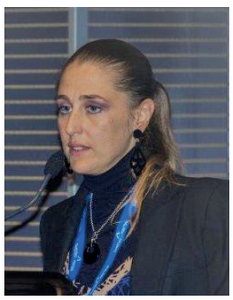
KEY WORDS
Kabuki syndrome, Niikawa-Kuroki syndrome,
Radiography, Case-control study

DENTOSKELETAL FEATURES OF KABUKI SYNDROME. A CASE-CONTROL STUDY



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PURPOSE. Kabuki syndrome, also known as Kabuki Makeup syndrome or Niikawa-Kuroki syndrome, is a rare genetic disorder characterized by multiple and heterogeneous congenital malformations and intellectual disability. The aim of this case-control study was to compare the dento-skeletal anomalies of Kabuki syndrome with those of non-syndromic population (control).

MATERIALS AND METHODS. Patients affected by Kabuki syndrome referred to the University of Florence were included in the present study. Patients who were able to undergo a lateral cephalogram were matched with a control group of patients of similar age and sex derived from the University of Michigan Growth Study. Several linear and angular cephalometric variables were compared with t-test for paired data.

RESULTS. A total of 10 patients with Kabuki syndrome were included in the study. Four patients had a history of cleft lip and palate. Eight patients showed at least one tooth agenesis. Lateral cephalograms were available for five patients. Regarding the craniofacial skeletal characteristics, the only statistically significant difference between the Kabuki group and the control group was represented by the inclination of the palatal plane to the cranial base (SN-PP). This was significantly higher in syndromic patients (3.8°, 95% CI from 2.1° to 5.4°, P = 0.003). The other variables were not statistically significant. The power of the study, however, was low.

CONCLUSIONS. Tooth agenesis, cleft lip and/or palate, and a steeper inclination of the palatal plane to the cranial base, were the most common dentoskeletal features detected in patients with Kabuki syndrome.

CONFLICT OF INTEREST STATEMENT
This study was completely self-funded, and no financial support was sought or obtained, not even in the form of free materials.

INTRODUCTION

Kabuki syndrome, also known as Kabuki Makeup syndrome or Niikawa-Kuroki syndrome, is a rare genetic disorder characterized by multiple and heterogeneous congenital malformations and intellectual disability. It was first described in 1981 by two Japanese geneticists, Yoshikazu Kuroki and Norio Niikawa[1,2]. They reported, in independent research groups, cases of individuals with peculiar facial and skeletal features, dermatoglyphic anomalies, reduced postnatal growth and mild to moderate intellectual disability[1,2]. Its name was suggested by the typical facial dysmorphism of this syndrome, which is reminiscent of the Kabuki masks used by actors in traditional Japanese theatre[2]. It is reported to have a prevalence of 1 in 32,000-86,000 people[3,4].

The aetiology of Kabuki syndrome is not yet fully understood. Two genes are commonly mutated in the Kabuki syndrome: KMT2D and KDM6[5]. For the first gene, the mutation is located on chromosome 12q13, while for the second gene, the mutation is located on chromosome Xp11.23[6]. Both gene products affect histone modification and chromatin activity and promote gene expression[7,8]. Considering the many possible variations, patients present different phenotypic spectra and severity of congenital anomalies[9-12].

Among the various manifestations observed, most patients had the following five cardinal manifestations:

1. a peculiar face characterized by eversion of the lower lateral eyelid, arched eyebrows, a depressed nasal tip, and prominent ears;
2. skeletal anomalies including brachydactyly and a deformed spinal column, with or without sagittal cleft vertebrae;
3. dermatoglyphic anomalies including increased digital ulnar loop and hypothenar loop patterns, absence of the digital triradius, and presence of fingertip pads;
4. mild to moderate mental retardation;
5. postnatal growth deficiency[3,13].

Kabuki syndrome can express a corollary of congenital malformations, which are accompanied by organ or systemic pathologies. The most common clinical findings are congenital anomalies of the heart, kidneys, and urogenital tract, neurological anomalies, and auxological problems[14-16].

The oral alterations include cleft lip and palate in 12%-86% of individuals and dental abnormalities of shape, size, position, and number[17,18]. In a recent systematic review among the 11 studies included, the most commonly reported finding was the absence or agenesis of teeth, observed by nine authors[6].

Several skeletal anomalies have been described in the Kabuki syndrome[19]. In a controlled study children with Kabuki syndrome exhibited larger heads and longer arms in proportion to their trunks compared to a control group[19].

To date, there have been few studies in the literature that have evaluated cephalometric analysis based on lateral radiographs of the skull of patients with Kabuki syndrome[20-22]. To the best of our knowledge, no study has hitherto compared the cephalometric characteristics of patients affected by Kabuki syndrome with those of non-syndromic subjects.

The aim of this matched case-control study was to compare the dento-skeletal anomalies of patients with Kabuki syndrome (Kabuki group) with those of a non-syndromic population (control group).

MATERIALS AND METHODS

Study design

The present study was a case-control matched study with a blind examiner. Subjects with Kabuki syndrome who underwent a lateral cephalogram were matched by age and sex with control patients from the University of Michigan Growth Study (https://www.aaoflegacycollection.org/aaof_home.html). The STROBE statement guidelines for reporting observational studies were followed[23].

Setting

The study included all patients with Kabuki syndrome who had undergone dental visits and/or treatments between years 2000 and 2020 at the Special Pediatric Odontostomatology Unit of the Anna Meyer University Hospital in Florence, Italy.

Participants

Patients suffering from Kabuki syndrome had to be between 7 and 20 years of age with the presence of a genetic diagnosis.

The patients with Kabuki syndrome included in the study who had offered their collaboration in the acquisition of a lateral cephalogram, were included in the Kabuki group. The control group consisted of non-syndromic subjects, matched 1:1 for age (plus and minus 3 months up to 18 years) and sex with the patients of the Kabuki group. The subjects of the control group were randomly selected from the collection of lateral cephalograms of the University of Michigan Growth Study, using as a search filter for untreated Class I malocclusion.

The University Michigan Growth Study consists of annual records of students enrolled at University School, a laboratory school housed in the School of Education on the Ann Arbor campus. Data collection began in 1935, when medical, dental, psychological, and anthropological data were collected. Collection of cephalograms began in 1953 and continued routinely until about 1970, when the University School closed and data collection was discontinued.

Variables, data sources/measurement, and quantitative variables

A comprehensive medical history was obtained for all patients. Through an oral examination and possibly with a panoramic radiograph, cleft palate or cleft lip and palate and dental agenesis were recorded in patients suffering from Kabuki syndrome.

In patients with Kabuki syndrome for whom a lateral cephalogram was available and in control subjects, a cephalometric analysis was performed with the following angular and linear variables:

- Variables related to the cranial base
  - SN (mm), sagittal dimension of the anterior cranial base;
  - NSBa (°), angle of the cranial base.
- Sagittal skeletal variables
  - SNA (°), angle that describes the position of the maxilla on the sagittal plane with respect to the cranial base;
  - SNB (°), angle that describes the position of the mandible on the sagittal plane with respect to the cranial base;
  - ANB (°), angle obtained from the difference of SNA minus SNB. It describes the intermaxillary relationship on the sagittal plane;
  - Wits index (mm), linear distance of the projections of points A and B on the occlusal plane.

- Vertical skeletal variables
  - SN-Palatal Plane (°) (SN-PP), angle that describes the inclination of the palatal plane to the cranial base;
  - SN-Mandibular Plane (°) (SN-MP), angle that describes the inclination of the mandibular plane to the cranial base;
  - Palatine Plane-Mandibular Plane (°) (PP-MP), angle that describes the intermaxillary divergence;
  - ANS-Me (mm), linear dimension of the lower anterior facial height;
  - N-Me (mm), linear dimension of the total anterior facial height.
- Mandibular variables
  - CoGn (mm), linear dimension of the total mandibular length;
  - CoGo (mm), linear dimension of the mandibular ramus;
  - CoGoMe (°), mandibular angle that describes the angulation of the mandibular ramus to the mandibular corpus.
- Dento-alveolar variables
  - OVJ (mm), linear distance measured parallel to the occlusal plane, from the incisal edge of the most protrusive upper central incisor to the most facial aspect in the incisal third of the crown of the most protrusive lower central incisor;
  - OVB (mm), vertical distance perpendicular to the occlusal plane between the incisal edges of the most protrusive upper and lower central incisors;
  - Molar relationship (mm), distance measured parallel to the occlusal plane between the mesial contact heights of the contours on the maxillary and mandibular first permanent molars;
  - Upper Incisor-Palatal Plane (°) (UIPP), angle that describes the inclination of the most protrusive upper central incisor to the palatal plane;
  - Lower Incisor-Mandibular Plane (°) (LIMP), angle that describes the inclination of the most protrusive lower central incisor to the mandibular plane.

Bias

The cephalometric data examiner (LF) was masked to the group (Kabuki syndrome or control).

Study size

All patients with Kabuki syndrome who were willing to perform a lateral cephalogram were included in this study. A sample size calculation was not possible due to the rarity of the disease.

Statistical methods

Descriptive statistics were performed for all variables (frequency and percentage for qualitative variables and mean and standard deviation for quantitative variables). Paired t-tests were used to compare Kabuki syndrome patients with matched control subjects.

RESULTS

Participants

The patients affected by Kabuki syndrome who were included in this study were 10 in total, with seven being male (M) and three female (F). The patients were aged between 8 and 20 years. Of the 10 patients included with Kabuki syndrome, only five, including three males and two females, who had offered their collaboration in the acquisition of a lateral cephalogram,

were recruited to constitute the Kabuki group, for the study of craniofacial skeletal characteristics. Consequently, a control group comprising five subjects was established, matched for age and gender with the five patients in the Kabuki group.

Descriptive data

A brief description of the pathological history, remote and immediate, of each patient affected by Kabuki Syndrome with radiographic documentation was reported in **TABLE 1**.
Four patients (40%) had a history of cleft lip and palate, which had been successfully treated surgically (**TABLE 1**). Eight patients (80%) presented multiple agenesis of elements of the permanent series, more often affecting the upper lateral incisors and the lower lateral incisors. Six patients (60%) exhibited a malocclusion with a tendency towards skeletal III malocclusion. Furthermore, multiple dental caries were found with high frequency (60% of cases) (**TABLE 1**).

TABLE 1 SYSTEMIC AND DENTOSKELETAL CHARACTERISTICS OF PATIENTS WITH KABUKI SYNDROME

	P. 1	P. 2	P. 3	P. 4	P. 5	P. 6	P. 7	P. 8	P. 9	P. 10
Gender	M	M	M	M	F	M	F	M	M	F
Systemic anomalies										
Intellectual disability	+	+	+	+	+	+	+	+	+	+
Hearing impairment	+	+								
Visual impairment or strabismus	+		+	+		+		+		+
Epilepsy			+							
Kidney anomalies			+		+	+				
Tonsillar hypertrophy		+		+				+		
Heart defects							+			+
Dentoskeletal anomalies										
Panoramic x-ray	+			+	+	+	+	+	+	+
Lateral cephalogram					+	+		+	+	+
Cleft palate/cleft lip and palate	+	+	+				+			
Agenesis	+ (1.8, 2.8)		+ (1.2, 2.2)		+ (5.2, 6.2, 1.2, 2.2, 3.3, 4.2)	+ (1.2 2.2)	+ (1.2)	+ (1.2, 2.2., 4.1)	+ (1.2, 2.2, 3.3, 4.2)	+ (1.2, 1.5, 2.2)
Multiple dental caries	+		+	+	+		+		+	
Malocclusion	+		+		+			+	+	+

M: Male; F: Female.

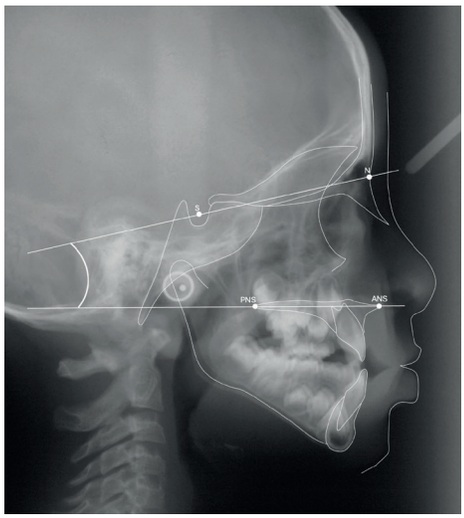

FIG. 1: *cephalometric tracing of a case with kabuki syndrome (male patient, 8 years) showing an increased angulation (14 degrees) of the palatal plane (passing through points anterior nasal spine, ans, and posterior nasal spine, pns) to the sella (s)-nasion (n) plane*

Main results (matched case-control study)

The statistical analysis of the comparison between the five patients who had offered their collaboration to perform the lateral cephalogram and the five subjects of the control group is shown in **TABLE 2**.

In relation to the craniofacial skeletal characteristics the only statistically significant difference between the Kabuki group and the Control group was represented by the inclination of the palatal plane to the cranial base (SN-PP). This angle was significantly greater in syndromic patients (3.8 degrees, 95% CI from 2.1 to 5.4, P = 0.003). No statistically significant differences were identified between the two matched groups for any other variables (**TABLE 2**). A cephalometric tracing of a case with Kabuki syndrome is presented in **FIG. 1**.

TABLE 2 COMPARATIVE CEPHALOMETRIC ANALYSIS BETWEEN KABUKI AND CONTROL GROUP

Variable	Kabuki N=5	Control N=5	Difference	95%CI	P-value
Age	11.8 (4.6)	11.4 (4.0)	0.3	-0.5; 1.1	0.348
Variables relating to the skull base					
SN (mm)	63.3 (1.7)	65.8 (3.1)	-2.5	-6.2; 1.2	0.132
NSBa (°)	135.6 (10.2)	130.8 (3.4)	4.8	-6.2; 15.9	0.290
Sagittal skeletal variables					
SNA (°)	79.6 (3.3)	80.6 (3.1)	-1.0	-6.1; 4.0	0.605
SNB (°)	75.0 (1.3)	77.3 (2.6)	-2.3	-5.8; 1.3	0.150
ANB (°)	4.7 (2.6)	3.3 (0.8)	1.3	-2.1; 4.7	0.340
Wits (mm)	-1.7 (1.4)	-1.5 (2.1)	-0.2	-3.5; 3.1	0.900
Vertical skeletal variables					
SN-PP (°)	**10.5 (2.8)**	**6.7 (3.6)**	**3.8**	**2.1; 5.4**	**0.003**
SN-MP (°)	40.3 (8.7)	33.7 (3.0)	6.6	-6.8; 20.0	0.241
PP-MP (°)	29.8 (9.4)	26.9 (1.1)	2.9	-9.0; 14.8	0.532
ANS-Me (mm)	60.1 (8.2)	58.4 (4.8)	1.8	-7.8; 11.4	0.633
N-Me (mm)	103.5 (6.8)	101.9 (6.7)	1.6	-9.3; 12.5	0.711
Mandibular variables					
CoGn (mm)	96.8 (5.4)	99.7 (6.9)	-2.9	-8.8; 3.0	0.242
CoGo (mm)	45.3 (3.0)	46.9 (5.0)	-1.6	-4.4; 1.1	0.177
CoGoMe (°)	128.5 (7.1)	124.2 (3.8)	4.3	-8.5; 17.0	0.404
Dento-alveolar variables					
OVJ (mm)	1.9 (2.9)	4.7 (1.4)	-2.5	-6.3; 0.8	0.101
OVB (mm)	0.5 (2.3)	1.3 (1.4)	-0.8	-4.7; 3.1	0.581
Molar relation (mm)	1.0 (1.6)	1.7 (1.3)	-0.7	-2.5; 1.1	0.367
U1-PP (°)	108.7 (8.1)	112.7 (6.1)	-4.0	-15.0; 7.0	0.367
L1-MP (°)	88.3 (10.2)	90.3 (4.4)	-2.0	-15.8; 11.8	0.708

DISCUSSION

The aim of this matched case-control study was to compare the dentoskeletal features of Kabuki syndrome (Kabuki group) with those of non-syndromic population (control group).

A total of 10 patients diagnosed with Kabuki syndrome were enrolled in the study. Four patients exhibited cleft lip and palate while eight patients showed agenesis (congenitally missing teeth) in at least one location.

The observed frequency of cleft lip and palate in this study (40%) is comparable to that reported in other studies which ranged from 12% to 86%[17,18,24]. This study also corroborates the findings of Barbosa-Lima (2020) that tooth absence or agenesis were the most commonly observed oral findings in individuals with Kabuki syndrome[6].

Lateral cephalograms were available for five patients in this study. The only statistically significant craniofacial skeletal difference between the Kabuki and control groups involved the inclination of the palatal plane (SN-PP) relative to the cranial base. This angle was significantly steeper in patients with the syndrome (3.8 degrees, 95% CI: 2.1 to 5.4, P = 0.003), suggesting a relatively greater upper anterior facial height compared to the lower facial height in Kabuki syndrome.

Midface hypoplasia and mandibular hypoplasia were frequently observed in the Kabuki syndrome[17]. There are few studies in the literature that have performed cephalometric analysis on lateral cephalograms of patients with Kabuki syndrome[20-22]. To our knowledge, this is the first study that compared the cephalometric characteristics of patients with Kabuki syndrome with those of control subjects in a case-control study.

In a study[20], craniofacial growth in a patient with Kabuki syndrome was assessed with lateral cephalograms with an interval of 12–15 months. These cephalograms were taken from 6 years and 9 months to 14 years and 2 months. Angular and linear measurements of the craniofacial region showed a hypoplastic maxilla and a constricted maxillary basal arch width. This patient showed a Class III skeletal pattern with a steep mandibular plane angle (SN–MP), a relatively short ramus, and a large gonial angle. The SN-PP angle was not reported in this study[20].

In another study, a patient was followed for nine years with lateral cephalograms [22]. Bimaxillary retrusion and a skeletal Class I relationship, with increased lower facial height and severe anterior open bite were observed[22]. Analysis based on only a single case is insufficient to describe the dentoskeletal features of Kabuki patients[22].

Matsune *et al.* (2001) analysed lateral cephalograms in six patients[21]. They found that the angle of convexity (NA to APog) was small in all patients, but they did not measure the SN-PP angle. This finding corroborates our result because it could indicate presence of maxillary hypoplasia in the Kabuki syndrome.

A major limitation of this study is the low power for all the variables examined as a result of the low sample size. Unfortunately, cephalometric analysis was performed in only 50% of patients with Kabuki syndrome. In any case, despite the limited statistical power, it was possible to identify an increase in the SN-PP angle in subjects with Kabuki syndrome. Nevertheless, it is conceivable that other cephalometric variables may differ between patients with Kabuki syndrome and the non-syndromic population. The limited sample size, however, may have prevented the precise detection of such differences.

CONCLUSIONS

Tooth agenesis, cleft lip and/or palate, and a steeper inclination of the palatal plane to the cranial base were the most common dentoskeletal features detected in patients affected by the Kabuki syndrome.

REFERENCES

1. 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(4):570-3.
2. Niikawa N, Matsuura 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(4):565-9.
3. Niikawa N, Kuroki Y, Kajii T, Matsuura N, Ishikiriyama S, et al. Kabuki make-up (Niikawa-Kuroki) syndrome: a study of 62 patients. Am J Med Genet 1988;31(3):565-89.
4. White SM, Thompson EM, Kidd A, Savarirayan R, Turner A, et al. Growth, behavior, and clinical findings in 27 patients with Kabuki (Niikawa-Kuroki) syndrome. Am J Med Genet A 2004;127A(2):118-27.
5. Miyake N, Koshimizu E, Okamoto N, Mizuno S, Ogata T, et al. MLL2 and KDM6A mutations in patients with Kabuki syndrome. Am J Med Genet A. 2013 ;161A(9):2234-43.
6. Barbosa-Lima R, Lopes A, de Moura JN, Ribeiro SN., Cardoso MS. Dental findings in Kabuki syndrome: a systematic review for dentistry. Odovtos 2020;22(2):62-71.
7. Shpargel KB, Starmer J, Wang C, Ge K, Magnuson T. UTX-guided neural crest function underlies craniofacial features of Kabuki syndrome. Proc Natl Acad Sci USA 2017;114(43):E9046-E9055.
8. Shpargel KB, Mangini CL, Xie G, Ge K, Magnuson T. The KMT2D Kabuki syndrome histone methylase controls neural crest cell differentiation and facial morphology. Development 2020;147(21):dev187997.
9. Geneviève D, Amiel J, Viot G, Le Merrer M, Sanlaville D, et al. Atypical findings in Kabuki syndrome: report of 8 patients in a series of 20 and review of the literature. Am J Med Genet A 2004;129A(1):64-8.
10. Shangguan H, Su C, Ouyang Q, Cao B, Wang J, et al. Kabuki syndrome: novel pathogenic variants, new phenotypes and review of literature. Orphanet J Rare Dis 2019;14(1):255.
11. Di Candia F, Fontana P, Paglia P, Falco M, Rosano C, et al. Clinical heterogeneity of Kabuki syndrome in a cohort of Italian patients and review of the literature. Eur J Pediatr. 2022;181(1):171-87.
12. Hennocq Q, Willems M, Amiel J, Arpin S, Attie-Bitach T, et al. Next generation phenotyping for diagnosis and phenotype-genotype correlations in Kabuki syndrome. Sci Rep 2024;14(1):2330.
13. Adam MP, Banka S, Bjornsson HT, Bodamer O, Chudley AE, et al. Kabuki Syndrome Medical Advisory Board. Kabuki syndrome: international consensus diagnostic criteria. J Med Genet 2019;56(2):89-95.
14. Schrander-Stumpel CT, Spruyt L, Curfs LM, Defloor T, Schrander JJ. Kabuki syndrome: Clinical data in 20 patients, literature review, and further guidelines for preventive management. Am J Med Genet A 2005;132A(3):234-43.
15. Schott DA, Blok MJ, Gerver WJ, Devriendt K, Zimmermann LJ, et al. Growth pattern in Kabuki syndrome with a KMT2D mutation. Am J Med Genet A 2016;170(12):3172-79.
16. Digilio MC, Gnazzo M, Lepri F, Dentici ML, Pisaneschi E, et al. Congenital heart defects in molecularly proven Kabuki syndrome patients. Am J Med Genet A 2017;173:2912–22.
17. Do Prado Sobral S, Leite AF, Figueiredo PTS, Ferrari I, Safatle HPN, Cordoba MS, et al. Craniofacial and Dental Features in Kabuki Syndrome Patients. Cleft Palate-Craniofacial J 2013;50:440–7.
18. Pinto LC, Kokitsu-Nakata NM, da Silva Dalben G, de Azevedo Silva LJ, de Almeida ALPF. Systemic and oral abnormalities in Kabuki syndrome: a case series. Oral Surg Oral Med Oral Pathol Oral Radiol 2024;137(5):e91-e98.
19. Penders B, Schott N, Gerver WJ, Stumpel CT. Body proportions in children with Kabuki syndrome. Am J Med Genet A 2016;170(3):610-4.
20. Kobayashi ET, Maruyama Y, Kobayashi K. A longitudinal evaluation of craniofacial growth in a patient with Kabuki make-up syndrome: a case report. Eur J Orthod 2001;23(2):205-13.
21. Matsune K, Shimizu T, Tohma T, Asada Y, Ohashi H, et al. Craniofacial and dental characteristics of Kabuki syndrome. Am J Med Genet 2001;98(2):185-90.
22. Tuna EB, Marşan G, Gençay K, Seymen F. Craniofacial and dental characteristics of Kabuki syndrome: nine years cephalometric follow-up. J Clin Pediatr Dent 2012;36(4):393-400.
23. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med 2007;147(8):573-7.
24. Petzold D, Kratzsch E, Opitz Ch, Tinschert S. The Kabuki syndrome: four patients with oral abnormalities. Eur J Orthod 2003;25(1):13-9.