COMPLETE TRISOMY 9: CASE REPORT AND LITERATURE REVIEW

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INTRODUCTION

Trisomy 9 is a rare genetic alteration that represents 2.7% of all trisomies. (1,2,7) It was reported for the first time in 1973 by Feingold and Atkins, through the study of lymphocytes in the blood of a male newborn, with multiple congenital anomalies (4,5). Complete gain of chromosome 9 has a fatal prognosis and usually results in first trimester miscarriage. (2) However, in exceptional cases, pregnancies that reach term die in the early neonatal period (4).

From the cytogenetic point of view, cases of trisomy 9 present completely, which is not mosaicism, or in a state of mosaicism. The spectrum of this syndrome, in addition to trisomy 9, includes partial trisomies of the short arm 9p, of the long arm 9q, mosaicisms, mosaicisms confined to the placenta and pseudo mosaicisms. (4,5). In the case of trisomy 9, most correspond to de novo mutations. Mosaicisms are related to balanced rearrangement mutations (5). However, phenotypic heterogeneity, as well as the incidence and severity of associated malformations, are directly related to the variable size of the duplicated segment and the frequent concomitant monosomy (2,3,4,6).

Most of the cases of trisomy 9 reported in the literature occurred in women under 35 years of age, which makes evident the usefulness of screening for congenital anomalies, even in low-risk populations (1,2). Fetal screening in the first and second trimesters allows early detection of fetal structural abnormalities associated with genetic alterations. In this way, it offers the opportunity to advise the patient, with the aim of carrying out early interventions regarding the prenatal prognosis and postnatal management, even if it is available and for this specific case, the interruption of the pregnancy. (1)(6).

This chromosomal abnormality is characterized by a constellation of multiple phenotypic abnormalities that mainly involve craniofacial, central nervous system, cardiovascular, musculoskeletal, and genitourinary abnormalities (1,4,5,7). The main structural anatomical alterations include, for ultrasound screening at 11-13.6 weeks, an increase in the thickness of nuchal translucency (1), then microcephaly and brachycephaly become evident, fontanelles and wide cranial sutures, bulbous nose, lip and cleft palate, short nasolabial fold , hypertelorism, micro-retrognathia, short and wide neck and low implantation of the ears. In the central nervous system, it is common to find associated Dandy Walker Malformation characterized by hydrocephalus, alterations in the development of the cerebellar vermis and ventriculomegaly (4,2). At the cardiovascular level, it is common to find ventricular septal defects, cardiomegaly, valvular dysplasia or even the right aortic arch. Regarding the musculoskeletal system, camptodactyly, clubfoot , hypoplasia or agenesis of the fingers

and nails of the hands and feet (4), and dislocation of the hip or knees can be found. In genitourinary organs, horseshoe kidney, renal hypoplasia or dysplasia as well as renal cysts, short penis or bicornuate uterus become evident . Other case reports include abnormal lung lobulation, malrotation, hypoplasia or agenesis of the gallbladder and biliary tract, and hypoplasia of the adrenal gland. In addition, this pathology incorporates within its recognition pattern growth restriction, low birth weight and delayed neurological development. (2,7) Other authors mention that, when faced with elevated serum levels of alpha-fetoprotein in the context of trisomy 9, the finding of spina bifida should be ruled out (1). Serum markers such as the free fraction of BhCG and PAPP-A are found to be decreased in concentration in trisomies 9 and 18. In addition, different abnormal phenotypic findings overlap in both chromosomopathies; however, the genetic study can discern the final diagnosis (1,4).

CASE REPORT

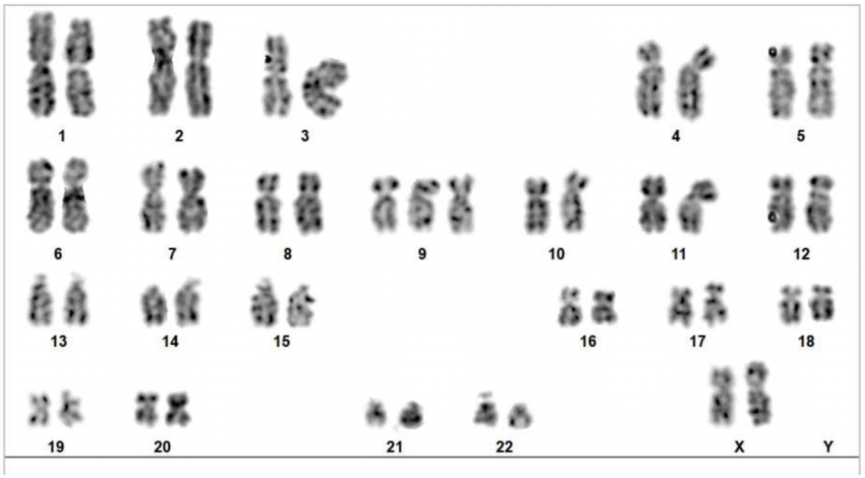
A 42-year-old patient in her fourth pregnancy, with no particular personal, obstetric, or family history, with a single pregnancy of 25 weeks and 5 days, presented to the high-risk obstetric consultation, in the maternal-fetal medicine department of the Colombia University Clinic in Bogotá, Colombia, conceived spontaneously, with an anatomical detail ultrasound report taken at 23 weeks of pregnancy documenting mild bilateral ventriculomegaly, colpocephaly , and abnormal cisterna magna, suggesting an arachnoid cyst in the posterior fossa; in addition, the evaluation of the facial profile presents micrognathia. Other anomalies include altered echogenicity of the liver parenchyma and a fetus with abnormal growth curve, with altered fetoplacental circulation parameters, for stage I intrauterine growth restriction (IUGR). However, with gestational age greater than 14 weeks it was not possible to calculate the risk of aneuploidy. Neither were abnormalities identified in the early obstetric ultrasound performed at that time.

In the high-risk obstetric consultation, she was referred to the medical board of congenital anomalies and defects to corroborate the diagnosis and define the management plan; including invasive genetic study, neurosonography and fetal echocardiography, previous advice and authorization from the patient.

Amniocentesis was performed for the study by Fluorescence in Situ Hybridization (FISH), Karyotype and Microarray at 27 weeks; then echocardiography and fetal neurosonography are performed at 28 weeks. Fetal neurosonography presents parameters for biparietal diameter, occipitofrontal diameter and head circumference in percentile less than 1, resulting in microcephaly diagnosis, with moderate ventriculomegaly and colpocephaly, cerebellar hypoplasia and agenesis of the corpus callosum. Evaluation of the midface profile shows micrognathia and fetal echocardiography shows cardiomegaly, but with a structurally and functionally normal heart. Pachygyria and lissencephaly were observed at 30 weeks of pregnancy as a result of altered neuronal migration patterns, which were corroborated later by fetal brain magnetic resonance. In addition, the echocardiographic assessment showed loss of valvular offset with an incomplete atrioventricular canal, due to ventricular septal defect. The fetal growth profile remains at a growth percentile of less than 1, with an altered hemodynamic pattern for stage I IUGR.

The result of the genetic study by amniocentesis reported a FISH with two signals for X, no signal for chromosome Y, two signals for chromosomes 13, 18 and 21, resulting in a male fetus without numerical alteration in chromosomes 13, 18 and 21. Karyotype did not present cell growth for obtaining metaphases and their subsequent analysis. However, the microarray comparative genomic hybridization (aCGH) study was positive for two pathogenic variants with a gain at the 9p24.3p13.1 loci and another gain at the 9q21.11q34.3 loci, confirming a complete gain of chromosome 9 for a trisomy 9. (Figure 1)

Figure 1: Results of the comparative genomic hybridization study by microarrays (aCGH)



Resultados de la Célula:

Karyotyped: 47,XX,+9

Nivel de Resolución:

Estimated Band Resolution:350

Lámina N°: 1 - 1/3

At the consultation, within the department of maternal-fetal medicine, counseling on the diagnosis and implication on the prognosis and complications of pregnancy was carried out. After a week of reconciling with her partner, the decision was made to terminate the pregnancy at 35 weeks, accepted by Colombian regulations in sentence C 355 of 2006 for cause II given the structural anomalies and fetal genetic alteration incompatible with life. The patient did not agree to the autopsy of the fetus, therefore the phenotypic characteristics at birth are unknown.

MATERIALS AND METHODS

The literature search was carried out in the PUBMED database with the MeSH terms ((" Chromosome 9, trisomy " [Supplementary Concept]) AND "Prenatal Diagnosis" [Mesh]) AND " Ultrasonography , Prenatal" [Majr]; a publication year filter was not applied. The result yielded a total of 23 articles, of which 5 were selected by title, two were discarded due to abstract , and 1 eliminated due to content. Finally, 3 were selected for review. In addition, five articles on the trisomy 9 spectrum were included. All these were added due to their relevance in the description of this case.

DISCUSSION

Trisomy 9 is considered as a rare chromosomal abnormality, frequently associated with spontaneous pregnancy loss in the first trimester of pregnancy (2). The first reported case of trisomy 9 was in 1973 by Feingold and Atkins in a male neonate who died in the neonatal period (2). Since then, it is not frequent to find new publications on the appearance of this phenomenon. However, the literature offers a greater number of cases on mosaicisms of this trisomy.

Tonni et al., in 2014 reported two cases of trisomy 9. The first referred to a 37-year-old primigravida with a 12-week pregnancy, high obstetric risk due to intermediate risk of aneuploidies. An anatomical detail ultrasound was performed at 20 weeks, documenting a general decrease in growth patterns, diagnosed as intrauterine growth restriction, as well as an elevated tentorium and a hypoplastic cerebellar vermis, a wide cleft between the cerebellar hemispheres, and direct communication between the cerebellar hemispheres. the fourth ventricle and the cisterna magna, findings that were associated with Dandy Walker malformation. Other relevant defects included cleft lip and palate, VSD heart disease and right aortic arch, hyperechogenic and multicystic kidneys suggesting dysplastic kidney disease. Given multiple congenital anomalies, the mother underwent a cytogenetic study by amniocentesis. The result of the karyotype showed a complete trisomy 9, in a male fetus. Finally, the pregnancy was terminated at 22 weeks. The other reported case, a 28-year-old multiparous woman, was diagnosed during pregnancy with Dandy Walker malformation, cleft lip, palate, and cardiac and renal anomalies; the amniotic fluid karyotype concluded a female fetus with complete gain of chromosome 9. This last case was also interrupted at week 23. (2)

Prenatal ultrasound was one of the main screening tools to reach the diagnosis of aneuploidies (5). Bencaerraf and Alabama reported for the first time clenched hands in their case of trisomy 9 in a 31 week pregnancy, in addition to rigid extension to the metacarpal joints, but with contraction in the proximal and distal phalanges, and abnormal angulations in the hands and feet (4). Mine Yeo and researchers report the most frequent ultrasound findings associated with trisomy 9 and mosaicism cases, as well as a review of the literature on these phenomena. Like Sepúlveda, they conclude that phenotypic heterogeneity is the product of the variability of the duplicated segment and the frequent concomitant monosomy (4)(5)(3). It is worth mentioning that there are important similarities in the ultrasound findings between trisomy 9 and trisomy 18, however, the differential diagnosis can be discerned with a genetic examination. (4)

The complete gain of chromosome 9 encompasses a constellation of phenotypic abnormalities such as increased Nuchal Translucency, craniofacial dimorphisms, heart disease, and skeletal defects such as spina bifida (1,5). Although it does not seem to be directly related to age, it is common in women under 35 years of age (2). Early ultrasound is one of the main tools for aneuploidy screening, since abnormal findings should be subjected to a cytogenetic study (5). However, genetic studies such as PCR on DNA extracted from amniotic fluid or chorionic villus cells are considered accurate for the diagnosis of specific aneuploidies, but do not detect mosaicism or microarray spectra (5)(6). Therefore, in patients with markers and suspicion of aneuploidies, it is opportune to take a complete karyotype and microarrays in conjunction with FISH technology, which demonstrate translocations or minor deletions. This is important to submit for prenatal counseling and inform the prognosis of the pregnancy (1) (3).

In case of diagnosing complete trisomy of chromosome 9, it is possible to offer the termination of the pregnancy, since this condition is incompatible with life. On the other hand, counseling in cases of trisomy 9 mosaicism is more difficult, since the development and prognosis is uncertain, and will depend on the degree

of genetic penetrance of the genetic disease (5). The evaluation of these pregnancies must be interdisciplinary and include timely genetic counseling, together with therapeutic options available early, since it is directly related to the cost of public health that generates the disability of the disease, specifically in matters of special education, rehabilitation , not to mention the social and labor gap. (6)

CONCLUSIONS

Trisomy 9 is a rare chromosomal disorder that is incompatible with life. Frequently, pregnancies with complete gain of chromosome 9 end in an abortion in the first trimester. However, those that reach term die at birth or in the early postnatal life. Currently, the diagnosis is carried out by the cytogenetic study, in pregnancies with a high risk of presenting aneuploidies when finding different structural anomalies, in the ultrasound screening between 11 and 14 weeks, or in anatomical detail ultrasound between 20 and 24 weeks. It is essential that a multidisciplinary team that includes the prenatal control group includes a general physician, gynecologist and obstetrician, a doctor specializing in maternal-fetal medicine, and mental health specialist, offering both the mother and the couple post-diagnosis genetic counseling of the disease, with the aim of knowing the therapeutic options available early. Finally, the actions aimed at the early diagnosis and management of genetic anomalies during pregnancy have a direct impact on the quality of life of the family nucleus, and on the reduction of public health costs.

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Image 1: Results of the comparative genomic hybridization study by microarrays (aCGH)