Variable Expressivity in a Family with Kabuki Make-up (Niikawa-Kuroki) Syndrome

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Kabuki make-up syndrome (KS), also called Niikawa-Kuroki syndrome, is a rare congenital disorder of unknown etiology. Most KS cases occur sporadically and familial KS had never been reported in Taiwan. I describe four individuals in one family with KS. Significant intrafamilial variability in the clinical expression of this syndrome is evident. In addition to the typical craniofacial dysmorphism and cleft palate and/or cleft lip that the three children inherited from their father, rare anomalies such as lower lip pits and growth hormone deficiency in one girl and right-sided acrotia in one boy were noted. High-resolution banding did not detect any chromosomal structural anomalies. These findings further suggested the autosomal inheritance (from the father to two sons and one daughter) in KS and highlighted the overlapping phenotype with van der Woude syndrome. *(Chang Gung Med J 2004;27:307-11)*

Key words: **Kabuki make-up syndrome, Niikawa-Kuroki syndrome, lip pit, van der Woude syndrome.**

Kabuki make-up syndrome (KS), also known as Niikawa-Kuroki syndrome (OMIM#147920), was independently reported in 1981 by Niikawa et al. and Kuroki et al.[1,2] This syndrome was called "Kabuki make-up syndrome" because the faces of the patients resembled the make-up of Japanese Kabuki actors with peculiar features including long palpebral fissures, broad eyebrows which are sparse in the lateral half, prominent eyelashes, lower lateral palpebral ectropia, and depressed nasal tips.[1,2] Major associated features include moderate mental retardation, susceptibility to infection, and growth retardation. Lower lip pit, a common feature of van der Woude syndrome, has been reported in very rare cases of KS.[3,4] Failure to thrive with confirmed growth hormone deficiency (GHD) in KS was also noted.[5,6] Here, I report a Taiwanese family of which the father had a mild form of KS and transmitted this disorder to his three children. The daughter presented with previously unreported GHD and lower lip pits. High-resolution chromosome banding and fluorescence in situ hybridization (FISH) study were performed to detect the existence of some syndromic oral-facial defects.

CASE REPORT

A 5-year-old female Taiwanese patient was brought to the genetic outpatient clinic due to developmental delay and short stature. She was born to a healthy and nonconguineous 29-year-old G2P1 mother and a 30-year old father at 40 weeks of gestation, after an uneventful pregnancy. Her birth weight was 2500g. She has a submucous cleft palate and underwent two courses of palatoplasty at 12 months and 14 months of age, respectively. Frequent episodes of respiratory tract infection and acute otitis media were noted from when she was 1 year old.

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Closure for the oro-nasal fistula was performed when she was 3 years old. She also suffered from poor weight gain, short stature (below the 3rd percentile), retarded bone age (delayed over 2 years), and epilepsy. Mental retardation with IQ 31 was noted at the age of 5 years. Physical examination showed typical features of KS including arched eyebrows with sparse or dispersed lateral half, long palpebral fissures, eversion of the lower lateral eyelids, long eyelashes, epicanthal folds, depressed nasal bridge, short nasal septum, long and prominent ears, and micrognathia (Fig. 1). In addition, she had ptosis, strabismus (exotropia), hypodontia, umbilical hernia, two pits over the lower lip (Fig. 2), short 5th fingers, fingertip pads, scoliosis, poor visual acuity, velopharyngeal insufficiency, motor delay, and hyperactivity. Her speech was not very structured. Her body height was always below the 3rd percentile (104 cm at 7 years old). GHD was confirmed after insulin and clonidine provocative tests. Recombinant human growth hormone therapy was started when she was 10 years old.

Her elder brother (2 years older) had normal growth but became obese. He also has epilepsy, mental retardation (IQ 57), history of hypocalcemia, speech delay, poor dentition, and acanthosis nigricans. Her younger brother (2 years younger) showed similar features with additional anomalies including right-sided hemifacial microsomia, right acrotia with bilateral hearing impairment, unilateral cleft palate and cleft lip, seizure, attention deficit, velopharyngeal insufficiency, frequent otitis media, initial poor weight gain (body weight around 3-10th percentile) with retarded bone age (about 2 years' delay) but obesity developed after the age of 7 years. Her father has some characteristics of KS (long palpebral fissures, broad eyebrows which are sparse in the lateral half, and prominent eyelashes), history of epilepsy, borderline mentality, and cleft palate. All three children have features of KS (Fig. 1 and Table 1).

The results of chromosome studies using high resolution banding for each patient were normal. FISH with the Oncor probe N25 (D22S75) revealed no submicroscopic deletion of 22q11.2 in these

Fig. 1 The Kabuki family (from the front to the back): the proband, her younger brother, older brother, and father.

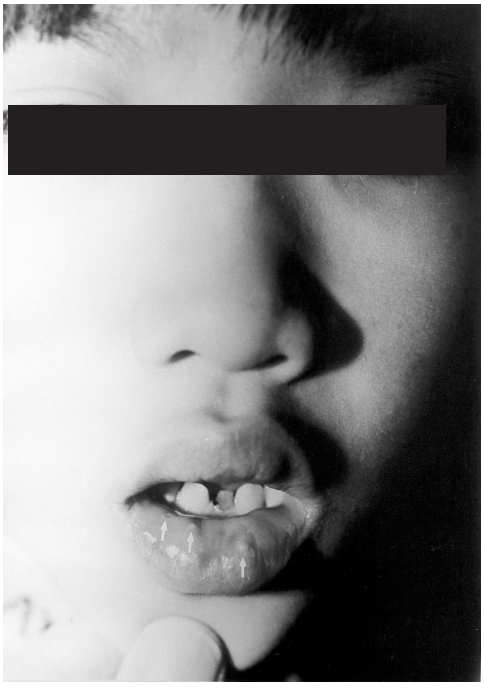

Fig. 2 Bilateral lower lip pits in the proband.

Table 1. Clinical Features of the Kabuki Family

Features / Patient	Son 1	Daughter	Son 2	Father
Mentality (IQ)	moderate (57)	severe (31)	moderate (48)	borderline
Microcephaly	+	+	+	−
Failure to thrive	−	+	+~−	−
Strabismus	−	+	−	−
Hypernasality dyslalia	+	+	+	−
Cleft lip	−	−	+	−
Cleft palate	−	+	+	+
Lower lip pits	−	+	−	−
Hypodontia	+	+	+	+
Microtia	−	−	+	−
Frequent otitis media	+	+	+	+
Hearing impairment	−	+	+	+
Seizure	+	+	+	+
Growth hormone deficiency	−	+	−	−
Delayed skeletal age	−	+	+	ND
Umbilical hernia	−	+	+	−
Joint laxity	+	+	+	+
Kyphoscoliosis	−	+	+	−
Acanthosis nigricans	+	−	−	−
Obesity	+	−	+	−

Abbreviations: ND: not done.

patients. The complete blood cell counts, immunoglobulin levels, and thyroid function were all normal.

DISCUSSION

Most cases of KS are sporadic. In this family, the father had mild symptoms married and reproduced and the disease was transmitted to a second generation where more severe and variable manifestations occurred. This report further supports the autosomal dominant inheritance with different expressivity in KS. Patients of KS have characteristic facies and associated features such as 1) neonatal hypotonia and feeding difficulties, 2) recurrent infections, 3) congenital heart disease, 4) reno-urinary malformations, 5) small mouth, micrognathia, cleft or high arched palate, hypodontia, 6) obesity, 7) premature thelarche, and 8) deafness.[1,2,5,7,8]

Rare associations or complications have included autistic behavior, partial epilepsy, polymicrogyria,[9] congenital hypothyroidism, thrombocytopenic purpura, autoimmune hemolytic anemia, hypogammaglobulinemia,[7] abnormal upper incisor teeth shape, missing premolars,[10] and lip pits.[3,4] The lower lip pits, known as congenital sinuses or fistulas that occur between the 40th and 50th day of embryonic life, are frequently seen in patients with van der Woude syndrome (VDWS) and popliteal pterygium syndrome and occasional in those with branchio-oculo-facial syndrome and oral-facial-digital syndrome I.[11] VDWS is an entity of autosomal dominant genetic etiology and variable expressivity. Clinically there may be one or more pits in the lower lip, cleft palate with or without cleft lip, cleft uvula, and other signs. In the present family report, the cleft lip/palate, hypodontia and/or, lower lip pits were consistent with VDWS. A Brazilian girl with KS and lower lip pits and anovestibular fistula was reported.[4] Such lip lesions in a patient with KS were also reported by Franceschini et al.[3] Possibly those two patients have VDWS and KS. However, there was one report that excluded this possibility by microsatellites close to the VDWS critical region at 1q32-41. Rather, this sign may represent a rare manifestation of the KS spectrum.

Ligmentous laxity and joint hyperextensibility have been described in 74-96% of KS patients.[12] Joint dislocation is also present in up to 50% of these patients, including patella dislocation, which may

result in significant disability and require surgical repair. Some risk factors for patella dislocation include female, adolescence, young adulthood, obesity, and joint laxity.[13] Some endocrinological problems have been reported in KS, they included premature thelarche or precious puberty,[3] hypoglycemia, and short stature with GHD.[5,6] The administration of growth hormone therapy in the patient is expected to promote her growth and enhanced her cognition.

The pathogenesis of KS is still unknown. Autosomal dominant or X-linked transmission has been thought after the genetic analysis or chromosomal anomalies in only a few cases.[8,14,15] The candidate genes such as TUBA2 (on13q11), SHOX/PHOG (on pseudo-autosomal region of X or Y chromosome) have been speculated but have not been proven yet.[8,14] Further studies of the occurrence of the cleft lip and palate and genetic changes of the parents' family members may elucidate the pathogenesis of this rare disease.

REFERENCES

1. Niikawa N, Matsura N, Fukushima Y, Ohsawa T, Kajii T. Kabuki make-up syndrome: a syndrome of mental retardation, unusual facies, large and protruding ears, and postnatal growth deficiency. J Pediatr 1981;99:565-9.
2. Kuroki Y, Suzuki Y, Chyo H, Hata A, Matsui I. 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 1981;99:570-3.
3. Franceschini P, Varden MP, Guala A, Franceschini D, Testa A, Corrias A, Chiabotto P. Lower lip pits and complete idiopathic precocious puberty in a patient with Kabuki make-up syndrome. Am J Med Genet 1993;47:423-5.
4. Kokitsu-Nakata NM, Vendramini S, Guion-Almeida ML. Lower lip pits and anorectal anomalies in Kabuki syndrome. Am J Med Genet 1999;86:282-4.
5. Bereket A, Turan S, Alper G, Comu S, Alpay H, Akalin F. Two patients with Kabuki syndrome presenting with endocrine problems. J Pediatr Endocrinol Metab 2001;14:215-20.
6. Devriendt K, Lemli L, Craen M, de Zegher F. Growth hormone deficiency and premature thelarche in a female infant with Kabuki make-up syndrome. Horm Res 1995;43:303-6.
7. Kawame H, Hannibal MC, Hudgins L, Pagon RA. Phenotypic spectrum and management issues in Kabuki syndrome. J Pediatr 1999;134:480-5.
8. 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. Kabuki make-up (Niikawa-Kurokii) syndrome: a study of 62 patients. Am J Med Genet 1988;31:565-89.
9. Roccella M. Niikawa-Kuroki syndrome. Minerva Pediatr 1999;51:271-8.
10. Mhanni AA, Cross HG, Chudley AE. Kabuki syndrome: description of dental findings in 8 patients. Clin Genet 1999;56:154-7.
11. Schinzel A, Klauser M. The van der Woude syndrome (dominantly inherited lip pits and defects). J Med Genet 1986;23:291-4.
12. Wilson GN. Thirteen cases of Niikawa-Kuroki syndrome: report and review with emphasis on medical complications and preventive management. Am J Med Genet 1998;79:112-20.
13. Kurosawa K, Kawame H, Ochiai Y, Nakashima M, Tohma T, Ohashi H. Patellar dislocation in Kabuki syndrome. Am J Med Genet 2002;108;160-3.
14. McGinniss MJ, Brown DH, Burke LW, Mascarello JT, Jones MC. Ring chromosome X in a child with manifestations of Kabuki syndrome. Am J Med Genet 1997;70:37-42.
15. Tsukahara M, Kuroki Y, Imaizumi K, Miyazawa Y, Matsuo K. Dominant inheritance of Kabuki make-up syndrome. Am J Med Genet 1997;73:19-23.

一歌舞伎症 (Niikawa-Kuroki 二氏症) 家族之臨床變異

侯家瑋

歌舞伎症，又名Niikawa-Kuroki二氏症，是一種成因不明的罕見先天疾病，乃以其特殊臉型五官類似歌舞伎劇演者爲名，本病多爲散發性，家族內發生在台灣尚未報告過。本文描述在同一家庭4名歌舞伎症之臨床變異，除了類似的臉部特徵外，其中3名有顎裂或唇裂，1名則有極罕見的下嘴唇小孔合併生長激素缺乏症，另1名則有單側小耳症。高解析度染色體檢查並無異常。這些發現顯示歌舞伎症常染色體顯性遺傳，而且與van der Woude氏症表現型有重疊。(長庚醫誌 2004;27:307-11)

關鍵字： 歌舞伎症，Niikawa-Kuroki二氏症，嘴唇小孔，van der Woude氏症。

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