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Kabuki Syndrome: Clinical Data in 20 Patients, Literature Review, and Further Guidelines for Preventive Management

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The Kabuki syndrome, or Niikawa–Kuroki syndrome, is a clinically recognizable syndrome of unknown etiology. Clinical findings include early hypotonia, joint laxity, developmental delay, facial dysmorphism, persistent fetal fingertip pads, cleft palate, hypodontia, lip nodules, heart defects, and a variety of other structural defects. Behavior in general is social and pleasant. In collaboration with the Dutch Kabuki Network, we evaluated the medical data of 20 individuals diagnosed with the syndrome and compared them with data from the literature. In our literature review we used convincing cases only. Frequent findings in the oral region are under-reported in the literature: apart from the cleft palate (in about 50%), hypodontia with predominantly absence of the upper lateral incisors, and a full lower lip with symmetrical nodules, or (in a minority) lip-pits are frequent findings. Also under-reported is the presence of a thickened nuchal fold during pregnancy and hydrops in the neonatal period. Clinical recognition in the neonate is difficult. Towards early puberty acute and serious weight excess has been experienced. We suggest that a cytogenetic abnormality should be ruled out in all cases. We provide further guidelines for preventive management.

KEY WORDS: Kabuki syndrome; medical data; preventive management

INTRODUCTION

The Kabuki syndrome or Niikawa–Kuroki syndrome was first described in 1981 independently by Niikawa et al. and Kuroki et al. They reported ten Japanese patients aged 4–16 years. Kabuki is a traditional form of Japanese theater. The eyebrows are one of the most important features expressing the role. The resemblance between the characteristic faces seen in these patients and the make-up of the actors in the Japanese traditional Kabuki theater gave this syndrome its alternative name: Kabuki make-up syndrome [Niikawa et al., 1981; Mhanni and Chudley, 1999]. These facial features give a Caucasian child an "oriental" look [Schrander-Stumpel et al., 1994]. The term 'Kabuki make-up syndrome' is not easily acceptable in Europe, so we prefer the term 'Kabuki syndrome.' As long as the basic mechanism is unknown, an etiologic term for the condition is not available. Patients have the following cardinal manifestations: a characteristic face (100%), skeletal anomalies (over 90%), including brachydactyly V, dermatoglyphic abnormalities (over 95%), and the presence of fetal fingertip pads, mild to moderate mental retardation (over 90%), pre- or post-natal growth deficiency (over 70%), and various structural anomalies [for reviews of the clinical data see Niikawa et al., 1988; Philip et al., 1992; Schrander-Stumpel et al., 1994; Wessels et al., 2002; and Matsumoto and Niikawa, 2003].

The etiology of the syndrome is not known and a diagnostic laboratory test is not available. Recently, Milunsky and Huang reported an 8p22-8p23.1 duplication in 6/6 patients with the syndrome [2003]. However, Miyake et al. [2004] did not confirm this duplication in the 28 patients they studied. Clinical diagnosis up to now is made on the basis of the "facial gestalt" in combination with the mild to moderate developmental delay, the hand anomalies, and a variety of other features.

In the present report we focus on the medical aspects of the condition. We describe the clinical features in 20 patients with Kabuki syndrome (7 males and 13 females). We review the data of over 300 patients in the literature. These data are compared and discussed. Based on all available data, we suggest further guidelines for preventive management.

METHODS

In collaboration with many patients, their families and the Dutch network of Kabuki syndrome, 20 individuals were examined in a standardized way by the first two authors. There were 7 males and 13 females, ranging in age from 1 year to 34 years. Written consent for publication of the medical data and the pictures was given in all cases. The clinical manifestations in the patients are listed in Table I. Patient number 1 is the youngest patient, number 20 the oldest. Clinical pictures of all patients are included in Figures 1 and 2. Patient 18 was reported before [as an "unknown" in Schrander-Stumpel et al. [1991, 1993, 1994] as was patient 10. The ophthalmologic features in patient 19 were reported by Kluijt et al. [2000]. A general review of the psychological data and speech data have been presented as posters [Curfs et al., 2002; Defloor et al., 2003] and speech data are further reported in this issue.

An extensive literature review was performed. We excluded a number of papers/patients because of insufficient data and/or lack of clinical pictures or because of disagreement with the proposed reported clinical diagnosis of Kabuki syndrome

This article contains supplementary material, which may be viewed at the American Journal of Medical Genetics website at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html.

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TABLE I. Clinical Features in the Present Group

Patient number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	Total[a] pos/inf
Sex 7 m;13 f	f	f	m	m	f	m	f	m	f	f	f	m	f	m	f	f	f	f	m	f	
Age at evaluation	1	2	3	6	7	7	7	7	8	9	9	10	11	11	11	12	13	20	24	34	
Length at birth ≤C3	−	−	−	−	+	−	+	+	−	+	+	−	+	−	+	+	+	+	+	+	13/20
Actual height ≤C3	+	−	+	−	+	+	−	+	−	+	+	+	+	−	+	−	+	+	+	+	14/20
OFC at birth ≤C3	+	−	−	−	−	−	−	−	−	−	−	−	−	−	+	+	−	−	+	+	5/20
Actual OFC ≤C3	+	−	+	−	−	−	−	+	−	−	−	−	−	−	+	+	+	−	−	+	8/20
Mental retardation	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Characteristic face	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Preauricular pit	−	+	−	−	−	−	−	−	+	−	+	−	−	−	−	−	−	+	−	−	4/20
Coloboma of the eye	−	−	−	−	−	−	−	+	−	−	−	−	−	−	−	−	−	−	+	−	2/20
Blue sclerae	+	−	+	+	−	+	+	+	+	−	+	+	+	+	−	+	+	−	+	−	14/20
Rec. otitis media	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Hearing loss	+	−	−	+	+	−	−	−	−	−		+	+	−	−	+	+	−	+	+	9/20
Cleft palate	−	+	−	+	−	−	−	+	−	−	−	−	+	−	−	+	−	+	−	+	9/20
Oligodontia	?	?	?	+	+	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	16/16
Thin upper lip	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	+	19/20
Full lowerlip [b]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Hip dysplasia	+	−	−	+	−	−	−	−	+	−	+	+	−	−	−	+	+	−	+	−	7/20
Joint hypermobility	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	18/20
Brachydactyly (5th)	+	+	+	+	+	−	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Fetal fingertip pads	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	20/20
Neonatal hypotonia	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	−	+	−	18/20
Seizures	−	−	+	−	−	−	+	−	−	−	−	−	−	−	−	+	−	−	−	+	4/20
Feeding problems	+	+	+	+	+	+	+	+	+	+	+	−	+	+	+	+	+	−	+	+	18/20
Aortic dilation				+																	1/20
Coarctation aorta/bicuspid aortic valve	+					+															2/20
Ventr. septal defect	+				+											+					3/20
Undescended testicle								+											+		2/7
Renal abnormalities					+			+							+	+			+		5×
Early breasts (girls)	+	+					+		+	+			+								7/13
Diaphragmatic abn.			+					+											+		3×
GH deficiency										+					+						2×
Hypothyroidism																	+				1×

?, too young; C3, 3rd centile.
[a]Total: positive/informative.
[b]Symmetric lower lip nodules and, in some children, pits.

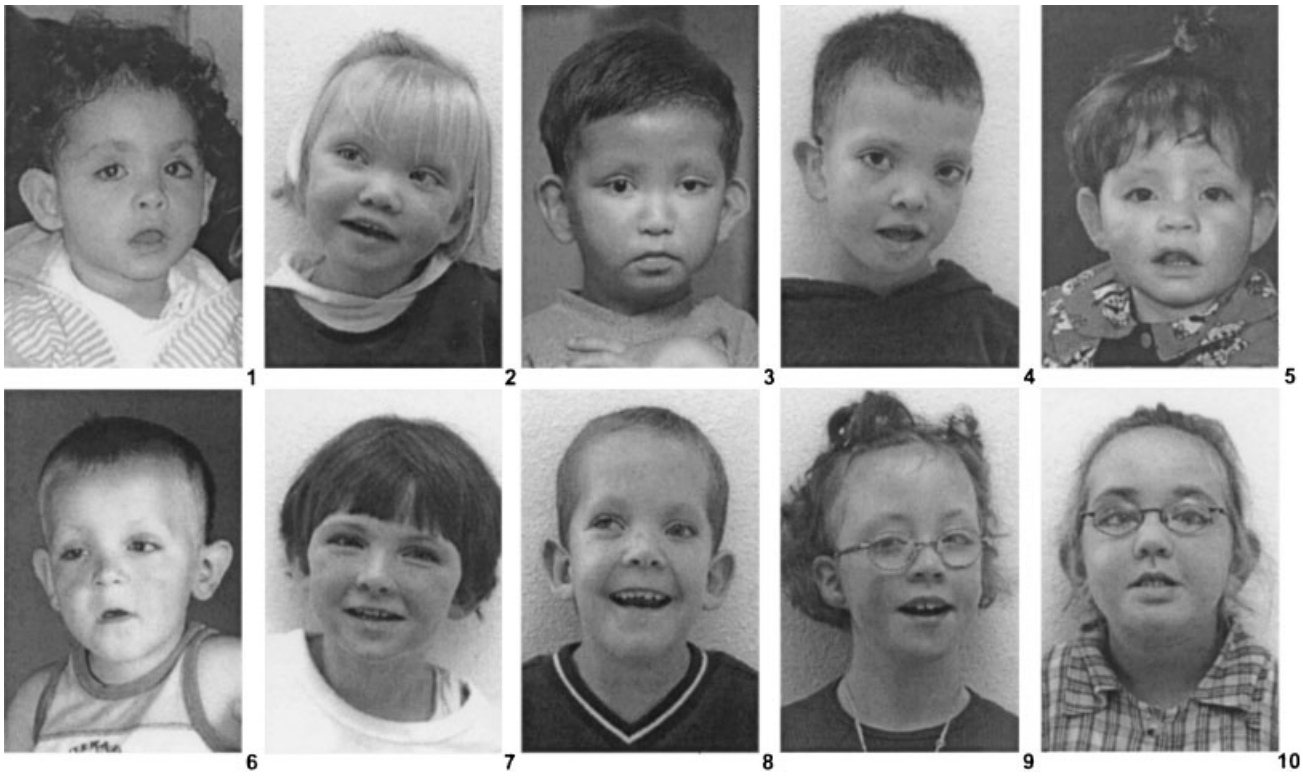

Fig. 1. Picture gallery of patients 1–10 according to age (see Table I).

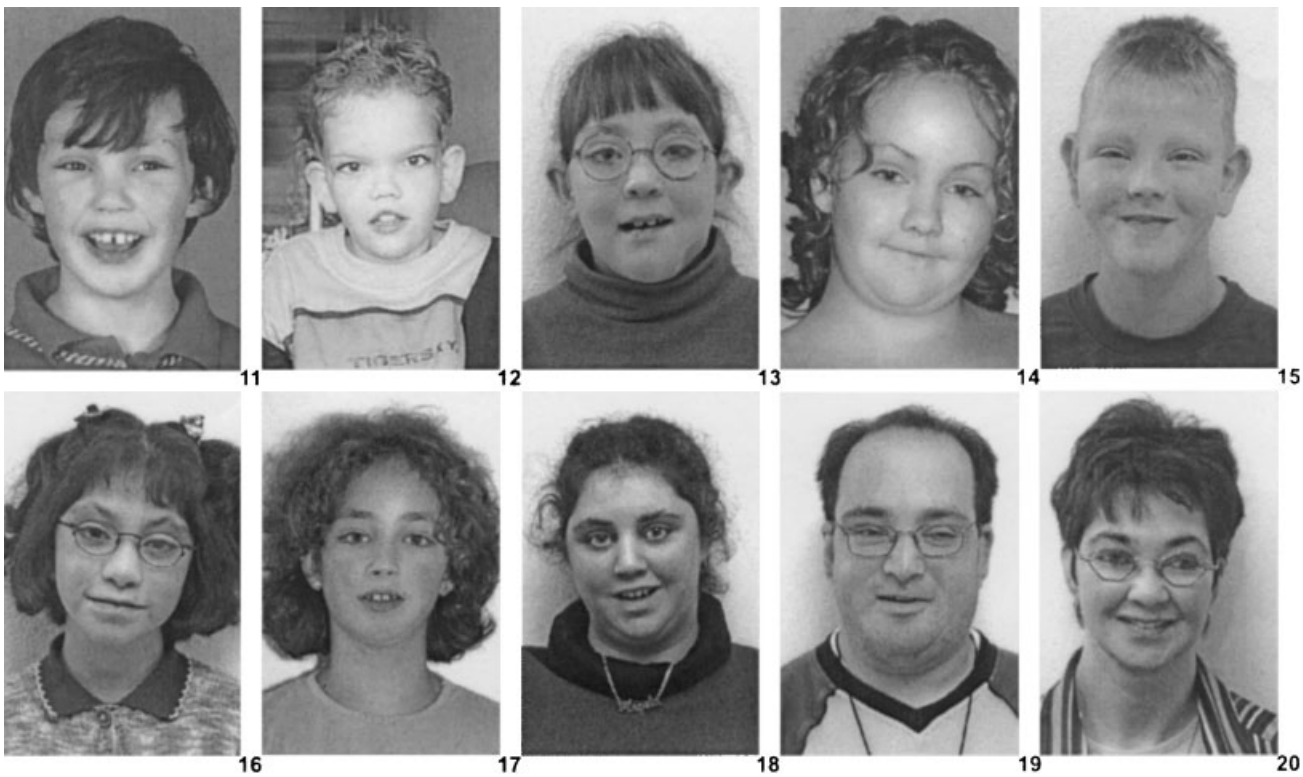

Fig. 2. Picture gallery of patients 11–20 according to age (see Table I).

[Handa et al., 1991; Ilyina et al., 1995; Chu et al., 1997; Ewart-Toland et al., 1998; Roccella, 1999; Courtens et al., 2000; Donadio et al., 2000; Gabrielli et al., 2000; Frediani et al., 2001; Mihci et al., 2002].

However, it was possible to review the medical data of over 300 (306) patients in the literature [see listing in literature review references]. There were 154 males and 152 females, ranging from 5 months to 43 years. Table II lists the clinical features in our group compared to those in literature.

RESULTS AND DISCUSSION

Comparing the medical features in our patient group versus the data in the literature (Tables I and II), we generally discuss the clinical features and highlight striking issues. Clinical diagnosis in neonates and young infants appears to be difficult, and most cases have been diagnosed after age 2 years. In 3/20 patients in the presently reported series, neonatal hydrops was present, indicating that this is an important feature in the neonatal period. Notable features in early life are summarized in Addendum A (see the online Addendum A at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html).

All patients were diagnosed on the basis of their facial features in combination with a developmental delay. Generally, affected individuals have a pleasant character and pose no specific behavioral problems. Height is below the 3rd centile in about 70% of patients with a prenatal onset in about half of our cases. Adult height, using data from some case reports and three of our patients over 18 years of age, is close to the third centile for age.

Postnatal growth retardation may be caused by growth hormone deficiency, which was documented in two patients of our group. It has been reported at least six times in literature [Niikawa et al., 1988; Satoh et al., 1993; Tawa et al., 1994; Devriendt et al., 1995; Makita et al., 1999; Gabrielli et al., 2002].

In Kabuki syndrome, premature activation of the hypothalamic-gonadal axis is a frequent finding, since many girls with this syndrome present premature thelarche. Premature breast development (as a toddler) was found in 7 of our 13 female patients (54%), and was reported in 33 of 81 female patients (41%) in literature. Apparently girls with Kabuki syndrome have increased sensitivity to estrogens during infancy [Bereket et al., 2001].

Towards puberty, patients may become very obese (weight for height ratio above the 97th centile), a weight gain of 10 kg in 6 months being no exception. No endocrinological explanation has been given for this phenomenon so far [Schrander-Stumpel et al., 1994]. In the present study, we found this feature in 3/9 individuals over 10 years of age. The fat distribution is mainly truncal. Whether this situation in young people with Kabuki syndrome is different from the general problem of obesity in the population is not clear.

Early hypotonia hampered motor development in all of our patients. With time and physiotherapy, hypotonia improved and motor milestones were reached with walking between 2 and 3 years of age. Feeding problems are very common and underemphasized in literature; the feeding problems are clearly related to hypotonia and may require gavage feeding for many weeks, sometimes a grastrostomy tube has to be placed. Speech development is delayed with first words after 2 years of age. Mental retardation is a common feature and developmental assessment reveals that most individuals have a mild to moderate delay—100% in our group and 90% in the literature. Severe mental retardation is uncommon with only two case reports in the literature [PeBenito and Ferretti, 1989; Gilles et al., 1990].

The facial features are very typical, the long palpebral fissures being the most constant finding, together with eversion of the lateral part of the lower eyelid and arched eyebrows, sparse or notched in the lateral one-third. Depressed/flat nasal tip is also a frequent finding.

Some ocular features occur more frequently in patients with the syndrome than in the general population, for example, blue sclerae, strabismus, and ptosis [Kluijt et al., 2000]. Blue sclerae were present in 14/20 individuals (70%) in our group, and in 52/156 patients (33%) in the informative literature. Amblyopia, refractive anomalies, and other eye anomalies have been reported also. One specifically reported eye anomaly is coloboma of the iris or retina: seen three times in our group and five times in literature cases [Philip et al., 1992; Tutar et al., 1994; Kluijt et al., 2000; McGaughran et al., 2000].

The ears in patients with Kabuki syndrome are large, 9 of 20 patients (45%) in our group and 90% in literature. This difference in percentages can be explained, because we actually measured the ears instead of obtaining an impression. The ears are dysplastic and/or simply formed in most patients. Preauricular pits were seen in 4 of 20 patients (20%) in our group and 33% in literature.

In our group, all patients had recurrent otitis media and hearing loss of all types was present in half. No inner ear malformations were documented in our group, but not all individuals had an MRI of the inner ear. The hearing loss in our group as well as in the literature has usually been attributed to otitis media, although several cases have been described with sensorineural [Kuroki et al., 1981; Burke and Jones, 1995] or mixed hearing loss [Carcione et al., 1991; Philip et al., 1992; Burke and Jones, 1995]. Mondini dysplasia was the most common reported malformation of the inner ear [Toutain et al., 1997; Igawa et al., 2000].

Eight of twenty individuals in our group had a cleft palate, a feature present in 51% of the cases in literature. Niikawa et al. [1988] reported clefts of all types. However, in our series and reported by Burke and Jones [1995], the majority of patients had a cleft palate and a cleft lip/palate was rare. Lip pits have been reported in Kabuki syndrome [Shotelersuk et al., 2002], but in our experience symmetrical lower lip nodules, with or without pits, are very common (see Fig. 3A). A thin upper lip was also very common. Abnormal dentition was present in all of our informative patients, and in 83% in the literature. Many reported Kabuki syndrome patients have spaced teeth, perhaps caused by tooth hypoplasia and/or conical teeth and/or hypodontia (absence of central/lateral incisors) (Fig. 3B) [Halal et al., 1989; Li et al., 1996; Lerone et al., 1997; Mhanni et al., 1999; Matsune et al., 2001; Petzold et al., 2003]. Hypodontia with absence of the upper lateral incisors is present in all informative patients in our series.

The hands feel soft and are short with short fingers, especially the fifth fingers. In general the middle phalanx of the 5th finger is short. Mild cutaneous syndactyly is common, usually between fingers II/III or III/IV. Persistance of fetal fingertip pads is highly characteristic of, but this feature is not specific. Fingertip pads can be seen in various syndromes, fetal alcohol syndrome being one of the most common.

Abnormal vertebrae are documented in three patients in our group, and in 33/88 cases (38%) in the literature. Scoliosis is found in 5 of 20 patients (25%) in our group, and 38% in the literature. Hip dysplasia was a serious problem in 8/20 patients (40%), and 65/178 patients (37%) in literature.

Neurologic manifestations other than cognitive impairment include hypotonia, microcephaly, and seizures. These features are under-reported in the Japanese patients [Philip et al., 1992; Schrander-Stumpel et al., 1994]. Many patients have hypotonia in combination with feeding difficulties (90% in our group and up to 70% in literature); the severity was variable. Some patients require gastrostomy tube placement because of poorly coordinated sucking and swallowing [Kawame et al., 1999; presently reported patients]. Joint hyperlaxity was present in 18/20 patients (90%) in our group, and 73% in the

TABLE II. Clinical Features in Literature, Compared to Our Patient Group

	Literature, n = 306		Present group, n = 20		Total, n = 326	
	Pos/inf	Percentage	Pos/inf	Percentage	Pos/inf	Percentage
154 m:152 f (5 months–43 years)						
Length at birth ≤C3	6/14	43	13/20	65	19/34	56
Actual length ≤C3	156/221	71	14/20	70	170/241	71
OFC at birth ≤C3	4/8	50	5/20	25	9/28	32
Actual OFC ≤C3	42/134	31	8/20	40	50/154	32
Mental retardation	210/227	90	20/20	100	230/253	91
Characteristic face						100
Long palpebral fissures	150/150	100	20/20	100	170/170	100
Eversion of the lateral third of the lower eyelid	204/217	94	17/20	85	221/237	93
Arched eyebrows, sparse in lateral one-third	189/212	89	16/20	75	205/232	88
Depressed/flat nasal tip	166/202	82	18/20	90	184/222	83
Large ears	165/183	90	9/20	45	174/203	86
Dysplastic ears	117/137	85	20/20	100	137/157	87
Preauricular pit	52/160	33	4/20	20	56/180	31
Malar hypoplasia	5×					
Ophthalmologic findings						
Eye anomaly (coloboma)	8×		3×			
Blue sclerae	52/156	33	14/20	70	67/176	38
Ptosis	40×		2×			
Otologic findings						
Otitis media	90/134	67	20/20	100	110/154	70
Hearing loss	64/151	42	10/20	50	73/170	43
Oral abnormalities						
Cleft palate or bifid uvula	112/220	51	8/20	40	120/240	50
Abnormal dentition	111/134	83	16/16	100	127/150	85
Hypodontia	22/25	88	16/16	100	38/41	93
Thin upperlip	5×		19/20	95	ND	
Lipnodules	15/29	52	20/20	100	35/49	72
Skeletal abnormalities						
Scoliosis	62/163	38	5/20	25	67/183	37
Hip dysplasia	65/178	37	8/20	40	73/198	37
Patellar dislocation	14/42	33	0/20		14/62	23
Joint hypermobility	77/105	73	18/20	90	95/125	76
Hands						
Brachydactyly (5th finger)	141/164	86	20/20	100	161/184	88
Fetal fingertip pads	201/221	91	20/20	100	221/241	92
Neurological problems						
Neonatal hypotonia	73/159	46	18/20	90	91/179	51
Seizures	41/171	24	4/20	25	45/191	24
Feeding problems	46/66	70	18/20	90	64/86	74
Cardiovascular						
Coarctation aorta/bifid aortic valve	24/108	22	2/20	5	26/128	20
Ventricular septal defect	22/104	21	3/20	15	25/124	20
Atrial septal defect	22/124	18	0/20		22/144	15
Aortic dilatation	ND		1/19	5		
Urogenital						
Undescended testicles	19/44	43	2/7	29	21/51	41
Renal abnormalities	41/131	31	5/20	25	46/151	30
Early breast development	33/81	41	7/13	54	40/94	43
Immunological						
Increased susceptibility to ear Infections	79/123	64	20/20	100	99/143	69
Diaphragmatic hernia/eventration	8×		3/20	15		
Anal atresia	11/70	16	0/20		11/89	12
Endocrinological						
GH deficiency	5/64	8	2×			
Hypothyroidism	3/19	16	1×			
Hyperbilirubinemia	21/78	27	8/20	40	29/98	30
Other						
Hydrops fetalis	2×		3×			

ND, not documented; pos/inf, positive/informative; C3, 3rd centile.

Kuroki et al. [1981, 1987]; Niikawa et al. [1981, 1982, 1988]; Koutras and Fisher [1982]; Braun and Schmid [1984]; Ohdo et al. [1985]; Kaiser-Kupfer et al. [1986]; Pagon et al. [1986]; Iwama et al. [1987]; Halal et al. [1989]; Meinecke and Rodewald [1989]; Mulvihill and Kaiser-Kupfer [1989]; PeBenito and Ferretti [1989]; Gilles et al. [1990]; Carcione et al. [1991]; Handa et al. [1991]; Matsumura et al. [1992]; Philip et al. [1992]; Franceschini et al. [1993]; Ikegawa et al. [1993]; Satoh et al. [1993]; Schrander-Stumpel et al., [1993, 1994]; Devriendt and Fryns [1994]; Fryns et al. [1994]; Hughes and Davies [1994]; Tawa et al. [1994]; Tutar et al. [1994]; Watanabe et al. [1994]; Burke and Jones [1995]; Devriendt et al. [1995, 1996]; Galan-Gomez et al. [1995]; Lan et al. [1995]; Hostoffer et al. [1996]; Ijichi et al. [1996]; Kobayashi and Sakuragawa [1996]; Li et al. [1996]; Silengo et al. [1996]; Ho and Eaves [1997]; Lerone et al. [1997]; McGinniss et al. [1997]; Mitsudome et al. [1997]; Peterson-Falzone et al. [1997]; Toutain et al. [1997]; Tsukahara et al. [1997]; Yano et al. [1997]; Chrzanowska et al. [1998]; Fryns and Devriendt [1998]; Kasuya et al. [1998]; Wilson [1998]; Di Gennaro et al. [1999]; Kawame et al. [1999]; Kokitsu-Nakata et al. [1999]; Makita et al. [1999]; Mhanni et al. [1999]; Igawa et al. [2000]; Kluijt et al. [2000]; McGaughran et al. [2000, 2001]; van Haelst et al. [2000]; Bereket et al. [2001]; Cetinkaya et al. [2001]; Digilio et al. [2001]; Fong et al. [2001]; Kobayashi et al. [2001]; Matsune et al. [2001]; Milunsky and Cheney [2001]; Selicorni et al. [2001]; Gabrielli et al. [2002]; Kurosawa et al. [2002]; Shotelersuk et al. [2002]; Fujishiro et al. [2003]; Kokitsu-Nakata and Guion-Almeida [2003]; Ming et al. [2003]; Petzold et al. [2003].

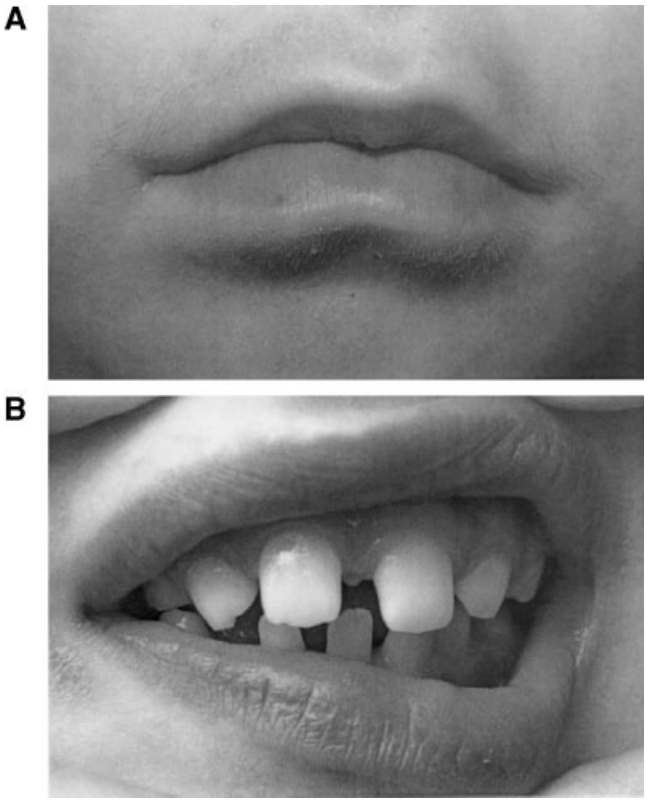

Fig. 3. The oral region with lower lip nodules (**A**) and hypodontia (**B**).

literature. Joint hyperextensibility also contributes to gross motor delays [Kawame et al., 1999, and in our experience]. Muscular biopsy was performed in some cases but failed to detect any significant muscular abnormality [Philip et al., 1992; Schrander et al., 1997: in the presently reported patient number 4]. Patellar dislocation was present in 14 of 42 patients in the literature [e.g., Kurosawa et al., 2002] and in our patient 4; most patients were post-pubertal when this problem occurred.

Microcephaly is noted in 8/20 (40%) patients in the present group, and in 42 of 134 (31%) patients in the literature. In 5/8 microcephalic patients in our group, the origin is prenatal. In the literature, it was not possible to evaluate the percentage that are pre- or post-natal onset. Seizures were recognized in 4/20 patients (25%) in our group, and 41/171 patients (24%) in the literature.

Commonly reported cardiovascular abnormalities in Kabuki syndrome are coarctation of the aorta, atrial, and ventricular septal defects. One of our males (patient number 4) had an aortic dilatation; he also had severe hip dysplasia and joint laxity.

Increased susceptibility to infections is frequently diagnosed in Kabuki patients. All our patients were susceptible for recurrent ear infections as were 90 of 134 patients (67%) in the informative literature, especially at a young age. Part of this susceptibility can be explained by cleft palate and anatomic structure. In our opinion and experience, there is no significant difference, apart from otitis media, from normal toddlers, who have about 11 upper respiratory infections a year [Behrman et al., 2000]. In general, no specific immunological abnormality has been documented in our group, and there was no indication for a systematic immunological study. Three patients in the literature had hypogammaglobulinemia and thrombocytopenia [Watanabe et al., 1994; Hofstoffer et al., 1996; Kawame et al., 1999].

One patient, described by Ijichi et al. [1996], developed an abdominal malignant lymphoma at the age of 3 years. The tumor was histologically diagnosed as Burkitt's lymphoma and Epstein-Barr virus was detected by in situ hybridization. Recently, acute lymphatic leukemia was documented in a child with Kabuki syndrome [Scherer et al., 2003].

Some patients with Kabuki syndrome have autoimmune diseases [Schrander-Stumpel et al., 1993, the presently reported patient 17; Hofstoffer et al., 1996; Kawame et al., 1999; Ming et al., 2004]. Autoimmune hypothyroidism was documented in patient number16. The association between Kabuki syndrome and diabetes type I in a patient was suggested to be an autoimmune phenomenon as well [Fujishiro et al., 2003].

Diaphragmatic defects, such as herniation and eventration, have been reported in 3/20 patients in the present group of patients, and at least eight times in literature.

Hirsutism and/or hypertrichosis is mentioned in 12 of 66 patients (18%) in literature. In our group, most female patients are noted to have abundant head hair with some also on the arms, legs, and back; this was abundant compared to their mothers and female siblings.

Van Haelst et al. [2000] described two Kabuki patients with unusual life-threatening complications; stenosis of the central airway, extrahepatic biliary atresia, and congenital diaphragmatic hernia. In a series of 18 patients 3 died before they reached adulthood [Kawame et al., 1999]. Causes were different in each case; one was related to developmental delay and recurrent aspiration, another was due to malabsorption, and the third was due to immunodeficiency.

DIFFERENTIAL DIAGNOSIS AND POSSIBLE ETIOLOGY

Until very recently, etiology of Kabuki syndrome was unknown and diagnosis was based on clinical findings only. Heterogeneity cannot be excluded. In our opinion, it is a diagnosis of exclusion. Most specific is the face with long palpebral fissures (most prominent from the profile), the full lower lip with symmetrical nodules, and hypodontia. Growth retardation and mild developmental delay are prominent. The skin feels soft and joint tend to be lax; young children are hypotonic. The combination of blue sclerae, joint hyperlaxity, hip dysplasia and, in one child in our series, aortic dilatation, suggests a connective tissue component in the etiology of Kabuki syndrome [see also, Kawame et al., 1999].

Before making the diagnosis, a cytogenetic anomaly must be ruled out. Girls with a mosaic X chromosome abnormality may show a clinical overlap of Kabuki syndrome and Turner syndrome [Niikawa et al., 1988; Wellesley and Slaney, 1994; van Hagen et al., 1996; McGinniss et al., 1997; Stankiewicz et al., 2001].

Several other cytogenetic conditions have clinical overlap with Kabuki syndrome as well. Fryns et al. [1994] and Schrander-Stumpel et al. [1994] described a child with the phenotype of Kabuki syndrome and a paracentric inversion of the short arm of chromosome 4 (46, XX, inv(4)(p12pter)). They suggested that Kabuki syndrome is a chromosomal syndrome with partial duplication and/or deficiency of the short arm of chromosome 4. Kabuki syndrome-like features were described in monozygotic twin boys with a pseudodicentric chromosome 13. Their phenotypically normal mother carried the same pseudodicentric chromosome 13 [Lynch et al., 1995]. Dodé et al. [1998] suggested involvement of the *TUBA2* gene at 13q11 in Kabuki syndrome. Some patients with Kabuki syndrome demonstrate overlap with the 22q11.2 deletion syndrome

(e.g., cleft palate, congenital heart defects, urinary tract anomalies). However, a 22q11.2 deletion has been ruled out in patients with Kabuki syndrome [our series, Li et al., 1996; Kawame et al., 1999]. A child with partial 6q monosomy/partial 12q trisomy was reported as having Kabuki syndrome features [Jardine et al., 1993].

In our opinion, however, no cytogenetic condition reported to date represented a true Kabuki phenotype. Recently an 8p22-8p23.1 duplication was reported as common etiologic basis [Milunsky and Huang, 2003]. This finding is the first cytogenetic anomaly truly associated with the phenotype. Our patients had normal cytogenetic findings so far, but had been examined for the 8p inversion–duplication as well [Engelen et al., 2004].

Lip-pits are common in van der Woude syndrome (VWS) and are found in some Kabuki syndrome patients suggesting the possibility of a contiguous gene syndrome involving the putative genes for both syndromes. Fluorescence in situ hybridization and microsatellite analyses using PAC clones and dinucleotide repeat markers spanning the VWS1 critical region at 1q32-q41 have been carried out. No deletion was detected at the VWS1 critical region. It remains to be seen whether the patient has a microdeletion in the VWS type 2 critical region at 2q34-q36 [Makita et al., 1999].

Hardikar syndrome comprises the combination of sclerosing cholangitis, cleft lip and palate, and pigmentary retinopathy. The children may present with prolonged hyperbilirubinemia.

Hyperbilirubinemia was described in 8 of 20 patients (40%) in our group, and in 21 of 78 patients (27%) in the literature. Persistent hyperbilirubinemia has led to the diagnosis of extrahepatic biliary atresia in four patients in literature, so this has to be considered a rare but associated anomaly of Kabuki syndrome. Biliary atresia can be due as well to choledochal cysts [van Haelst et al., 2000]. Clinical overlap between Hardikar and Kabuki syndrome has been reported [e.g., Cools and Jaeken, 1997; McGaughran et al., 2000; van Haelst et al., 2000]. No gene location has been suggested for either syndromes, so the similarity to Kabuki syndrome remains in doubt.

The sex ratio in Kabuki syndrome is almost equal [Lerone et al., 1997]. The rate of consanguinity among the parents is not increased [Niikawa et al., 1988; Tsukahara et al., 1997]. There is no correlation with birth order. Most individuals with the syndrome have been sporadic, suggesting new autosomal dominant mutations [Kuroki et al., 1981; Niikawa et al., 1988]. Parent–child transmission of the Kabuki syndrome has been reported, suggesting autosomal dominant inheritance [Halal et al., 1989; Kobayashi and Sakuragawa, 1996; Silengo et al., 1996; Tsukahara et al., 1997; Courtens et al., 2000]. Most reports, however, were not convincing to the authors of this report. Most parents reported to be affected had an incomplete form of the syndrome, with more mothers than fathers showing a partial (facial) phenotype. In one family autosomal dominant transmission by the mother was suggested by Kluyt et al. [2000; the mother of presently reported patient 19], but these authors find this questionable.

Although paternal ages were not significantly increased in some studies [Niikawa et al., 1988; Schrander-Stumpel et al., 1994], recent studies suggest an increase [Armstrong et al., 2003; this issue]. The mean paternal age in the presently reported series is 33.7 years, which is increased for the Netherlands. The recurrence risk for unaffected parents is very low. In our series, we have seen no recurrences.

PREVENTIVE MANAGEMENT

After a clinical diagnosis of Kabuki syndrome, parents, families, and caretakers face many questions, concerning health, mental development, and behavior. Follow up of anyone with a genetic syndrome should be well coordinated by an experienced professional. In children the paediatrician generally takes this central role. Preventive management in an individual with a genetic syndrome is a multidisciplinary and continuous effort. At an adult age, the medical doctor specialized in the care of people with mental disabilities, the general physician, and/or the clinical geneticist may play a central role. Follow up is useful to learn about the natural course of the condition, to discuss any questions regarding the syndrome, and to inform the family of any new clinical or scientific findings in this specific syndrome.

General guidelines for children/adults with a Kabuki syndrome diagnosis are available in the book by Wilson and Cooley [2000]. More specific guidelines for individuals with Kabuki syndrome were reported by Wilson [1998] and Kawame et al. [1999].

Based on all available data, and including our long-term experience in the Netherlands in close collaboration with the lay organization, we give a synopsis of the medical features and further specify guidelines for preventive management in Kabuki syndrome in Addenda A and B (see the online Addenda A and B at http://www.interscience.wiley.com/jpages/0148-7299/suppmat/index.html). We summarize relevant guidelines for each age category.

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