

Speech Characteristics in the Kabuki Syndrome

Sheila Upton,¹ Carmella S. Stadter,¹ Pat Landis,² and Eric A. Wulfsberg^{1*}

¹*Division of Pediatric Genetics, University of Maryland, School of Medicine, Baltimore, Maryland*

²*Cleft Palate Diagnostic Program, Kernan Hospital, Baltimore, Maryland*

Six children with Kabuki syndrome were studied to investigate speech patterns associated with the syndrome. Each child's speech was characterized with regard to articulation (types of errors and intelligibility), pitch (high or low), loudness (volume of speech), and prosody (general quality of speech that combines rate and inflection). All six children had a history of delayed speech and language acquisition and were receiving speech services. All individuals had articulation errors and abnormal oral resonance, which appeared to be due to poor oral-motor coordination and hypotonia and were not felt to be due to structural abnormalities such as velopharyngeal insufficiency, dental malocclusion, or cleft palate. An intriguing finding, noted in the two individuals followed from childhood into adolescence with serial speech evaluations, was that pitch, loudness, and prosody did not mature over time and what was age appropriate performance at younger ages became inappropriate in adolescence. This raises a challenge for speech services, as by adolescence, while articulation had improved, the pitch and loudness of these individuals' speech had not and so was noticeably different from peers. Distinctive speech characteristics with a lack of normal maturation during childhood can be added to the extensive list of clinical features associated with the Kabuki syndrome and hopefully will lead to improved speech/language treatment for individuals with this syndrome.

© 2002 Wiley-Liss, Inc.

KEY WORDS: Kabuki syndrome; Niikawa-Kuroki syndrome; speech characteristics; cleft palate

INTRODUCTION

Kabuki syndrome, first described in 1981 [Kuroki et al., 1981; Niikawa et al., 1981] is a multiple malformation syndrome characterized by five cardinal manifestations including: (1) a characteristic face with long palpebral fissures, large protruding ears, arched eyebrows, and a depressed nasal tip; (2) skeletal anomalies including brachydactyly and scoliosis; (3) dermatoglyphic abnormalities including increased digital ulnar loops and persistence of fetal fingertip pads; (4) mild to moderate mental retardation with average IQs of 50–62; and (5) postnatal growth deficiency. Severe mental retardation is uncommon, as is normal intelligence. Other commonly reported anomalies have included cleft palate (CP), congenital heart defects, and early breast development in girls [Kuroki et al., 1981; Niikawa et al., 1981; Koutras and Fisher, 1982; Niikawa et al., 1988; Wilson, 1998].

While the physical phenotype is well characterized, limited information is available about speech abilities in individuals with Kabuki syndrome. Ilyina et al. [1995] reported that four of ten patients ranging in age from 4 to 15 years of age had hypernasal speech or dyslalia. Burke and Jones [1995] reported dysarthria and dyspraxia in six of eight patients studied and suggested that it resulted from oral motor problems having a neurological component. The purpose of our study was to characterize the speech production in individuals with this syndrome and follow its development over time.

METHODS AND MATERIALS

Patients were recruited from the Pediatric Genetics Clinic at the University of Maryland and the Kabuki Syndrome Network Family Support Group (8060 Struthers Crescent, Regina, Saskatchewan S4Y 1J3 Canada). Seven patients were identified at the University of Maryland and three additional patients contacted us through the Kabuki Syndrome Network. Of the ten patients, two were non-verbal and two were unable to come in for a full evaluation. The remaining six patients were examined and had their diagnosis made or confirmed by the same clinical geneticist and all speech

*Correspondence to: Eric A. Wulfsberg, M.D., Division of Pediatric Genetics, University of Maryland, School of Medicine, 100 North Greene Street, Room 414, Baltimore, MD 21201.
E-mail: ewulfsberg@pediatrics.umaryland.edu

Received 5 February 2002; Accepted 31 July 2002
DOI 10.1002/ajmg.a.10039

consultations were performed by the same speech pathologist.

The University of Maryland, Baltimore IRB Committee approved the study and informed consent was obtained from all families. The speech consultation was performed by a speech pathologist experienced in the evaluation of children with cleft lip and/or CP. The consultations were each about 15–20 min long and consisted of having each child say a number of specific words and phrases and engage in conversation with the speech pathologist. The child's speech was characterized with regard to articulation (types of errors and intelligibility), pitch (high or low), loudness (volume of speech), and prosody (general quality of speech that combines rate and inflection).

The results were compared among children with Kabuki syndrome with and without CP to determine if distinctive speech patterns could be recognized in this syndrome and whether they are influenced by the presence of oral clefting. Speech characteristics were also compared between males and females to determine whether or not sex-dependent speech characteristics exist. A control population was not used in this study but the patients were compared to known standards for same age children. A brief medical and family history was obtained and the clinical geneticist performed a physical examination on each individual to confirm the diagnosis.

CLINICAL REPORTS

The clinical findings of the patients are summarized in Table I and the speech characteristics in Table II.

Patient 1 (Fig. 1a) is an 11-year-old boy who was the 3.2 kg product of a term pregnancy to a 25-year-old Para 0 mother. At 3 days of age, he developed seizures requiring anticonvulsant medication. During a 3-week nursery stay aortic stenosis, hydronephrosis, a CP, and

a right cloudy cornea (possibly representing congenital glaucoma) were discovered. He had an iridectomy of the right eye at age 6 months, CP repair at age 9 months, right hydronephrosis surgery at age 1 year, and aortic stenosis repair at age 2½ years. Lymphocyte karyotype was normal 46, XY. At 4 years of age, he was diagnosed with Kabuki syndrome. IQ at age 11 years was in the mild mentally retarded range. The family history is noncontributory. Examination at age 11 years showed a height of 127.5 cm (<5th centile), weight 37.4 kg (50th centile), and OFC was 53.5 cm (50th centile).

Patient 2 (Fig. 1b) is a 6½-year-old girl who was the 2.3 kg product of an uncomplicated non-identical twin pregnancy born at 37 weeks gestation to a 25-year-old Para 0 mother. An unusual appearance was noted in the nursery. Lymphocyte karyotype was normal 46, XX. She was diagnosed with Kabuki syndrome at age 5 months. She was recently found to have a horseshoe kidney. Family history is noncontributory. Examination at 6½ years showed a height of 108 cm (<5th centile), weight 23 kg (75th centile), and OFC 55.5 cm (25th centile).

Patient 3 (not pictured) is a 10-year-old girl who was the 3.5 kg product of a term pregnancy to a 27-year-old Para 5005 mother. Pregnancy was uncomplicated with a normal fetal ultrasound. In the nursery, she exhibited poor feeding but went home after 1 day. She returned at age 6 days when a critical coarctation of the aorta was detected and repaired. She has hypoplasia of the musculature of her upper lip and maxilla. She has mild mental retardation and is in special education. Family history is noncontributory. Examination at age 9 11/12 years of age showed a height of 145 cm (75th centile), weight 29.9 kg (25th centile), and OFC 54 cm (75th centile).

Patient 4 (Fig. 1c) is a 16-year-old young woman who was the 3.1 kg product of an uncomplicated term pregnancy to a 33-year-old Para 1001 mother. At birth,

TABLE I. Pertinent Clinical Features in Six Patients Compared to Previous Reports

Patient	1	2	3	4	5	6	Total	Lit (%) ^{a,b,c}
Gender	M	F	F	F	F	M		
Developmental delay/MR	+	+	+	+	+	+	6/6	92
Short stature	+	+	–	–	+	+	4/6	73
Long palpebral fissures	+	+	+	+	+	+	6/6	100
Arched eyebrows	+	+	+	+	+	+	6/6	100
Ptosis	–	+	–	+	–	–	2/6	22
Broad/flat nasal tip	+	+	+	+	+	+	6/6	79
Large/protruding ears	+	+	+	+	+	+	6/6	85
Cleft palate	+	–	–	+	+	–	3/6	41
Heart defect	+	+	+	–	–	+	4/6	32
Kidney defect	+	+	–	–	–	+	3/6	12
Precocious breast development (females)	NA	–	+	–	+	NA	2/4	23
Clindactyly of 5th finger	+	+	–	–	+	+	4/6	89
Fetal fingertip pads	+	+	+	–	+	+	5/6	89
Joint hyperextensibility	–	+	+	++	+	+	5/6	50
Hypotonia	+	+	+	+	+	+	6/6	89
Immune thrombocytopenic purpura	–	–	–	+	–	–	1/6	Rare
Scoliosis	–	–	–	+	–	–	1/6	49
Seizures	+	–	–	–	–	–	1/6	16

^aNiikawa et al. [1988].

^bKawame et al. [1999].

^cSchrander-Stumpel et al. [1994].

TABLE II. Speech Characteristics in Six Patients

Patient	Ages evaluated (years)	Language acquisition	Articulation	Pitch	Loudness	Prosody	
						Inflection	Rate
1	11	Delayed	Abnormal	High	Decreased	Decreased	Slow
2	6	Delayed	Abnormal	Normal	Decreased	Normal	Normal
3	10	Delayed	Abnormal	Normal	Normal	Normal	Normal
4	10, 12, 14	Delayed	Abnormal	High	Decreased	Decreased	Slow
5	4, 8, 9, 14	Delayed	Abnormal	High	Decreased	Decreased	Slow
6	9	Delayed	Abnormal	Normal	Normal	Increased	Slow

she was noted to have a CP, low muscle tone, and poor feeding. Lymphocyte karyotype was normal 46, XX. She was diagnosed with Kabuki syndrome at 11 years of age. She has mild scoliosis and recurrent patellar dislocations. She has bilateral hearing loss but only wears a hearing aid in one ear. She is currently being treated for immune thrombocytopenic purpura. Family history is noncontributory. She is in regular classes, but is having increasing difficulty keeping up with peers and is estimated to have borderline normal cognitive function. Physical examination at age 15 years showed a height of 157.5 cm (25th centile), weight 53.5 kg (25th centile), and OFC 56 cm (75th centile).

Patient 5 (Fig. 1d) is a 16-year-old young woman who was the 3.0 kg product of a term pregnancy to a 42-year-old P1061 mother. Pregnancy was complicated by threatened miscarriage, which was controlled with medication. Labor and delivery were prolonged and forceps were required for delivery. At birth, she was found to have a CP, an unusual facial appearance, and a small ventricular septal defect. Lymphocyte karyotype was normal 46, XX. She was diagnosed with Kabuki syndrome at 7 11/12 years of age. She currently has

hearing difficulties and wears a hearing aid in her right ear. She also has severe dental malocclusion. She has mild mental retardation and is in special education. Examination at age 16½ years showed a height of 140.3 cm (<5th centile), weight 39.7 kg (<5th centile), and OFC 53.3 cm (25th centile).

Patient 6 (Fig. 1e) is an 8 1/12-year-old male who was the 3.13 kg product of a term gestation to a 23-year-old Para 0 mother. He was adopted from Russia at approximately age 3 years. Upon arrival in the United States, he was evaluated and found to have developmental delay, bicuspid aortic valve with mild aortic insufficiency, and a horseshoe kidney. Lymphocyte karyotype was normal 46, XY and he was diagnosed with Kabuki syndrome. He has mild mental retardation and is in special education. Examination at age 7 5/12 years showed a height of 122.5 cm (25th centile), weight 28.7 kg (75th centile), and OFC 54.2 cm (75th centile).

DISCUSSION

Speech characteristics were evaluated in six children with Kabuki syndrome, ranging in age from 6 to 16 years, including three with CP. Two of these individuals had been followed over time by the speech pathologist and had three to four speech evaluations over periods ranging from 4 to 10 years. The physical characteristics of our patients as detailed in Table I are typical of previously reported series [Niikawa et al., 1988; Kawame et al., 1999] with a remarkably similar facial appearance (Fig. 1). While mild to moderate joint hyperextensibility was common (5/6), serious skeletal abnormalities including scoliosis and recurrent patellar dislocation were seen in only one patient. Patellar dislocations while uncommon in Kabuki syndrome have been reported [Ikegawa et al., 1993] and caused significant pain and disability in our patient. An uncommon, but interesting feature of this condition is immune thrombocytopenic purpura, which was seen in one of our patients and has been reported in at least three other patients [Watanabe et al., 1994; Kawame et al., 1999]. Whether a gene or genes important for immune function is part of the genetic alteration causing this condition is currently unknown. We also had one patient with early onset seizures, which have previously been reported in 16% of patients [Niikawa et al., 1988].

All six individuals had a history of delayed speech and language acquisition and were receiving speech services. All had articulation errors, which appeared to be



Fig. 1. Patients with Kabuki syndrome. a: Patient 1 at age 11 years. b: Patient 2 at age 5 years. c: Patient 4 at age 16 years. d: Patient 5 at age 12 years. e: Patient 6 at age 8 years.

due to oral-motor hypotonia and poor coordination and were not felt to be due to structural abnormalities such as velopharyngeal insufficiency, dental malocclusion, or CP. All patients also had abnormal oral resonance, which again was felt to be a result of oral-motor hypotonia. Abnormal resonance is frequently misinterpreted as hypernasality. Thus, the reduced projection and precision in articulation skills seen in our patients with the Kabuki syndrome are consistent with oral-motor hypotonia, which may explain their resistance to treatment.

Of the four patients with abnormal prosody, three had a decreased inflection pattern characterized by dull, flat speech, whereas one had an increased inflection pattern characterized by a singsong manner of speech. Additionally, the prosody and articulation errors often became more pronounced as spontaneous, verbal utterances increased in length and complexity and so intelligibility was negatively impacted. One of the more intriguing findings, noted in the two girls followed from childhood into adolescence with serial speech evaluations (Patients 4 and 5), was that pitch, loudness, and prosody did not mature significantly over time. Therefore, what was age appropriate performance at younger ages became inappropriate in adolescence. This certainly raises a challenge for speech services, as by adolescence, while articulation had improved, the pitch and loudness of these girls had not and so was noticeably different from peers despite ongoing speech services. As no boys were followed into adolescence, we do not know if this feature can be generalized to both sexes nor do we know if this was related to the fact that both of the adolescent girls had CPs. Otherwise there were no sex-dependent or cleft-dependent speech characteristics observed.

One limitation of this study was the small number of patients and the lack of longitudinal follow-up on all patients. The evaluation of additional patients over longer periods of time will enable confirmation of these findings and the discovery of age-dependent, sex-dependent, or cleft-dependent speech characteristics. In summary, we suggest that there is a characteristic speech pattern in individuals with the Kabuki syndrome that combines features of abnormal oral resonance and articulation errors due to oral-motor hypotonia. Further, this pattern shows a lack of normal maturation throughout childhood, so that abnormalities of pitch,

loudness, and prosody result in inappropriate and difficult to understand speech production by adolescence. Speech characteristics can be added to the extensive list of clinical features associated with this syndrome. Recognition of this distinctive speech pattern will hopefully aid in tailoring speech-language remedy for individuals with the Kabuki syndrome.

REFERENCES

- Burke LW, Jones MC. 1995. Kabuki syndrome: Underdiagnosed recognizable pattern in cleft palate patients. *Cleft Palate Craniofac J* 32:77-84.
- Ikegawa S, Sakaguchi R, Kimizuka M, Yanagisako Y, Tokimura F. 1993. Recurrent dislocation of the patella in Kabuki make-up syndrome. *J Pediatr Orthop* 13:265-267.
- Ilyina H, Lurie I, Naumtchik I, Amoashy D, Stephanenko G, Fedotov V, Kostjuk A. 1995. Kabuki make-up (Niikawa-Kuroki) syndrome in the Byelorussian register of congenital malformations: Ten new observations. *Am J Med Genet* 56:127-131.
- Kawame H, Hannibal MC, Hudgins L, Pagon RA. 1999. Phenotypic spectrum and management issues in Kabuki syndrome. *J Pediatr* 134:480-485.
- Koutras A, Fisher S. 1982. Niikawa-Kuroki syndrome: A new malformation syndrome of postnatal dwarfism, mental retardation, unusual face, and protruding ears. *J Pediatr* 101:417-419.
- Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. 1981. A new malformation syndrome of long palpebral fissures, large ears, depressed nasal tip, and skeletal anomalies associated with postnatal dwarfism and mental retardation. *J Pediatr* 99:570-573.
- Niikawa N, Matsuura N, Fukushima Y, Ohsawa T, Kajii T. 1981. Kabuki make-up syndrome: A syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. *J Pediatr* 99:565-569.
- Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, Tonoki H, Ishikawa N, Yamada Y, Fujita M, Umemoto H, Iwama Y, Kondoh I, Fukushima Y, Nako Y, Matsui I, Urakami T, Aritaki S, Hara M, Suzuki Y, Chyo H, Sugio Y, Hasegawa T, Yamanaka T, Tsukino R, Yoshida A, Nomoto N, Kawahito S, Aihara R, Toyota S, Ieshima A, Funaki H, Ishitobi K, Ogura S, Furumae T, Yoshino M, Tsuji Y, Kondoh T, Matsumoto T, Abe K, Harada N, Miike T, Ohdo S, Naritomi K, Abushwereb AK, Braun OH, Schmid E. 1988. Kabuki make-up (Niikawa-Kuroki) syndrome: A study of 62 patients. *Am J Med Genet* 31:565-589.
- Schrander-Stumpel C, Meinecke P, Wilson G, Gillessen-Kaesback G, Tinschert S, Konig R, Philip N, Rizzo R, Matt-Kievit A, van der Burgt I, van Essen T, Latta E, Hillig U, Verloes A, Journal H, Fryns JP. 1994. The Kabuki (Niikawa-Kuroki) syndrome: Further delineation of the phenotype in 29 non-Japanese patients. *Eur J Pediatr* 153:438-445.
- Watanabe T, Miyakawa M, Satoh M, Abe T, Oda Y. 1994. Kabuki make-up syndrome associated with chronic idiopathic thrombocytopenic purpura. *Acta Paediatr Jpn* 36:727-729.
- Wilson GN. 1998. Thirteen cases of Niikawa-Kuroki syndrome. *Am J Med Genet* 79:112-120.