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Mini Review

Kabuki syndrome: a review

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Kabuki syndrome (KS) (Kabuki make-up syndrome, Niikawa–Kuroki syndrome) is a multiple malformation/mental retardation syndrome that was described initially in Japan but is now known to occur in many other ethnic groups. It is characterized by distinctive facial features (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears), skeletal anomalies, dermatoglyphic abnormalities, short stature, and mental retardation. A number of other manifestations involving other organ systems can aid in the diagnosis and management of KS. This review will focus on the diagnostic criteria, the common and rare features of KS by organ system, and the possible etiology of this interesting condition.

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Kabuki syndrome (KS) (Kabuki make-up syndrome, Niikawa–Kuroki syndrome) is a multiple congenital anomaly/mental retardation syndrome that was first described simultaneously by two groups in Japan, Niikawa et al. (1) and Kuroki et al. (2). They described a group of patients who had characteristic facial features, skeletal anomalies, dermatoglyphic abnormalities, short stature, and mental retardation. Because the facial features of the patients resembled the make-up of actors in Kabuki, the traditional Japanese play, the term 'Kabuki make-up syndrome' was suggested by Niikawa et al. (1). This condition has also been referred to as the Niikawa–Kuroki syndrome, after the two groups who initially described it. However, the most common name by which this condition is currently known in the literature is KS; the 'make-up' portion of the original name has been discarded secondary to concern that it might cause parental confusion or offense.

The most striking aspects of KS are the unique facial features, which usually prompt the clinician to consider this diagnosis. Patients often have long palpebral fissures with eversion of the lateral one-third of the lower eyelid, arched eyebrows with sparseness of the lateral one-third, short columella with depressed nasal tip, and prominent ears (Figs 1 and 2). There is also a range of other congenital anomalies and health-related issues, which accompany this syndrome. The purpose of this article is to review both common and rare manifestations of KS and to discuss the possible underlying genetic etiology responsible for this condition.

Prevalence

Based on a total of 10 patients identified in a specific prefecture of Japan in a 16-year period, the prevalence of KS in the Japanese population has been estimated to be 1/32,000 (3). Because all of the initial reports originated from Japan, it was thought that this condition was much more common in the Japanese population. However, since 1981, there have been increasing reports of KS in a wide variety of ethnic groups, including patients of Northern European, Brazilian, Filipino, Vietnamese, Arab, East Indian, Chinese, Mexican, and African descent (4–12). Until recently, this condition was almost certainly underdiagnosed outside of the Japanese population, and now that information about KS has become available worldwide, the true prevalence of this syndrome outside of Japan will hopefully be forthcoming.

A recent article by White et al. estimated the minimal birth prevalence of KS in Australia and New Zealand to be 1/86,000 (13). However, they felt that this may actually be an underestimate of the prevalence of KS in their population because of under-recognition of the diagnosis. Based on the many reports from other populations, we would presume that the prevalence will approximate that seen in the Japanese population.

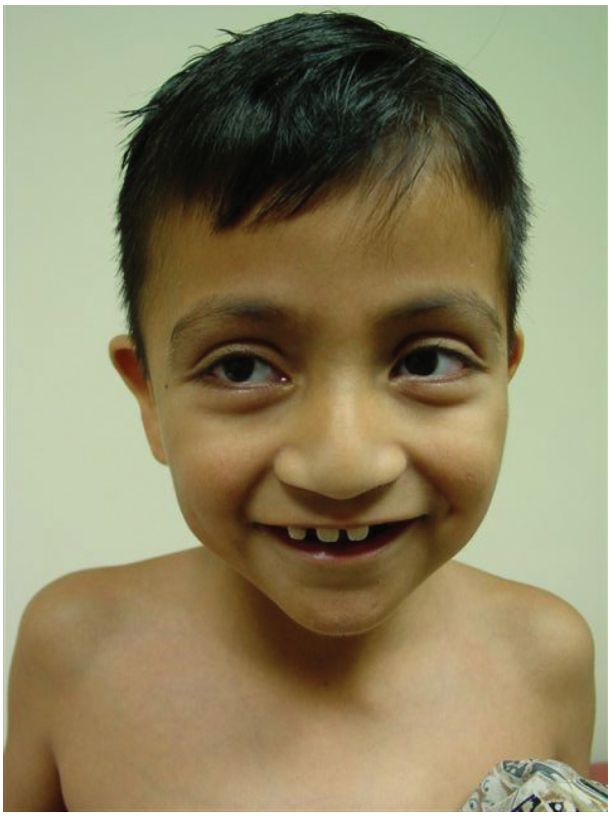

Fig. 1. Facial features of Kabuki syndrome. Note the long palpebral fissures with lower lateral eyelid eversion, dispersed lateral one-third of the eyebrows, and widely spaced teeth.

Diagnostic criteria

Currently, there are no consensus diagnostic criteria for KS and there is no clinically available genetic test to confirm the diagnosis. In 1988, Niikawa et al. reported on the clinical findings in 62 patients diagnosed with KS (3). Based on the findings in these patients, five cardinal manifestations were defined. These included a 'peculiar face' (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears) in 100% of their patients, skeletal anomalies (deformed spinal column with or without sagittal cleft vertebrae, and brachydactyly V) in 92% of their patients, dermatoglyphic abnormalities (fingertip pads, absence of digital triradius c and/or d, and increased digital ulnar loop and hypothenar loop patterns) in 93% of their patients, mild to moderate mental retardation in 92% of their patients, and postnatal growth deficiency in 83% of their patients. There have also been a number of less frequent findings reported in KS, including visceral abnormalities, premature breast development in females, and susceptibility to frequent infections. Table 1 summarizes some of the major and minor features found in KS.

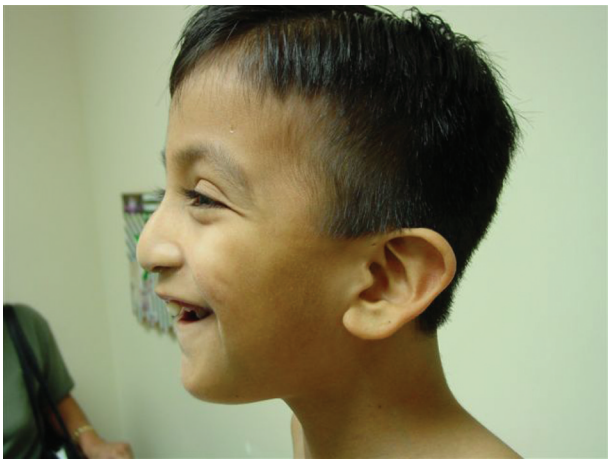

Fig. 2. Profile of patient with Kabuki syndrome. Note the ear pit and the short columella leading to a depressed nasal tip.

In the literature, there has been discussion as to whether the phenotype of KS varies based on ethnic background. Most authors agree that the facial phenotype of KS is easily recognizable in patients from all ethnic backgrounds (10, 11). The exception to this is a report of an American black male who had the external eyelid findings typical of KS without the arched eyebrows. The authors felt that his nasal configuration was heavily influenced by his racial background, such that it was not classical for KS (14). This patient was excluded from the review of KS by Niikawa et al. based on the fact that he lacked the characteristic facial features of KS (3). A follow-up letter from the original authors reaffirmed their diagnosis in this patient and again suggested that the racial background of the patient obscured the full facial phenotype of KS in this instance (15).

Other manifestations of this condition also appear to vary somewhat based on ethnic background. Philip et al. reported findings in 16 non-Japanese patients with KS (10). In their review, 11/16 patients had significant neurological symptoms aside from mental retardation, including hypotonia and seizures, compared with only 8/62 patients reported by Niikawa et al. (3). Joint hypermobility also appeared to be more common in the non-Japanese population. This is supported by data from Schrander-Stumpel et al. in which 29 non-Japanese patients were studied (16). In this group, again there appeared to be an increase in hyperlaxity and neurological problems including neonatal hypotonia, feeding problems, and microcephaly. Wilson et al. similarly reported an increased incidence of neonatal complications, abnormal dentition, hypotonia, and microcephaly in non-Asian KS patients (17).

Despite these racial differences, it has been suggested that minimal criteria for the diagnosis of

Table 1. Summary of major and minor features of Kabuki syndrome (KS)

Clinical feature	Patients with KS (cumulative percent)[a]
Major features	
Characteristic face	100
Long palpebral fissures	99
Abnormal dermatoglyphics	96
Short nasal septum	92
Persistent fingertip pad	89
Malformed ear	87
Arched eyebrows	85
IQ < 80	84
Prominent ears	84
Depressed nasal tip	83
Short 5th digit	79
Joint laxity	74
High-arched palate	72
Abnormal dentition	68
Hypotonia	68
Short stature (<2.0 SD)	55
Ptosis	50
Minor features	
Cardiovascular anomaly	42
Cleft lip and/or cleft palate	35
Scoliosis	35
Deformed vertebra/rib	32
Blue sclerae	31
Kidney/urinary tract malformation	28
Premature thelarche	28
Hearing loss	27
Lower lip pits	27
Cryptorchidism	24
Preauricular pits	22
Hip dislocation	18
Seizures	17

[a]Cumulative data for patients with KS are derived from Matsumoto et al. (20).

KS be as follows: long palpebral fissures with eversion of the lateral portion of the lower eyelids; broad, arched eyebrows with lateral sparseness; short nasal columella with depressed nasal tip; large, prominent or cupped ears; and developmental delay or mental retardation (18). In addition, prominent fingertip pads are a frequent and relatively specific finding (19). In the authors' experience, the majority of patients with KS have at least several of these features that lead to an overall gestalt suggestive of KS. The remainder of this article will focus on both frequent and rare aspects of KS, differential diagnosis, possible etiology, and prognosis.

Manifestations by organ system

Table 2 summarizes the suggested evaluations and management of patients with KS by organ system.

Growth and feeding

Patients with KS often demonstrate normal growth parameters at birth. However, most patients develop failure to thrive and postnatal growth retardation during the first year of life, which becomes more pronounced with age. It is not uncommon for patients to have height 2 standard deviations or more below the mean (20). Recently, a study by White et al. found that over half of the patients with failure to thrive in infancy went on to develop an increased body mass index or obesity in middle childhood or adolescence (13). In support of this, Kluijt et al. described a male with KS who developed obesity at age 13 despite a normal diet (21). Medical practitioners should be aware of this increased risk for obesity in adolescence and consider referral to a nutritionist, if necessary.

Microcephaly is found in approximately one-quarter to one-third of patients with KS (5, 16, 20). However, as mentioned previously, there may be an increased incidence of microcephaly in non-Japanese patients of up to 60% *vs* as low as 6% in Japanese patients (3, 17). However, head size does not appear to be a predictor of final developmental outcome in patients with KS (13).

Complete or partial growth hormone deficiency has been rarely reported (3, 22–24). At least two of the patients reported with partial growth hormone deficiency had a somewhat efficacious response to exogenous growth hormone therapy, with one patient's height velocity increasing from 3.5 cm/year to 5.3 cm/year and another patient's height velocity increasing from 3.6 cm/year to 11.2 cm/year after instituting growth hormone therapy (22, 24). Growth problems may be exacerbated by feeding difficulties, which are quite common (approximately 70%), gastroesophageal reflux, or malabsorption (18). Patients who exhibit poorly coordinated suck and swallow may require gastrostomy tube placement.

Neurological

As mentioned previously, hypotonia is a frequent feature of KS and may be more common in non-Japanese patients. This feature may be exacerbated by joint hyperextensibility and tends to improve with age. The issue of an underlying neuromuscular abnormality in KS patients has been raised because of the observation that some patients with KS have ptosis, an expressionless face, and a drooping lower lip. In a study by Burke et al., dysarthria and dyspraxia were common features (11). When performed, muscle biopsies in KS patients have been normal (10, 16). In

Table 2. Summary of suggested evaluations and management of patients with KS by organ system

Organ system	Evaluation	Management
Growth and feeding	Monitor height, weight, and head circumference	Consider referral to endocrinology if growth velocity abnormal Consider pH probe study if there is evidence of gastroesophageal reflux Consider barium study in those with abnormal suck or swallow Consider gastrostomy tube placement in those with severe feeding difficulties Consider nutrition consult if patient develops obesity in later childhood
Neurological	Evaluate for hypotonia and seizures	Consider referral to pediatric neurology Consider physical therapy evaluation for hypotonia Standard epileptic treatment for patients with seizures
Otolaryngologic findings and hearing	Follow expectantly for otitis media	Consider ear, nose, throat (ENT) referral for chronic otitis media Annual hearing evaluations Amplification is indicated for those patients with hearing loss
Craniofacial and dental	Careful examination of palate at time of diagnosis Dental evaluation as a toddler	Consider ENT referral in those with palatal issues Consider referral to orthodontics if hypodontia or malocclusion detected
Ophthalmologic	Formal ophthalmology examination at time of diagnosis	Any ocular abnormalities detected should be treated and/or followed by an experienced pediatric ophthalmologist Annual vision screening
Cardiovascular	Echocardiogram at time of diagnosis	Referral to cardiology or cardiovascular surgery as indicated
Respiratory	Monitor for obstructive sleep apnea	Consider a sleep study Consider referral to ENT
Renal and genitourinary	Renal ultrasound at time of diagnosis Careful physical examination for cryptorchidism	Consider referral to nephrology or urology, as indicated
Gastrointestinal (GI)	Careful physical examination in neonates for GI anomalies	Standard surgical correction of GI abnormalities
Musculoskeletal	Radiographs of the spine at diagnosis Monitor for the development of scoliosis	Consider referral to orthopedics for spinal abnormalities, scoliosis, or recurrent joint dislocations
Endocrinologic	In females, follow expectantly for possible premature thelarche	Extensive endocrinologic workup for premature thelarche is unnecessary
Immunologic/hematologic	Monitor for frequent sinopulmonary infections, evidence of ITP, or autoimmune hemolytic anemia	Immunoglobulin levels in those patients with multiple infections Consider referral to pediatric immunology Consider IVIG in those patients with documented immunodeficiency
Development and behavior	Monitor developmental milestones Psychoeducational testing in all patients who demonstrate cognitive difficulties	Consider referral to a developmental pediatrician or psychiatrist Early intervention services should be instituted in infancy In the older child, special education services may be warranted

ITP, idiopathic thrombocytopenic purpura; IVIG, intravenous administration of IgG.

those patients with hypotonia, dysarthria, or dyspraxia, physical therapy and speech therapy can be helpful.

Approximately 10 to 39% of patients with KS have seizures (16, 18). There does not appear to be a specific seizure type associated with KS, although the majority of patients have localization-related epilepsy with a favorable seizure outcome (25). The age of onset of seizures can vary from the neonatal period up to 12 years of age (10, 18, 25).

Recently, Oksanen et al. reported three patients who had bilateral spikes or polyspikes in the temporo-occipital regions on electroencephalograms (EEGs) (26). The authors suggested that such posterior focal spikes may be a typical finding in KS, despite the fact that other EEG findings have been reported in patients with KS (18, 25).

Fig. 3. Female patient with Kabuki syndrome. Note the long palpebral fissures, bilateral ptosis (left greater than right), and prominent, cupped ears.

However, none of the patients reported by Oksanen et al. developed these EEG findings before the age of 8 years, and only two of the three patients had clinical seizures (26). Therefore, EEG studies done in early infancy or childhood might miss this finding. Further evidence for this includes a report of a patient who developed seizure activity at the age of 10 years and was also found to have polyspikes and polyspike/slow wave complexes over the left temporoparietal region associated with bilateral occipital polymicrogyria (27). Therefore, Oksanen et al. suggested that disorders of cortical development, including subtle abnormalities that might be missed with modern imaging techniques, could be the cause of the EEG findings and seizures in KS patients (26).

Head-imaging studies in KS patients have often demonstrated non-specific cerebral atrophy or enlarged ventricles (18). Major structural brain abnormalities, including polymicrogyria, aqueductal stenosis resulting in hydrocephalus, and large arachnoid cyst requiring removal, have all been rarely reported (27–30).

Otolaryngologic findings and hearing

Dysmorphic pinnae, otitis media, and hearing loss are some of the most common otolaryngologic findings in KS (20, 31). Prominent, large, and cup-shaped ears characterize the type of ear dysmorphia (Fig. 3). Ear pits have also been described in approximately 20% of patients (16, 18, 20) and can aid in the diagnosis. Otitis media appears to be a frequent complication, which can be exacerbated by the finding of cleft palate in approximately one-third of patients (18, 20) and by the finding of increased susceptibility to infections in up to two-thirds of patients (3, 16). It should be noted that while frequent infections are common in KS, laboratory evidence of immune dysfunction has been documented only rarely (see section on *Immunologic/hematologic*). Hearing loss has been reported in up to 82% of patients ascertained through a multidisciplinary craniofacial clinic (31), but the true prevalence of hearing loss is probably closer to 20–30% (3, 10, 18, 20). Hearing loss has been characterized as conductive, sensorineural, or mixed (11, 31, 32).

Craniofacial and dental

In addition to the typical facial features mentioned previously, Kawame et al. identified a unique configuration of the philtrum, which they described as trapezoidal in shape (18). By this, they meant that the prolabium was flared as it met the upper portion of the vermilion border in some patients.

Cleft palate or cleft lip/palate has also been described in approximately one-third of patients, while high arched palate has been seen in almost two-thirds of patients (3, 11, 18, 20, 33, 34). Burke et al. was the first group to suggest that KS is an underdiagnosed condition in the cleft lip/palate population (11). Lip pits have also been described in several patients with KS (7, 20, 35) and will be discussed further under the section entitled *Differential diganosis*.

Dental anomalies are seen in over 60% of patients with KS (33). The most common finding is hypodontia, particularly of the central and lateral incisors and the premolars. Other manifestations include malocclusion, microdontia, and a small dental arch. In addition, widely spaced teeth with abnormal shape, including screw driver-shaped incisors and conical teeth, have been described and may aid in the diagnosis (12, 33, 36, 37). Maxillary recession and mid-face hypoplasia may predispose patients with KS to the development of a small dental arch and malocclusion (33).

Ophthalmologic

Ophthalmologic abnormalities have been found in approximately one-third to one-half of patients with KS. The most common findings include ptosis, strabismus, and blue sclerae (Fig. 3) (20, 21). Less common findings have included refractive errors, delayed visual maturation with nystagmus, Peters' anomaly, palsy of the third cranial nerve, Marcus Gunn's phenomenon (involuntary eyelid closure with jaw movement),

cataracts, optic nerve hypoplasia, megalocornea, microcornea, and retinal and ocular colobomas (5, 18, 20, 21, 38–40). Because many of these findings have the potential to significantly impact vision, it has been suggested that all patients with KS undergo an initial ophthalmologic examination (21).

Cardiovascular

In the original series of patients reported by Niikawa et al. (1) and Kuroki et al. (2), only one patient was noted to have a congenital heart defect that consisted of an atrial septal defect (ASD) and hypertrophic cardiomyopathy. Ohdo et al. was the first group to suggest that there may be an increased incidence of congenital heart defects in patients with KS (41). They reported on two patients with KS and heart defects. The first patient had a ventriculoseptal defect (VSD) which closed spontaneously and the second patient had a complex heart defect consisting of a double outlet right ventricle, a patent ductus arteriosus, and a coarctation of the aorta. Since that time, there have been many different congenital heart defects described in patients with KS and the prevalence of heart defects in this population has been estimated to be between 28 and 80% (16, 39, 42), although the true incidence of such defects is more likely to be around 40–50% (18, 20, 31). The most common finding appears to be juxtaductal coarctation of the aorta, a relatively rare heart defect, followed by VSD and ASD (39, 43). Interestingly, coarctation of the aorta in KS appears to be much more common in males than in females. The sex distribution of VSD and ASD is not as straight forward, with some authors noting an increased incidence of both VSD and ASD in female patients with KS and other authors finding no sex difference (39).

Respiratory

Respiratory abnormalities in KS are relatively uncommon, although Peterson-Falzone et al. reported airway problems in 58% of patients who presented to a multidisciplinary craniofacial clinic (31). Recurrent pneumonia appeared to be the most common problem, but this may actually be related to immune dysfunction, which will be discussed in a separate section, as opposed to true airway abnormalities. Obstructive sleep apnea requiring either tonsillectomy or tonsillectomy with adenoidectomy was found in several patients. Two patients have been reported with stenosis of the central airways (32).

Diaphragmatic abnormalities have also been rarely reported, including congenital diaphragmatic hernia, eventration of the diaphragm, and paralysis of the diaphragm (6, 10, 19, 32, 44–46). Diaphragmatic abnormalities appear to be much more commonly found in non-Asian patients (45).

Renal and genitourinary

Renal anomalies are present in over 25% of patients with KS (20) and include malposition of the kidneys, hydronephrosis, renal hypoplasia or dysplasia, and fusion defects of the kidneys, such as horseshoe kidney (3, 5, 18). One patient with markedly dysplastic kidneys required transplantation (47). Iwama et al. was the first group to report a patient with KS and ureter abnormalities, which consisted of a megaureter (48). Since then, duplication of the collecting system, ureteropelvic junction obstruction, and hydroureter have also been reported (18, 47).

Cryptorchidism has been reported in approximately 25% and small penis has been described in approximately 10% of males with KS (3, 5, 10, 20). Hypospadias has also been reported in males (9).

Gastrointestinal

Gastrointestinal abnormalities in KS are rare, with an incidence of approximately 5% (3, 20). While malrotation of the intestines has been reported in several patients (3, 29, 40), the majority of patients have abnormalities of the anus or rectum in the form of anal atresia, anovestibular fistula, or anteriorly placed anus (7, 18, 49). Biliary atresia has also been reported, as has neonatal sclerosing cholangitis that required a liver transplantation (20, 32, 47).

Musculoskeletal

Skeletal abnormalities are common in KS and are used as part of the diagnostic criteria for this condition. The initial reports by Niikawa et al. (1) and Kuroki et al. (2) sited short and incurved fifth digits with short fifth metacarpals, cone-shaped epiphyses of the proximal second through fifth phalanges, dislocation of the hip joints, and various vertebral anomalies (butterfly vertebra, sagittal cleft, narrow intervertebral disc space, and scoliosis). Cranial abnormalities including coronal synostosis, metopic synostosis, incomplete development of the frontal and/or maxillary sinuses, digital impression of the skull, and

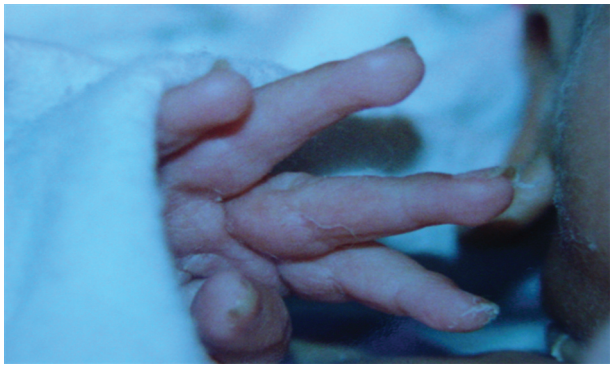

Fig. 4. Fingertip pads in an infant with Kabuki syndrome.

underdevelopment of the mastoid processes have been found in a handful of patients (3, 18, 47).

Joint hypermobility is seen in one-half to three-quarters of patients, and joint dislocations are not uncommon, particularly of the hips, patellae, and shoulders (18, 20, 50). Procollagen studies in at least one patient were normal (18). The finding of joint hypermobility tends to improve with age. Inguinal and umbilical hernias have also been reported in approximately 10% of patients (3, 10, 20).

Dermatoglyphics

Over 90% of patients with KS have unusual dermatoglyphic patterns, including fingertip ulnar loop patterns, absence of digital triradius 'c' or 'd', interdigital triradius 'bc' or 'cd', hypothenar loop patterns, and ulnar loop patterns in the fourth interdigital area. In addition, the vast majority of patients have also been found to have persistent fingertip pads (Fig. 4), which are clue to the diagnosis (1–3, 20, 51).

Ectodermal

Aside from dental abnormalities which have already been discussed in the section entitled *Craniofacial and dental*, patients with KS can have other abnormalities of the hair and nails similar to findings in patients with various types of ectodermal dysplasias. Specifically, absent, hypoplastic and/or fragile nails, brittle hair with trichorrhexis nodosa, twisting of the hairshafts, irregularity of the hair diameter, and congenital alopecia areata have been noted (5, 6, 8, 11, 37, 52). In addition, hypopigmented and hyperpigmented skin lesions have been rarely reported (5, 52).

Endocrinologic

A number of endocrinologic abnormalities have been described in patients with KS. The most common finding, which is present in about one-quarter of females with KS, is isolated premature thelarche, with breast development as early as 4 months of age (3, 10, 20, 22, 52, 53); however, true central precocious puberty has also been rarely reported (28, 35, 53). Pescovitz et al. theorized that premature thelarche and central precocious puberty represented different ends of the spectrum of precocious activation of the hypothalamic luteinizing hormone-releasing hormone (LHRH) neurons (54). Not surprisingly, elevated gonadotropin levels, particularly isolated increases in follicle-stimulating hormone (FSH), have been reported in KS patients with either premature thelarche or central precocious puberty (35, 53). Although the underlying etiology for the precocious sexual maturation is unknown, Kuroki et al. postulated that it could be secondary to low hypothalamic sensitivity to the suppressive effects of sex hormones on gonadotropin secretion (53).

Growth hormone deficiency, hypoglycemia, congenital hypothyroidism, and insulin-dependent diabetes mellitus are all rare findings in KS (3, 13, 18, 20, 22, 52, 55), and at least one patient has been reported with primary ovarian dysfunction resulting in markedly delayed sexual development (38).

Immunologic/hematologic

An increased susceptibility to infections has been reported in approximately 60% of patients with KS (3, 16). In particular, KS patients have a propensity to the development of otitis media, upper respiratory tract infections, and pneumonia. It is unclear whether the otitis media is truly secondary to an underlying immunologic abnormality or whether it is related to the finding of cleft palate or other craniofacial abnormalities, such as Eustachian tube anomalies, that could predispose to middle ear infections (9). However, recurrent otitis media has been reported in a number of patients without cleft palate (31). Severe immunodeficiency with hypogammaglobulinemia requiring intravenous administration of IgG (IVIG) has been reported in several patients (18, 56, 57). In addition, acquired hypogammaglobulinemia with anti-IgA antibody, autoimmune hemolytic anemia, polycythemia, and idiopathic thrombocytopenic purpura (ITP) have each been rarely reported (3, 18, 52, 57). There has also been one report of a patient with IgA deficiency which was felt to manifest as an autoimmune disease consisting of both Hashimoto thyroiditis and vitiligo (47).

One patient has been reported with low levels of IgG and IgA, a history of recurrent infections, and pre-B-cell acute lymphoblastic leukemia (46). The authors speculate that immunodeficiency in KS might predispose patients to the development of malignancies. However, further studies evaluating this possible association need to be performed.

Development and behavior

Mental retardation, defined as an intelligence quotient (IQ) of <70, is considered a cardinal manifestation of KS. In a review of 62 patients with KS by Niikawa et al., 92% had some degree of mental retardation (which they defined as an IQ of <80), mainly in the mild to moderate range (3). Of the patients without mental retardation, all patients had an IQ of 83 or less. Since the time of that review, there have been multiple reports of patients with KS and normal intelligence (5, 30, 33, 58), such that a more recent review by Matsumoto et al. estimates that one-sixth of patients with KS have normal intelligence (20). However, there have also been reports of more severely affected individuals, including individuals with IQs of <35 (8, 38, 50). No consistent cognitive pattern has been described in KS but a decline in IQ over time has been rarely reported (8, 38).

Patients with KS appear to have particular delays in speech and language acquisition as well as articulation abnormalities. Articulation problems may be exacerbated by oral-motor hypotonia, poor coordination, and craniofacial anomalies (11, 59). A recent study of speech characteristics by Upton et al. demonstrated that pitch, loudness, and prosody did not mature over time in two adolescent patients despite improvements in articulation (59). Therefore, maturation of speech characteristics may be delayed or absent in KS patients, making speech noticeably different from adolescent peers.

Several patients have been found to have autism or autistic-like behavior, with difficulties in both communication and peer interactions (8, 26). However, a recent study of 27 patients with KS revealed good socialization skills, ease with strangers, and an affable nature despite the existence of poor eye contact (13). In addition, parents of these patients reported excellent long-term memory for faces, music lyrics, events, and dates. Many patients appeared to have a particular love of music with musical aptitude outside that found in their families. In several children, music proved to be an excellent tool to teach new concepts or skills. Knowledge of this may help parents and teachers devise more effective educational plans for patients with KS.

Differential diagnosis

There are a number of genetic syndromes that each shares some characteristics with KS. Patients with 22q11 deletion syndrome (velocardiofacial syndrome, DiGeorge syndrome) can have cleft palate, cardiac malformations, and renal anomalies, which are all features that can be seen in KS. However, when evaluated, patients with KS have not been found to have microdeletions in the 22q11 region, making a common etiology and pathogenesis for these two disorders unlikely (43, 56, 60).

Patients with KS can have clinical features in common with patients who have van der Woude's syndrome (VWS), an autosomal dominant condition in which cleft lip/palate, lip pits, and hypodontia are found. In 1999, however, Makita et al. demonstrated that KS was not caused by a microdeletion in the VDS1 critical region on chromosome 1q32–q41 (23).

One of the more unusual features of KS is the persistent fingertip pads. This feature has also been reported in FG syndrome, Rubinstein–Taybi syndrome, Fryns syndrome, and Weaver syndrome (19). However, the distinctive facial features of KS should allow one to distinguish it from these other conditions.

KS and Turner's syndrome also share many features, including a propensity for patients to have coarctation of the aorta. In fact, there have been multiple reports of patients with KS or KS-like features and either abnormalities of the X chromosome or 45,X cell lines, which will be discussed further in the next section (3, 61–64).

Etiology, pathogenesis, and genetics

The cause of KS is currently unknown. Numerous cytogenetic abnormalities have been reported in patients with KS or KS-like features, including an interstitial duplication of 1p [dup(1)(p13.1p22.1)], an inherited balanced translocation between chromosomes 3 and 10 [t(3;10)(p25;p15)], an inherited paracentric inversion of the short arm of chromosome 4 [inv(4)(p12pter)], a partial 6q monosomy with partial 12q trisomy [der(6)t(6;12)(q25.3;q24.31)], an inherited pseudodicentric chromosome 13, an inherited balanced translocation involving 15q and 17q [t(15;17),(15q;21q)], a pericentric inversion of the Y chromosome, ring Y, ring X, and 45,X (3, 39, 42, 61–68) (Table 3). However, the only cytogenetic abnormalities that have been found repeatedly are those that involve the X chromosome, which have led some authors to postulate that KS may be due to abnormalities

Table 3. List of previously reported chromosome anomalies in patients with Kabuki syndrome (KS) or KS-like features

Chromosome aberration	De novo/familial	Reference
dup(1)(p13.1p22.1)	De novo	(65)
t(3;10)(p25;p15)	Familial	(39)
inv(4)(p12pter)	Familial	(66)
der(6)t(6; 12)(q25.3;q24.31)	De novo	(67)
dup 8p22–8p23.1	De novo[a]	(72)
psu dic(13)	Familial	(68)
t(15;7)(15q;1q)	Familial	(42)
inv(Y)(p11.2q11.23)	Familial	(3)
45X,r(X)(p11.2q13) or r(Y)(p11.2q11.2)	Not stated	(3)
45X/46,X,r(X)	Presumably de novo	(62, 64)
45X/46,X,r(X)(p11.2q13)	Presumably de novo	(63)
45, X	Presumably de novo	(61)

[a]Two parents of two different KS patients with this duplication were found to have a heterozygous inversion at 8p23.1.

involving the pseudoautosomal region of the X chromosome (3, 39). Interestingly, Matsumoto et al. pointed out that those patients with KS-like features and ring X tend to have more severe manifestations than is typical for KS without ring X (20). Therefore, they postulated that ring X may lead to KS-like features but is most likely causally different from KS.

The majority of cases of KS are sporadic and the sex ratio is nearly equal. A recent review by Matsumoto et al. found the male-to-female ratio among 251 patients with KS to be 1.16 : 1 (20).

A number of familial cases have been reported, which document vertical transmission of KS or KS-like features from mothers to sons and daughters and father to daughter (5, 6, 44, 58, 69, 70). Two pairs of monozygotic twins have been reported; in one pair, the twins were concordant for KS and in the other pair, the twins where discordant for KS (68, 71). For the discordant pair, a postzygotic mutation in the affected twin could have led to the condition, but multifactorial inheritance cannot be ruled out. Given the number of familial cases, autosomal dominant inheritance seems likely.

Recently, using comparative genomic hybridization (CGH) and fluorescence *in situ* hybridization (FISH), Milunsky et al. reported a duplication of 8p22–8p23 in six unrelated patients with KS (72). The duplicated region was found to be approximately 3.5 Mb in size. This duplication was not found in two parents or in 20 control individuals. Two mothers of KS patients and one control individual were found to have a heterozygous submicroscopic inversion involving 8p23.1, which may contribute to the occurrence of this duplication. Because of these findings, Milunsky et al. felt that this duplication could represent a common etiology for KS (72).

To date, at least one KS patient has been reported without any aberration found on CGH (46), and recently, 28 patients with typical KS did not have any detectable duplication of the 8p22–8p23.1 region by FISH (73). Miyake et al. speculate that perhaps the patients studied by Milunsky et al. had either atypical KS or possibly an '8p23.1–p33 duplication syndrome' with features similar to KS (73). Therefore, further studies will need to be done to confirm this association and to more fully evaluate this chromosomal region in order to define the underlying genetic etiology of KS. Certainly, it is possible that KS is a heterogeneous disorder and abnormalities not only on chromosome 8, but also on other chromosomes, such as the X chromosome, could lead to similar KS features.

Prognosis/natural history

KS was only recently recognized as a genetic syndrome; therefore, a complete study of the natural history of this condition has not been performed. It appears that the facial features of KS may evolve over time, such that the diagnosis is difficult to make in the neonatal period (10, 11). Similarly, it is unclear whether continued evolution of the phenotype may also make the diagnosis difficult in adulthood, particularly in those patients who are more mildly affected. This may lead to an ascertainment bias in the literature for those patients with more severe manifestations.

Because KS is not typically associated with severe medical complications, it is presumed that the prognosis for survival into adulthood is good, particularly if congenital anomalies, such as congenital heart defects, and infections are properly managed in childhood. Reports of vertical transmission of KS from both females and males imply that fertility may not be affected by this condition.

Conclusions

KS is a multiple malformation/mental retardation syndrome characterized by distinctive facial features (eversion of the lower lateral eyelid, arched eyebrows with the lateral one-third dispersed or sparse, depressed nasal tip, and prominent ears), skeletal anomalies, dermatoglyphic abnormalities including persistent fingertip pads, mild to moderate mental retardation, and postnatal growth deficiency. A number of visceral,

endocrinologic, and immunologic/hematologic abnormalities can accompany this condition and can aid in the diagnosis. This diagnosis should particularly be considered in those patients found to have cleft palate with a congenital heart defect and/or renal anomalies. Recently, duplication of the 8p22–8p23 region has been demonstrated by CGH in six patients with KS. Hopefully, as our understanding of this chromosomal region improves, the underlying etiology of this complex condition will become clear.

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