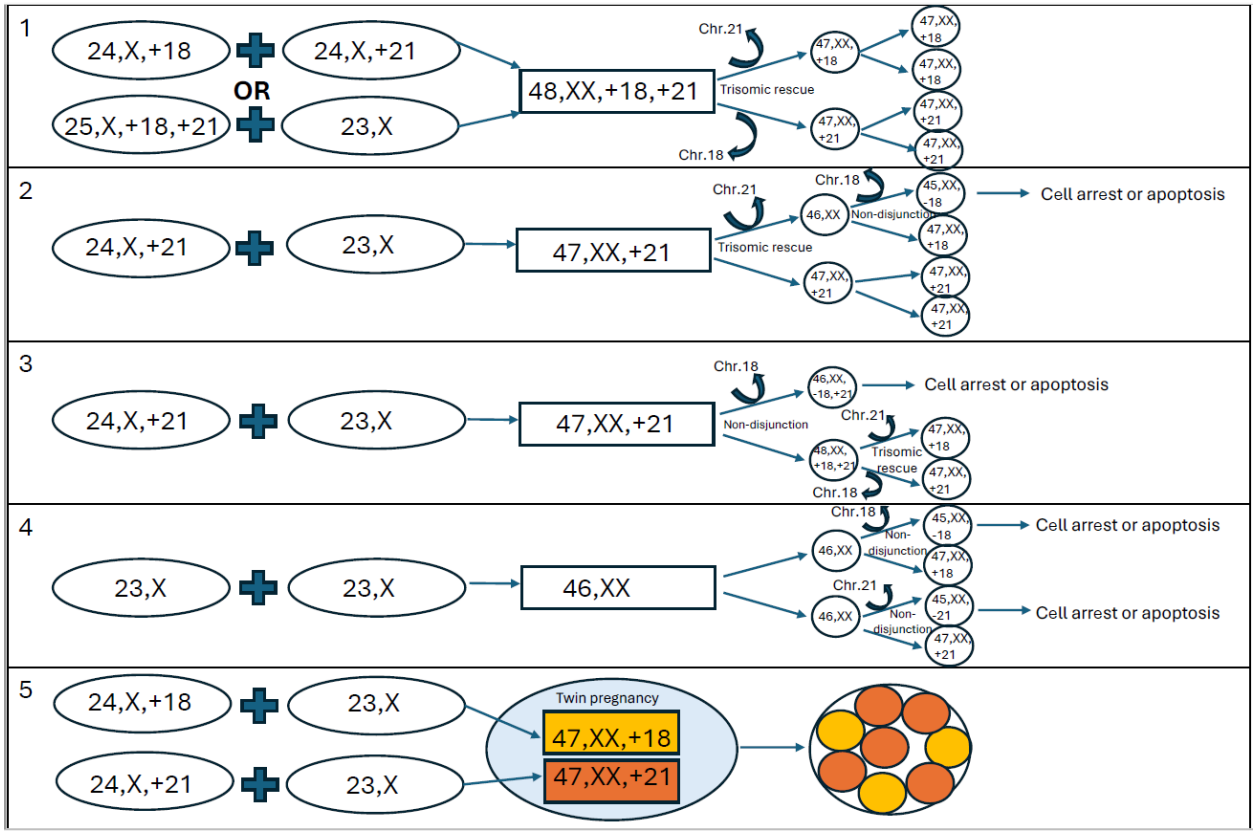

Figure 3. Possible mechanisms of double aneuploidy trisomy 18 and trisomy 21.

The first possible pathway is error during meiosis, in which nondisjunction involving two chromosome pairs happen during gametogenesis in one or both parents. This subsequently produces gametes carrying an extra chromosome 18 or 21 or both chromosomes 18 and 21. Fertilization between these abnormal maternally or paternally derived gametes results in production of a zygote with 48,XX,+18,+21. During the first postzygotic mitotic cell division, trisomy rescue takes place leading to the loss of chromosome 18 or 21 in either of the two cells, respectively, resulting in 47,XX,+18 and 47,XX,+21 cells.

The second possibility is meiotic nondisjunction resulting in 47,XX,+21 zygote, which is then corrected by subsequent mitotic events (such as nondisjunction or anaphase lag). The mitotic loss of one copy of chromosome 21 in the first post-zygotic cell division produces 47,XX,+21 and 46,XX cells, respectively. In the subsequent second cell division, the corrected (rescued) 46,XX cell undergoes mitotic nondisjunction involving chromosome 18, followed by negative selection of the monosomy 18 cell resulting in 47,XX,+18 cell.

The third possible pathway is when the original zygote with 47,XX,+21 undergoes mitotic non-disjunction of chromosome 18 at the first cell division instead of undergoing trisomy rescue subsequently producing both 48,XX,+18,+21 and 46,XX,-18,+21 cells. Cells with monosomy 18 will undergo negative selection. In the subsequent mitotic cell division, the 48,XX,+18,+21 cell will have lost chromosome 18 or 21 in either of the two cells, resulting in 47,XX,+18 and 47,XX,+21 cells.

The fourth possible pathway is by sequential mitotic segregation error occurring in a normal zygote (46,XX). The possible mechanisms for mitotic segregation errors have been well explained above. These mitotic segregation errors likely occur in the early postzygotic stage as there is absence of normal cell lines in the present case. However, there is a possibility that a normal cell line might be present at a much lower level as compared to 47,XX,+18 and 47,XX,+21 cells. In this case, only 23 metaphases were analyzed, thus the lowest percentage of mosaicism excluded with 95% confidence is 13% [16]. Therefore, there is a possibility of uncaptured normal cell lines in the present case. The presence of a normal cell line is an important indicator to gauge the timing of mitotic segregation error and helps in predicting the possible pathways leading to double mosaic aneuploidy.

The last possible pathway is chimerism, in which the different cell lines observed originated from two different zygotes that fuse into one during the early embryonic stage producing a mixture of completely unrelated two cell lineages. In the present case, the mother is unsure regarding the date of her last menstrual cycle, and a revised estimated date of delivery (REDD) was given after the first ultrasound scan at week 7. Subsequently, the baby was born prematurely at 35 weeks of gestation. The possibility of vanishing twin syndrome could not be totally excluded. Assuming that this mother was pregnant with fraternal twins, one of the embryos with trisomy 18 died in utero very early on, the other surviving embryo with trisomy 21 who had "absorbed" its twin's cells would end up with two sets of deoxyribonucleic acid (DNA) i.e., 47,XX,+21 (own DNA) and 47,XX,+18 (DNA from the other twin).

Chimerism resulting from post-zygotic fusion of the two different embryos is known as tetragametic or dispermic chimerism [17], a condition that arises from four gametes: two eggs fertilized by two sperms, resulting in dizygotic twins who fuse into one individual. Most chimeras remain undetected especially if both zygotes in a chimera are of the same sex and have a normal phenotype [18].

Chimerism and double mosaic aneuploidy can produce two different sets of karyotypes in an individual. Molecular analysis such as single nucleotide polymorphism (SNP) microarray, chromosome polymorphic markers, DNA microsatellite and short tandem repeats (STR) markers on different body tissues are essential to delineate the actual mechanism of double mosaic aneuploidy as well as to differentiate it from chimerism.

Limitations in this case include the inability to perform Fluorescence in situ hybridization (FISH) or high-resolution chromosome microarray studies for the proband and the absence of parental cytogenetic results. Cytogenetic analysis of other tissue types or at a different age are not routinely available in Malaysia. These investigations, if performed, may shed light as to the mechanism and expression of the aneuploidy, aiding the understanding of the phenomenon of double aneuploidy in liveborns.

Conclusion

This report reiterates the importance of conventional cytogenetic analysis in children with Down Syndrome even if the phenotype is typical, so that any associated abnormality may be detected.

List of Abbreviations

DNA: deoxyribonucleic acid
FISH: Fluorescence in situ hybridization
MRI: magnetic resonance imaging
NICU: neonatal care intensive unit
SNP: single nucleotide polymorphism
STR: short tandem repeats

Declarations

Ethics approval and consent to participate**:** Not applicable.

Consent for publication

Written informed consent was obtained from the parents of the patient.

Availability of data and material

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that there are no conflicts of interest.

Funding

The authors declare that no funding was available for the manuscript writing and publication.

Authors' contributions

AMK, AWAR, LYS, FE and HAH were involved in the writing of the manuscript. AMK and AWAR extensively reviewed the manuscript. All authors were involved in revision of the manuscript. We declare that the manuscript represents honest work and fulfills the journal requirements.

Acknowledgements

We thank the Paediatric Department, Ampang Hospital for the opportunity to write this case.

References

[1] Huete-García A, Otaola-Barranquero M. Demographic Assessment of Down Syndrome: A Systematic Review. International Journal of

Environmental Research and Public Health. 2021 Jan 5;18(1):352.

[2] Vaniawala S, Gadhia P. Mosaic Double Aneuploidy with Edwards-Klinefelter Syndromes (48,XXY, +18/46XY). American Journal of Medical Sciences and Medicine. 2014 Nov 24;2(6):131–3.

[3] Ford C. The Chromosomes In A Patient Showing Both Mongolism And The Klinefelter Syndrome. The Lancet. 1959 Apr;273(7075):709–10.

[4] Kovaleva NV, Mutton DE. Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. American Journal of Medical Genetics Part A. 2005;134A(1):24–32.

[5] Reddy KS. Double trisomy in spontaneous abortions. Human Genetics. 1997 Dec 11;101(3):339–45.

[6] Micale M, Insko J, Ebrahim SAD, Adeyinka A, Runke C, Van Dyke DL. Double trisomy revisited-a multicenter experience. Prenatal Diagnosis. 2009 Dec 29;30(2):173–6.

[7] Matheson JKB, Matheson VA, McCorquodale M, Santolaya-Forgas J. Prenatal Diagnosis of Double Autosomal Mosaicism (47,XX,+8/47,XX,+14): Phenotype and Molecular Cytogenetic Analysis on Different Tissues. Fetal Diagnosis and Therapy. 2003;18(1):29–32.

[8] McGregor-Schuerman M, Lo Fo Sang A, Bihari S, Ramdajal N, F Suijkerbuijk R, van Ravenswaaij-Arts C. A child with complementary mosaic trisomy 8 and mosaic trisomy 21; clinical description of Warkany-Down syndrome and mechanism of origin. European Journal of Medical Genetics [Internet]. 2020 Jun 1;63(6):103922. Available from: https://www.sciencedirect.com/science/article/pii/S1769721220301105

[9] Wilson MG, Fujimoto A, Alfi OS. Double Autosomal Trisomy and Mosaicism for Chromosomes No. 8 and No. 21. Journal of Medical Genetics. 1974 Mar 1;11(1):96–101.

[10] Abe K, Itoh NH, Hirakawa O, Niikawa N. Trisomy 13/trisomy 18 mosaicism in an infant. Clinical Genetics. 2008 Jun 28;50(5):300–3.

[11] Marks JF, Wiggins KM, Spector BJ. Trisomy 21-trisomy 18 mosaicism in a boy with clinical Down's syndrome. The Journal of Pediatrics. 1967 Jul;71(1):126–8.

[12] Jenkins MB, Kriel RL, Boyd L, Barnwell A. Trisomy 21 with 47,+18 lymphocyte cell line: double mitotic nondisjunction. Journal of Medical Genetics. 1978 Oct 1;15(5):395–8.

[13] Thomas IM, Sayee R, Shavanthi L, Sridevi H. Trisomy 18 and trisomy 21 mosaicism in a Down's syndrome patient. Journal of Medical Genetics. 1994 May 1;31(5):418–9.

[14] Mendiola C, Ortega V, Britt A, Fonseca R, Velagaleti G. Double aneuploidy mosaicism involving chromosomes 18 and 21 in a neonate. Molecular Cytogenetics. 2022 Jan 24;15(1).

[15] Yu-Feng Hsu L, Schwager AJ, Nemhauser I, Sobel EH. A case of double autosomal trisomy with mosaicism: 48/XX (trisomy 18+21) and 46/XX. The Journal of Pediatrics. 1965 Jun;66(6):1055–60.

[16] Hook E. Exclusion of chromosomal mosaicism: tables of 90%, 95% and 99% confidence limits and comments on use. American Journal of Human Genetics . 1977;29(1):94–7.

[17] Ankathil R, Eva F, Bakar ZA, Yunus NM, Nawi NA, Annuar A, et al. A Dual Gender Rare Case with 47,XY, + 18/46,XX Karyotype: Chimera or Mosaic? Journal of Child Science. 2021 Jan;11(01):e41–4.

[18] Madan K. Natural human chimeras: A review. European Journal of Medical Genetics. 2020 Sep;63(9):103971.

