Craniosynostosis in Kabuki syndrome

Case report

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Niikawa-Kuroki, or Kabuki syndrome (KS), is characterized by distinctive facial features, skeletal anomalies, persisting fingertip pads with dermatoglyphic abnormalities, short stature, and mental retardation. Neurological manifestations and CNS anomalies have been described in some patients with this condition. However, craniosynostosis has been documented in only 4 patients with KS who did not undergo operations. The authors report a case of KS with unicoronal synostosis that constitutes the first documented instance of a patient with this syndrome submitted to surgery. Previous reported instances of craniosynostosis occurring in KS are briefly reviewed. Although rarely documented, craniosynostosis might represent a relatively frequent feature of this syndrome. Kabuki syndrome should be considered at the time of evaluating children with craniosynostosis. The diagnosis of KS can be suspected from the patients' characteristic facial features. Kabuki syndrome appears to be an underdiagnosed condition in the craniosynostosis population. Given that most patients with this syndrome suffer from only mild to moderate mental retardation, surgical correction can be considered in instances of KS with craniosynostosis. (DOI: 10.3171/2010.5.PEDS09286)

Key Words • craniosynostosis • Niikawa-Kuroki syndrome • Kabuki syndrome • craniofacial dysmorphism • skull deformity

In 1981, Niikawa et al.12 and Kuroki et al.10 reported a multiple anomaly/mental retardation syndrome characterized by distinctive facial features, skeletal anomalies, short stature, mental retardation, and dermatoglyphic abnormalities. The condition was named Kabuki makeup syndrome, referring to the resemblance of the patients' characteristic facial expression with that of the makeup used in Kabuki, a traditional Japanese theater.12 The entity is at present best known as Niikawa-Kuroki syndrome or KS (Online Mendelian Inheritance in Man 147920). The molecular basis of KS remains unknown.

The reported prevalence of KS in Japan was estimated to be 1 of every 32,000 people. Although initially regarded as a disease exclusive to the Japanese, there have been several reports that support a widespread ethnic distribution of KS.1,2,6,7,12 Skeletal abnormalities constitute a cardinal feature of the syndrome.10,12 Microcephaly has been reported in 65% of affected individuals and craniosynostosis has been documented in approximately 6% of cases.2 Some reviews of KS do not even mention craniosynostosis as constituting part of the syndrome.13 To our knowledge, there have been only 4 detailed reports of craniosynostosis in the context of KS.5-8 Two of these instances corresponded to trigonocephaly5,7 and 1 each to scaphocephaly8 and bicoronal synostosis.6 None of these patients was submitted to surgery. Thus, our patient represents the first instance of unilateral coronal synostosis in KS and the first patient with this syndrome and craniosynostosis submitted to surgery.

After reviewing the current literature, we believe that KS may be an underdiagnosed condition in the population with craniosynostosis. Because many patients with KS suffer from only mild to moderate mental delay, surgical treatment should be considered in instances of KS with craniosynostosis.

Abbreviation used in the paper: KS = Kabuki syndrome.
Case Report

History and Presentation. This 6-month-old girl presented at the outpatient clinic because of flattening of her right frontal region with a protruding right eye. She was the third child born to a nonconsanguineous and healthy couple. Her 2 live brothers (ages 9 and 4 years) were unaffected. The mother had previously experienced 2 abnormal gestations, ectopic and hydatiform molar pregnancies. The mother’s pregnancy was complicated by gestational diabetes and preterm delivery risk. Corticosteroids were used to induce lung maturation. Polyhydramnios was detected by prenatal ultrasonography. The child was born by vacuum extraction at Week 31 of gestation. Her birth weight was 1650 g and her Apgar score was 8 and 9 at 1- and 5 minutes, respectively. Head circumference at birth was 29 cm. Psychomotor development was slightly delayed for her age. She had 2 previous hospital admissions, one for acute gastroenteritis and failure to thrive, and the other for bronchiolitis.

Examination. The girl's head circumference, height, and weight were below the fifth percentile. There was a flattening of her right frontal region with a mild right-eye proptosis. An osseous ridge was palpated on the baby’s right coronal suture. Most remarkable was the appearance of the child's face (Fig. 1a) with long palpebral fissures, lateral arched eyebrows, eversion of the lateral part of her lower eyelids, blue sclerae, flat nasal base, downturned corners of the mouth, and prominent and posteriorly rotated ears. The girl’s face resembled her mother’s. She also had a small abdominal angioma, an umbilical hernia, and an anteriorly placed anus. Prominent fingertip pads were also present (Fig. 1b). The child's neurological examination was unremarkable except for generalized hypotonia.

A CT head scan showed closure of the right coronal suture and a normal brain (Fig. 1c–e). Perimembranous ventricular septal defect and mild aortic regurgitation were detected by echocardiogram. The skeletal survey showed scoliosis and hypoplastic ulnae. The patient had a normal high-resolution karyotype and normal subtelomeres screening performed using multiplex ligation probe amplification. She also underwent analysis for a craniosynostosis genes panel and the Pro250Arg mutation in fibroblast growth factor receptor 3 (FGFR3) gene, linked to Muenke syndrome. Crouzon fibroblast growth factor receptor 2 (FGFR2)–related mutations and twist gene mutations (linked to Saethre-Chotzen syndrome) have been excluded. In an attempt to rule out submicroscopic rearrangements underlying the Kabuki phenotype, an array-based comparative genomic hybridization study is ongoing.

Operation and Postoperative Course. A bicoronal zig-zag skin incision was performed followed by a standard right frontal craniotomy with orbital advancement. The girl's postoperative period was uneventful. After a follow-up of 18 months, the girl's development is evolving satisfactorily and her facial appearance has improved in regard to craniofacial features of her coronal synostosis (Fig. 1a). However, the child's growth and psychomotor development are mildly delayed. A recent MR imaging
study (Fig. 1f) has shown a small zone of delayed periaxial myelinization within a normal brain.

**Discussion**

**Niikawa-Kuroki (Kabuki) Syndrome**

Kabuki syndrome is a multiple anomaly/mental retardation syndrome characterized by 5 cardinal manifestations: distinctive facial features, skeletal anomalies, short stature, mental retardation, and dermatoglyphic abnormalities. The facial expression is most characteristic and has been compared with the makeup used in Kabuki, a traditional Japanese theater. This appearance explains the initial proposed designation of the condition as “Kabuki makeup” syndrome. Kabuki syndrome may evolve with development of cardiovascular problems as ventricular and atrial septal defects and coarctation of the aorta. The patients often present with feeding difficulties and malabsorption, intestinal malrotation, and anal anomalies. The skeletal defects consist of scoliosis, vertebral abnormalities, congenital hip dislocation, joint hyperextensibility, and short fifth fingers. Anomalous dermatoglyphs and persistence of fetal fingertip pads can be encountered as well. A variety of genitourinary, hematological, and endocrine manifestations have also been reported as part of the syndrome.

The cause of KS is presently unknown and it may possibly be due to sporadic mutations without familial history. Inherited transmission has been reported with some facial resemblance in mothers of patients with KS, suggesting an autosomal dominant inherited condition with variable expressivity. Numerous cytogenetic abnormalities have been reported in KS but none has been definitely regarded as responsible for the syndrome. The role of previously reported chromosomal anomalies in KS etiology, including recently reported duplication of 8p22–8p23, has been discussed elsewhere and is beyond the scope of our paper. Kabuki syndrome has an almost equal sex distribution and is found in all ethnic groups. Initially reported in Japan, an increasing number of patients with KS has been recognized in non-Japanese children. At present, there is no prenatal screening, genetic test, or consensus criteria for the diagnosis of this syndrome. The condition is diagnosed based on the characteristic facial appearance and the other signs reported by Niikawa et al. These peculiar facial features of patients with KS observed by the attending neurosurgeon should prompt a genetics consultation for diagnostic and clinical evaluation of the affected individuals.

**Central Nervous System Anomalies in KS**

Developmental delay, hypotonia, seizures, and mental retardation have often been found in patients with KS. There were no neurologically normal individuals in the Spanish series of 18 cases. Reported neuroimaging findings include arachnoid cysts, enlarged ventricles, aqueduct stenosis with hydrocephalus, Chiari malformation Type I, Dandy-Walker anomaly, cerebellar and brainstem atrophy, polymicrogyria, periventricular heterotopia, and corpus callosum dysgenesis. Our patient had a mild mental retardation but her postoperative MR imaging study did not disclose any major brain abnormality with the exception of a small zone of delayed periaxial myelinization.

**Craniosynostosis in KS**

We have already mentioned that skeletal anomalies constitute one of the cardinal features of KS, scoliosis and vertebral defects are present in 35% and 32% of patients, respectively. Armstrong et al. reported a 65% incidence of microcephaly and 6% craniosynostosis in their reviewed cases of KS. Other cranial anomalies have been reported, including incomplete formation of the frontal bones and digital impressions of the skull. Gillis et al. documented (for the first time) a 2-year-old boy diagnosed with KS with scaphocephaly, enlarged ventricles, scoliosis, and grand mal seizures. Ewart-Toland et al. reported a 9-month-old boy with bicoronal synostosis. David et al. and Geneviève et al. have published 1 case each of trigonocephaly in children with KS. However, according to these reports, none of these patients was submitted to surgery. The origin of coronal synostosis in our patient appears to be related to a primary sutural involvement of probable mesenchymal origin, as no other causes for craniosynostosis, such as uterine abnormalities, oligohydranios, or metabolic diseases, were observed. The child’s phenotype also ruled out the usual features that characterize other known syndromes that evolve with craniosynostosis. After a thorough discussion with the child’s parents, surgical treatment was undertaken mainly for cosmetic reasons, having especially considered the girl’s mild mental delay, and hoping to improve her future social and school integration. In addition, surgery also appeared to be indicated for prevention of the eventual neurological damage that may occur in patients affected with craniosynostosis.

We have reported on a child who received a diagnosis of KS, was affected by coronal craniosynostosis, and underwent an operation. We believe KS may be an underdiagnosed condition in the population with craniosynostosis. The facial features of patients with KS are characteristic and should raise suspicion of the condition by the treating neurosurgeon. However, children suspected of having KS should undergo analysis by a geneticist for definitive diagnosis and further evaluation of other possible systemic anomalies. Patients with KS who present with craniosynostosis can be offered surgical treatment because many individuals with this syndrome present with only mild to moderate mental delay.

**Disclosure**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following: Conception and design: Martínez-Lage, Navarro, Guerrero. Acquisition of data: Navarro, Almagro, Pérez-Espejo. Analysis and interpretation: All authors. Drafting the article: Navarro, Pérez-Espejo. Reviewed final version of the manuscript and approved it for submission: All authors. Study supervision: Martínez-Lage.
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