



Case Study

Otolaryngologic Manifestations of Kabuki Syndrome

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Introduction

Kabuki syndrome is a genetic disorder first described in Japan in the 1980s. It was so named because characteristic facial features of the disorder were thought to resemble the facial features and makeup of actors in the Kabuki Theater [1].

Diagnosis

Diagnostic criteria were established in an international consensus statement from 2019 [2]. Based on this consensus, a diagnosis of Kabuki syndrome can be made at any age in a patient with a history of infantile hypotonia, developmental delay/intellectual disability, and at least one of the following major criteria: a variant found in genes KMT2D or KDM6A - OR - characteristic dysmorphic facial features or other clinical features. The specified clinical findings include arched and broad eyebrows with notching or sparseness of the lateral third, short columella and depressed nasal tip, large, prominent, or cupped ears, and persistent fingertip pads.

A probable diagnosis of Kabuki syndrome can be made in a patient with infantile hypotonia, developmental delay AND at least three supportive clinical features. Supportive features include hearing loss, cleft palate, lip pits, immunologic disorders, short stature, microcephaly, feeding abnormalities and congenital heart defects.

Etiology

Abnormalities in the KMT2D gene are the most common cause of Kabuki syndrome and occur in approximately 75% of patients. Abnormalities in the KDM6A gene, which follow an X-linked dominant inheritance pattern, account for approximately 5% of cases with the remainder of cases being of unknown etiology [3].

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Prevalence

Kabuki syndrome is extremely rare and is estimated to occur in one out of every thirty-two thousand live births. It is not associated with an increased prevalence in persons of in East Asian descent or any other ethnicity. There are no known prenatal risk factors and family history is often unremarkable with the exception of KDM6A gene abnormalities which may exhibit an X-linked dominant inheritance pattern.

Otolaryngologic Clinical Manifestations

Cardinal dysmorphic facial features include arched and broad eyebrows with notching or sparseness of the lateral third, short columella and depressed nasal tip, and large, prominent or cupped ears. Characteristic facies are observed in 100% of patients with Kabuki syndrome, hence making these features a major criterion for diagnosis. Severe midface hypoplasia with maxillary recession may be observed with or without associated mandibular hypoplasia in some patients. These abnormal facial features appear to be the result of defective osteochondral progenitor differentiation as observed in mouse models of this disease.

Cleft palate is found in 35-70% of patients, with the submucous cleft palate being slightly less prevalent (15-50%). Lower lip pits and nodules are seen in up to 70% of patients and may lead to a misdiagnosis of Van der Woude syndrome. A low posterior hairline is observed in 50% of patients and preauricular dimples are seen in approximately 40% of patients. Infantile hypotonia, a key supportive feature, most commonly presents as oral hypotonia with a resultant inability to suck, chew and swallow in a normal fashion.

The ear is often affected by Kabuki syndrome, and dysmorphism of the external ear is found in at least 80% of patients. Hearing loss is found in 24-65% of patients and is frequently associated with speech delay. Both recurrent otitis media and chronic otitis media are observed in greater than 50% of patients with an even higher prevalence in those who also have a cleft palate [2]. Many patients with Kabuki syndrome also have an abnormal immune response due to defective B lymphocyte terminal differentiation and associated low IgA and IgG levels. Therefore, early diagnosis and early consideration of the medical or surgical treatment of middle ear disease is important in this patient population. External ear abnormalities including microtia occur in a small fraction of patients.

Inner abnormalities such as Mondini dysplasia associated with a high-frequency sensorineural hearing loss have been reported but are rare. Audiologic testing may confirm a suspected hearing loss, typically conductive or mixed, in up to 65% of patients. Most cases of hearing loss are related to either recurrent otitis media or chronic otitis media. For patients without evidence of middle ear effusion, other potential causes of conductive hearing loss observed in this patient population include tympanosclerosis, tympano-ossicular fixation, and congenital antroatticotomy. Abnormal vestibular testing is present in less than 5% of patients. Speech delay in patients with Kabuki syndrome, although frequently a direct result of hearing loss, may be

multifactorial as intellectual disability and other developmental/neurologic abnormalities may play a significant role.

Finally, 90% of children with Kabuki syndrome have significant ligamentous laxity. This may be of particular concern to otolaryngologists and anesthesiologists alike if general anesthesia is required, as excessive ligamentous laxity may result in cervical spine instability with neck extension.

Case Report

A 19-month-old female was evaluated by pediatric genetics due to a history of multiple congenital anomalies, including dysmorphic facial features, congenital hip dysplasia, ventricular septal defect, proportionate growth retardation, premature thelarche, and a history of ear infections. Despite these anomalies, the patient was achieving her developmental milestones. She had initially been tested for genetic disorders including Smith-Lemli-Opitz (SLO) syndrome, cystic fibrosis, celiac disease, and thyroid disease, the results of which were normal. Family history was only significant for Factor V Leiden in her mother and maternal grandmother.

Physical exam findings included the 4th percentile for height, less than the 1st percentile for weight, and the 2nd percentile for head circumference. Facial features included up-slanting palpebral fissures, eversion of the lateral eyelids, and sparse lateral eyebrows. The patient also had simplified, cupped, and prominent ears, a square nasal tip, and a trapezoid-shaped philtrum. At the time of the first exam by pediatric genetics, she had a few teeth and palpable breast tissue bilaterally. Hand features included brachydactyly, short fifth digits with clinodactyly, and persistent fetal fingertip pads. Her second toes were shortened and overlapped her third toes.

Due to the physical exam findings and her history, the team was suspicious that the patient may have Kabuki syndrome. Genetic testing was sent for gene sequencing, which identified a heterozygous mutation of the gene *KMT2D* and helped secure a diagnosis of Kabuki syndrome.

Before being diagnosed with this syndrome, the patient had presented to the otolaryngology clinic with a history of suspected hearing loss and otorrhea at 19 months. The patient failed her newborn hearing screen which was followed by repeat auditory brainstem response (ABR) testing that demonstrated a mild bilateral conductive hearing loss (CHL) at one month of age. She underwent a myringotomy with tube placement at six months of age. On follow-up exam, the tympanic membranes (TMs) were translucent, and opalescent with patient tubes bilaterally. By four years of age, her speech was improving and her tympanostomy tubes had extruded. At age six, she returned to the otolaryngology clinic for evaluation after failing a school hearing screen. At that time, there was no report of recent episodes of otitis media, and her TMs were found to be intact, translucent, opalescent, and mobile. She underwent additional audiologic testing which demonstrated a mild to moderate conductive hearing loss (CHL) on the right and mild CHL on the left with normal tympanometry and speech discrimination scores. A CT scan of the temporal bone showed no anatomic abnormalities other than opacification of the right mastoid air cells without bony destruction. Hearing aid evaluation,

preferential seating, and the use of an FM system loop system at school were recommended. The patient obtained a hearing aid for the right and her hearing loss has remained stable.

The patient has been followed regularly by the otolaryngology, audiology, infectious disease, and endocrinology services. She has not developed any detectable immunodeficiency and has received all age-appropriate vaccines. She has received speech therapy, physical therapy (following repair of hip dysplasia), and occupational therapy in addition to the implementation of an individual education plan for educational support through her school.

Discussion

This patient's diagnosis of Kabuki syndrome occurred relatively early in life due to genetic testing, which identified a mutation in the gene *KMT2D*. *KMT2D* has been found to encode a histone methyltransferase involved in epigenetic regulation and neural crest cell migration [4]. Specific pathways affected have yet to be fully elucidated but are shown to affect the differentiation of neural crest cells into craniofacial cartilage and bone, such as the temporal bone and ear structures.

Similar to other craniofacial disorders, abnormal development of the eustachian tube is thought to lead to recurrent acute and chronic otitis media resulting in conductive hearing loss. Sensorineural hearing loss has been identified in patients with Kabuki syndrome less frequently as a result of anatomic anomalies of the inner ear including Mondini dysplasia. Recurrent infections have also been linked to *KMT2D*'s effect on B cell development resulting in immune deficiency [3]. This patient's development has progressed appropriately despite her complex medical history, in part, due to early intervention and interdisciplinary medical care. Early intervention to restore hearing and improve speech development has aided in her transition from special education into a traditional classroom setting.

Kabuki syndrome is often associated with abnormalities of the external ear, recurrent and chronic otitis media, and hearing loss. Early and frequent otolaryngologic and audiologic assessment is critical to restoring normal hearing and speech development in this patient population. Common interventions include hearing aids, aural rehabilitation, and treatment of chronic or recurrent infections.

Reference

1. Niikawa N, Matsuura N, Fukushima Y, Ohsawa T, Kajii T (1981) Kabuki make-up syndrome: a syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. *J Pediatr* 99: 565-569.
2. Adam MP, Banka S, Bjornsson HT, Bodamer O, Chudley AE, et al. (2019) Kabuki syndrome: international consensus diagnostic criteria. *J Med Genet* 56: 89-95.
3. Boniel S, Szymańska K, Śmigiel R, Szczałuba K (2021) Kabuki Syndrome-Clinical Review with Molecular Aspects. *Genes (Basel)* 12: 468.
4. Schwenty-Lara J, Nehl D, Borchers A (2020) The histone methyltransferase *KMT2D*, mutated in Kabuki syndrome patients, is required for neural crest cell formation and migration. *Hum Mol Genet* 29: 305-319.



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