RESEARCH NOTE

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

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Running title: Double trisomy.

Key words: Down syndrome, Triple X syndrome, double trisomy, developmental delay.

Research note

"Double trisomy (XXX+21 karyotype) in a six years old girl with Down phenotype"

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 (Balwan et al. 2008; Li et al. 2004; Park et al. 1995). 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 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.

The occurrence of double trisomy is due in most cases to a non-disjunctional error in maternal meiosis II and it usually leads to miscarriage, when this anomaly involves autosomes Diego-Alvarez et al. 2006; Park et al. 1995).

In regard to live births reported with double trisomy, one of the duplicated chromosomes was the sexual pair, and the other has been either 21 or18 and less frequently 7, 8 ,10, 15 and 16. (Kovaleva and Mutton 2005; Li et al. 2004; Micale et al. 2010).

Key words: Down syndrome, Triple X syndrome, double trisomy, developmental delay.

CASE HISTORY

We evaluated the neurological development in a six-year-old girl, daughter of a non-consanguineous couple without medical or family history of relevance. This case was selected from a database constructed in a previous study to evaluate Down 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 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 onward due to uterine bleeding and threat of miscarriage.

According to the mother report the ultrasound study suggested fetal Down 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 9 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 control was achieved at 5 years of age. In relation to language development, babbling appeared at eight months and first words at 18 months. Currently, her vocabulary is scant (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 age four, and since five years 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 schoolwork, 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 stablished 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). 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 (Photo 1- frontal view and Photo 2- Side view). Brachydactyly in both hands, single palmar crease, and bilateral clinodactyly of the fifth finger, was 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, Stock, and Wnek, 2009) served to assess her general developmental. The global score obtained by the girl corresponded to a developmental age of 32 months.

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 results 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 months of 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 7 months: 15-16 months in receptive and 3 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 behavior. 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 at 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 (XXXX, + 21), with a Down phenotype. This double trisomy is a rare condition described in isolated cases in the literature (Balwan et al. 2008; Day et al. 1963; Li et al. 2004; Park et al. 1995). Studies in a population with Down syndrome, such as that of Flores-Ramirez and Mandava, do not mention this specific type of chromosomal condition (Flores-Ramirez et al. 2015; Mandava et al. 2010).

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 syndrome (Balwan et al. 2008; Iliopoulos et al. 2004). Nevertheless, the association of Klinefelter syndrome and Down (48, XXY +21 karyotype) has been reported more frequently than triple X syndrome and Down (48, XXX +21 karyotype) (Kovaleva and Mutton 2005; Li et al. 2004).

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 6 years of age in our patient showed an impairment in all the tests performed, and most of the responses were below 3 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.

COMPETING INTERESTS, FUNDING.

The authors declare no conflict of interest.

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