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Case Study Report On Kabuki Makeup Syndrome

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Abstract
Kabuki make-up syndrome is a rare genetic disorder characterized by distinctive facial features, growth delay, skeletal abnormalities, and possible developmental or intellectual disability. Given the rarity of Kabuki syndrome and the lack of treatment research, there is a paucity of literature describing the signs, symptoms, and impacts experienced by patients and the overall burden of living with Kabuki syndrome. We discuss the case of a patient presenting with typical clinical findings suggestive of this syndrome, highlighting the importance of early recognition, clinical evaluation, and supportive multidisciplinary care. The condition is most commonly associated with mutations in the KMT2D and KDM6A genes. To identify new treatment pathways, we must first understand Kabuki syndrome as an epigenetic disorder.

Keywords:
Kabuki make-up syndrome, genetic disorder, Growth delay, dysmorphic features, KMT2D, KDM6A

1. Introduction

Kabuki make-up syndrome is a rare congenital multisystem disorder characterized by distinctive facial dysmorphism, postnatal growth retardation, skeletal anomalies, and variable developmental delay. It was first described in Japan and is named for the facial appearance resembling Kabuki theater makeup. Because of its broad clinical spectrum and occasional associated congenital anomalies, early recognition is important for timely diagnosis and multidisciplinary care. We report this case to highlight the characteristic features of Kabuki make-up syndrome and to emphasize the value of clinical suspicion in early identification. Kabuki Count is the global Kabuki syndrome census and contact registry designed to drive research to treatments for Kabuki syndrome. Kabuki syndrome affects approximately 1 in 32,000 newborns worldwide. Because it is a rare genetic disorder, exact population totals remain unknown. However, global tracking efforts—such as the Kabuki Count Global Census—have documented over 1,500 affected individuals across 75 countries.

History

In 1969, Norio Niikawa MD, a geneticist in Japan, was treating a child patient presenting with unique facial characteristics and various health problems. Never having seen this constellation of symptoms before, Dr Niikawa wondered if he was faced with an undiagnosed condition, a disorder with a genetic basis. Over the next several years, this physician treated several other patients with the same symptoms in his outpatient genetics clinic, furthering support for a disorder never before diagnosed.
Dr Niikawa coined the term 'Kabuki syndrome' (also known as Kabuki make-up syndrome or Niikawa–

Kuroki syndrome) as a reference to traditional Japanese theatre which he respected greatly. As reported by Dr. Niikawa "The name, 'Kabuki make-up', of the syndrome was given by myself, because the facial appearance of patients, especially eversion of their lower eyelids, is reminiscent of the makeup of actors in Kabuki, the traditional form of Japanese theater. Kabuki was founded early in the 17th century in Japan and over the next 300 years developed into a sophisticated form of theater. Kabuki actors usually apply traditional makeup to strengthen their eyes, especially in a hero play, and they are very proud of their performing art."

Case report

A 3-year-old female child who was admitted with complaints of vomiting for three episodes. She was the second twin child born through normal vaginal delivery to parents with a history of first-degree consanguineous marriage. The child was referred from a private hospital with a suspected diagnosis of Kabuki make-up syndrome. Genetic counseling had been provided prior to referral. On admission, the child was shifted t**o** Level II Pediatric Intensive Care Unit for further management.

Embryogenesis

Kabuki syndrome's embryogenesis is thought to involve disrupted epigenetic regulation during development, mainly from pathogenic variants in the KMT2D gene and less often, KDM6A. These genes help control embryonic gene expression through histone modification, so when they are altered, normal organ and tissue development can be disturbed.

2. Review of disease progress:

Definition

Kabuki syndrome, also called Kabuki make-up syndrome, is a rare genetic disorder that affects many parts of the body and is characterized by distinctive facial features, growth delay, intellectual disability, and congenital anomalies .

Symptoms

Each person with Kabuki syndrome is unique. Symptoms and their severity can vary widely between individuals. Some symptoms can be present at birth, while others can appear later in life.

Causes

- KMT2D (TYPE -I)
- KDM6A (TYPE -II)

KMT2D and KDM6A are the two main Kabuki syndrome genes, and they differ in a few key ways. KMT2D is on chromosome 12, is the more common cause, and acts as a histone H3K4 methyltransferase that usually affects embryonic gene activation; KDM6A is on the X chromosome, causes a smaller share of cases, and acts as a histone H3K27 demethylase that helps remove repressive marks. In August of 2010, a group of researchers at the University of Washington reported that pathogenic variants in the gene *KMT2D* (formerly *MLL2*) were responsible for Kabuki syndrome in most

affected individuals who were tested. In 2012, a group of researchers from Belgium identified a second gene, termed *KDM6A*, that causes Kabuki syndrome. Most cases of Kabuki syndrome, particularly those caused by variants of *KMT2D*, occur for the first time in the affected individual with no family history of the disorder (*de novo*). However, familial occurrence of Kabuki syndrome has been reported.

The University of Washington researchers confirmed that Kabuki syndrome caused by a dominant pathogenic variant in the *KMT2D* gene can then be passed on to the offspring of an affected individual. Dominant genetic disorders occur when only a single copy of an abnormal gene is necessary for the appearance of the disease. The abnormal gene can be inherited from either parent or can be the result of a new gene change in the affected individual (*de novo*). The risk of passing the abnormal gene from affected parent to offspring is 50 percent for each pregnancy. The risk is the same for males and females. Variable expressivity means that the disorder is expressed in dramatically different ways from one person to another, even within affected individuals from the same family.

Kabuki syndrome caused by *KDM6A* gene variants follows X-linked inheritance. Females typically have two X chromosomes and males typically have one X and one Y chromosome. Females who have a pathogenic variant in *KDM6A* on one X chromosome generally have milder features of Kabuki syndrome compared to males who have a pathogenic variant in this gene, although exceptions exist. It is also possible for a female with a variant in *KDM6A* to have no symptoms of Kabuki syndrome. Most cases of Kabuki syndrome caused by variants in *KDM6A* are the result of a new gene change. However, it is possible for a female with a variant in *KDM6A* to pass on the condition to her children, even if she herself has mild or no symptoms of Kabuki syndrome. For a female with a *KDM6A* variant, the risk of passing the abnormal gene to her offspring is 50 percent for each pregnancy. The risk is the same for males and females, however, female children may have milder or no symptoms of the condition. An affected male will pass on the abnormal gene to all his daughters but none of his sons.

KMT2D and *KDM6A* appear to work together to regulate gene expression. They are part of a newer class of conditions that impact the "epigenetic machinery", sometimes called Mendelian disorders of the epigenetic machinery (MDEMs). For a gene to be expressed (or read), the DNA must be in an "open" configuration. Proteins called histones are involved in keeping DNA "opened" (able to be read) or "closed" (unable to be read). Modifications to histones help determine if DNA will be read or not. *KMT2D* places activating marks on histones, so DNA can be read. It can "write" that DNA should be opened and to read these marks as well. *KDM6A* erases marks that keep DNA closed, so that DNA can be opened and read. However, more research is necessary to determine the specifics of how abnormal histone modification results in the development of the disorder and its associated symptoms.

Inheriting Kabuki Syndrome

Kabuki syndrome follows an autosomal dominant inheritance pattern—meaning an individual must only have one copy of the mutated gene to result in symptoms. There is a 50 percent chance of passing the syndrome on to future generations.

Contrarily, the cases caused by the KDM6A gene are X-linked, which occurs when the mutated gene is on the X-chromosome. Males tend to present more severely than females because they have one X chromosome, while females have two.

Incidence

- Worldwide incidence: about 1 in
- 32,000 to 1 in 86,000 live births
- More frequently reported in Japan, but occurs in all populations

Pathophysiology

Genetic mutation
↓
KMT2D gene mutation (chromosome 12) Or KDM6A gene mutation (X linked)
↓
Defective histone modification
↓
Abnormal gene expression
↓
Impaired embryonic development.
↓
Defective cell differentiation.
↓
Multisystem involvement.

Clinical manifestation

- Craniofacial anomalies.
- Growth retardation.
- Intellectual disability.
- Skeletal defect.
- Congenital heart disease.
- Immune dysfunction

BOOK PICTURE	CHILD PICTURE
Respiratory system ● Chronic cough. ● Dyspnea. ● Noisy breathing. ● Cyanosis. ● Respiratory rate and effort. ● Use of accessory muscle.	● RR: 30 Breath/min. ● No evidence of noisy breathing
Gastrointestinal system ● Fatigue during meals. ● GERD. ● Frequent vomiting or regurgitation. ● Constipation	● Presence of vomiting in 3 episodes. ● Weight:: 7 kg. ● Height: 62cm.
Cardio vascular system ● Cyanosis. ● Clubbing of fingers. ● Jugular vein distention. ● Apex beat. ● Thrills. ● Capillary refill time. ● Hepatomegaly. ● Heart rate. ● Heart sound. ● Heart murmur. ● Abnormal heart sounds.	● Heart rate: 82 beats/min. ● Capillary refill time: 2 second ● No thrill, abnormal heart sound detected
Craniofacial abnormalities ● Arched eyebrows. ● Long palpebral fissures. ● Eversion of lower eye lid. ● Prominent of cupped ears. ● Depressed nasal tip ● High arched palate. ● Bilateral ptosis.	● Presence of arched eyebrows, Depressed nasal tip,high arched palate.bilateral ptosis.

Growth and development ● Postnatal growth retardation ● Short stature ● Failure to thrive ● Delayed developmental milestones ● Intellectual disability (mild to moderate)	● Presence of global developmental delay
Genito urinary system ● Dysuria. ● Hematuria ● Oliguria/anuria. ● Enuresis. ● Masses, tenderness.	● No signs of hematuria.
Musculoskeletal system ● Kyposis ● Scoliosis ● Joint laxity. ● Brachydactyly. ● Clinidactyly ● Hypotonia.	● Presence of scoliosis.
Neurological behavior ● Level of consciousness. ● Muscle tone ● Posture. ● Gait. ● Muscle strength	● Hypotonia present

Diagnostic evaluation

NAME OF THE INVESTICATIONS	NORMAL VALUE	CHILD VALUE	INFERENCE
WBC	5000-15000/mm3	19000 mm3	Leukocytosis
HGB	10-14g/dL	8 g/dL	Anemia
BILIRUBIN	0.3-1.2 mg/dL	0.5 mg/dL	Normal
SGOT	10-40IU/L	30 IU/dL	Normal
SGPT	7-56 IU/L	27 IU/L	Normal
SODIUM	135-145 Meq/L	128 Meq/L	Hyponaremia
POTASSIUM	3.5 -5.5 Meq/L	4.7 Meq/L	Normal
CHLORIDE	96-106 meq/l	102 meq/l	normal
SR.UREA	7-18 mg/dL	10 mg/gL	Normal
SR.CREARININE	0.3-0.7 mg/dl	0.3 mg/dl	Normal
CRP	0.9- 1.0 mg/dl	0.3 mg/dl	Normal

Imaging Studies

Book picture	Child picture
Echo cardiography ● ASD ● VSD ● COA	● Presence of **ASD(**Moderate) ● Ostium secundum atrial septal defect measuring 6 mm ● Left-to-right shunt present ● Mild right atrial and right ventricular dilation ● No significant pulmonary hypertension
X ray spine	● X-ray spine shows lateral curvature of the vertebral column with a Cobb angle between 20°–40°, ● suggestive of moderate scoliosis, consistent with skeletal manifestation of Kabuki makeup syndrome. ● Orthopedic evaluation and follow-up are recommended

Management

BOOK PICTURE	CHILD PICTURE
Developmental and neurological management: ● Physiotherapy ● Occupational therapy ● Speech therapy	● Early intervention and speech therapy given

Cardiac management ● Small ASD/VSD: Observation. ● Large VSD/ASD: Surgery ● Treat heart failure if present	● No findings of any cardiac abnoprmality

Nursing diagnosis:

- Ineffective breathing pattern related to congenital heart defect (VSD)Secondary to Kabuki makeup syndrome as evidenced by tachypnea, chest retractions, abnormal breath sounds
- Imbalanced nutrition less Than Body Requirements related to feeding difficulties and gastroesophageal reflux as evidenced by poor weight gain, inadequate intake
- Impaired Verbal Communication related to developmental delay and hearing impairment secondary to Kabuki makeup syndrome as evidenced by delayed speech
- Disturbed Body Image (Child/Parents) related to facial features and physical abnormalities secondary to Kabuki makeup syndrome as evidenced by parental concern, social withdrawal.
- Risk for Aspiration related to feeding difficulties and hypotonia
- Impaired growth and development related to nutritional deficiency as evidenced by failure to thrive

3. Conclusion

Kabuki makeup syndrome is a rare genetic disorder characterized by distinctive facial features, developmental delay, intellectual disability, and multiple congenital anomalies affecting various body systems. It is primarily caused by mutations in the KMT2D and KDM6A genes, which play a key role in chromatin modification and gene expression during embryonic development. Early diagnosis through clinical evaluation and genetic testing is essential for timely intervention. Although there is no definitive cure, multidisciplinary management—including medical, surgical, developmental, and supportive therapies—can significantly improve the quality of life and functional outcomes. Long-term prognosis varies depending on the severity of associated anomalies, particularly cardiac, skeletal, and immune system involvement. Continuous monitoring, early rehabilitation, and family support are crucial in optimizing growth, development, and overall well-being of affected individuals.

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