CASE REPORT

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Declaration of ethical aspects

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Prenatal diagnosis of Pallister-Killian syndrome

Diagnóstico prenatal de síndrome de Pallister-Killian

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ABSTRACT

Pallister-Killian syndrome is a rare and sporadic disorder characterized by the presence of an extra 12p isochromosome in some body tissues. Its prenatal diagnosis is complex due to the absence of distinctive or pathognomonic ultrasonographic features, making it difficult to identify some malformations during the prenatal period. Among the most common prenatal findings are congenital diaphragmatic hernia, polyhydramnios, and rhizomelic limb shortening. Genetic diagnosis is also made difficult by the tissue mosaicism associated with this syndrome and the diminution of the abnormal isochromosome-bearing clone. Amniocentesis is considered the most appropriate procedure for genetic diagnosis since most of the cells in the amniotic fluid are epithelial cells shed from the fetal skin. A case of prenatal diagnosis of Pallister-Killian syndrome is presented.

Key words: Pallister-Killian syndrome, Genetic diseases, Prenatal diagnosis

RESUMEN

El síndrome de Pallister-Killian (SPK) es un trastorno poco común y esporádico que se caracteriza por la presencia de un isocromosoma 12p adicional en algunos tejidos del cuerpo. Su diagnóstico prenatal es complejo debido a la ausencia de características ecográficas distintivas o patognomónicas, lo que dificulta la identificación de algunas malformaciones durante el período prenatal. Entre los hallazgos prenatales más comunes se encuentran la hernia diafragmática congénita, el polihidramnios y el acortamiento rizomélico de las extremidades. El diagnóstico genético también se dificulta por el mosaicismo tisular asociado a este síndrome y la disminución del clon anómalo portador del isocromosoma. La amniocentesis se considera el procedimiento más adecuado para el diagnóstico genético, ya que la mayoría de las células en el líquido amniótico son células epiteliales desprendidas de la piel fetal. Se presenta un caso de diagnóstico prenatal del síndrome de Pallister-Killian.

Palabras clave. Síndrome de Pallister-Killian, Enfermedades genéticas, Diagnóstico prenatal

Introducción

Pallister-Killian syndrome (PKS), also known as tetraploid 12p syndrome or isobrachial chromatid 12p syndrome, is a rare genetic disorder. It is caused by the mosaic presence of an additional 12p isochromosome, the pathophysiological mechanisms of which are not yet fully understood. Consequently, four copies of the short arm of chromosome 12 are present in affected cells[(1)].

Prenatal diagnosis of PKS is challenging due to the absence of distinctive or pathognomonic ultrasound findings. Clinical manifestations can vary and present during the prenatal period with various congenital malformations and sonographic abnormalities. Among the most common manifestations are polyhydramnios, diaphragmatic hernia and rhizomelic limb shortening[(2)]. Genetic diagnosis also presents difficulties due to the variability of mosaicism and the rapid decrease of the supernumerary marker isochromosome during amniocyte subculture[(3)]. A case of prenatal diagnosis of Pallister-Killian syndrome is presented.

Case report

This was a 26-year-old patient, gestation III, para I, abortion I, who was referred to the high-risk prenatal consultation for presenting facial anomalies, nasal morphological alterations and suspicion of polyhydramnios in the ultrasound at 18 weeks. The patient denied any significant family or personal history, had no family history of congenital malformations and no consanguineous ties to her partner. The combined results of the first trimester screening tests, which included fetal trisomies 21, 13 and 18, indicated a low risk. Ultrasound evaluation at 9 and 12 weeks revealed no evidence of fetal alterations.

Ultrasound evaluation at the high-risk consultation revealed a fetus with a gestational age of 19 weeks. Flat facial profile with hypoplasia of the nasal bones, broad-flat nose and lateral ventriculomegaly (9-millimeter anterior horn of the ventricles) were the main findings. The stomach and intestines were in the thoracic cavity, displacing the fetal heart (Figure 1). Both femur and fetal humerus length were below the 5th percentile and head and abdominal circumference were at the 80th and 95th percentile, respectively, indicating asymmetric fetal growth. Body movements and cardiac activity were observed, although the latter appeared abnormal. The estimated fetal weight was 400 grams, and the amniotic fluid volume was increased (amniotic fluid index 25) for gestational age. Doppler evaluation of the maternal uterine, umbilical and fetal middle cerebral arteries was within normal limits.

The patient consented to ultrasound-guided amniocentesis, and genetic analysis showed a 47,XY karyotype with tetrasomy 12p (isochromosome 12p) in mosaic, confirming the diagnosis of PKS (Figure 2). The 12p isochromosome was found in 86% (26/30) of the cells, according to FISH analysis. The parents were informed of the possible relationship between these and other sonographic findings, with a severe clinical phenotype, such as mental retardation.

Due to the absence of cardiac activity in the ultrasound performed at 24 weeks, it was decided to perform cervical ripening with misoprostol with subsequent uterine curettage. The ultrasound findings were confirmed. The anatomopathological study of the stillborn revealed low-set ears, broad and flat nose, prominent forehead on the hands and short upper and lower limbs (Figure 3). Genetic analysis of the fetus resulted in 47,XY-,+i(12)(pIO).

Discussion

KPS is a rare and sporadic genetic disease, with an estimated incidence of 5.1 cases per million live births. It is caused by the mosaic presence of an additional 12p isochromosome (12p mosaic tetrasomy)[4,5]. To date, about 60 cases have been described in the literature.

Figure 1. Ultrasound images of Pallister-Killian syndrome anomalies. A) Fetal profile showing flat face with flat nose and nasal bone hypoplasia. B) Stomach and intestine in thoracic cavity displacing the fetal heart.

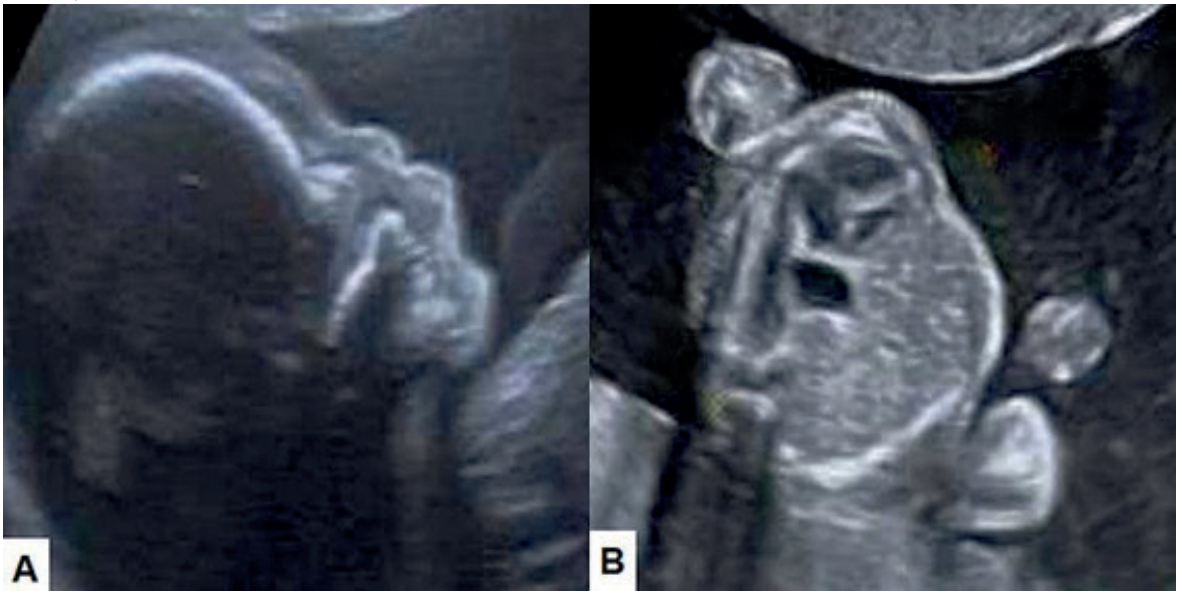


Figure 2. Karyotype 47,XY. The arrow indicates tetrasomy 12p (isochromosome 12p).

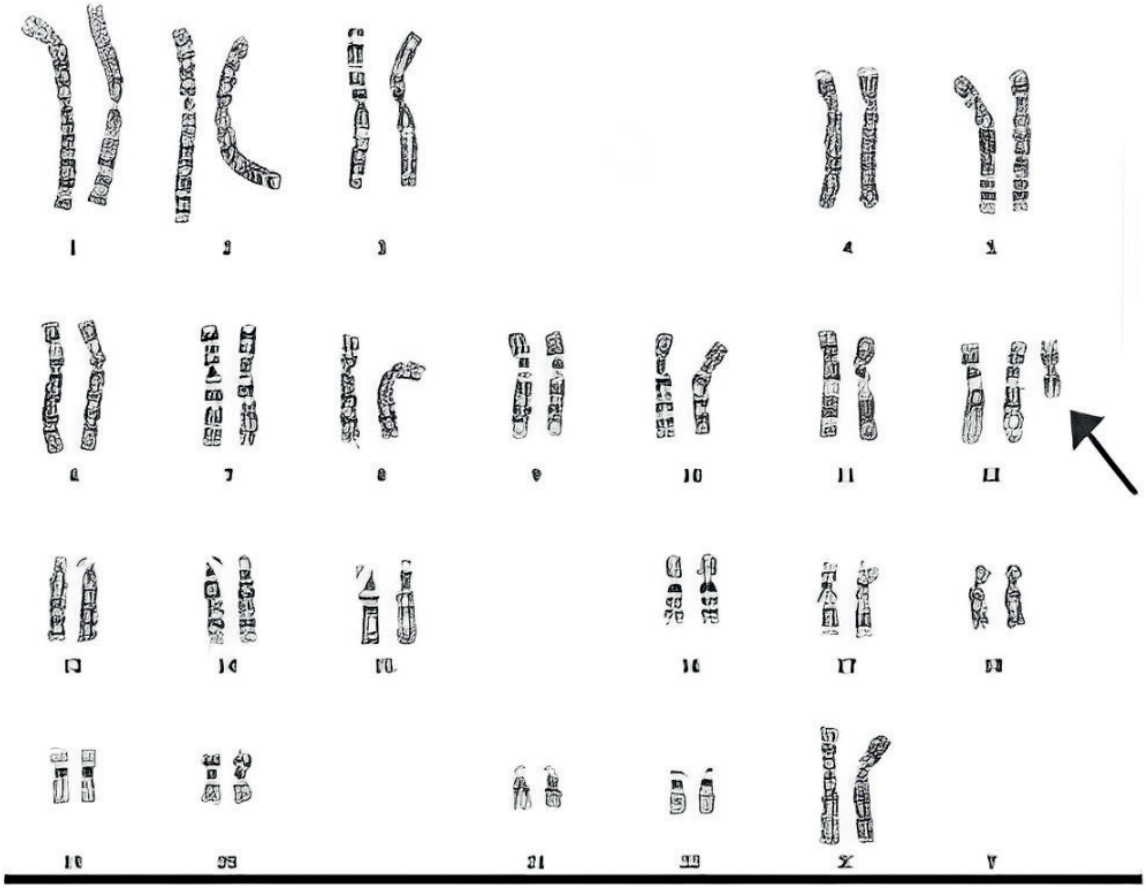
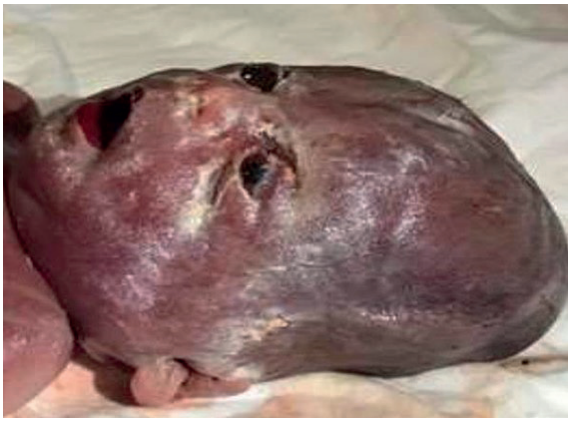


Figure 3. Pathologic image of the stillborn showing broad, flat nose, flat face, low-set ears, and prominent forehead.



The exact mechanism of 12p isochromosome generation is still unknown. Several theories have been proposed, most of which suggest that the lack of disjunction during maternal meiosis II produces a disomic gamete that subsequently gives rise to isochromosomes from chromosome 12. This mechanism of mosaic tetrasomy is similar to the effect of maternal age in pregnancies with aneuploidies[6,7]. Among the 26 potential genes that could be involved in PKS, ING4 and CHD4 are crucial for cellular transcription, chromatin reorganization, and cell cycle metabolism. However, there is no clear evidence of a relationship between genotype and phenotype of the syndrome, especially during the prenatal period[8]. In most of the reported cases, advanced maternal age (older than 35 years) has been identified as a risk factor[9].

Due to the wide range of anomalies associated with PKS, polyhydramnios (37% of cases), congenital diaphragmatic hernia (27%) and micromelia of predominantly rhizomelic type (34%) are three frequent ultrasound indicators that can guide the diagnosis of the syndrome[4,9-11]. Biparietal diameter and abdominal circumference measurements are usually above the mean in most cases, while fetal femur and humerus growth are usually below the normal percentiles for gestational age[3].

These findings may be absent in some cases of PKS, and the diagnosis should be suspected because of fetal craniofacial features including flat face, small nose with anteverted nostrils, and protruding lower lip. Hypertelorism, low-set ears, short neck and flat occiput are some of the additional anomalies. Increased nuchal translucency or edema, hydrops fetalis, fetal overgrowth, cardiovascular and central nervous system anomalies, omphalocele, hydronephrosis, small or absent gastric bubble, hyperechogenic bowel, ambiguous genitalia, and single umbilical artery are less common sonographic anomalies[12].

The typical fetal craniofacial features of PKS may be helpful in differentiating it from Fryns syndrome. These syndromes have several similarities, such as congenital diaphragmatic hernia, distal limb hypoplasia and polyhydramnios[4,10].

Currently, nuchal translucency and maternal serum biochemistry are widely used to detect chromosomal abnormalities in the first trimester of pregnancy, with the aim of increasing the likelihood of earlier diagnosis of these abnormalities. However, PKS is an example of a chromosomal disorder that may be missed during this type of screening[13].

Although possible, prenatal genetic diagnosis of PKS presents challenges. For cytogenetic diagnosis, chorionic villus sampling, amniotic fluid, or fetal blood can be obtained[4,9]. Amniocentesis is the most effective method, with detection rates of the 12p isochromosome ranging from 78% to 95%. Most of the cells in the amniotic fluid are epithelial cells shed from the skin of the fetus. Although isochromosome 12p is frequently found in fibroblast cultures, it is rarely detected in blood lymphocytes. Cytogenetic differences have been observed between placental and fetal tissues[2]. This variability could be due to a selective proliferative advantage of normal diploid cells over tetrasomal cells during embryogenesis, although tissue-dependent mechanisms have also been proposed. It has been shown that the 12p isochromosome is lost with patient aging in bone marrow, fibroblasts and lymphocytes. On the other hand, after successive trypsinization of cultured cells, a progressive decrease of the isochromosome 12p-bearing clone has been observed, independently of the tissue[14].

Genetic counseling for PKS is straightforward because it is generally considered a severe disease. Although some fetuses with severe structural anomalies such as severe diaphragmatic hernia, hydrocephalus, and hydrops fetalis may die during pregnancy or shortly after birth, survival and prognosis vary considerably among individuals[4,9,10]. Mental retardation, seizures, epilepsy, pigmented skin lesions, and brachydactyly are frequent manifestations in the postnatal period. Some individuals with mild to moderate intellectual disability can attend school, while others have profound intellectual disability and sensory deficits. Familial recurrence is rare but cannot be completely ruled out[15].

In conclusion, PKS is a nonhereditary genetic disease caused by the presence of an additional isochromosome of the short arm of chromosome 12. Prenatal ultrasound diagnosis is complex due to the wide variability of the anomalies present. The most common sonographic findings include polyhydramnios, congenital diaphragmatic hernia, and rhizomelic micromelia. Prenatal genetic diagnosis also presents challenges due to variability in the detection of the 12p isochromosome in fetal tissues. For proper prenatal ultrasound diagnosis, knowledge and recognition of this syndrome is crucial.

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