Kabuki Syndrome Diagnosed in utero: Clinical Case Reported in Santander, Colombia

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Abstract

Kabuki syndrome (KS) is a rare genetic disorder caused by mutations in the KMT2D or KDM6A genes, affecting development and leading to multiple malformations. Diagnosis is usually postnatal, although prenatal detection through ultrasound and genetic testing can be key. A case was presented in Santander, Colombia, where a male fetus exhibited anomalies on ultrasound, including cleft lip and palate, complex heart disease, and skeletal malformations. Due to the suspicion of KS, a chromosomal microarray was performed, confirming a mutation in KDM6A. The postnatal diagnosis corroborated the phenotypic characteristics of the syndrome. This case highlights the importance of prenatal ultrasound in detecting suggestive signs of KS and guiding confirmatory genetic studies. It is the first reported case with KDM6A in the region, expanding knowledge about KS in Latin America. Early identification enables optimized neonatal management and improved prognosis.

Keywords: kabuki syndrome, KMT2D, KDM6A, prenatal ultrasound, UTX gen, MLL2 gen.

RESUMEN

El síndrome de Kabuki (SK) es una enfermedad genética rara causada por mutaciones en genes KMT2D o KDM6A, afectando el desarrollo y provocando múltiples malformaciones. Su diagnóstico suele ser postnatal, aunque la detección prenatal mediante ecografía y pruebas genéticas puede ser clave. Se presentó un caso en Santander, Colombia, donde un feto masculino mostró anomalías en la ecografía, como fisura labio-palatina, cardiopatía compleja y malformaciones óseas. Ante la sospecha de SK, se realizó un microarray cromosómico que confirmó una mutación en KDM6A. El diagnóstico postnatal corroboró las características fenotípicas del síndrome. El caso resalta la importancia del ultrasonido prenatal para detectar signos sugestivos de SK y dirigir estudios genéticos confirmatorios. Es el primer caso reportado con KDM6A en la región, ampliando el conocimiento sobre SK en América Latina. La identificación temprana permite optimizar el manejo neonatal y mejorar el pronóstico.

Palabras clave: Sindrome de kabuki, KMT2D, KDM6A, ultrasonido prenatal, gen UTX, gen MLL2.

Introduction

Kabuki syndrome (KS), also known as Kabuki makeup syndrome and Niikawa-Kuroki syndrome, is a rare hereditary genetic disorder first diagnosed in Japan in 1980. It is caused by mutations in the lysine 4 methyltransferase H3 (KMT2D) gene or a histone H3 lysine 27 demethylase linked to the X chromosome (KDM6A)[1].

The KMT2D mutation affects normal growth and development by disrupting histone methylation associated with gene expression. This mutated gene was the first pathogenic gene recognized in Kabuki syndrome, also known as MLL2. Identified in 2010 (KMT2D), this is the most common genetic mutation in KS patients, found in 75% of cases[2]. In contrast, 5% of cases are attributed to variants in Lysine (K)-specific demethylase 6A (KDM6A), also known as UTX, which follows an X-linked dominant inheritance pattern. The etiology of the remaining 20% of cases remains unknown[2].

KS occurs in approximately 1 in 32,000 to 1 in 86,000 live births1. More than 400 cases have been described worldwide; in Latin America, published cases have increased significantly in recent years[4], and in Santander, Colombia, two confirmed clinical cases have been reported[5].

There are proposed diagnostic criteria defined by an expert panel, which establishes the diagnosis in patients of any age with a history of infantile hypotonia, developmental delay, or intellectual disability, and one or both of the following main criteria[4]: A pathogenic or likely pathogenic variant in KMT2D or KDM6A. Typical dysmorphic features at any point in life, including long palpebral fissures (equal to or greater than two standard deviations above the mean for age) with eversion of the lateral third of the lower eyelid, and at least two of the following: Arched and broad eyebrows with lateral notching or sparseness.
Short columella with a depressed nasal tip. Large, prominent, or cupped ears. Fleshy finger pads[3].

Additionally, other cardiac malformations, structural anomalies such as auricular pits, cleft lip and palate, anal atresia, hiatal hernia, and skeletal malformations including syndactyly and clinodactyly have been identified. Functional differences may include hearing loss, feeding problems, endocrinological abnormalities such as isolated premature thelarche in females, increased susceptibility to infections, autoimmune disorders, and seizures[1].

The diagnosis is usually confirmed postnatally; however, in the prenatal setting, congenital anomalies related to KS can be detected through routine prenatal ultrasound supplemented with available genetic testing[5].

The literature demonstrates the clear diagnostic power of ultrasound in fetuses to establish a diagnostic impression based on the studied fetus's phenotype[7]. Cases have been reported in which characteristic phenotypic abnormalities of KS can be identified, such as facial, skeletal, and cardiac anomalies[8], intrauterine growth restriction, polyhydramnios, and oligohydramnios, among others[6]. Reviews indicate that in more than half of the population, the diagnosis is made postnatally, highlighting the challenge of prenatal diagnosis. Molecular testing can confirm the diagnosis, which can then be corroborated after birth through phenotypic characteristics.

CLINICAL CASE

In Floridablanca, Santander, Colombia, a 20-year-old G1P0 patient began prenatal care at 6 weeks of gestation. The first genetic screening ultrasound was performed at 13.2 weeks, estimating a fetal weight of 98 grams, with a viable fetus growing at the 69.9% percentile and a low risk of chromosomal abnormalities.

Throughout the first, second, and third trimester prenatal check-ups, the TORCH infectious profile was negative, blood type A positive, and thyroid profile normal. A second detailed ultrasound was conducted on July 2, 2024, reporting a pregnancy of 20.4 weeks by biometry, with an estimated fetal weight of 368 grams, growing at the 38th percentile, amniotic fluid index of 12.2 cc, and anatomical findings of: cleft lip involving the lip and palate, levocardia with a 83-degree angle, severe right radial atresia with hand deviation, and only three identifiable fingers. Due to these findings, an amniocentesis was requested for genetic analysis.

A follow-up ultrasound was scheduled for August 9, 2024, revealing normal fetal growth, estimated fetal weight of 945 grams (60% percentile), amniotic fluid index of 22 cc, cleft lip and palate *(Picture 1),* complex congenital heart defect: truncus arteriosus type B, diaphragmatic hernia with absence of gastric chamber, right upper limb radial agenesis *(Picture 3),* and upper limb micromelia *(Picture 2)*. Given these findings, a neurosonography was performed on August 15, 2024, revealing: normal skull, face, and spinal column in the midline, normal-shaped and structured septum pellucidum and corpus callosum, symmetrical lateral ventricles (right: 7.8

mm, left: 6.9 mm), and normal-appearing choroid plexuses. The optic chiasm, cortical convolutions, and median eminence could not be evaluated.

The patient was evaluated by the perinatology team, who reviewed the genetic analysis results, which indicated: normal male fetal karyotype. Additionally, chromosomal microarray (CMA) analysis revealed a microdeletion at the Xp11.3 region associated with a mutation in the Lysine (K)-specific demethylase 6A (KDM6A) gene.

Subsequently, the patient underwent another transabdominal obstetric ultrasound performed by perinatology on October 19, 2024. The pregnancy was dated at 36.1 weeks by last menstrual period; however, biometry suggested 38.4 weeks, with an estimated fetal weight of 3,339 grams (91% percentile), an amniotic fluid index of 25 cc, normal Doppler evaluation of the uterine arteries, and normal hemodynamic profile. The fetus presented multiple malformations, including cleft lip and palate, complex congenital heart defect (truncus arteriosus), diaphragmatic hernia with absence of gastric chamber, right upper limb radial agenesis, syndactyly, and upper limb micromelia.

The patient was referred to an institution with pediatric cardiology services and pediatric cardiovascular surgery specialists in Santander. The mother states that surgical interventions were performed after birth and that her son has multiple disabilities. The mother reports that the physicians at the clinic where the cesarean section was performed confirmed phenotypic findings related to Kabuki syndrome. The mother also sent photographic records confirming the findings related to Kabuki syndrome; however, she states that she does not wish the photos to be published. These photos show long palpebral fissures, fleshy pads of the fingers and ear fossae, along with the skeletal diagnosis related to radial agenesis and finger abnormalities such as syndactyly.

DISCUSSION

Kabuki syndrome is characterized by variable phenotypic findings associated with a mutated genotype in one of two identified genes: lysine 4 methyltransferase H3 (KMT2D) or histone H3 lysine 27 demethylase linked to the X chromosome (KDM6A). In this clinical case, genetic diagnosis was achieved through karyotype FISH + chromosomal microarray (CMA), confirming the KDM6A mutation, which accounts for only 5% of KS cases[2].

KS malformations include facial, cardiac, skeletal, and gastrointestinal anomalies. In this case, some diagnostic characteristics were identified prenatally via ultrasound, including facial (cleft lip and palate), skeletal (radial agenesis, syndactyly, micromelia), and cardiac (common arterial trunk type B with perimembranous VSD) anomalies. Additional findings included polyhydramnios and fetal macrosomia.

Prenatal KS diagnostic suspicions were confirmed postnatally based on phenotypic characteristics. When the infant was born via cesarean section, pediatric cardiology evaluation confirmed KS-specific facial malformations, including long palpebral fissures, fleshy finger pads, and auricular pits, alongside the prenatally diagnosed skeletal and cardiac abnormalities.

CONCLUSION

I want to highlight the importance of ultrasound, as the timely diagnosis of phenotypic malformations associated with a particular syndrome can enable the examiner to develop a diagnostic suspicion and suggest confirmatory diagnostic tests, as was the case here. Additionally, it allows for the option of pregnancy termination if the mother so desires. In the above clinical case, the identification of phenotypic anomalies raised a diagnostic suspicion that led the examiner to request genetic testing, which confirmed their suspicion. Furthermore, the literature demonstrates that obstetric ultrasound can identify phenotypic characteristics that are sensitive for the diagnostic impression of Kabuki syndrome.

In this case, the confirmation of Kabuki syndrome (KS) was achieved through chromosomal microarray (CMA) analysis, which identified a microdeletion in the KDM6A gene. This finding is significant because mutations in KDM6A account for only 5% of KS cases, with the majority being caused by mutations in KMT2D.

The relevance of this case in Latin America and Colombia is notable, as the number of reported KS cases has been increasing but remains a rare condition. In Santander, Colombia, only two previous cases with KMT2D mutations had been recorded, making this the first documented case with a KDM6A mutation, bringing the total number of cases in the region to three.

The value of early diagnosis is crucial, as prenatal detection allows for proper medical management planning at birth, involving specialists in pediatric cardiology and genetics. This underscores the importance of combining ultrasound findings with genetic studies to improve diagnostic accuracy and patient prognosis.

The challenges in prenatal diagnosis are significant. Although diagnosing KS prenatally remains difficult due to the variability of its manifestations, this case highlights the crucial role of ultrasound and genetic testing in its early detection. Postnatal confirmation with typical phenotypic characteristics of the syndrome further reinforces the reliability of the prenatal diagnosis in this case.

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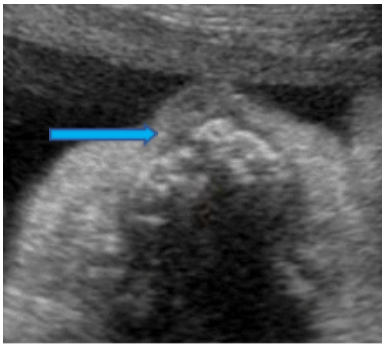
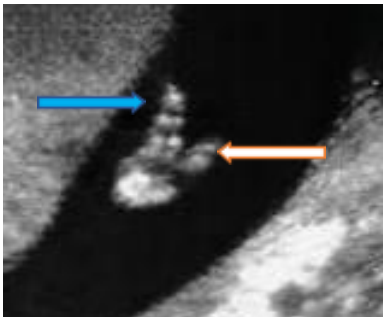
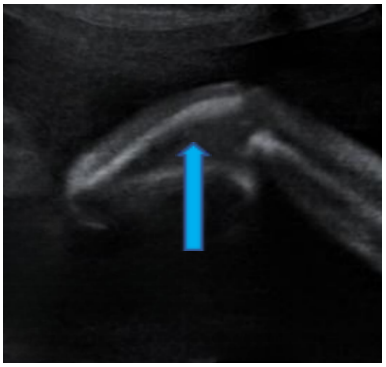
ATTACHED FILES



Picture 1: Cleft lip and palate

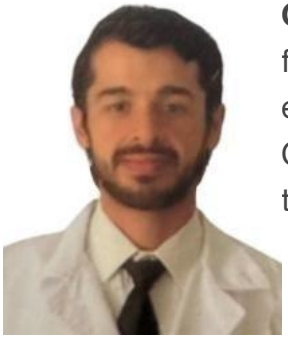


Picture 2: Syndactyly (blue arrow) and micromelia (orange arrow)



Picture 3: Radium agenesis (Blue arrow, the absence of the radius bone is evident)

About the Author



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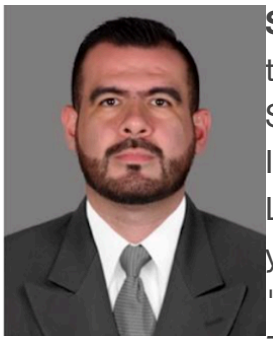

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