

Kabuki syndrome with ossification of the posterior longitudinal ligament requiring differentiation from Ehlers-Danlos syndrome: a case report with a literature review

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Abstract

Kabuki syndrome (KS) comprises multiple congenital abnormalities and the main symptoms include characteristic facial features, skeletal and spinal abnormalities, and mental retardation. The estimated incidence of KS is 1 in 32000, and mutations in the *KMT2D* gene (also known as *MLL2*) are considered to be involved. The details of such mutations, including the mode of inheritance, are unclear. A 40-year-old woman visited our hospital with back pain and urinary incontinence. The patient had been diagnosed with Ehlers-Danlos syndrome (EDS) in childhood, on the basis of physical findings including hip subluxation. Because of her characteristic facial features, we suspected KS instead. Genetic testing revealed the presence of a rare missense mutation in *KDM6A* that was suggestive of KS. Computed tomography showed that she had ossification of the posterior longitudinal ligament (OPLL). On the basis of her clinical presentation and genetic mutation in *KDM6A*, we made a diagnosis of KS with OPLL. Hereditary diseases may share similar clinical characteristics, as in the case of our patient with Kabuki syndrome, who was misdiagnosed in childhood as having an Ehlers-Danlos syndrome involving disordered connective tissue. Physicians should undertake a comprehensive consideration of multiple clinical features when diagnosing a hereditary disease.

Keywords: Genetic mutation; Kabuki syndrome; Ehlers-Danlos syndrome; *KDM6A*; Ossification of posterior longitudinal ligament.

Introduction

Kabuki syndrome (KS) is a syndrome of multiple congenital anomalies that was first reported in 1981, in

Japan [1]. The symptoms are classified as (a) general and (b) dermatoglyphic. The main symptoms of (a) are spinal and skeletal abnormalities and mental

retardation. However, the most characteristic symptom of the syndrome is facial malformations. They are similar to the 'Kumadori' face painting used by actors of the Japanese classical art form 'Kabuki'. That is why Kabuki syndrome is so named (Figure 1) [2].

There have been approximately 400 reports of KS worldwide, and the estimated morbidity is considered to be 1 in 32000 people [reference]. Most reports described isolated cases, with very few reports of family cases. According to previous studies, familial KS has been found in only 42 patients in 15 families [3-14] (Table 1).

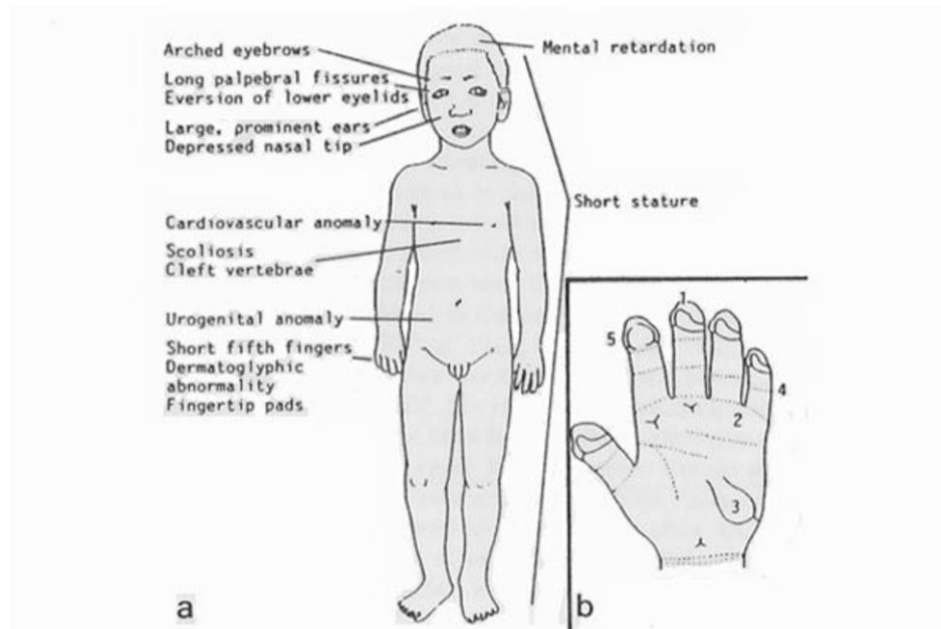
Mutation of the *KMT2D* gene (also known as *MLL2*) is found in approximately 70% of patients with a clinical diagnosis of KS. The *KMT2D* /

MLL2 gene encodes a histone methylase (H3K4) that interacts with KMT2D [1].

KS is regarded as the result of an abnormality in histone methylation in patients with mutation of *KDM6A*. Our patient, who had previously been diagnosed with Ehlers-Danlos syndrome (EDS) in childhood, presented with unidentified weight loss, back pain and urinary incontinence in adulthood [reference].

Ultimately, we diagnosed her with KS with ossification of the posterior longitudinal ligament (OPLL) instead of EDS. This case provided us with a valuable learning opportunity and may prove meaningful for the future diagnosis and treatment of hereditary disease groups with overlapping clinical characteristics.

Figure1. Characteristics of Kabuki syndrome.



Legend: A. General appearance of the patient with KS. B. Dermatoglyphic aspect of KS. Modified from Niikawa et al. [2].

Table 1. Previous studies of familial Kabuki syndrome.

Family numbers	Patient numbers	Hereditary pattern	Reference
1	8	X-linked	[2]
1	3	Autosomal dominant	[3]
0	0	none	[4]
2	no data	Autosomal dominant	[5]
1	2	Autosomal dominant	[6]
1	2	Autosomal dominant	[7]
1	3	X-linked	[8]
2	4	Autosomal dominant	[9]
1	2	unknown (twin)	[10]
1	2	Autosomal recessive	[11]
1	6	unknown	[12]
3	10	unknown	[13]

Case report

Chief complaints

A 40-year-old woman presented to our hospital with back pain and urinary incontinence.

History of present illness

The symptoms of back pain and urinary incontinence had been ongoing for 3 months.

History of past illness

Thirty-five years prior, at age 5, the patient had bilateral hip dislocations. She was diagnosed with EDS based on clinical findings including hip subluxation at the paediatrics department of another hospital and did not undergo genetic testing.

One year later, Suzuki-Binet Intelligence testing revealed an IQ of 42, and the patient was diagnosed with moderate mental retardation. Her family history included dementia in her mother and father, and uterine prolapse

in her mother. Her sister had died in her 40s from a type of collagenases (details unknown).

Physical examination

The patient exhibited certain facial features indicative of KS; namely, long palpebral fissures with eversion of the lateral third of the lower eyelid, and arched and broad eyebrows, with the lateral third displaying notching or sparseness (Figure 2).

Laboratory examinations

Genetic screening revealed one missense variant each in *KMT2D/MLL2* (Online Mendelian Inheritance in Man: 147920) and *KDM6A* (Online Mendelian Inheritance in Man: 300867) in the patient. The variant found in *KMT2D* is a synonymous substitution with low pathological significance, i.e., no amino acid substitution.

However, the mutation found in *KDM6A* corresponds to the Jumonji C (JmjC) protein domain. This mutation is

novel, highly pathogenic, and has not previously been registered in ClinVar, the Exome Aggregation Consortium, or the Human Gene Mutation Database. There were no abnormal findings on the patient's electroencephalogram or elec-

trocardiogram. Blood cell analysis, and examinations of blood electrolytes, glucose and lipids, and liver and renal function, also showed no abnormalities.



Figure 2. The patient's facial features were suggestive of Kabuki syndrome.

Imaging examination

Computed tomography of the spine showed OPLL in the spinal canal (Figure 3), which was considered to be the cause of back pain and urinary incontinence.

Final diagnosis

The patient was diagnosed with KS with OPLL.

Treatment

She was prescribed corsets and acetaminophen (1800 mg/day) to alleviate the symptoms of OPLL for 3 months.

Outcome and follow-up

The patient's back pain improved slightly, but she later developed numbness, sensory and motor

disturbances in both legs and became unable to walk well. If these neurological deficits persist, including the urinary incontinence, we may

consider surgical treatment of the OPLL, because corsets and acetaminophen are not fundamental treatments for OPLL.



Figure 3. Computed tomography of the patient's spine showing ossification of the posterior longitudinal ligament in the spinal canal (red oval).

Discussion and Conclusion

The mutation found in *KDM6A* in our patient represents a new missense variant in KS. The sequence change replaces glycine with glutamate at codon 3419 in the *KDM6A* protein. Glycine has a non-polar side chain, whereas glutamate has a polar

uncharged side chain with moderate physicochemical differences. This variant is predicted to be highly pathogenic according to the SIFT and PolyPhen-2 prediction tools in InterVar, a bioinformatics software for clinical interpretation of genetic variants based on the *American College of Medical Genetics and Genomics* and the Association

for *Molecular Pathology* 2015 guideline. Because the phenotypic details of the parents and siblings of this case are unknown, the variant must be formally classified as having "Uncertain Significance" (clinical significance unknown). However, given that the phenotype of the patient is typical of KS, the pathogenic potential for the variant is high.

When our patient was diagnosed with EDS in childhood, gene therapy in this area was poorly developed. It was difficult to perform genetic screening tests, even in patients who were suspected of having a genetic disorder. The fact that her sister suffered from collagenosis also probably impacted her initial diagnosis. It is possible that her attending physician at the time made the diagnosis of EDS based on physical assessment alone.

The main clinical symptoms of KS are characteristic facial features, short stature, various organ malformations, and a variable degree of intellectual disability. We were unable to obtain a photograph of the patient in childhood, but her friends stated that she had always had distinctive facial features, supporting our own assessment of her physical features as being typical of KS.

Most KS patients have mutations in *KMT2D/MLL2*, but mutations in *KDM6A* are comparatively rare. Pathogenic variants in the genes encoding the chromatin modifiers *KMT2D* and *KDM6A* are responsible for Kabuki

syndrome 1 (KS1) and Kabuki syndrome 2 (KS2), respectively. The patient had a mutation in both genes, therefore, it should be considered as KS1. [15].

A previous study showed that *KDM6A* is involved in the maternal inheritance of KS and that there is also an unidentified X-linked form of KS (type 2) [14]. In this case, the patient's sister died of an unspecified collagen disease. We considered the possibility that the patient's sister also had KS. This patient has a genetic mutation that is quite rare among patients with KS, making her KS diagnosis notable. If she has other living blood relatives besides her father and sister, they should also be tested for mutations in *KDM6A*. While there have been reports of skeletal abnormalities such as scoliosis in KS [2], to our knowledge this is the first reported case of KS with OPLL. Clinical symptoms related to OPLL include numbness of limbs, gait disturbance, back pain, and urination defecation disorder [16].

In this case, our patient was being cared for by helpers; therefore, she was not indicated for emergency surgery. However, there are no established guidelines for conservative therapy for OPLL. If her neurological symptoms worsen, she may be considered for surgery [1].

This case study highlighted three key messages. First, it is essential that we continue to consider other possible diagnoses in patients with heritable

disease syndromes. Second, we should consider that patients with genetic disorders may exhibit complications that have never been reported. Third, genetic screening tests and physical assessments are both important in the diagnosis of genetic disorders.

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