AMJ Australasian Medical Journal [AMJ 2021;14(7):202-206]

Kabuki Syndrome with Chiari malformation type II: A case report

Mohammed S. Alqarni[1,2], Ziad M. Bukhari[1,2], Abdulmalek Alzahrani[1,2], Abdulkarim W. Abukhodair[1,2], Albraa Abulhamail[2,3], Jubara Alallah[1-3], and Aiman Shawli,[1,2,4]

1. College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
2. King Abdullah International Medical Research Center, Jeddah, Saudi Arabia
3. Neonatology Section, Pediatric Department, King Abdulaziz Medical City-WR, Ministry of National Guard, Saudi Arabia
4. Departments of Clinical Genetics, King Abdulaziz Medical City, Jeddah, Saudi Arabia

CASE STUDY

Please cite this paper as: Alqarni MS, Bukhari ZM, Alzahrani A, Abukhodair AW, Albraa A, Jubara A, Aiman S. Kabuki Syndrome with Chiari malformation type II: A Case Report. AMJ 2021;14(7):202–206.
https://doi.org/10.35841/1836-1935.14.7.202-206

Corresponding Author:
Dr. Jubara Alallah, MD
College of Medicine, King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi Arabia
Email: AlallahJS@ngha.med.sa; Jalallah@gmail.com

ABSTRACT

Kabuki syndrome is a rare genetic disorder, characterized by typical facial features, hypotonia, developmental delay and intellectual disabilities. We report here a Saudi female infant diagnosed as a case of Kabuki syndrome clinically and confirmed by molecular genetic testing. She was admitted at birth to neonatal ICU due to hydrocephalus and meningomyelocele and found to have Chiari malformation type II on radiological evaluation of the brain. Whole exome sequencing (WES) was sent for her and showed pathogenic variant in KDM6A which confirm the diagnosis of Kabuki syndrome.

Key Words
Kabuki syndrome, congenital abnormalities, Chiari malformation type II, whole exome sequencing, KDM6A

Implications for Practice:

1. What is known about this subject?
Kabuki syndrome is a genetic disorder that was first described by Niikawa and Kuroki in Japan in 1981 through two independent case reports.

2. What new information is offered in this case study?
This is a case of Kabuki syndrome that was presented with Chiari malformation type 2 which has not been reported in literature previously.

3. What are the implications for research, policy, or practice?
It should be brought more attention to neonate with Arnold Chiari type 2 with no obvious etiologies, since it may be associated with Kabuki syndrome.

Background

Kabuki syndrome is a genetic disorder that was first described by Niikawa and Kuroki in Japan in 1981 through two independent case reports.[1,2] The worldwide prevalence of Kabuki syndrome is unknown but patients were mostly seen in Japan with 1/32,000 prevalence.[3] Later on, the prevalence was calculated in Australia and New Zealand, and it was 1/86,000.[4] In 1988, Niikawa and Kuroki have defined the five cardinal manifestations of Kabuki syndrome including characteristic facial features, skeletal abnormalities, dermatoglyphic abnormalities, mental retardation, and postnatal growth deficiency. Distinctive facial features consist of arched eyebrows, prominent ears, depressed nasal tip, and lower lateral eyelids eversion.[3] Also, multiple inconsistent anomalies such as congenital heart disease, dental anomalies, ocular manifestation have been reported in some cases of Kabuki patients.[5-7] In 2010, the underlying genetic cause of Kabuki syndrome was discovered to be a mutation in KMT6D gene, previously known as MLL2 gene.[8,9] Moreover, KDM6A mutation was also identified to be associated with Kabuki syndrome.[10] Arnold Chiari malformation is a structural defect in the posterior fossa that affect the hindbrain. It is characterized by downward herniation of the cerebellum into the

foramen magnum. Chiari malformation is classified into four distinctive types based on the severity.[11] Chiari malformation type 2 is characterized by cerebellar herniation along with myelomeningocele. Also, 80–90 per cent of type II may present with hydrocephalus.[12] The incidence of Chiari type 2 in Saudi Arabia, which is 1.27/10,000, is considered low compared to what reported by Hakami, which is 4.4/10,000.[13] Children with Chiari type 2 may suffer from fatal respiratory difficulties that require neurosurgical emergency.[12] Other symptoms include neurogenic dysphagia, hypotonia, nystagmus, and quadriparesis.[12,14] Chiari malformation type 2 has a 25 per cent mortality rate that occur commonly during the first year of life.[15] Structural brain anomaly is one of the uncommon atypical presentation of Kabuki patient. Few cases of Kabuki were reported with cerebellar atrophy, Dandy Walker syndrome, or type one Arnold Chiari malformation.[16-19] However, no cases of Kabuki accompanied with Arnold Chiari type 2 was reported in literature. Kabuki syndrome was underdiagnosed in countries other than Japan, but now more cases are being reported in the middle east due to the available information about the syndrome.[20-22] Only one case of Kabuki was reported in Saudi Arabia.[6] We are reporting this case of Kabuki syndrome which was presented with Chiari malformation type 2 which has not been reported in literature previously. We aim to report this rare case using theoretical concepts from our discipline and recommend a course of action for similar cases in the future.

Case details

Our patient was born at 38 weeks of gestation to a 28-year-old healthy mother. She is G3, P2. There is no previous similar cases and no family history of genetic or neurological diseases. The mother has another two older children with no complications, At the 25th week of gestation, ultrasound showed large ventricles, obliterated cisterna magnum, banana shape cerebellum, and spina bifida defect. Amniocentesis was done and showed normal female karyotype. Fetal Magnetic Resonance Imaging (MRI) showed ventriculomegally, cerebellar tonsil herniation, small posterior fossa, and large myelomeningocele. These MRI findings were consistent with Chirai 2 malformation. Baby born at 38th weeks of gestation through induction of labor due to the myelomeningocele. The delivery was spontaneous vaginal delivery with no complications. At birth, APGAR score of the baby was 9 at 1 and 5 minutes. The birth weight was 2.510kg (25th percentile), height was 49cm (50th percentile), and head circumference was 38cm (97th percentile). She was vitally stable and did not need intubation or resuscitation. On newborn assessment, ruptured myelomeningocele was seen at the lumbar region with 4cm diameter, and the anterior fontanelle was soft and full. Diagnosis of Arnold Chiari 2 was confirmed by post natal head MRI (Figure 1). Echocardiogram was done on the second day and showed normal heart with small patent foramen ovale. Three days after birth, surgical repair was done for the myelomeningocele. After the surgery, she required endotracheal intubation for two weeks.

At age of three months, she has prominent forehead, depressed nasal bridge, microphthalmia, long palpebral fissures with eversion of the lateral part of the lower eyelid, short columella with depressed nasal tip with frontal hemangiomas and hypotonia, which were more evolved (Figure 2). So whole exome sequencing showed a heterozygous variant c.1603A>Gp, (Thr535Ala) in KDM6A and this confirms diagnosis of Kabuki syndrome 2, (KABUK2; OMIM300867). An X-ray was done at the age of six months and showed an apparent cardiomegaly. During the hospital course, she suffered from multiple episodes of oxygen desaturations, and she became an oxygen dependent. Currently, she is discharged home on home oxygen at 12 months of age on stable condition with home oxygen and nasogastric tube feeding. Her weight was 6.620kg (25th percentile), height was 77cm (25th percentile), head circumference was 43cm (50th percentile). She was referred to multidisciplinary team for follow up, high risk neonatal clinic, pediatric pulmonology, pediatric neurology, pediatric neurosurgery, physiotherapy and occupational therapy. Informed consent was obtained from the parents.

Discussion

Most of Kabuki patients have a typical presentation that includes five cardinal manifestations which have been previously defined by Niikawa and Kuroki. These cardinal manifestations include distinctive fascial features (arched eyebrows, prominent ears, depressed nasal tip, and lower lateral eyelids eversion), skeletal abnormalities (short fifth finger, hip dislocation, hyperlaxity, or scoliosis), dermatoglyphic abnormalities (persistent fingertip or fetal pads), mental retardation, and postnatal growth deficiency.[3] In this case, these five cardinal manifestations have not been observed initially. This may be due to the young age of the case, eleven months old, as most of the cases were diagnosed after the age of two years.[7,16,17,23] Also, the classical facial features of Kabuki syndrome become more obvious after the age of three months, and it is very difficult to be seen in infants.[24] However, there are various manifestations other than the five cardinal manifestations that appear in various systems were reported. In our case, some central nervous system (CNS) manifestations have

been observed similar to other reported cases such as generalized hypotonia, feeding difficulties, and hydrocephalus.[7,16,17,23,25,26] The association of Kabuki syndrome with Arnold Chiari type 2 has not previously been reported in the world literature and is presented in this case history for the first time. Other CNS manifestations that have been reported in Kabuki patients include seizures, microcephaly, cerebellar atrophy, and Arnold Chiari Type 1.[16,17,26] Other manifestations have been mentioned in literature with Kabuki syndrome such as recurrent infections, cleft palate, cardiac anomalies, ocular manifestations, and urogenital anomalies.[7,16,17,23,25-27] Based on the international expert panel, a diagnosis of Kabuki syndrome can be made with the presence of either infantile hypotonia, intellectual disability, or delay in development accompanied by genetic confirmation of Kabuki syndrome or the presence of typical dysmorphic features.[29] In our case, a whole exome sequencing came positive for Kabuki gene in the third month of life when her with hypotonia and developmental delay. Prognosis and mortality of Kabuki syndrome were not assessed in literature yet, which may be due to the recent discovery of the syndrome in 1988, and the early diagnosis in childhood life.[3,17,23] However, few cases of Kabuki were reported at the twenties.[26,29,30]

Conclusion

We report this case to bring more attention to neonate whom presenting with Arnold Chiari type 2 and neurological abnormalities of with no obvious etiologies, since it may be associated with Kabuki syndrome. A genetic testing for those patients is recommended to predict the various manifestations of Kabuki syndrome early.

References

1. Niikawa N, Matsuura N, Fukushima Y, et al. Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. J Pediatr. 1981;99(4):565–9.
2. Kaye B. A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism in mental retardation. Plast Reconstr Surg. 1982;69(5):917.
3. Braun O, Schmid E. Niikawa-Kuroki-Syndrom (sog. Kabuki-make up-Syndrom). Klin Padiatr. 1986;198(01):65–8.
4. White SM, Thompson EM, Kidd A, et al. Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa–Kuroki) syndrome. Am J Med Genet A. 2004;127(2):118–27.
5. Yuan S. Congenital heart defects in Kabuki syndrome. Cardiol J. 2013;20(2).
6. Tini GF, Juvino AC, Atmanspacher MA, et al. Kabuki Syndrome: Case Study Report. J Dent Oral Disord Ther. 2017;5(1):1–3.
7. Chaudhry I, Shamsi F, Alkuraya H, et al. Ocular manifestations in Kabuki syndrome: the first report from Saudi Arabia. Int Ophthalmol. 2007;28(2):131–4.
8. Ng SB, Bigham AW, Buckingham KJ, et al. Exome sequencing identifies MLL2 mutations as a cause of Kabuki syndrome. Nat Genet. 2010;42(9):790.
9. Bögershausen N, Bruford E, Wollnik B. Skirting the pitfalls: a clear-cut nomenclature for H3K4 methyltransferases. Clini Genet. 2013;83(3):212–4.
10. Lederer D, Grisart B, Digilio MC, et al. Deletion of KDM6A, a histone demethylase interacting with MLL2, in three patients with Kabuki syndrome. Am J Hum Genet. 2012;90(1):119–24.
11. Horn SR, Shepard N, Vasquez-Montes D, et al. Chiari malformation clusters describe differing presence of concurrent anomalies based on Chiari type. J Clin Neurosci. 2018;58:165–71.
12. Stevenson KL. Chiari Type II malformation: past, present, and future. Neurosurg Focus. 2004;16(2):1–7.
13. Hakami WS, Majeed-Saidan MA. The incidence and spectrum of central nervous system malformations in newborns over a decade (2001-2010) in the Central Region of Saudi Arabia. Saudi Med J. 2011;32(11):1137–42.
14. Pollack IF, Pang D, Kocoshis S, et al. Neurogenic dysphagia resulting from Chiari malformations. Neurosurgery. 1992;30(5):709–19.
15. McDowell MM, Blatt JE, Deibert CP, et al. Predictors of mortality in children with myelomeningocele and symptomatic Chiari type II malformation. J Neurosurg Pediatr. 2018;1(aop):1–0.
16. Yano S, Matsuishi T, Yoshino M, et al. Cerebellar and brainstem “atrophy” in a patient with Kabuki make-up syndrome. Am J Med Genet. 1997;71(4):486–7.
17. Liu S, Hong X, Shen C, et al. Kabuki syndrome: a Chinese case series and systematic review of the spectrum of mutations. BMC Med Genet. 2015;16(1).
18. McGaughran J, Aftimos, S, Jefferies C, et al. Clinical phenotypes of nine cases of Kabuki syndrome from New Zealand. Clin Dysmorphol. 2001;10(4):257–62.
19. Ciprero K, Clayton-Smith J, Donnai D, et al. Symptomatic Chiari I malformation in Kabuki syndrome. Am J Med Genet. 2004;132A(3):273–5.
20. Abdel-Salam GM, Afifi HH, Eid MM, et al. Anorectal anomalies, diaphragmatic defect, cleft palate, lower lip pits, hypopigmentation and hypogammaglobulinemia A

in Kabuki syndrome: a rare combination. Genet Couns. 2008;19(3):309.
21. Abdel-Salam GM, Afifi HH, Eid MM, et al. Ectodermal abnormalities in patients with Kabuki syndrome. Pediatr Dermatol. 2011;28(5):507–11.
22. Suleiman J, Riedhammer KM, Jicinsky T, et al. Homozygous loss-of-function variants of TASP1, a gene encoding an activator of the histone methyltransferases KMT2A and KMT2D, cause a syndrome of developmental delay, happy demeanor, distinctive facial features, and congenital anomalies. Hum Mutat. 2019.
23. Gillis R, Klar A, Gross-Kieselstein E. The Niikawa-Kuroki (Kabuki make-up) syndrome in a Moslem Arab child. Clin Genet. 1990 ;38(5):378–81.
24. Dentici ML, Di Pede A, Lepri FR, et al. Kabuki syndrome: clinical and molecular diagnosis in the first year of life. Arch Dis Child. 2015;100(2):158–64.
25. Chu DC, Finley SC, Young DW, et al. CNS malformation in a child with Kabuki (Niikawa-Kuroki) syndrome: Report and review. Am J Med Genet. 1997;72(2):205–9.
26. Kasuya H, Shimizu T, Nakamura S, et al. Kabuki make-up syndrome and report of a case with hydrocephalus. Childs Nerv Syst. 1998;14(6):230–5.
27. Lung ZHS, Rennie A. Kabuki syndrome: a case report. J Orthod. 2006;33(4):242–5.
28. Adam MP, Banka S, Bjornsson HT, et al. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet. 2019;56(2):89–95.
29. Sattur A, Deshmukh PK, Abrahim L, et al. Kabuki make-up syndrome–A case report with Electromyographic study. J Clin Diagn Res. 2014;8(11):ZD03–ZD06.
30. Roma D, Palma P, Capolino R, et al. Spinal ependymoma in a patient with Kabuki syndrome: a case report. BMC Med Genet. 2015;16(1):80.

ACKNOWLEDGEMENTS

We like to thank the Research Unit of King Saud Bin Abdulaziz University for Health Sciences, Jeddah, Saudi and King Abdullah International Medical Research Center for their ethical approval.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

This research did not receive any specific fund from any agency of the public, commercial, or non-profit sector.

PATIENT CONSENT

The authors, Alqarni MS, Bukhari ZM, Alzahrani A, Abukhodair AW, Albraa A, Jubara A, Aiman S, declare that:

1. They have obtained written, informed consent for the publication of the details relating to the patient(s) in this report.
2. All possible steps have been taken to safeguard the identity of the patient(s).
3. This submission is compliant with the requirements of local research ethics committees.

Figures and Tables

Figure 1: Extensive bilateral hydrocephalus, with thinning of the periventricular parenchyma and changes of Chiari II malformation with crowding of the posterior fossa and tonsillar herniation (arrow). There is mass effect over the brainstem with narrowing of the fourth ventricle

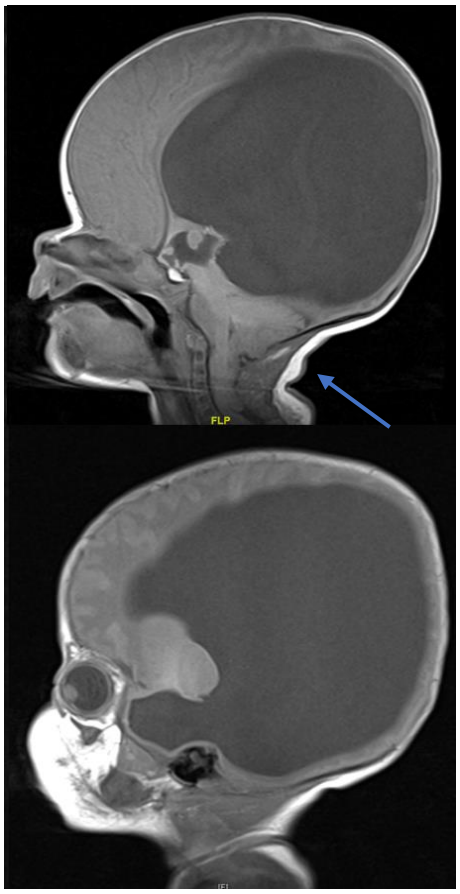

Figure 2: Prominent forehead, depressed nasal bridge, microphthalmia, long palpebral fissures with eversion of the lateral part of the lower eyelid and frontal hemangioma