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RESEARCH NOTE

Double trisomy (XXX+21 karyotype) in a six-year-old girl with down phenotype

LAURA DANIELA VERGARA-MENDEZ*, CLAUDIA TALERO-GUTIÉRREZ and ALBERTO VELEZ-VAN-MEERBEKE

Neuroscience research group (Neuros), School of Medicine and Health Sciences, Universidad del Rosario, Bogotá 111221, Colombia
*For correspondence. E-mail: Laura.vergara@urosario.edu.co.

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Abstract. We describe a case of a six-year-old girl who presents multiple dysmorphic features characteristic of Down's syndrome. She has a significant general developmental delay, with a score that correspond to 32 months of developmental age. This delay is especially in language, with a very scant vocabulary. She communicates with some hand sign words or pointing, although her auditory responses in hearing test were normal. Two previous karyotype studies showed 47, XXX, +21 anomalies. This double trisomy is a rare condition described in isolated cases in the literature and none of these refers to the developmental aspects of these children (Balwan *et al.* 2008; Li *et al.* 2004; Park *et al.* 1995; Day *et al.* 1963).

Keywords. Down's syndrome; triple X syndrome; double trisomy; developmental delay.

Introduction

Chromosomopathy presenting with double aneuploidy is infrequent (<2.8%), and even more so in live births (0.05%) (Diego-Alvarez *et al.* 2006; Flores-Ramirez *et al.* 2015). There are very few cases described in the literature, but none of these addresses the neurological development in these children (motor, language, social-personal and perception developmental skills), as they do not usually exceed one year of age (Park *et al.* 1995; Li *et al.* 2004; Balwan *et al.* 2008). There is only one case reported in an eight-year-old girl (Day *et al.* 1963), but authors did not describe the developmental characteristics. We describe a case of a six-year-old girl who presents multiple dysmorphic features characteristic of Down's syndrome. She has a significant general developmental delay, particularly in language with a very scant vocabulary. She communicates with some hand sign words or pointing, although her auditory responses in hearing tests were normal. Two previous karyotype studies showed 47, XXX, +21 anomalies.

In most cases, the occurrence of double trisomy is due to a nondisjunctional error in maternal meiosis II and it usually leads to miscarriage, when this anomaly involves autosomes (Park *et al.* 1995; Diego-Alvarez *et al.* 2006). Regarding live births reported with double trisomy, one of the duplicated chromosomes was the sexual pair, and the other was either 21 or 18 and less frequently 7, 8, 10, 15 and 16 (Li *et al.* 2004; Kovaleva and Mutton 2005; Micale *et al.* 2010).

Case history

We evaluated the neurological development in a six-year-old girl, daughter of a nonconsanguineous couple without medical or family history of relevance. This case was selected from a database constructed in a previous study to evaluate Down's syndrome characteristics in children from Bogota, Colombia. This study obtained an approval of the Institutional review board and ethics committee. Parents gave their consent to publish the patient's records.

She was the first child of a 27-year-old woman and her husband, a 40-year-old man. This was the mother's first pregnancy. During the first trimester, the mother had

persistent vomiting (hyperemesis gravidarum), and was successfully treated with metoclopramide. The pregnancy was considered as high-risk from the second trimester onwards due to uterine bleeding and threat of miscarriage.

According to mother's report, the ultrasound study suggested foetal Down's syndrome characteristics (this could not be confirmed as we never had access to the original report). An amniocentesis at 19 weeks, identified chromosomal alterations due to an additional copy of the X chromosome and an extra chromosome 21 on cytogenetic analysis (48, XXX, +21 karyotype). Anhydramnios presented at week 32, leading to an emergency Cesarean section surgery. The female newborn weighed 1279 g and measured 39 cm. At nine-days old, a new karyotype was performed (G-banded technique) that showed 48 chromosomes with two trisomies (trisomy-21 and triple-X) (figure 1).

The girl received physical, neurodevelopmental and language therapy until three years of age. Motor development was slow with sitting and crawling at 12 months, and walking at 48 months. Bowel and bladder controls were achieved at five years of age. In relation to language development, babbling appeared at eight months and first words at 18 months. Currently, her vocabulary is scanty (fewer than 10 words), but with good gestural expression; no onomatopoeias or imitation of sounds are present, and she is not able to combine two words. The patient attended nursery school from age two to four years, and since five-year-old to date, has attended formal school without significant progress in her academic skills. Apparently, the child is able to carry out some basic, everyday activities, such as eating and dressing, but needs help to do her school work, use the bathroom and brush her teeth.

At age six, the girl underwent a cognitive, language and motor development evaluation. The girl entered the office, walking on her own with her mother, who was concerned about the limited use of oral language. Her communication consisted mainly of some structured signs that were learnt in language therapy.

During the visit, appropriate contact with the examiner and engagement in exploratory conduct through didactic material, was established without structured play. Hearing was apparently normal, she responded to noises and to voice with orientation towards the sound source with comprehension and execution of some simple instructions, in spite of some difficulties. From a visual point of view, although the mother reported that her vision test was not normal, the child did not use corrective lenses.

Her anthropometric measurements were: weight 15.2 kg (<P3), height 97 cm (<P3; weight/height P50), and head circumference 47 cm (P3) (World Health Organization, The WHO Child Growth Standards. http://www.who.int/childgrowth/standards/en/). There were no body or functional asymmetries. Patient had a brachycephalic skull, hypertelorism, epicanthus, flat nasal bridge, low facial muscle tone without sialorrhea or oral breathing, and low-set ears and short neck (figure 2a, frontal view; figure 2b, side view). Brachydactyly in the hands, single palmar crease and bilateral clinodactyly of the fifth finger were found. Her feet showed a separation between the great toe and the second toe (sandal gap sign) and flat arches. A generalized symmetrical low muscle tone was present. Walking and object manipulation were functional, and had a normal standing posture; however, activities such as hopping on one foot, walking on a straight line, or walking on tip-toe, could not be performed.

An examination of the speech organs and articulation showed hypotonic half-opened lips and insufficient strength to form or imitate phonemes. There was no macroglossia, but the tongue was in an interdental position, vibratory and protrusion movements were also limited. The soft and hard palates were structurally normal, and dentition was complete, although there was irregularity in the form and organization of the teeth, as well as an altered bite.

Developmental assessment: The BATTELLE developmental inventory (Spanish version), designed to evaluate development in typical children (Newborg *et al.* 2009) served to assess her general development. The global score obtained by the girl corresponded to a developmental age of 32 months.

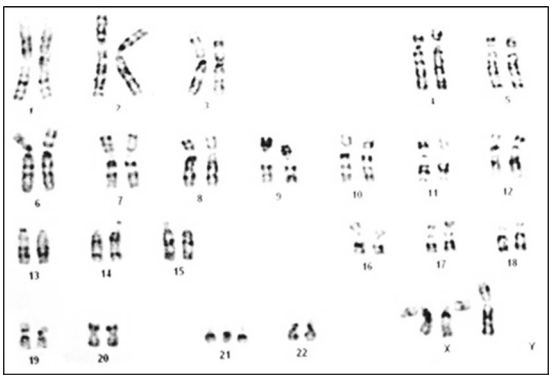
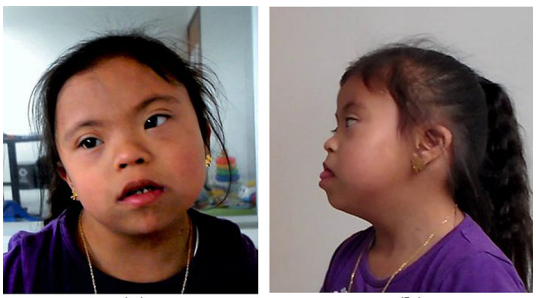


Figure 1. Peripheral blood karyotype of the girl: 48, XXX, +21.



(a) **(b)**

Figure 2. (a) Facial physical findings, frontal view. (b) Profile left side.

In the personal/social area, a direct score of 111 was achieved, which is equivalent to 35 months. Outstanding points in the test were her ability to recognize and greet familiar adults, ask for help when needed, establish a relationship with people, animals or objects, and participate in games. The child responded to her name, recognized herself in a mirror, and followed everyday life rules.

In the adaptive area, an equivalent result for an age of 40 months, was obtained. There is some degree of independence in feeding and dressing. Familiar environmental recognition, common danger avoidance and basic hygiene tasks were performed on her own.

In the motor area, a direct score of 87 was reached (gross 57 and fine 30), which is equivalent to a 28 month developmental age: 30 for gross-motor and 26 for fine-motor skills. The girl walked independently, ran without falling, went up and down stairs without assistance, but could not jump or catch a ball. In fine motor skills, the patient was in the scribbling phase, could turn pages and hold the paper, while drawing lines, and used her left hand preferentially.

In communication, a direct score of 16 was achieved, (receptive 12 and expressive 4), corresponding to an age of seven months: 15–16 months in receptive and three months in expressive. The girl presented arousal response and direction to the sound source, associate words with actions or objects and follow simple commands accompanied by gestures. In expressive language, had a limited repertoire of single words that were not always understandable (fewer than 10 words), used gestures to indicate her needs and knew some words in sign language.

In the cognitive area, 59 points were obtained, equivalent to an age of 46 months. She explored the environment, manipulated and showed object permanence with her behaviour. Recognized herself and identified familiar objects by their function, but did not have a concept of quantity, nor could handle basic operations.

Hearing assessment: An audiologist performed an evaluation using pure sounds in frequencies of 500–2000–4000 Hz through bone conduction and free field. An alerting response bone conduction at 20 dB in all frequencies and at 50 dB in all frequencies in free field, was found. According to these results, the severe language delay is probably due to her level of maturation rather than hearing loss.

Genetic study: A G-banding karyotype performed during the newborn period corroborated the double trisomy of chromosomes X and 21 (karyotype 48, XXX, +21) (figure 1).

Discussion

We described a girl with a double trisomy (XXX, + 21) with a down phenotype. This double trisomy is a rare condition described in isolated cases in the literature (Day *et al.* 1963; Park *et al.* 1995; Li *et al.* 2004; Balwan *et al.* 2008). Studies in a population with Down's syndrome, such as that of Flores-Ramirez *et al.* (2015) and Mandava *et al.* (2010), do not mention this specific type of chromosomal condition.

In cases described of double trisomy related to sex chromosomes (XXY or XXX) and chromosome 21 (Kovaleva and Mutton 2005), the phenotypic characteristics are primarily those of Down's syndrome (Iliopoulos *et al.* 2004; Balwan *et al.* 2008). Nevertheless, the association of Klinefelter syndrome and Down (48, XXY +21 karyotype) was reported more frequently than triple X syndrome and Down (48, XXX +21 karyotype) (Li *et al.* 2004; Kovaleva and Mutton 2005).

The survival rate of children with this double trisomy—48 XXX; +21—can be explained by the partial inactivation (around 85% of the genes), which is produced in the extra X chromosome, and the good prognosis of children with Down syndrome in the absence of heart disease (Otter *et al.* 2010).

The evaluation conducted at six years of age in our patient showed impairments in all the tests performed, and most of the responses were below three years in the majority of tested items. Personal/social, adaptive, communication, motor and cognitive abilities were severely limited. At present, verbal communication is so restricted that the child is receiving training for alternative communication through signs. The repertoire is still limited, but was able to communicate at home for basic activities.

As one of the X trisomy characteristics is a delayed development of speech and language skills, this poses a dilemma as to whether this situation is due to a more severe characteristic of Down syndrome, or to the fact that there is a combination of the two trisomies.

References

Balwan W. K., Kumar P., Raina T. R. and 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.

Day R. W., Wright S. W., Koons A. and Quigley M. 1963 XXX 21-trisomy and retinoblastoma. *Lancet* **2**, 154–155.

Diego-Alvarez D., Ramos-Corrales C., Garcia-Hoyos M., Bustamante-Aragones A., Cantalapiedra D., Diaz-Recasens J. *et al*. 2006 Double trisomy in spontaneous miscarriages: cytogenetic and molecular approach. *Hum. Reprod.* **21**, 958–966.

Flores-Ramirez F., Palacios-Guerrero C., Garcia-Delgado C., Morales-Jimenez A. B., Arias-Villegas C. M., Cervantes A. *et al*. 2015 Cytogenetic profile in 1,921 cases of trisomy 21 syndrome. *Arch. Med. Res.* **46**, 484–489.

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

Kovaleva N. V. and Mutton D. E. 2005 Epidemiology of double aneuploidies involving chromosome 21 and the sex chromosomes. *Am. J. Med. Genet. A.* **134a**, 24–32.

Li S., Hassed S., Mulvihill J. J., Nair A. K. and Hopcus D. J. 2004 Double trisomy. *Am. J. Med. Genet. A.* **124a**, 96–98.

Mandava S., Koppaka N., Bhatia V. and Das B. R. 2010 Cytogenetic analysis of 1572 cases of Down syndrome: a report of double aneuploidy and novel findings 47,XY, t(14;21)(q13;q22.3)mat,+21 and 45,XX,t(14;21) in an Indian population. *Genet. Test Mol. Biomarkers* **14**, 499–504.

Micale M., Insko J., Ebrahim S. A., Adeyinka A., Runke C. and Van Dyke D. L. 2010 Double trisomy revisited: a multicenter experience. *Prenat. Diagn.* **30**, 173–176.

Newborg J., Stock J. and Wnek L. 2009 *Battelle developmental inventory, Spanish Edition*, 3rd edition. TEA Editors, Madrid.

Otter M., Schrander-Stumpel C. T. and Curfs L. M. 2010 Triple X syndrome: a review of the literature. *Eur. J. Hum. Genet.* **18**, 265–271.

Park V. M., Bravo R. R. and Shulman L. P. 1995 Double non-disjunction in maternal meiosis II giving rise to a fetus with 48,XXX,+21. *J. Med. Genet.* **32**, 650–653.

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