Craniofacial and Dental Characteristics of Kabuki Syndrome: Nine Years Cephalometric Follow-Up

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Objective: *Kabuki syndrome is a rare autosomal dominant trait with variable clinical expression. Common dental manifestations of Kabuki syndrome are high-arched palate, micrognathia, malocclusion, microdontia, small dental arches, hypodontia, severe maxillary recession and mid-facial hypoplasia.* ***Study design:*** *This report includes the oral manifestations of a Turkish patient with Kabuki syndrome with consideration of the long-term craniofacial prognosis for this patient based on the physical, clinical and radiological findings in 9 years follow-up period. General appearance of the patient was characterized by postnatal growth retardation, moderate mental retardation, peculiar face characterized by long palpebral fissures with eversion of the lateral third of the lower eyelids, prominent and cup-shaped ears, broad and depressed nasal tips, short fifth fingers, psychomotor retardation and dermatologic abnormalities.* ***Results and conclusion:*** *Cephalometric analysis revealed skeletal open bite; periapical and panoramic radiographic examinations showed agenesis permanent teeth. A patient with Kabuki syndrome, who may lead to a better understanding of the abnormalities, playing an important role in clinical diagnosis, planning and dental management is presented.*

Keywords: *craniofacial growth, Kabuki syndrome, dental characteristics, cephalometric analysis.*
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INTRODUCTION

Kabuki syndrome (KS) (Niikawa-Kuroki syndrome; OMIM #147920) is a multiple congenital anomaly/mental retardation syndrome. Its name is derived from the resemblance of the resulting facial features of the made-up faces of Kabuki actors in traditional Japanese theatre.[1,2] Kabuki syndrome was first reported simultaneously by two independent groups, Niikawa *et al*[3] and Kuroki *et al*, in 1981. Although the majority of early cases were reported in Japanese, it has now been described among a number of ethnic groups.[1]

The majority of reported cases have been sporadic, but parent-to-child transmission in more than half a dozen instances suggests that Kabuki syndrome is an autosomal dominant disorder.[5] Chromosomal abnormalities have been shown in few patients.[1,6,7] Recently, Ng *et al,*[5] suggest that mutations in *MLL2* are a major cause of KS.

A clinical diagnosis of KS is based on the following 5 major manifestations:

1. Peculiar facial features (100%) characterized by eversion of the lower lateral eyelid, high-arched eyebrows with a sparse or dispersed lateral third, a broad and depressed nasal tip and large prominent earlobes;
2. Skeletal anomalies (92%), including shortness of the fifth finger and toes, deformed vertebrae or ribs, and dislocation of the hip joints;
3. Dermatoglyphic abnormalities (93%), including increased digital ulnar and hypothenar loop patterns, absence of the digital c and/or triradii, and presence of fingertip pads;
4. Mild to moderate mental retardation (83%);
5. Postnatal growth deficiency (83%).

Oral anomalies are common (over 60%) in KS, and include abnormalities of the dentition such as widely spaced teeth, a high palate, hypodontia, conical incisors, screw driver-shaped incisors and ectopic upper permanent first molars.[8-10] Hypodontia in KS is usually observed at the central and lateral incisors.[9,11] A clinical case with fusion and germination was also reported by Adam *et al*.[1]

Additional manifestations of KS are early breast development in infant girls (23%) and congenital heart defects

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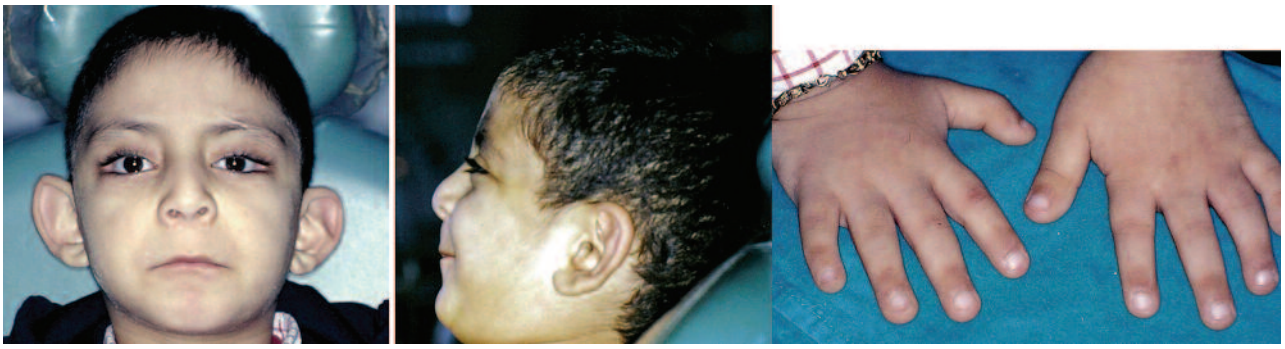

Figure 1. Frontal (A) and lateral view (B) of the patient with Kabuki Syndrome showing prominent malformed ears and retrognathia and hands of patient demonstrating short and single flexion crease in fifth fingers (C)

(31%) such as single ventricle with a common atrium, ventricular septal defect, and tetralogy of Fallot.[7,12] Recurrent otitis media and persistent middle ear fluid are common (82%), and more than half of children with KS have hearing loss.[13]

The present report describes a 9-year follow up of craniofacial growth based on longitudinal cephalometric radiographic analysis of a Turkish boy with KS aged 5 years 4 months at his initial visit.

CASE REPORT

A Turkish boy with KS aged 5 years 4 months was referred from genetic department to our faculty for dental care management. He is the fourth child born to non-consanguineous parents, and has three healthy siblings, 13- and 15-year-old brothers and an 18-year-old sister. His family history was unremarkable, showing neither KS, nor any other congenital anomaly.

His medical records showed that at 4 months of age he had been evaluated for dysmorphic features, hypothyroidism and renal anomaly; his weight at that time was 6400 grams; height 63 centimeters; and circumference of head (OFC), 40 centimeters. He was re-evaluated at the age of 5 years in the genetic department, at which time his weight was 18500 grams, his height 109 centimeters, and circumference of head (OFC), 50.5 centimeters.

Physical examination revealed peculiar facial appearance, with long and everted lateral and palpebral fissures and dysplastic prominent ears, blue sclera, a short nasal septum, depressed nasal tip; he also showed hypermobility of the joints. He had a short fifth finger and small middle phalanges, and hyperelastic finger joints (Figure 1). His karyotype was normal (46 XY). At 5 years and 4 months of age, his skeletal age was 3 years 6 months according to the evaluation of his hand-wrist X-rays. Table 1 shows the physical and clinical findings in the present case in comparison with those of the other cases reported in the literature.

Intraoral examination revealed skeletal anterior open bite and primary dentition. There were multiple carious teeth and missing lower primary incisors. His palate was highly arched and narrow. No periodontal disease or other anomalies were noted. Panoramic examination confirmed the clinical findings and also revealed congenitally absent teeth: 12, 14, 22, 24, 32, 33, 35, 42, 43 and 45 (Figure 2). Table 2 shows the position of the missing teeth compared with those in previously reported patients with KS.

Before taking radiographs, parental consent was obtained after explaining the potential risks and benefits of serial cephalometric radiographs. After informed consent was obtained, lateral cephalometric radiographs were taken at initial visit, at 3 years after initial visit and once a year after that for 2 years.

Cephalometric evaluation

The craniofacial growth of the patient from 5 years 3 months to 11 years 8 months was analyzed based on the lateral cephalometric radiographs. Radiographs were taken on initial visit, 36 months later and once a year for the following 2 years. Analysis of craniofacial growth was based on the linear and angular measurements of each radiograph. The long-term cephalometric evaluation of the patient between the ages of 5 years 4 months and 14 years 8 months is shown in Table 3. Cephalometric superimposition was carried out to ascertain the direction of craniofacial growth (Figure 3). Bimaxillary retrusion and a skeletal Class I relationship (SNA: 70º, SNB: 67º, ANB: 3º), with increased lower facial height (LFH: 66 mm) and severe anterior open bite were observed. Skeletal relationship changed to Class I ten years after the first observation (SNA:72º, SNB:72º, ANB:0º). The maxilla and mandible were retropositioned due to underdevelopment.

In this case, sagittal growth of the maxilla and mandible showed improvement according to cephalometric findings.[14] Intermaxillary relationship changed to skeletal Class III from skeletal Class I during the follow-up period (Table 3). Anterior, upper and lower face height increased during these 5 years (Figure 4).

Infected carious anterior primary teeth (51, 52, 61) were extracted. Carious maxillary and mandibular molar teeth were restored, and prophylaxis with flouride treatment was performed subsequently. The patient was scheduled for regular fluoride applications every 6 months. During this long-term restorative treatment, extractions were performed according to the treatment plan.

Table 1. Comparison of physical and clinical findings in four different report and in the presented case

	Niikawa et al, 1998	Galan-Gomez et al, 1995	Ilyina et al, 1995	Halal et al, 1989	Kobayashi et al, 2001	Present case
Facial findings						
Characteristic face	62/62	5/5	10/10	3/3	1/1	+
Lower palpebral eversion	61/62	5/5	10/10	3/3	1/1	+
Long palpebral fissures	62/62	5/5	10/10	3/3		+
Arched eyebrows	51/58	5/5	7/9	1/3	1/1	+
Epicanthus	35/57	5/5	4/10	1/3		+
Strabismus	21/43	5/5	4/10		1/1	+
Short nasal septum		50/54	5/5			+
Depressed nasal tip	45/47	5/5			1/1	+
Abnormal dentition	35/45	5/5			1/1	+
Spaced teeth	26/29	3/5			1/1	-
High arced palate	24/38	5/5			1/1	+
Cleft lip/palate	23/56		2/10		1/1	-
Prominent ears	51/60	5/5	10/10	3/3	1/1	+
Low posterior hair line	27/51		6/9	2/3	1/1	+
Skeletal abnormalities						
Short 5th finger	47/53	2/5	5/10		1/1	+
Clinodactyly of 5th finger		2/5	7/10			-
Short middle 5th finger	35/44	2/5			1/1	+
Hip dislocation	18/55					-
Scoliosis	26/53	2/5				-
Dermatoglyphic abnormalities						
Presence of fingerpads	35/45	5/5	7/7	2/3	1/1	+
Occasional abnormalities						
Cardiovaskular anomalies	19/59		1/10		1/1	-
Blue sclera	14/52		4/10	1/3	1/1	+
Hearing loss			4/10	1/3		-

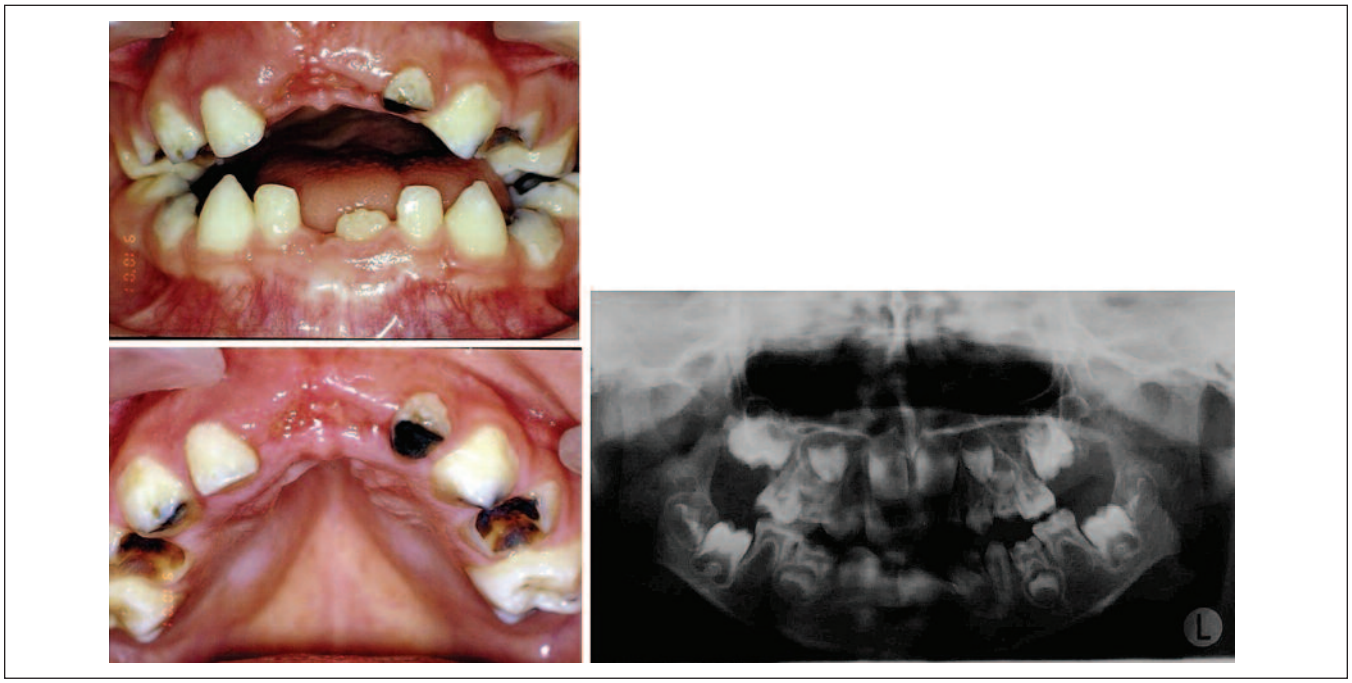

Figure 2. Intraoral view showing the anterior open bite (A), highly arched and narrow palate and multiple carious lesions (B) and panoramic radiograph showing congenital missing teeth (C)

Table 2. Hypodontia in the patient compared with the other cases in the literature

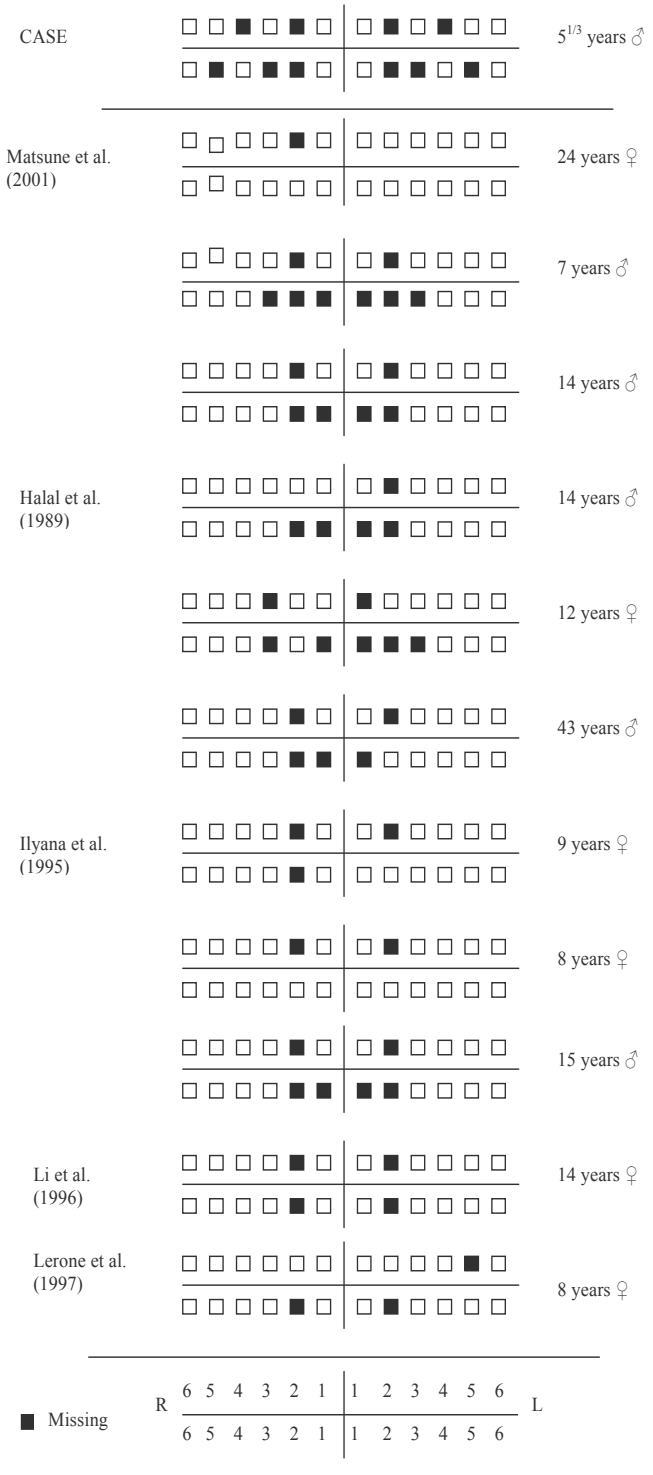

Table 3. Cephalometric measurements of the patient

	Sept 2001	June 2004	May 2007	Feb. 2008	Jan 2011
Cranial base					
S-N (mm)	67	71	72.5	72.5	76
Spatial maxillary relationship					
SNA (º)	70	68	69	71	72
A-Ptm (mm)	41	44	45	45	47
Spatial mandibular relationship					
SNB (º)	67	69	69	73	72
Pog-Go (mm)	55	66	75	75	77
Cd-Go (mm)	52	54	59	66	69
Cd-Gn (mm)	100	108	120	128	132
SN-MP (º)	46	41	42	39	41
Intermaxillary relationship					
ANB (º)	3	-1	0	-2	0
Vertical relationship					
Anterior face height (mm)	108	115	123	123	134
Upper face height (mm)	45	49	55	55	59
Lower face height (mm)	66	68	72	72	75

Cephalometric landmarks:
1-Sella **(S):** Geometric center of the pituitary fossa, located by visual inspection, 2-Nasion **(N):** Located on the most anterior aspect of the frontonasal suture, 3-Anterior nasal spine **(ANS):** Anterior tip of the nasal spine, 4-Pterygomaxillary **(Ptm):** The lowermost pont of pterygomaxillary fissure, 5-Point **A**: The most posterior point in the concavity between ANS and the maxillary alveolar process, 6-Point **B**: The most posterior point in the concavity between the chin and mandibular alveolar process, 7-Gonion **(Go):** Using two lines, one tangent to the inferior border of the mandible and the other tangent to the posterior border of the ramus, locating gonion on the curvature of the mandibular angle by bisecting the angle formed by the two lines, 8-Menton **(Me):** Using a line parallel to horizontal reference line, move the straight edge upward until it first touches the inferior border of the symphysis of the mandible. The first touch point is menton, 9-Pogonion **(Pog):** Move the perpendicular line to horizontal reference line forward then back to where it first touches the chin, this first touch point is pogonion, 10-Gnathion **(Gn):** A midway between pogonion and menton on the outline of the symphysis, 11-Articulare **(Ar):** The intersection of the posterior border of the ramus and the inferior border of the cranial base, 12-Condylion **(Cd):** The uppermost point of the mandibular condyle.

Hard tissue angular measurements:
1-SNA (º): The angle between sella, nasion and point A, 2-SNB (º): The angle between sella, nasion and point B, 3-ANB (º): The angle between point A, nasion and point B, 4-SN-MP (º): The angle between S-N line (anterior cranial base) and Go-Me line (mandibular plane), 5- CdGoMe (º): The angle between condylion, gonion and menton points.

Hard tissue sagittal linear measurements:
1-S-N (mm): Sella to nasion distance (anterior cranial base length), 2-Cd-Go (mm): Condylion to gonion distance, 3-Cd-Gn (mm): Condylion to gnathion distance, 4-A-Ptm (mm): Pterygomaxillary point to point A distance.

Hard tissue vertical linear measurements:
1-AFH (mm): Nasion to menton distance (anterior face height), 2-UFH (mm): Nasion to anterior nasal spine distance (upper anterior face height), 3-LFH (mm): Anterior nasal spine to menton distance (lower anterior face height)

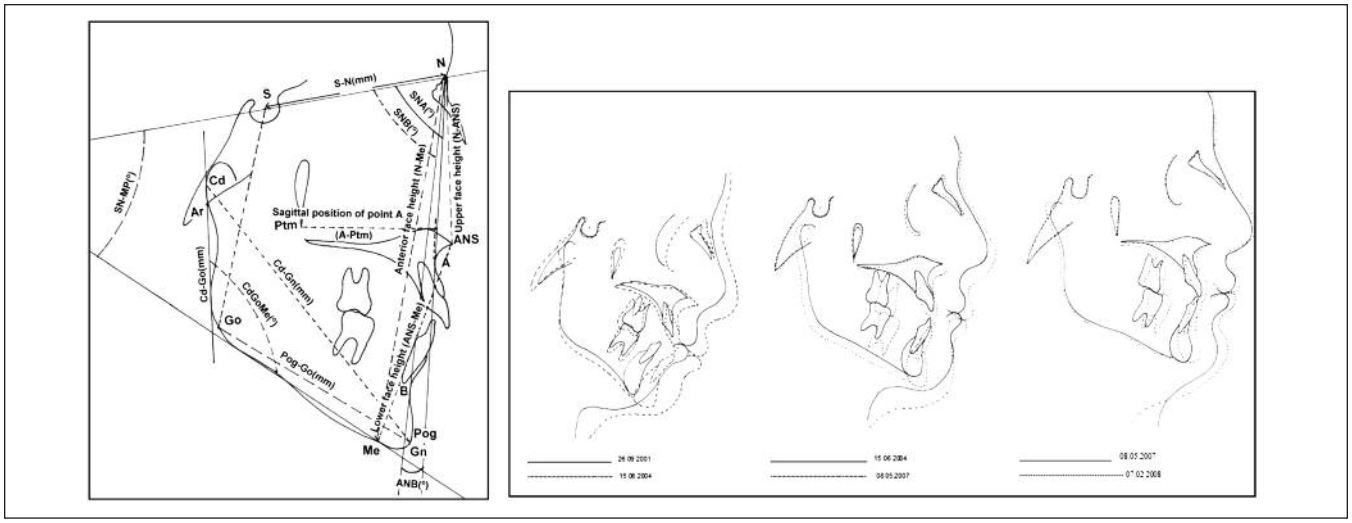

Figure 3. Cephalometric measurements and superimpositions

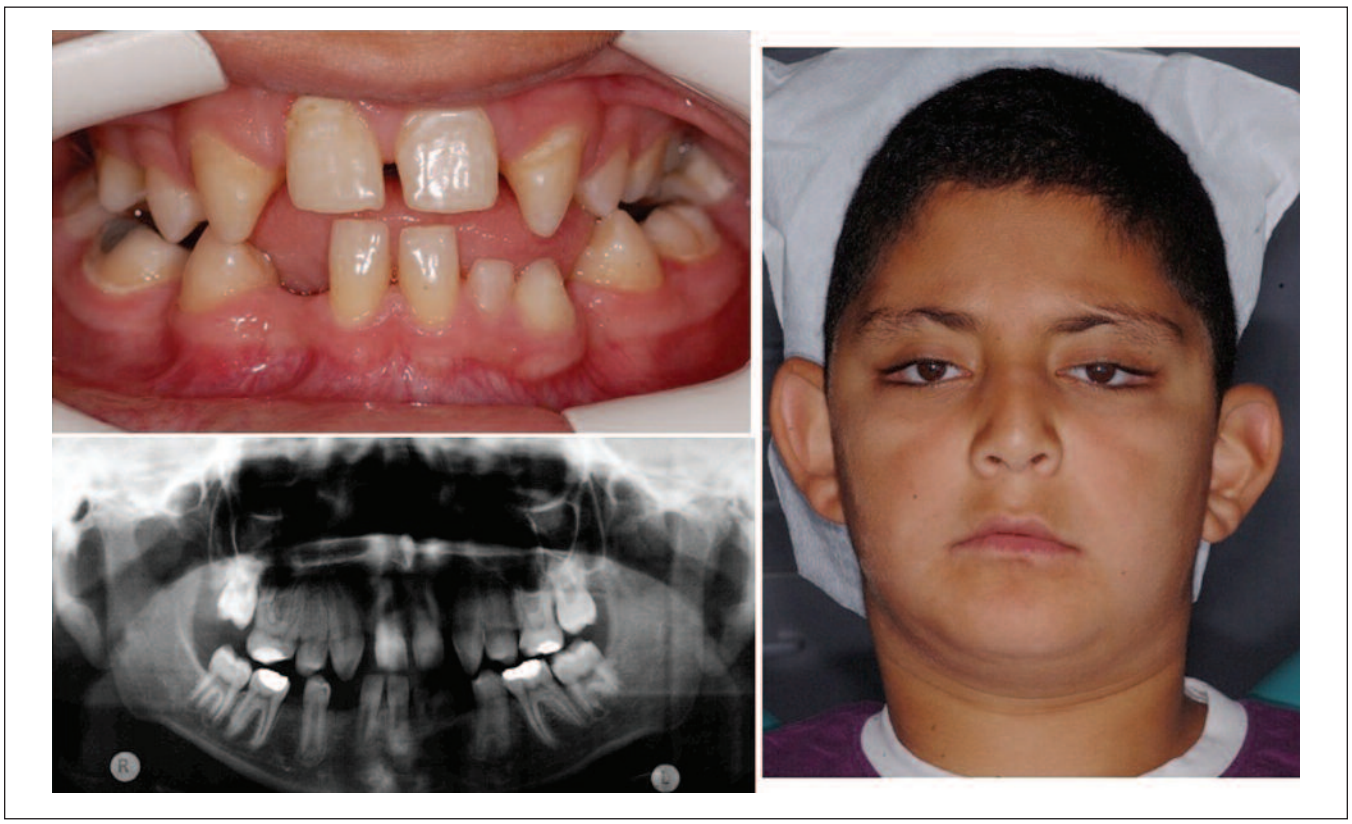

Figure 4. Intraoral (A) and frontal view (B) and panoramic radiograph (C) of the patient after nine years

DISCUSSION

KS was initially reported in Japan in 1981 as a sporadic entity characterized by mental and growth retardation with specific craniofacial malformations such as long palpebral fissures with eversion of the lateral part of the eyelids and depressed nasal tip.[15] The incidence of the disorder has been estimated as 1 in 32.000 live births in the Japanese population. Now, it appears that it is more common in the non-Japanese population than previously expected, particularly in the cleft palate population.[15,16]

Gillis *et al*[17] described the disorder in an Arab child with cervical rib, scaphocephaly, hyperelastic joints, who also presented thalassemia minor. They concluded that the facial phenotype was specific and easily recognizable, regardless of ethnic origin.

Galan-Gomez *et al*[18] reported this syndrome in five Spanish children with psychomotor retardation, postnatal growth deficiency, distinctive facial appearance, sagittal vertebral clefts and dermatoglyphic abnormalities. Congenital heart defects were present in four patients. They hypothesized that the prevalence of KS could be much higher than previously suggested.

Recently, Lung and Rennie[19] reported the disorder in an Afro-Caribbean child with short stature, long palpebral fissures, ectropium of the lateral third of the lower eyelids, eyebrows with sparse lateral halves, depressed nasal tip, large and prominent ears, micrognathia, mid-facial hypoplasia, prominent finger tip pads and learning difficulties.

The Turkish boy presented here supports previous observations of KS in different ethnic groups. He had the clinical signs of this syndrome, including long palpebral fissures, sparse eyebrows, large and prominent ears, blue sclera, micrognathia, short stature, and mental retardation. No cleft lip or palate, hip dislocation, congenital heart defect or foot deformities were observed in this patient although they are frequently encountered in this syndrome. The typical facial features of the syndrome, combined with systemic medical and dental examinations, are very important for confirmation of diagnosis.

Facial dysmorphism is a common craniofacial finding detected in many patients with this syndrome. Other characteristic findings of KS are a high arched palate, malocclusion, microdontia, a small dental arch, hypodontia and mid-facial hypoplasia. In this case, facial dysmorphism continued to show highest expression in the middle and lower third of the face throughout the evaluation period. From 5 years 3 months to 11 years 8 months, the SNA angle increased from 70 to 71 degrees and SNB angle increased from 67 to 73 degrees. The greatest increase in mandibular growth was found between the ages of 11 years and 11 years 9 months. ANB angle changed to a Class I (3º) relationship from a Class III (-2º) relationship during facial growth. And the dental malocclusion was also changed from Class III to Class I relationship. In this case, the severity of skeletal and dental malformation was dental malformation decreased and skeletal relationship changed from Class III to Class I with the growth.

Kobayashi *et al*[8] reported a girl with this syndrome, whose craniofacial growth has been assessed by analysis of lateral cephalograms at an interval of 12-15 months. They suggested that the facial dysmorphism observed in the maxilla and mandible could have been influenced by several factors, and possible etiologic factors contributing to anteroposterior deficiency of the maxillary arch, lower tongue posture, and tongue thrust swallowing were identified.

In this report, long-term cephalometric analysis supported the clinical diagnosis obtained by clinical examination. The comparison between his cephalometric data and average population norms helped quantify the severity of his skeletal craniofacial deviations.

Cleft palate or cleft lip/palate has also been described in approximately 1/3 of such patients, while high arched palate has been seen in almost 2/3.[15,16] Burke *et al*[16] was the first group to suggest that KS was an underdiagnosed condition in the cleft lip/palate population. Lip pits have also been described in several patients with KS.[2,11,20] Although cleft palate was not confirmed in our patient, he showed similar characteristics, including a narrow maxillary arch and high palate, to those described in the literature.[10,21]

Maas *et al*[22] reported a Belgian girl with this syndrome: she had cleft palate, mental and motor retardation, abnormal sexual development, renal abnormalities, habitual bladder and bowel disturbance and ophthalmologic findings. Recurrent middle-ear infections and extremity anomalies were also described such as short fifth fingers with clinodactyly and persistent fetal pads on the fingertips. Her facial appearance was distinct, with long palpebral fissures and everted lower eyelids, a broad nasal tip, cleft palate, oligodontia and pre-auricular pits.

Normal growth and development have been described before in some cases with KS.[9,12,19,23] White *et al*[24] also reported that low stature in KS was actually less common than previously assumed. In contrast with these reports, the child presented here showed mild growth retardation with skeletal age. He has also some degree of delayed mental development, although not to a point where social interaction was impeded.

Apart from dental abnormalities, patients with KS may have other abnormalities of the hair and nails such as trichorrhexis nodosa, caliber irregularities and twisting of the hair shaft. Mental retardation defined as an intelligence quotient of <70 is considered a cardinal manifestation of KS.[1]

There has been some discussion about whether the phenottype of KS varied based on ethnic background. Most authors agree that the facial phenotype of KS is easily recognizable in patients from all ethnic backgrounds.[1,16] Most of the cases reported have been sporadic, with the exception of a few families in which one of the parents had an incomplete form of the disorder.[25-27] Many etiologic factors may have contributed to the anteroposterior/tranverse deficiency of the maxillary arch in the patient in this study. However, it was not possible to determine which factor directly contributed to the dysmorphism of the maxillary structure. Some authors have reported that connective tissue disorder may be related to facial growth.[8,16]

Halal *et al*,[25] Silengo *et al*[27] and Tsukahara *et al*[28] reported individuals with typical findings of KS. They suggested that the condition could be inherited as an autosomal dominant trait with variable clinical manifestations in familial cases. Dominant inheritance with variable expressivity was also supported by the mother and child reported by Courtens *et al.*[29] The 18-month-old girl had characteristic facial findings of KS such as prominent fingertips, a midsagittal cleft of vertebral body, hypodontia and psychomotor retardation. The mother had a similar facial appearance, and microscopic examination of the hair showed abnormalities consisting of trichorrhexis nodosa. Li *et al*[30] also reported five patients (three Japanese and two non-Japanese children) with KS. They speculated that the condition might have a common molecular cause with the 22q11.2 deletion syndrome, as some cases present with congenital heart defects. Recently, Ng *et al*[5] identified genomic structure and allelic spectrum of *MLL2* mutations that cause Kabuki syndrome.

In KS cases, both esthetic and functional treatment to rehabilitate tongue habits and vertical occlusion, especially

to improve mastication, phonetics and facial appearance have great importance. This case illustrated oral findings and orthodontic growth characteristics of KS in a patient followed over a 5-year period. In most KS cases, it is difficult to treat and communicate with the patient due to mental retardation. In this case, the patient was uncooperative due to his young age and mental retardation. In evaluating long-term treatment options in such cases, the paediatric dentist needs to take a number of factors into account, including the patient's projected growth and development, management of hypodontia and interaction with other related conditions.

CONCLUSIONS

Common dental manifestations of KS are a high-arched palate, microdontia, hypodontia, malocclusion and mid-facial hypoplasia. These craniofacial and dental abnormalities may serve as indicators of a clinical diagnosis of this syndrome.

Cephalometric analyses can provide information on craniofacial growth in KS and assist with treatment management. However, such an analysis based on only a single case is insufficient to describe the growth pattern in KS patients.

Dental professionals need to be aware of this syndrome and its implications for oral dental care. This will lead to a better understanding of the abnormalities that play a distinct role in clinical diagnosis, and the planning and execution of orthodontic treatment.

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