v. 3, n. 5, 2023

International Journal of Biological and Natural Sciences

TRISOMY 21 AND PERICENTRIC INVERSION OF CHROMOSOME 9 AND THEIR ROLE IN EARLY FETAL LOSS

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Abstract: Pericentric Chromosome Inversionsthey result from a two-break event with a break in each arm, including the centromere (1).It is known that the inversion of chromosome 9 is frequently found in human karyotypes with structural chromosomal alterations (2); however, it is unusual to find it associated with another disorder such as trisomy 21 (numerical malformation), both evidenced in this case, which was obtained from a database of 5,000 amniocentesis reports performed at the Caracas Metropolitan Polyclinic center between the years 2005 and 2018, where the samples were centrifuged at 800 rpm according to the institution's protocol. This article seeks to highlight the relationship between these chromosomal abnormalities and recurrent fetal losses, as well as the importance of prenatal check-ups and early diagnosis of chromosomal abnormalities in order to mitigate the social impact linked to this type of genetic alterations; where the study of amniotic fluid becomes very important for this purpose.

Keywords: Inversion chromosome 9, trisomy 21, prenatal diagnosis, recurrent miscarriage, chromosome abnormalities.

INTRODUCTION

Chromosomal aberrations are as old as the existence of the genome itself, which is why it has been the subject of numerous studies highlighting the incidence of pericentric inversion of chromosome 9 in the general population between 1-3%; being more frequent in the Afro-descendant population with 3.57%, followed by Hispanics with 2.42%, whites with 0.73% and finally Asians with 0.26% (variable percentage depending on the study performed) (3). Given its relatively high incidence, it has been involved in a number of pathologies that are part of all specialties, including, although infrequently, genetic diseases such as Down syndrome, a genetic

malformation of the aneuploidy group, being the most frequent cause of mental retardation of genetic origin, also characterized by specific and well-defined phenotypic changes. The theory of the close relationship between inversion of chromosome 9 as a relevant risk factor for the development of trisomy 21 was promoted in an important way in the second half of the 20th century, but later on this theory lost strength thanks to studies such as the one carried out by Francisco Flores-Ramirez et al. where a sample of 1900 cases was reported in which one evidenced the coexistence of these two chromosomopathies (4). Therefore, the aim of this work is to highlight the role of cytogenetic prenatal diagnosis and thus promote early and timely counseling.

METHODOLOGY

The methodology used consisted of a sample of 5,000 amniotic fluids extracted by genetic amniocentesis, which were centrifuged at 800 rpm, discarding the supernatant, and then the cells were resuspended up to 3 milliliters of cell culture medium (CHANG Amnio, Irvine Scientific). 1.5 milliliters for each cell culture flask with a final volume of 4.5 millimeters and finally a G banding was carried out, analyzing 20 metaphases.

Of these 5,000 amniotic fluids, 417 women had recurrent fetal loss; Of those studied, only 1 case showed trisomy 21 associated with pericentric inversion of chromosome 9.

Subsequently, it was decided to carry out a search in the literature on the relationship of these chromosomal alterations with early fetal loss and the importance of prenatal diagnosis.

RESULTS

This is a karyotype study in amniotic fluid as indicated by the treating physician in 417 women with recurrent fetal loss, one of whom presented trisomy 21 as a chromosomal alteration associated with pericentric inversion of chromosome 9 (p12,q12) (Figure 1).

DISCUSSION

As previously mentioned, trisomy 21 is a chromosomal aberration first described by John Langdon Down in 1886; characterized by alterations such as generalized hypotonia, ligamentous laxity, brachycephaly, short neck, presence of epicanthus, small and flattened nose, macroglossia, small hands with short metacarpals and phalanges, single palmar groove, among others. In addition, the presence of congenital heart disease is common, as well as malformations of the gastrointestinal tract such as esophageal and duodenal atresia (5). Down syndrome is considered a chromosomopathy caused, generally, by maternal nondisjunction errors in the first division of meiosis in 90-95% of cases, to a lesser extent Robertsonian translocation (4%) and mosaicism (1). %) (6). On the other hand, there are chromosomal alterations of a structural type, such as the inversion of chromosome 9, considered one of the most common chromosomal anomalies within the balanced structural ones, which occurs when two breaks occur in a chromosome whose most common locations are inv(9) (p11q12) / inv(9) (p11q13) (1). The segment originating from these breaks is inverted and reinserted on the same chromosome. These genetic type alterations are considered relatively frequent individually, however the finding of these two malformations (numerical and structural) simultaneously is an unusual event and for which there is not enough literature to support it. However, it is worth noting the contradiction of ideas about the coexistence of these two anomalies; being initially defended in the 70s, by A. Serra et. al., who describe that there is an effect of the inversion of 9 on non-disjunction in the first division of meiosis (7), found predominantly in pregnant

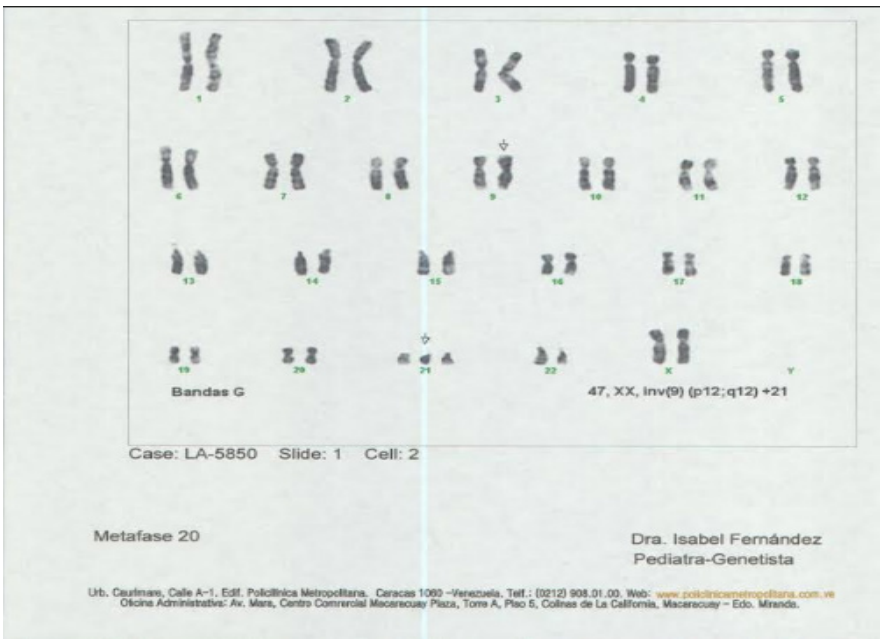

Figure N° 1. Karyotype 47, xy, inv (9) (p12;q12) + 21 of 1 amniotic fluid (metaphase 20).

women aged over 35 years (8), a theory that was refuted in the last years.

Additionally, a close relationship has been found between certain chromosomal alterations and recurrent fetal losses, mainly related to numerical chromosomopathies, up to 90%, in most cases caused by malformations of the group of aneuploidies and polyploidies, among which prevail trisomies and tetraploidies (9). In turn, a relationship has been found between recurrent spontaneous abortion and some structural chromosomal abnormalities such as chromosome 9 inversion, although it is worth mentioning that it has been observed in a lower proportion (8% of cases) compared to numerical chromosomal abnormalities (6). This situation makes it possible to establish a direct relationship between early fetal loss with the presence of both chromosomopathies (numeric and structural).

It should be noted that to obtain fetal cells there are different techniques such as amniocentesis, chorionic villus biopsy and cordocentesis, all of which are effective for the study and detection of chromosomopathies, obtaining this case using the first mentioned technique. The criteria for performing amniocentesis include advanced maternal age (>35 years), a previous child with a diagnosis of chromosomal disease, a parent with a balanced chromosomal aberration, suspicion of ultrasound signs of fetal chromosomal disease, among others (10). Due to the aforementioned throughout this writing, it is considered to highlight the importance of carrying out prenatal check-ups and cytogenetic prenatal diagnosis, taking into account the high incidence of recurrent early miscarriages associated with fetal chromosomal abnormalities (gestational age less than 24 weeks), thus generating an impact on improving detection in order to initiate early counseling and possible therapeutic interventions (11).

CONCLUSIONS

This case reinforces the idea that concomitant structural and number chromosomal abnormalities have a low incidence, as evidenced in the reviewed literature; however both increase the risk of recurrent early fetal loss. Since our sample is invalid to make statements in this regard, it is considered that more studies are needed to establish the relationship between the existence of pericentric inversion of chromosome 9 as a cause and/or association with trisomy 21, in addition to its impact on fertility. . Additionally, the importance of prenatal check-ups and cytogenetic prenatal diagnosis is emphasized to guide higher quality genetic counseling.

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