Carotid artery occlusion in Kabuki syndrome: Case report and literature review

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Abstract

Background: Kabuki syndrome is a rare multiple congenital anomaly syndrome whose main diagnostic findings are craniofacial phenotypic changes and mental retardation. Organic structural lesions in the central nervous system are rare, although have been described already. Systemic vascular changes have also been reported rarely.

Case Description: We report the case of a young patient with Kabuki syndrome who had a transient ischemic attack due to dissection of the internal carotid artery and a likely gliosis area on the white matter.

Conclusion: Association of cervical arterial disease with this syndrome has never been described, and its pathophysiology is not yet established; however, it can direct future research and maybe treatment.

Key Words: Carotid arterial disease, carotid artery dissection, Kabuki syndrome, Niikawa-Kuroki syndrome, transient ischemic attack, vascular anomaly

INTRODUCTION

Kabuki (make-up) syndrome (KS), also known as Nikawa–Kuroki syndrome (named after its independent description in a case series by two authors in 1981), is a rare disease not fairly common outside Japan, with more than 350 cases described after 20 years of its first description.¹³

KS has a variable prevalence in part due to the lack of consensus on diagnostic criteria and the phenotype that tends to evolve over time based on five cardinal characteristics – mild-to-moderate mental retardation, dermatoglyphic abnormalities, skeletal anomalies, postnatal growth deficiencies, and principally on craniofacial anomalies.⁶¹²¹³ Larger heads, long palpebral fissures with an eversion of the lower eyelid, long, dense eyelashes, and arched eye-brows are the common characteristic features, in addition to the thin upper and full lower lip and the corners of the mouth slant downwards.⁷¹５

The genetic causes of the disease are diverse mutations in the KDM2T or in KDM6A genes that encode proteins histone modifiers which play an important role in immune system and embryogenic development;¹⁹

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however, how pathological molecular pathways influence in development remains unclear.[8]

**CASE REPORT**

We present the case of a female born with birth weight 3.300 g by cesarean delivery in the 38th week due to labor dystocia after uneventful first pregnancy of a healthy 26-year-old (y-o) mother without addiction or continuous use of medication. Non consanguineous father; absence of neurological disease in the family. Left-hand was dominant. There was normal neuropsychomotor development until 5 years of age, when marked learning difficulties were observed at school. At 8 years, KS was diagnosed due to characteristic phenotypic traits such as eversion of the lower eyelid, elongated eyelid closure, arched eyebrows, long eyelashes, nasal tip facing down, high palate, and large and protruding pinna and fingertips with fetal aspect [Figure 1]. Furthermore, she had moderate conduction hearing loss and mild scoliosis, and scored 51 points on the intelligence quotient (IQ) test. Ophthalmologic evaluation was normal. At age 15, she had an unexplained episode of transient global aphasia with no trigger history of infection, cranial or cervical trauma, or pain. After referral to our service, the patient showed improvement of the transient deficit, presenting preservation of language (though with poor content, due to cognitive impairment). Physical examination did not detect motor deficit or other focal alterations. Magnetic resonance imaging (MRI) of the brain showed a hyperintense lesion in right posterior white matter, as shown in Figure 2. A Doppler ultrasound of cervical vessels suggested severe right internal carotid artery (ICA) stenosis. A brain computer tomography demonstrated a bilateral patent carotid foramen, indicating a noncongenital ICA occlusion [Figure 3]. Digital subtraction angiography (DSA) showed right ICA occlusion at the bulb portion, with compensatory perfusion of the ipsilateral hemisphere through anterior communicating artery, external carotid artery, and temporal branches anastomoses from the posterior circulation [Figure 4], suggesting ICA dissection. Investigation of cardiologic and thrombophilic diseases were negative; her mother did not allow biopsy due to surgical risks (mainly visuals). Oral acetylsalicylic acid (ASA) was taken for 6 months, and no further treatment was recommended. Follow-up was done with MRI every 6 months to evaluate white matter, which did not show growth and pattern change, ruling out demyelinating, inflammatory, or neoplasic disease, and supporting primarily diagnostic hypothesis of gliosis. On 2-years follow-up, 3D-CTA identified complete spontaneous recanalization of ICA [Figure 5]. No other intercurrence was observed on the long-term follow up, but at age 16 a benign polyp of the gallbladder was removed.

Research was performed using PubMed database on articles published before 2016 September, using the following MESH terms: Kabuki syndrome, Kabuki makeup syndrome, Kabuki make-up syndrome, Kabuki make up syndrome or Niikawa-Kuroki syndrome combined with stroke, brain ischemia, brain hypoxia–ischemia, transient ischemic attack, cerebral infarction, carotid artery stenosis, carotid stenosis narrowing, vascular malformation, vascular anomaly, carotid arterial diseases, carotid arterial injury, or dissection. Only articles in English, Spanish, or Portuguese were included. A few
articles met the review criteria. Other articles were included by decision of the authors aiming to improve discussion.

**DISCUSSION**

Structural central nervous system (CNS) anomalies in KS are rare, and comprise hydrocephalus, caused or not by aqueductal stenosis, cortical dysplasia, cursing or not with epilepsy, microcephaly, cerebellar atrophy, Dandy-Walker malformation, Arnold-Chiari malformation, syringohydromyelia, dysgenesis/agenesis of the corpus callosum, hippocampal atrophy, polymicrogyria, pachygyria, subarachnoid cysts, and periventricular heterotopias. Despite rare, the association with variable CNS disorders justify brain image study, even if no clinical finding is detectable. In this patient, no other abnormality beyond the microcephaly and white matter lesion was found; the last one probably related to a previous asymptomatic ischemic insult. Otherwise, the lesion was clinically and radiologic monitored, principally because biopsy was not consented and follows without progression or pattern changes.

Congenital heart and great vessels are relatively common, mostly aorta coarctation. Nevertheless, there are some reports addressing associated rare great vessels anomalies such as partial anomalous left pulmonary artery, partial anomalous right pulmonary venous drainage with dilatation of main pulmonary artery and aorta, and double aortic arc. Other rare vascular anomalies also include tortuous retinal vessels and Galen vein dilatation; however, occlusion of an ICA with KS is unprecedented.

This is the first case report, to our knowledge, involving an ischemic transient attack in a young patient with KS. Despite of a report of 25-year-old patient with KS and an acute myocardial infarction in the absence of classical risk factors, suggesting premature atherosclerosis, no one can relate this cause to this patient because subsequent and ample investigation indicates an anatomical anomaly cause, an internal carotid artery occlusion with adequate cerebral perfusion by other arteries and branches.
Spontaneous carotid artery dissection is an important cause of stroke in young adults with a gender predisposition to male sex and mainly risk factor hypertension.[5] Our patient was a 15y-o female during the event, with no hypertension history or minor cervical trauma or manipulation trigger. The principal element in this specific case may be the KS genetic predisposition to connective tissue abnormality, although vessel dilatation be extremely rare.[10] Cervical carotid dissections mostly can safely be conservatively managed,[16] with no difference in efficacy of antiplatelet and anticoagulant drugs,[1] with low rates of recurrence.[16] The patient was discharged with oral AAS for 6 months and rigorous follow up, with an ICA spontaneous recanalization.

CONCLUSION

Kabuki is a rare multiple congenital anomaly syndrome. The characteristic syndromic findings should be recognized so that a comprehensive investigation can be performed. Case reports associated with other anomalies have been important, and can direct future research and maybe treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/ their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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