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CLINICAL CASE

Turner syndrome associated with Down syndrome: about a case

Síndrome Turner asociado a Síndrome Down: a propósito de un caso

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Abstract

The coexistence of double aneuploidy of Down and Turner syndromes is rare; most cases have been due to double mitotic errors. The objective of the study was to report a case with monosomy of the X chromosome and trisomy of chromosome 21, in mosaic variety, highlighting the phenotypic effect that the presence of different chromosomal abnormalities can produce and compare with those reported in the literature. A 10-year-old Ecuadorian female, born to a multipregnant mother with 46 years at conception, is seen in consultation with a predominant clinical phenotype of Down syndrome, associated with menarche, presence of pubic and axillary villu, where a karyotype is verified 45 X[7]/47XX+ 21 [3]/46, X, der (X)(: p11.1-> q11.1)[1]/46,XX [1]. The present case is a double Turner-Down aneuploidy, with predominantly X monosomy cell line, who shows important mental retardation and some signs of puberal development not usually in Turner syndrome. These features highlight the clinical importance of doing a karyotype in mental retardation cases and searching low mosaics of another aneuploidies in atypical cases. Its complex chromosomal formula and support with molecular cytogenetics allowed diagnostic confirmation and genetic counseling.

Keywords: *Turner syndrome. Down syndrome. Double aneuploidy. Chromosomal mosaicism.*

Resumen

La coexistencia de doble aneuploidía de los síndromes de Down y Turner es rara; la mayoría de los casos se han debido a dobles errores mitóticos. Reportar un caso con trisomía del cromosoma 21 y monosomía del cromosoma en X, en variedad mosaico, que curiosamente presenta un despertar puberal precoz y comparar con los reportados en la literatura. Paciente ecuatoriana de sexo femenino, de 10 años de edad, nacida de madre multigesta con 46 años a la concepción, que es vista en consulta con fenotipo clínico predominante de Síndrome Down, asociado a menarquia y telarquia, donde se constata un cariotipo. El presente caso es el primero informado de mosaicismo de doble aneuploidía de Turner-Down asociado con un despertar puberal precoz. Su fórmula cromosómica compleja y el apoyo con la citogenética molecular permitió la confirmación diagnostica y la asesoría genética.

Palabras claves: *Síndrome de Turner. Síndrome de Down. Doble aneuploidía. Mosaicismo cromosómico.*

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Introduction

Down syndrome (trisomy 21, DS) is the most common chromosomal disorder in humans with an incidence of one in 770 live births[1]. On the other hand, Turner syndrome has a birth prevalence of 1/2000 to 1/5000 female live NBs[1,2]. However, the combination of Down syndrome and Turner syndrome is very rare (estimated frequency is 1 in 2,000,000); the 1st time, it was described in 1971[2]. This phenomenon is relative rare; the estimated frequency is 1 in 2,000,000 births[2-8].

A double aneuploidy is an uncommon condition in which two or more chromosomal abnormalities come together in the same individual, usually as a consequence of meiotic errors, where two different numerical chromosomal abnormalities occur simultaneously or sequentially in the same cell line, however, it can also happen that two different anomalies involve different cells in the first post-zygotic divisions, finding cases of mosaic double aneuploidy. It is pointed out that the association of autosomal trisomy and abnormality in the number of sexual chromosomes are the most frequent types of duplicated aneuploidies, the most representative being the Down-Turner and Down-Klinefelter cases[1].

The work aims to present the case of an Ecuadorian girl with an X chromosome monosomy in addition with chromosome 21 trisomy, showing the phenotypic effect of combination aneuploidies. We discuss its clinical phenotype and compare it with similar cases presented in the literature.

Clinical case

A 10-year-old female patient is referred for a conventional karyotype due to a clinical phenotype of Down syndrome. She is the last daughter of a phratry of seven and the parents were not blood relatives. There is no relevant family or hereditary history. She was a product of conception at a maternal age of 46 years, with poor prenatal care and was born from a cephalovaginal delivery at term with a weight of 2300 g and congenital heart disease type small interventricular communication.

Neurodevelopmental milestones were acquired late, achieving independent walking at 2½ years of age; at that age, there was also a marked language delay. At the time of the study, he presented a picture of moderate intellectual disability with an IQ of 56 and a behavioral disorder due to self-injury.

Physical examination revealed that the girl had a height of 124 cm (age-height slightly below the 5th percentile) and a weight of 27 kg (age-weight 10th percentile) and a head circumference of 49.5 cm. On clinical examination, he presented brachycephaly, upward slanting palpebral fissures, facial freckles, low-set ears, and wide and short hands with bilateral clinodactyly. At the level of the genitalia, she presented thelarche, pubarche P2-3, and axillary, drawing attention to the fact that just at the age of 10, she had begun to menstruate.

Echocardiography and renal ultrasound performed at the age of 6 years did not confirm anatomical defects.

The hormonal studies did not confirm the classic gonadotropic hypogonadism and presented the following values: follicle-stimulating hormone 6.17 mIU/mL, luteinizing hormone (LH) 2.35 mIU/mL, and estradiol (E2) 116.30 pq/mL.

The gynecological ultrasound could not be performed due to the patient's failure to attend periodic check-ups and the discontinuity of her medical care at the Baca Ortiz Pediatric Hospital.

Band cytogenetic analysis

The girl's karyotype was performed by culture of peripheral blood lymphocytes in RPMI-1640 medium (GIBCO). Chromosome preparations were obtained using standard techniques and analyzed by GTG banding at 50 metaphases. The karyotype of the parents was not performed.

Fluorescent in situ hybridization (FISH)

FISH analysis was performed according to standard procedures, on metaphases derived from cultured lymphocytes, applying commercially available probes for centromeric regions of chromosomes 21 and X (Wcp X and 21 [EH]) (Abbott, Wiesbaden, Germany).

Ethical aspects

This study was conducted in accordance with the Declaration of Helsinki as amended in 2013. Informed consent was obtained from the mother for genetic testing and Hospital Ethics Committee approval was obtained for publication of this article.

Results

Conventional cytogenetic analysis revealed a female karyotype with mosaic double aneuploidy: 45X[50]/47XX+21[40]/46,XX[2] (Fig. 1A).

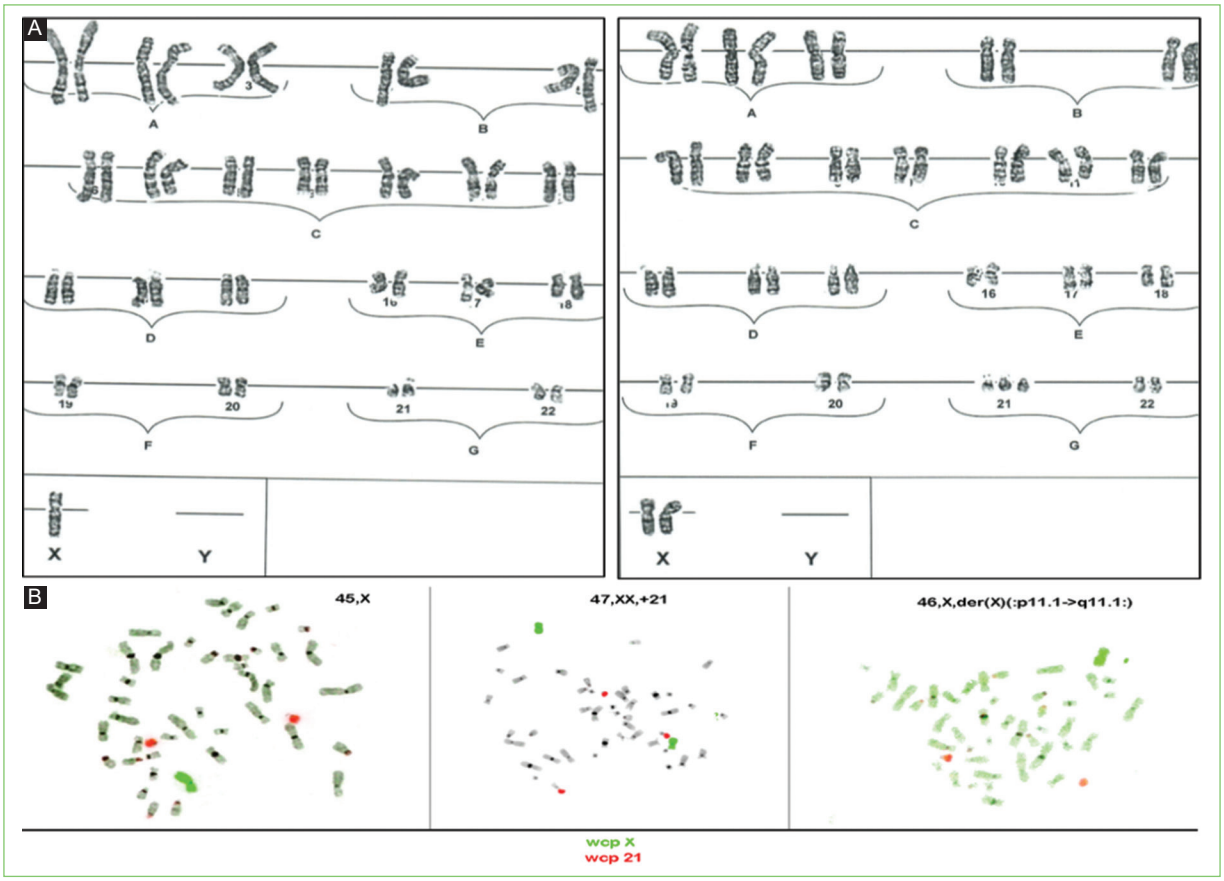

Figure 1. A: conventional G-band karyotype showing mosaic double aneuploidy with loss of the X chromosome and enhancement of chromosome 21. mos 45 X [50]/47XX+ 21 [40]/46,XX [2]. **B:** FISH analysis with centromeric X probe (DXZ1; green spectrum) and chromosome 21-specific LSI DNA probe (D21S259, D21S341, and D21S342; red spectrum) showing mosaic: 45X[7]/47XX+21[3] / 46, X, rh (X)(: p11.1-> q11.1)[1]/46,XX [1].

The FISH karyotype resulted: 45 X [7/47XX]+ 21 [3/46], X, right (X)(: p11.1-> q11.1)[1/46,]XX [1] (Fig. 1B).

Discussion

We described a female case of double aneuploidy affecting chromosome X and chromosome 21 and compared it with the majority of the similar cases previously described[1-21] (Table 1). There are many other descriptions of different types of double aneuploidy.

It has been reported that in cases of double aneuploidy, where autosomes and sex chromosomes are involved, clinical manifestations related to autosomes regularly predominate and clinical manifestations related to sex chromosomes tend to be hidden[9-21]. The Down-Turner presentation behaves like mosaicism in most cases and the Down phenotype predominates. Note that it was present in almost 100% of the cases in table 1. This occurs in the case we present.

Authors have pointed out that the prevalence of the Down phenotype may also be related to the fact that the expression of Turner syndrome tends to become more evident towards puberty. Apparently, in Down-Turner syndrome, the ratio of trisomy 21 versus monosomy X cells does not always correlate with the phenotype, which can probably be explained by a different mosaic distribution in various somatic tissues[21]. Regarding the clinical predominance according to the monoclonal or polyclonal origin of the aneuploidy, it is not predictable, as shown in the comparison table.

The phenotypic effects of the Down-Turner mosaic chromosomal formula combinations have been diverse, such as capillary hemangioma of the orbit, joints dislocations, and severe hypotonia, although the classic signs of autosomal anomaly have prevailed in all[3,5,6].

The mechanism of the production of double aneuploidy is closely related to errors in meiotic divisions in either parent. Although the factor that is most closely related to

Table 1. Comparison of the karyotype and phenotype of 23 patients with Turner-Down syndrome described above and our case

References	Karyotype	Phenotype
Cohen et al.[9]	47,XX,+21/45X	Down
Mikel'saar et al.[10]	47,XX,+21/47,XXp-q-,+21	Down-Turner
Hustinx et al.[11]	45,X/47,XX,+21	Down
Townes et al.[3]	46,X,+21/45X	Down-Turner
Singh et al.[12]	47,XX,+21/46,XX/46,X,+21	Down
Martsolf et al.[13]	47,X,del(X)(p11),+21	Turner
Chen et al.[14]	45,X/48,XXX,(t12;21)	Down
Macfaul et al.[7]	46,X,+21/47,X,i(X),+21	Down
Macfaul et al.[15]	46,X,+21/47,XX,+21	Down-Turner
Gatrad et al.[6]	46,X,+21/47,XX,+21	Down-Turner
Jansen et al.[16]	45,X/47,XX,+21	Down-Turner
Prieur et al.[17]	45,X/47,XY,+21	Down
Van Buggenhout et al.[4]	45,X/46,X,+21/47,XY,+21	Down-Turner
Digilio et al.[18]	45,X/46,XX,i(21q)	Down-Turner
Harada et al.[19]	45,X/47,XX,+21	Down-Turner
Musarella et al.[5]	5,X/47,XX,+21/46,XX/47,XXX	Down
Zaki et al.[23]	45,X/47,XY,+21	Down-Turner
Zaki et al.[23]	46,X,+21/47,XX,+21	Down-Turner
Jeong et al.[20]	47,X,del(X)(p11),+21/47,XX,+21	Down-Turner
Ryu et al.[1]	45,X/47,XY,+21	Down
Bergamaschi et al.[24]	45,X/47,XY,+21	Down-Turner
Manassero-Morales et al.[2]	47,X,r(X),+21-	Down-Turner
Salwati et al.[21]	45,X/47,XY,+21	Down
Llamos et al. (present case)	45 X [7]/47XX+ 21 [3]/ 46, X, der (X)(: p11.1-> q11.1)[1]/46,XX [1]	Down

the pathogenesis of aneuploidy is advanced maternal age, due to the high level of meiotic instability documented during oogenesis[22], what is curious about this case is that despite the high risk of meiotic non-disjunction due to maternal age, the complex mosaicism is produced by successive mitotic errors. Given the proportions of the different cell lines found, we postulate the following as a possible production mechanism: a female embryo, originally euploid, suffered two errors independently in the second post-zygotic cell division, which led to the existence of a clone with trisomy of the chromosome 21 and another clone with loss of an X chromosome, with subsequent degradation of the same (Fig. 2).

The proposed mechanism would be more related to the demonstration that the large amount of cytoplasm present in oocytes and embryos in the cleavage stage induces error-prone chromosome segregation by dilution of spindle assembly checkpoint proteins, contributing to two successive segregation errors at this stage in a single zygote, leading to the development of mosaic double aneuploidy[22-24]. It is noteworthy that the majority of reported cases of double aneuploidies occur in young women, our case being an exception to this.

A significant clinical aspect of the presented case is the presence of secondary sexual characteristics, which disagrees with its main karyotyping constitution, since

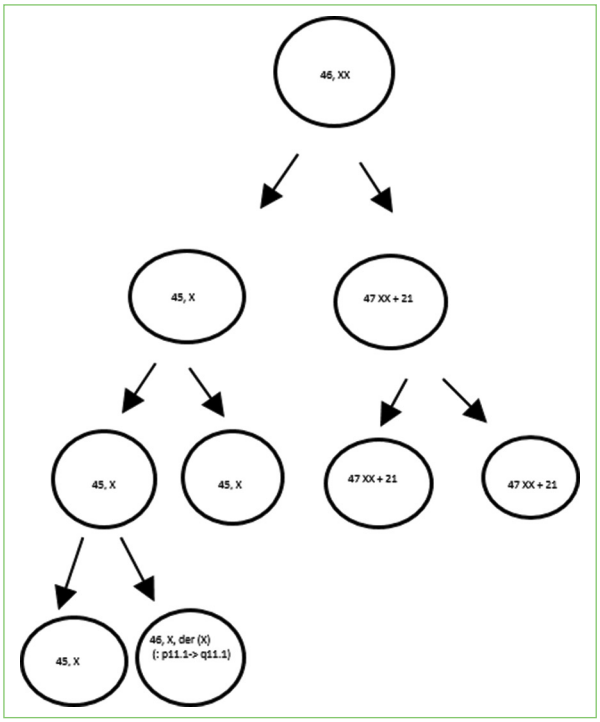

Figure 2. Sequence of mitotic errors proposed as a mechanism of double aneuploidy in this case.

in both Turner syndrome and Down syndrome, there is usually a notable delay in sexual development, especially if we take into account that the euploid cell line 46 XX is hardly significant, similar to the line with the structural abnormality of the X chromosome. Although distal deletions of the short arm of the X chromosome are usually accompanied by normal ovarian functions, the deletion detected in this case is quite small and is practically limited to the pericentromeric region whose content in functional genes is insignificant.

Some reports, regarding the incidence of menarche in Turner syndrome, showed a percentage of 3-16.1% depending on whether it is a pure or mosaic monosomy[25-27].

In the case presented, a limitation is the non-performance of gynecological ultrasound; it will show the measures of utero and ovaries, as an important sign of estrogenic function, nevertheless given the normal behavior of gonadotropic hormones and the presentation of menarche, we think that the degree of ovarian dysfunction could not be very important. On the other hand, the cytogenetic study of various tissues was not performed, which could indicate the tissue distribution of the different cell lines present and their possible correlation with the phenotype presented.

Conclusions

A karyotype is always an important test regarding mental retardation, looking for classic or complex chromosomal formulas, even when phenotype appears as classic Down syndrome. In this case, its proper management is particularly important, with emphasis on its high reproductive risk given its normal ovarian functions and the possibility of pregnancy, in a very unfavorable socioeconomic environment such as the one it presents.

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Conflicts of interest

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Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Ryu SW, Lee G, Baik CS, Shim SH, Kim JT, Lee JS, et al. Down-Turner syndrome (45, X/47, XY, + 21): a case report and review. Korean J Lab Med. 2010;30:195-200.
2. Manassero-Morales G, Álvarez-Manassero D, Merino-Luna A. Down-turner syndrome: a case with double monoclonal chromosomal anomaly. Case Rep Pediatr. 2016;2016:8760504.
3. Townes PL, White MR, Stiffler SJ, Goh K. Double aneuploidy. Turner-Down syndrome. Am J Dis Child. 1975;129:1062-5.
4. Van Buggenhout GJ, Hamel BC, Trommelen JC, Mieloo H, Smeets DF. Down-Turner syndrome: a case report and review. J Med Genet. 1994;31:807-10.
5. Musarella MA, Verma RS. An infant with downturn aneuploidy and massive capillary hemangioma of the orbit: a case report with review. Ann Genet. 2001;44:67-70.
6. Gatrad AR. Congenital dislocation of the knees in a child with Down syndrome-mosaic Turner. J Med Genet. 1981;18:148-51.

7. Macfaul R, Turner T, Mason MK. Double aneuploidy as a rare cause of missed prenatal diagnosis of chromosomal abnormality. Arch Dis Child 56(12): 962-3.
8. Gumus E. Two rare variants of down syndrome: down-turner syndrome and down syndrome with (13;14) translocation: a case report. Iran J Public Health. 2019;48:2079-82.
9. Cohen, M.M, Davidson, R.G. 1972. Double aneuploidy (47,XX,21+/45,X) arising through simultaneous double nondisjunction. J Med Genet 9(2): 242-4.
10. Mikel'saar AV, Blyumina MG, Kuznetsova LI. A double chromosomal aberration of the 47,XX,21+/47,XX p-q-,21+ type in a girl with features of down's and turner's syndromes. Genetika. 1971;5:156-61.
11. Hustinx TW, Haar BG, Scheres JM, Rutten FJ. Autsomal/heterosomal mixoploidy: a case report on two patients, a female with a 45,X/47,XX+21 and a male with a 45,X/47,XY, +21 chromosome constitution. Ann Genet (Paris). 1974;17:225-34.
12. Singh DN, Osborne RA, Hennigar GR, Barnett CD. Mosaic double aneuploidy of X and G chromosomes. Am J Ment Defic. 1975;79:644-7.
13. Martsolf JT, Ray M, Bauder F, Boychuk R, Armstrong JD. Down and turner syndromes in a female infant with 47, X, del (X) (p11),+21. Hum Genet. 1977;39:103-8.
14. Chen H, Tyrkus M, Woolley PV. Double aneuploidy: partial trisomy 21 and XO/XXX in a family with 12/21 translocation. Ann Genet. 1978;21:177-80.
15. Macfaul R, Turner T, Mason MX. Down's Turner's mosaicism: double aneuploidy as a rare cause of missed prenatal diagnosis of chromosomal abnormality. Arch Dis Child. 1981;56:962-3.
16. Jansen S, Kruger AJ, Liebenberg G. Turner/down mosaicism. S Afr Med J. 1991;79:731-2.
17. Prieur M, Dutrillaux B, Carpentier S, Berger, R., Raoul, O., Rethore, M., Lejeune, J. 1972. Mosaique 45,X/47,XY,+ 21. Ann Genet (Paris). 1972;15:195-6.
18. Digilio MC, Mingarelli R, Marino, Giannotti A, Melchionda S, Dallapiccola B. Congenital cardiac defect in a patient with mosaic 45,X/46,XX,i(21q) karyotype. Clin Genet. 1994;46:268-70.
19. Harada N, Abe K, Nishimura T, Sasaki K, Ishikawa M, Fujimoto M, et al. Origin and mechanism of formation of 45,X/47,XX,+21 mosaicism in a fetus. Am J Med Genet. 1998;75:432-7.
20. Jeong HJ, Lee ES, Choi KH, Park YH. A case of down-turner syndrome. J Korean Soc Pediatr Endocrinol. 2005;10:120-4.
21. Salwati S, Bador KM, Aida MI. A rare case of a male infant with down-turner syndrome and review of cases. Med Health. 2019;14:234-43.
22. Kato T, Kawai M, Miyai S, Suzuki F, Tsutsumi M, Mizuno S, et al. Analysis of the origin of double mosaic aneuploidy in two cases. Cytogenet Genome Res. 2020;160:118-23.
23. Zaki MS, Kamel AA, El-Ruby M. Double aneuploidy in three Egyptian patients: Down-Turner and Down-Klinefelter syndromes. Genet Couns. 2005;16(4):393-402. PMID: 16440882.
24. Bergamaschi, C., Giavoli, E., Profka, E., Ferrante, R., Fortuna, S., Guerneri D., Milani, F., Menni, M., Cerutti, G., Manzoni, A., Berrettini, S., Vallasciani, A., Spada, P. Beck-Peccoz. 2012. A particular phenotype in a case of Down-Turner syndrome. Abstract in the 15th International & 14th European Congress of Endocrinology Florence. Italy.
25. Martin Campagnea, C. Roa Llamazaresb. Letter to the editor: Spontaneous puberty and menarche in a patient with Turner syndrome and 45X monosomy. Annals of Pediatrics. Vol. 70. No. 2. pages 200-202 (February 2009) DOI: 10.1016/j.anpedi.2008.09.008
26. Mirela Mačkić-Đurović, PhD, 1 Meliha Stomornjak-Vukadin, MD, 2 and Slavka Ibrulj, PhD, Turner syndrome: a unique mosaic case with 45,X/47,XX, +21/46,XX cell lines . Iran J Med Sci. 2018 July; 43 (4): 436–439.
27. AM Pasquino, F. Passeri, I. Pucarelli, M. Segni, G. Municchi. Spontaneous pubertal development in Turner's syndrome. J Clin Endocrinol Metab, 82 (1997), p. 1810-1813 http://dx.doi.org/10.1210/jcem.82.6.3970 | Medline[4]