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 abnormalities 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
Kabuki syndrome with ossification of the posterior longitudinal ligament requiring 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.

![Characteristics of Kabuki syndrome](image)

**Legend:** A. General appearance of the patient with KS. B. Dermatoglyphic aspect of KS. Modified from Niikawa et al. [2].
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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 pediatrics 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
Kabuki syndrome with ossification of the posterior longitudinal ligament requiring 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 electrocardiogram. 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*
Kabuki syndrome with ossification of the posterior longitudinal ligament requiring surgery 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.

References

[1] Japan Intractable Diseases Information Center. Kabuki syndrome (designated intractable disease 187). (https://www.nanbyou.or.jp/entry/4663) reference 2021.8.9.

[2] Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. Am J Med Genet. 1988 Nov;31(3):565-89.

[3] Lederer D, Shears D, Benoit V, Verellen-Dumoulin C, Maystadt I. A three generation X-linked family with Kabuki syndrome phenotype and a frameshift mutation in KDM6A. Am J Med Genet A. 2014 May;164A(5):1289-92. doi: 10.1002/ajmg.a.36442.

[4] Belengeanu V, Rozsnyai K, Farcaș S, Velea I, Fryns JP. Familial transmission of a dysmorphic syndrome: a variant example of Kabuki syndrome? Genet Couns. 2005;16(2):167-71.

[5] Paulussen AD, Stegmann AP, Blok MJ, Tserpelis D, Posma-Velter C, Detisch Y, Smeets EE, Wagemans A, Schrander JJ, van den Boogaard MJ, van der Smagt J, van Haeringen A, Stolte-Dijkstra I, Kerstjens-Frederikse WS, Mancini GM, Wessels MW, Hennekam RC, Vreeburg M, Geraedts J, de Ravel T, Fryns JP, Smeets HJ, Devriendt K, Schrander-Stumpel CT. MLL2 mutation spectrum in 45 patients with Kabuki syndrome. Hum Mutat. 2011 Feb;32(2):E2018-25.

[6] Hannibal MC, Buckingham KJ, Ng SB, Ming JE, Beck AE, McMillin MJ, Gildersleeve HI, Bigham AW, Tabor HK, Mefford HC, Cook J, Yoshiura K, Matsumoto T, Matsumoto N, Miyake N, Tonoki H, Naritomi K, Kameji T, Nasai T, Ohashi H, Kurosawa K, Hou JW, Ohta T, Liang D, Sudo A, Morris CA, Banka S, Black GC, Clayton-Smith J, Nickerson DA, Zackai EH, Shaikh TH, Donnai D, Niikawa N, Shendure J, Bamshad MJ. Spectrum of MLL2 (ALR) mutations in 110 cases of Kabuki syndrome. Am J Med Genet A. 2011 Jul;155A(7):1511-6.

[7] Kokitsu-Nakata NM, Petrin AL, Heard JP, Vendramini-Pittoli S, Henkle LE, dos Santos DV, Murray JC, Richieri-Costa A. Analysis of MLL2 gene in the first Brazilian family with Kabuki syndrome. Am J Med Genet A. 2012 Aug;155A(8):2003-8.

[8] Badalato L, Farhan SMK, Dilliott A, Care4Rare Canada Consortium, Bulman DE, Hegele RA, Goobie SL. KMT2D p.Gln3575His segregating in a family with autosomal dominant choanal atresia strengthens the Kabuki/CHARGE connection. The American Journal of Medical Genetics - Part A. 2017;173;183–189.
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[9] Kim J, Lee CG. Coinheritance of Novel Mutations in SCN1A Causing GEFS+ and in KDM6A Causing Kabuki Syndrome in a Family. Ann Clin Lab Sci. 2017 Mar;47(2):229-235.

[10] Tsukahara M, Kuroki Y, Imaizumi K, Miyazawa Y, Matsuo K. Dominant inheritance of Kabuki make-up syndrome. Am J Med Genet. 1997 Nov 28;73(1):19-23.

[11] Lynch SA, Ashcroft KA, Zwolinski S, Clarke C, Burn J. Kabuki syndrome-like features in monozygotic twin boys with a pseudodicentric chromosome 13. J Med Genet. 1995 Mar;32(3):227-30. doi: 10.1136/jmg.32.3.227.

[12] G-Gómez E., C-Pérez J.M., C-García J.J., et al. 2004 A diagnostic conundrum: two siblings with features overlapping the Kabuki and Malpuech syndromes. A new MCA syndrome? The American Journal of Medical Genetics - Part A. 2004;25A:306–9.

[13] Shotelersuk V, Punyashtthiti R, Srivuthana S, Wacharasindhu S. Kabuki syndrome: report of six Thai children and further phenotypic and genetic delineation. Am J Med Genet. 2002 Jul 15;110(4):384-90. doi: 10.1002/ajmg.10474. PMID: 12116214.

[14] Ilyina H, Lurie I, Naumtchik I, Amoashy D, Stephanenko G, Fedotov V, Kostjuk A. Kabuki make-up (Niikawa-Kuroki) syndrome in the Byelorussian register of congenital malformations: ten new observations. Am J Med Genet. 1995 Mar 27;56(2):127-31. doi: 10.1002/ajmg.1320560202.

[15] Bögershausen N, Gatinois V, Riehmer V, Kayserili H, Becker J, Thoenes M, Elcioglu NH, Wieczorek D, Tinschert S, Sarrabay G, Strom TM, Fabre A, Baynam G, Sanchez E, Nürnberg G, Altunoglu U, Capri Y, Isidor B, Lacombe D, Corsini C, Cormier-Daire V, Sanlaville D, Giuliano F, Le Quan Sang KH, Kayirangwa H, Nürnberg P, Meitinger T, Boduroglu K, Zoll B, Lyonnet S, Tzschach A, Verloes A, Di Donato N, Touitou I, Netzer C, Li Y, Geneviève D, Yigit G, Wollnik B. Mutation Update for Kabuki Syndrome Genes KMT2D and KDM6A and Further Delineation of X-Linked Kabuki Syndrome Subtype 2. Hum Mutat. 2016 Sep;37(9):847-64.

[16] Kawaguchi Y, Imagama S, Iwasaki M, Kaito T, Koda M, Chikuda H, Hasegawa T, Mori K, Yoshiii T; 2019 Clinical Practice Guideline for Ossification of Spinal Ligaments working group. Japanese Orthopaedic Association (JOA) clinical practice guidelines on the management of ossification of the spinal ligament, 2019. J Orthop Sci. 2021 Jan;26(1):1-45. doi: 10.1016/j.jos.2020.07.027.

Conflict of interest: The author declares no conflicts of interest associated with this manuscript. The patient has
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