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Kabuki syndrome: oral and general features seen in a 2-year-old Chinese boy

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Summary. This report describes the case of a young Chinese boy with Kabuki syndrome (KS). KS is a congenital condition characterized by multiple anomalies, especially of the face, and is usually associated with mild to moderate mental retardation. The patient presented with the characteristic facial features of KS and some skeletal and neurological anomalies including a butterfly vertebrae with scoliosis, cerebral atrophy, and irregular dentition. Dental examination revealed screwdriver-shaped incisors and a high arched maxilla, features typical of patients with KS, as well as very poor oral hygiene and early childhood caries. This report includes discussion of the aetiology of KS as well as discussion of the long-term prognosis for this particular patient, and patients with KS in general, with consideration of associated dental and medical issues.

Introduction

Kabuki syndrome (KS; Mendelian Inheritance in Man %147920) is also known as Kabuki make-up syndrome, as sufferers mimic the facial makeup of actors in the Japanese Kabuki theatre. It is a congenital condition characterized by multiple anomalies and usually associated with mild to moderate mental retardation [1,2]. Kabuki syndrome was first identified in the Japanese population [3,4], but has since been reported in many other non-Japanese and non-Asian populations [5–9]. The key features seen in KS are its peculiar facies. Facial features most commonly identified in patients with KS include long palpebral fissures, eversion of the lower eyelids, large ears, highly arched eyebrows, and a flat nasal tip. In addition to these facial features, patients diagnosed with KS also commonly have a short stature and persistent foetal pads on the fingertips and less commonly exhibit numerous other visceral, skeletal, and neurological anomalies [1,8]. In some cases, KS has been accompanied by critical visceral anomalies of the heart [5,10], liver [11], kidneys [11–13], central bronchial airways [14], and diaphragm [14–19].

The development of abnormal dentition associated with abnormal oral anatomy is a skeletal manifestation often reported in patients with KS that may benefit from treatment [20]. Over 60% of patients with KS present with oral anomalies such as widely spaced teeth, screwdriver-shaped or conical incisors, high palate or cleft palate, maxillary recession, microdontia, hypodontia, ectopic upper molars, and malocclusion [2,21,22]. Speech difficulties in patients with KS are thought to be associated with poor oral–motor coordination and hypotonia rather than these structural anomalies [23,24].

This case report describes a Chinese boy diagnosed with KS at an early age. Summaries of his clinical and dental features are included. The possible aetiology of KS and the long-term prognosis for the current patient and for others with KS in general are discussed.

Clinical report

A 2-year-old Chinese boy, diagnosed with Kabuki syndrome, was referred to the Prince Philip Dental Hospital in Hong Kong from a local dental clinic. The reason for referral was that his mother was worried that his front teeth were 'growing together'.

A medical history investigation revealed that the patient was born at 37 weeks gestation and weighed

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2·5 kg. He was admitted neonatally, to a large teaching hospital in Hong Kong, because of meconium aspiration syndrome and was treated with oxygen supplementation via nasal cannulae. He was kept in the hospital for 54 days because of poor feeding ability and hypotonia. Subsequent follow-up visits revealed marked delays in his growth. He was found to be chromosomally normal (46, XY) and did not present with any metabolic disorders. Skeletal dysmorphic features including a butterfly vertebrae at T9 with associated thoracolumbar scoliosis were identified. In addition, a magnetic resonance imaging (MRI) evaluation revealed cerebral atrophy. His facial characteristics were described as typical of KS. Growth retardation, hypotonia, and reduced brain matter such as observed in this case are associated with approximately 73% of KS sufferers [25], 30% and 25% of KS diagnoses, respectively [8]. Therefore, the genetic team at the teaching hospital came to the diagnosis of KS. The clinical genetic service also gave genetic counselling to the mother, and her son's prognosis remains 'guarded'.

Since his diagnosis, he had received ongoing occupational therapy and physiotherapy. He had undergone eye surgery for strabismus and had received oral motor training at a local children's hospital.

Facial characteristics commonly associated with KS were evident on extra oral examination (Figs 1 & 2). Most notably, there were long palpebral fissures, eversion of the lower eyelids, large ears, highly arched eyebrows, and a flat nasal tip. Intraoral examination revealed very poor oral hygiene and symptoms of early childhood caries. Early erupting primary dentition was observed. Central incisors, lateral incisors, and first molars were erupted in all four quadrants. He is not expected to exhibit hypodontia as these are the normal complement of erupted teeth at his age. Notably, the central incisors in the upper jaw showed the screwdriver shape often reported in patients with KS. The exam and radiographs showed no other abnormal or pathological dentition beyond the screwdriver-shaped incisors (Fig. 3). Like the majority (approximately 72%) of patients with KS, our patient had a high arched palate, but he did not have micrognatia, a condition commonly (approximately 40%) found in patients with KS [1].

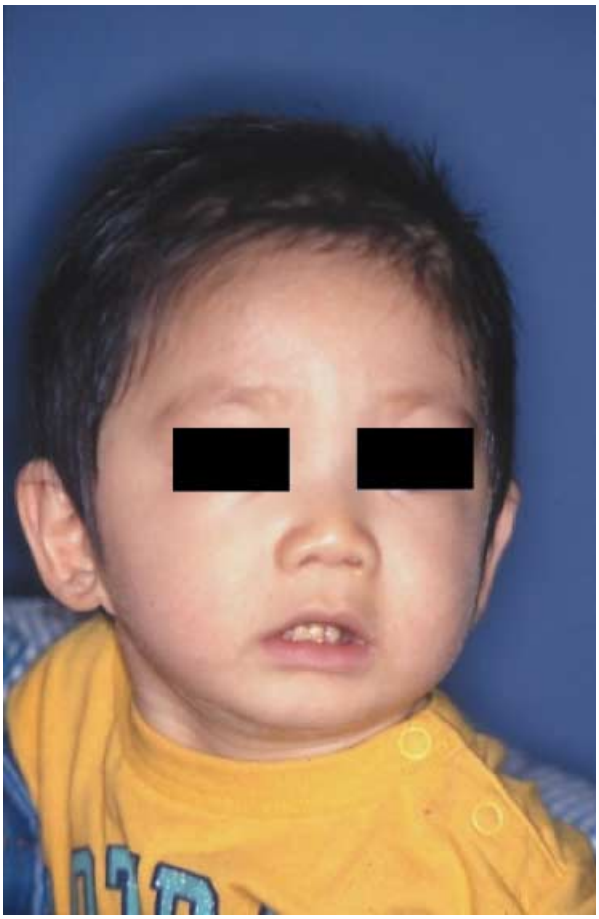

Fig. 1. Facial characteristics of patient diagnosed with KS. Frontal view. Photos were taken at Prince Philip Dental Hospital in Hong Kong on 12/06/2002.

Discussion

Case summary

The cardinal facial manifestations of KS were apparent in this patient. These included long palpebral fissures, eversion of the lower eyelids, large ears, highly arched eyebrows, and a flat nasal tip. In addition to these common features, he also had some skeletal anomalies that resulted in scoliosis and the neurological anomaly of cerebral atrophy. The oral manifestations of KS in the patient thus far were limited to his screwdriver-shaped incisors and high-arched maxilla. Intraoral examination revealed very poor oral hygiene and evidence of early childhood caries. As KS features become more prominent with further development, it is possible that additional anomalies may become apparent as the patient matures.

Aetiology

At present, the aetiology of KS remains undetermined. Recent studies, however, are providing some insight. Patients with KS are generally reported to be euploid with no obvious chromosomal abnormalities.

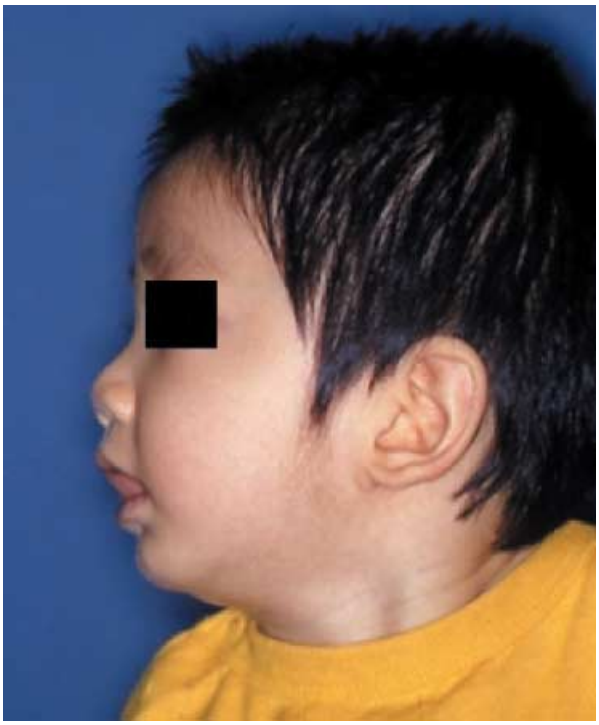

Fig. 2. Facial characteristics of patient diagnosed with KS. Profile. Photos were taken at Prince Philip Dental Hospital in Hong Kong on 12/06/2002.

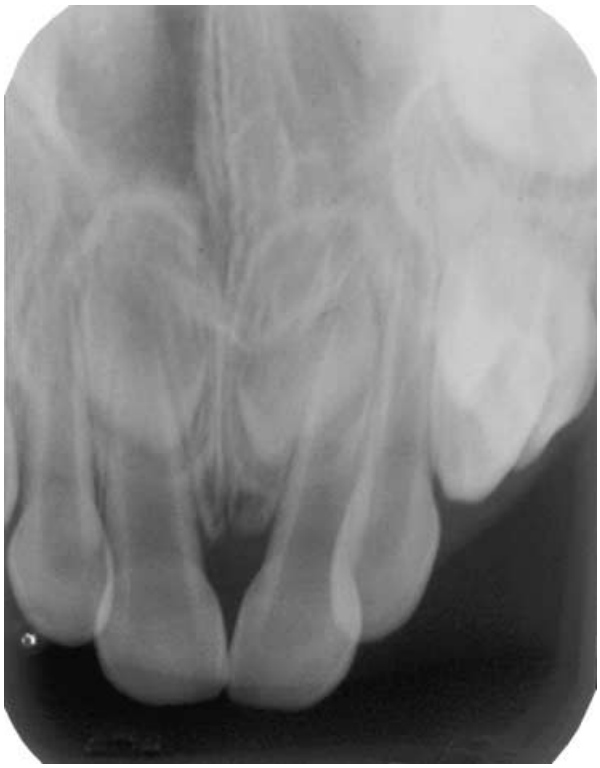

Fig. 3. Radiograph of patient's upper incisors. Note the screwdriver shapes of the upper central incisors, an observation commonly reported in patients with KS. Radiograph was taken at Prince Philip Dental Hospital in Hong Kong on 12/06/2002.

There is no evidence for sex-linked transmission of KS or gender-modulated expression of KS [1]. Observations of possible mild KS-like symptoms in family members, especially parents, of KS-affected individuals are consistent with the view that KS may be a genetic disorder with a low or variable penetrance [1,22,25,26].

If the development of KS is inherited, an identical twin of a KS-affected person would be expected to be affected as well. Both concordant [27] and discordant pairs of twins, however, have been reported [7]. Thus, a genetic mutation obligatory to the KS phenotype in the case of the discordant twins would have to have occurred post-zygotically. These findings and the most often sporadic incidence of KS are difficult to fit with the hypothesis that KS may be transmitted by simple autosomal dominant inheritance. If an autosomal dominant allele accounts for sporadic and familial KS cases, it may have quite low and variable expressivity [26,28]. It may be that an increased likelihood for the development of KS is inherited and that an inherited genetic factor may interact with multifactorial influences in development.

A recent study by Milunsky and Huang [29] presents compelling evidence that a genetic microduplication may cause KS. Comparative genetic hybridization revealed that six of six unrelated patients across multiple ethnic groups with sporadic KS had duplications of chromosome 8p22–8p23·1. The findings were confirmed by bacterial artificial chromosome–fluorescent *in situ* hybridization (BAC–FISH) genetic analysis. Notably, the 20 control subjects and the unaffected parents of the patients with KS did not exhibit this duplication. Thus, these findings indicate that sporadic KS may result from spontaneous microduplication in the region of chromosome 8p22–8p23·1 during gametogenesis [29]. It remains to be determined whether this genetic defect occurs more broadly in the patient population with KS and whether it ever occurs in the absence of the KS phenotype. It is possible that the exact region duplicated within chromosome 8p22–8p23·1 may determine which of the variable features of KS are expressed in the individual. Additionally, the severity of phenotype expressed with gene duplication disorders may depend on the number of repeats, as in Huntington's disease. These features of the relationship

between the chromosome 8p22–8p23·1 microduplication and the incidence and expression of KS remain to be determined.

Prognosis

Of particular concern in this case was the observations that he had very poor oral hygiene and evidence of early childhood caries. His mother was advised of the importance of maintaining good dental hygiene together with regular dental care to prevent his nursing bottle syndrome from progressing into severe tooth decay. She was also educated about the dangers of allowing him to fall asleep with sweet liquids left on his teeth for extended periods of time and given the recommendation that if the child needs to be soothed, a pacifier, or bottle containing water would be preferable. He will continue as a patient at Prince Philip Dental Hospital for his ongoing dental care. The long-term outlook for this child's dental health is dependent on proper compliance with these recommendations.

Recent findings suggest that patients with KS may be more susceptible to many other general medical concerns as they mature. There is evidence that patients with KS may be prone to obesity and diabetes mellitus during adolescence and adulthood [9,13,30,31]. Diabetes mellitus is associated with loss of calcium and phosphorus in tooth enamel and antidiabetic medication may alleviate this problem [32]. Therefore, it is critical that patients and their caregivers be advised to be aware of signs of the development of diabetes. Moreover, this link underscores the importance of regular medical and dental care and appropriate preventive care for tooth decay in patients with KS.

Several reports have also indicated that KS may be accompanied by a weakened immune system and increased susceptibility to infection [8,11,25,31]. In addition, depression in early adulthood has been reported in patients with KS [13]. It is not known whether there is an organic predisposition for depression associated with KS or if it manifested independently. However KS patients with depression have been reported to respond well to antidepressive medication [13]. With proper regular medical care, the development of serious infections and/or depression may be averted.

Although patients with KS exhibit mild to moderate mental retardation, they are capable of developing sufficient work and life skills to live relatively independently. Thus, occupational and speech therapy may greatly improve quality of life in these patients. They have been reported to exhibit very good memory, to have affable temperaments, and to respond especially well to music therapy and music-associated training [9]. The long-term prognosis of this patient remains guarded; however, with access to continued medical, dental, and behavioural support, his prognosis is improved and he may enjoy a good quality of life.

What this paper adds

- Kabuki syndrome is a rare syndrome and this report adds further insight into the condition and its interaction with other more common conditions.

Why this paper is important for paediatric dentists

- It is important that non specialist and specialist dental surgeons be kept aware of rare syndromes they may encounter from time to time in their practice, and the relevant treatment options as these syndromes may interact with several common conditions such as diabetes mellitus.
- The prognosis for children with Kabuki syndrome is guarded, and they may never see adulthood.
- Paediatric dentists will therefore be the ones they rely on for dental care.

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