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The Kabuki syndrome: four patients with oral abnormalities

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SUMMARY The aim of this paper is to report the oral signs and symptoms of four patients with Kabuki syndrome. All had oral abnormalities affecting the palate, teeth, and/or lips, including wide spacing between the teeth, screwdriver-shaped upper incisors, hypodontia, delayed tooth eruption, narrow spacing in the upper canine area, large pulp chambers of the upper incisors and permanent molars, external root resorption of the upper central incisors and permanent molars, a division of the lower third of the root canal in normally one-rooted teeth, tooth retention, retrognathia of the upper jaw, a high palate or cleft lip/palate, and microforms of lower lip fistula.

Introduction

Kabuki (Niikawa–Kuroki) syndrome was first reported by Niikawa *et al*. (1981). The faces of the patients are similar to the make-up of traditional Japanese Kabuki actors: long palpebral fissures, an ectropium of the lateral third of the eyelids, and arching eyebrows with sparse lateral halves. Craniofacial findings include a depressed nasal tip, short nasal septum, large and prominent ears, and micrognathia. Other main features are mild to moderate mental deficiency, short stature, skeletal and dermatoglyphic abnormalities, including prominent finger tip pads. Wilson (1998) described 183 patients with the syndrome, more than 50 per cent of whom (108) were of non-Asian origin.

The increased occurrence of cleft lip and palate or the development of a high palate has been described by a number of authors (Niikawa *et al*., 1981; Schrander-Stumpel *et al*., 1994; Burke and Jones, 1995; Chu *et al*., 1997; Peterson-Falzone *et al*., 1997; Chrzanowska *et al*., 1998; Wilson, 1998; Kawame *et al*., 1999). Franceschini *et al*. (1993), Kokitsu-Nakata *et al*. (1999) and Makita *et al*. (1999) reported on patients with fistulae in the lower lips.

The aetiology of this syndrome remains unknown. Most cases have been sporadic. In a few families possible parent–child transmission of the syndrome has been reported (Halal *et al*., 1989; Schrander-Stumpel *et al*., 1994; Kobayashi and Sakuragawa, 1996; Tsukahara *et al*., 1997). Thus, autosomal dominant inheritance with variable expressivity is suggested.

Apart from brief references to problems with the dentition or spacing between the teeth (Niikawa *et al*., 1981; Philip *et al*., 1992; Schrander-Stumpel *et al*., 1994; Lerone *et al*., 1997; Wilson, 1998), Mhanni *et al*. (1999) were the first to report in detail on dental anomalies. They observed agenesis of the teeth in eight children, screwdriver-shaped upper incisors with flat crowns in five patients, and ectopic first molars in three subjects.

The aim of this research was to detail the oral and dental features of Kabuki syndrome.

Clinical reports

The clinical features of Kabuki syndrome reported in the literature and of the four patients in this study are summarized in Tables 1 and 2. The facial features of the patients are illustrated in Figure 1 and the typical fingertip pads in Figure 2.

There were no similar signs in any of the families of the patients, indicating sporadic occurrence.

Chromosomal analyses performed on blood lymphocytes revealed normal karyotypes.

Patient 1

Neonatal features and physical/mental development. A girl born in 1987 after 8 months gestation, with a birth weight of 3050 g and length of 50 cm. It was noticed that the amniotic fluid appeared cloudy. A heart defect was diagnosed post-natally (aortic co-arctation), and required surgery several times in the first year of life. Both kidneys had double attachments. There were particular difficulties in feeding and this was partially carried out via a naso-gastric tube. Impaired growth was still evident at 3 years of age. Psychomotor development was delayed. Speech started at 24 months. Walking independently only occurred at the end of the fourth year.

Chromosomal analysis showed a normal female karyotype 46,XX.

Currently aged 13 years, her height is 136 cm (below the third centile). Partial deafness in both ears requires the use of a hearing-aid. The girl attends a special-needs school.

Clinical dental/oral features. The dental status was reported in 1996 as being unusual. The wide spaces

Table 1 Kabuki syndrome: summary of general clinical features. Comparison of data from the literature and from the present study.

Clinical features	Niikawa *et al.* (1988)	Schrander-Stumpel *et al.* (1994)	Patient 1	Patient 2	Patient 3	Patient 4
Characteristic face	62/62	29/29	+	+	+	+
Lower palpebral eversion	61/62	24/29	+	+	+	+
Long palpebral fissure	62/62	29/29	+	+	+	+
Arched eyebrows	51/58	23/29	+	+	+	+
Strabism	21/43		+	+	+	–
Short nasal septum	50/54		–	+	+	+
Depressed nasal tip	45/47	23/29	–	+	+	+
Prominent ears	51/60		+	+	+	+
Malformed ears	37/47	29/29	+	+	+	+
Fingertip pads	35/45	28/28	+	+	+	+
Short fifth finger	47/53	19/26	+	+	+	+
Susceptible to infections	29/49	12/24	–	+	+	+
Mental retardation	Mild–mod.	Mild–mod.	+	+	+	+

–, feature not present; +, feature present; blank space, no indication given.
Mild–mod., mild to moderate.

Table 2 Kabuki syndrome: compilation of occasional features reported in the literature and from the present study.

Further abnormalities	Niikawa *et al.* (1988)	Schrander-Stumpel *et al.* (1994)	Patient 1	Patient 2	Patient 3	Patient 4
Cardiovascular anomalies	19/59	8/29	+	+	–	+
Postnatal growth failure	30/40	18/29	+	+	+	+
Kidney/urinary tract malformations		9/27	+	–	–	–
Ptosis	7/58		+	+	+	+
Hypernasality/dyslalia			+	+	+	+
Hearing loss		12/24	+	+	+	+
Cleft lip/palate	37/47	20/29	–	+	+	+
Abnormal dentition	35/45	17/24	+	+	+	+

–, feature not present; +, feature present; blank space, no indication given.

between the incisors in the upper and lower arches indicated that the teeth were not deformed. The crowns of 11 and 21 were flattened, with slight convergence incisally, so that the largest circumference of the teeth was at the gingival border. The maxilla was retrognathic. The eruption of the teeth was delayed. The primary teeth and the crown of 36 were destroyed by caries.

At 11 years 8 months of age tooth 11 had to be extracted due to resorption of the root. Histological examination of the tooth fragment showed no anomalies in dentine or enamel structures (Figure 3a,b).

Radiographic findings. The dental tomogram (DPT) obtained at the start of treatment (Figure 3c) confirmed that the teeth were normal in appearance. Tooth buds 12, 22, 31, and 41 were missing.

Radiographs showed a denticle in the relatively large pulpal tissue of the first molars and unusual root development of 45 and 34; the large pulp chamber and the lower root third division gave the appearance of a taurodont molar. Root development of the teeth was incomplete. The roots of 32 and 42 were shortened. Both upper and lower arches were less developed than usual at 9 years of age. In addition the appearance of the lower arch was very narrow.

The DPT prior to extraction of 11 (Figure 3c) showed nearly complete resorption of the root of this tooth, probably as a result of undermining resorption by 13. A wide-open apical foramen and the relationship of the length between the crown and the root of 21 also indicated the start of root resorption. Other features noted at that time were a deposition of hard tissue in the pulp of both second permanent molars and development of 35 with division of the lower third of the root.

Oral therapy. To support development of the dentition, tooth 36 and all the remaining primary teeth were extracted. Tooth 11 was extremely loose, and was removed and replaced with a fixed prosthesis to prevent

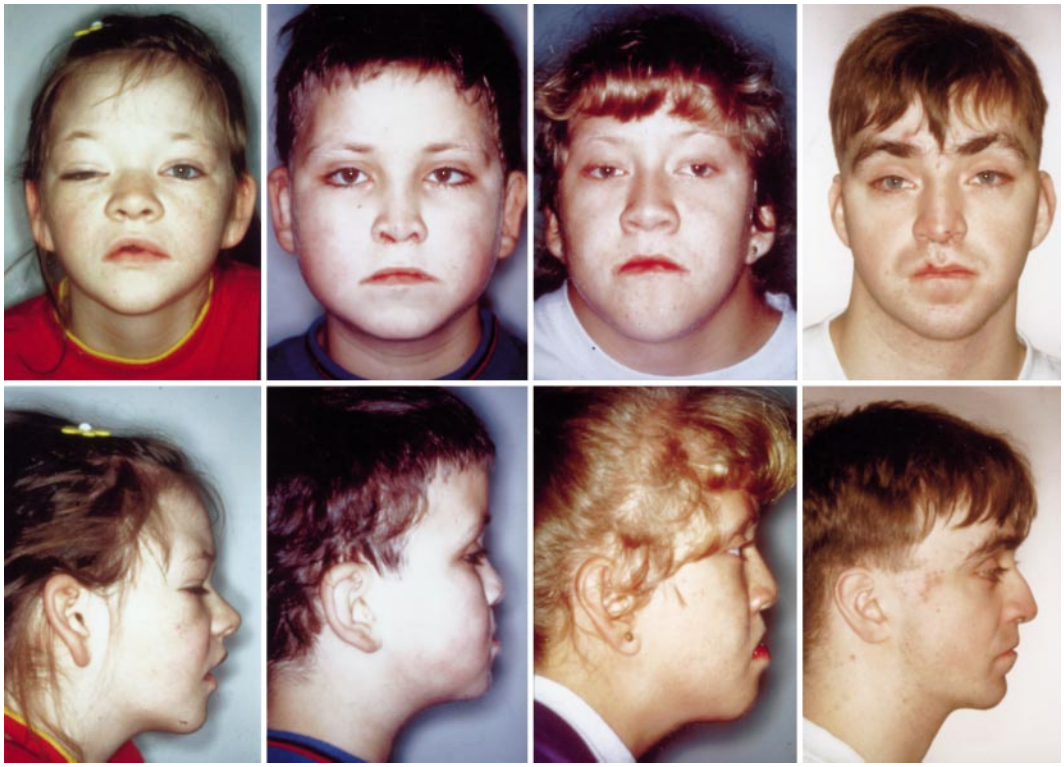

Figure 1 Frontal and lateral photographs of four patients with the typical features of Kabuki syndrome. The short nasal septum and the associated wide flat tip of the nose was only present in some patients. Patients 1–4 are shown from left to right.

the risk of accidental inhalation. Orthodontic treatment to correct the arch discrepancy will commence on complete eruption of the premolars.

Patient 2

Neonatal features and physical/mental development. A boy born in 1981 following a normal pregnancy. The birth occurred at term; birth weight was 4100 g and length was 55 cm. It was noted that the amniotic fluid appeared green-tinged. After birth, a sub-mucosal cleft palate, lower lip fistulae and an aortic co-artation were diagnosed. In 1986, at 4 years of age, the palate was closed surgically. Heart surgery was performed in 1988. Speech and motor development were delayed. The patient was only able to walk unaided at 2½ years. At 18 years of age there is evident intellectual impairment and he attends a special-needs school. At this time his height is below the tenth centile. Chromosomal analysis showed the normal male karyotype 46,XY.

Clinical dental/oral features. The crowns of the upper incisors had a smooth conical shape. The eruption of these teeth was delayed, with wide spacing. Tooth 22 was rotated by 90 degrees. There was a retrognathia of the upper arch (Figure 4a,b).

Figure 2 The hand of patient 3 with finger tip pads characteristic of Kabuki syndrome.

Radiographic findings. The DPT at 10 years of age showed the condition of the early mixed dentition (Figure 4c). Root development of the upper anterior teeth was incomplete. The division of the lower third of the normally one-rooted tooth (53) was unusual. All tooth buds were present except for the third molars. The most recent radiograph taken at 16 years of age showed the permanent dentition and the tooth buds of the third molars (Figure 4c). Tooth 27 had not erupted. The large

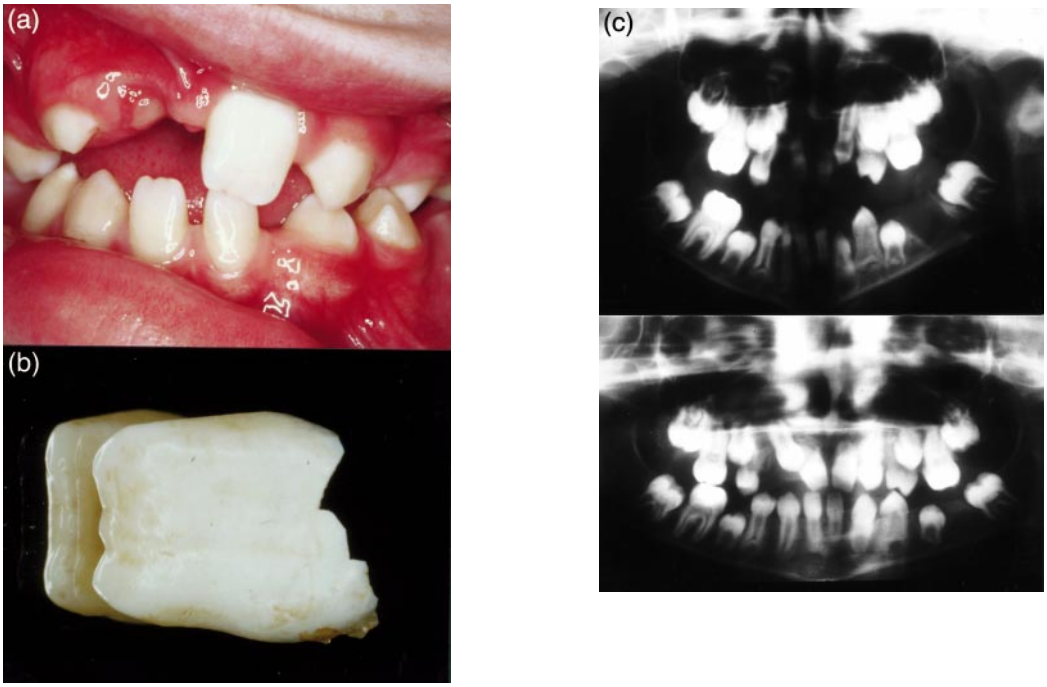

Figure 3 (a) The oral cavity of patient 1 and (b) the tooth fragment after extraction of 11 at eleven years of age: the pictured tooth was taken on a mirror. The screwdriver shape of the crown is clearly visible. (c) Dental tomograms of patient 1 at (top) 9 and (bottom) 11 years of age with non-attachment of 12, 22, 31, 41, and large pulp lumen in the remaining molars with denticle deposits. Of note is the division of the lower third of the roots of teeth 45, 34, 35, the root resorption of 11 and 21, and the shortened roots of 32 and 42.

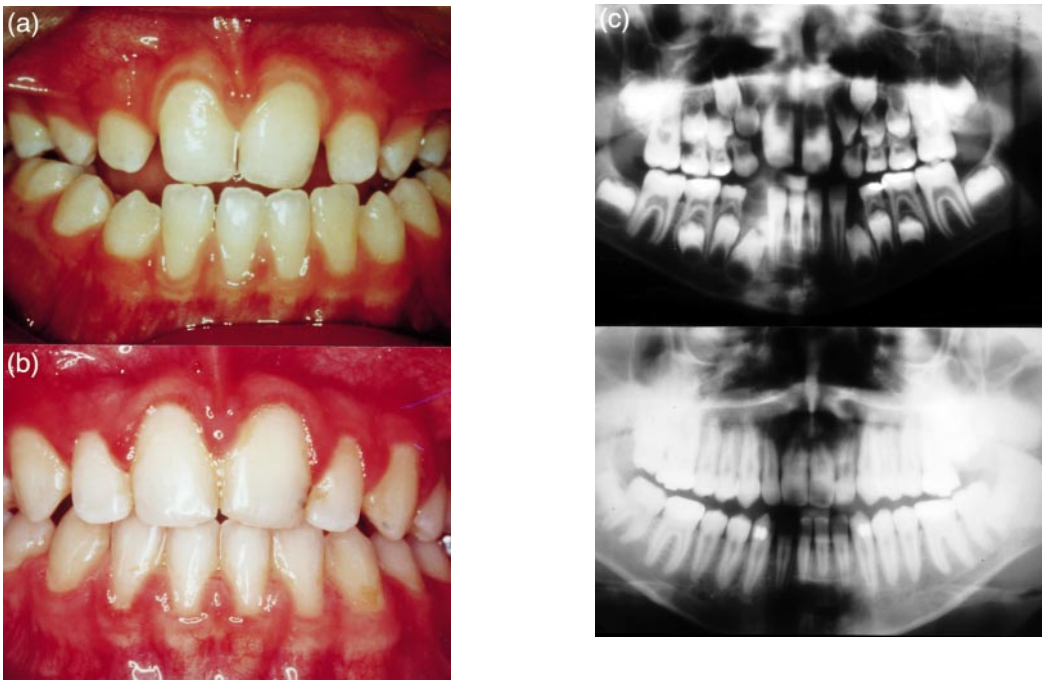

Figure 4 The oral cavity of patient 2 (a) before and (b) after orthodontic treatment. The shape of the crowns of the upper incisors are typical of Kabuki syndrome. There are early signs of crowding of the canines and upper arch retrognathia. (c) DPT of patient 2 at (top) 10 and (bottom) 16 years of age: the features are similar to those seen in patient 1. The root of tooth 53 is split in the lower third, there is a hard tissue deposit in the wide pulp lumen of the remaining molars and in the medial incisors, and early external resorption of 21. Hypodontia is not present.

pulp lumen in the first molars with denticle deposits were still present. The second remaining molars were identical. Teeth 11 and 21 had shortened roots with wide pulp chambers, similar to internal granuloma, also containing deposits of hard tissue. Root development on tooth 11 was incomplete. The start of external resorption was evident on tooth 21.

Orthodontic diagnosis and therapy. Analysis of the lateral cephalogram confirmed upper arch retrognathia and a normal lower jaw position with a prognathic jaw relationship. There was an open bite relationship. The upper arch was proclined.

At 9 years 9 months of age a Class III malocclusion was present. In addition, there was a crossbite from tooth 15 to 25 and an anterior open bite. The space for 13 and 23 was almost completely occupied by the lateral incisors. The long axis of 11 and 21 diverged. In the lower arch, no particular features were noted other than retrusion of the lower anterior segment.

Orthodontic therapy began at 12 years of age with a Fränkel III appliance. As the patient found it difficult to adapt to this, a Delaire facemask was used. Space for the canines was created.

Patient 3

Neonatal features and physical/mental development. The patient, a girl, was born 3 weeks before term, in 1980. Her birth weight was 2250 g and length 48 cm. A cleft palate, diagnosed post-natally, made tube feeding until the sixth week of life necessary. Fistulae in the area of the lower lip were also observed. In 1984 the cleft was closed. Physical development was below normal at 18 months of age. Psychomotor development was delayed. The patient was able to sit at 12 months, but was not able to walk unaided until 2 years of age. Language development was also very late and had not developed beyond very basic sentence structure.

At 12 years 2 months her height was 135 cm (below the third centile). Chromosomal analysis showed normal female karyotype 46,XX.

Clinical dental/oral features. At 6 years 5 months of age teeth 11 and 21 presented with aspects typical of the syndrome: screwdriver-style flattened conical shaped crowns. There was a delay in the appearance of further teeth. At 14 years 3 months, 17 and 27 and the third molars were unerupted. Tooth 22 had rotated nearly 90 degrees. Maxillary retrognathia was present (Figure 5a).

Radiographic findings. All tooth buds were evident. The high position of the tooth germs of 17 and 27 implied late maturation of these teeth (Figure 5b).

Orthodontic diagnosis and therapy. Cephalometrically, the upper and lower arch were retrognathic.

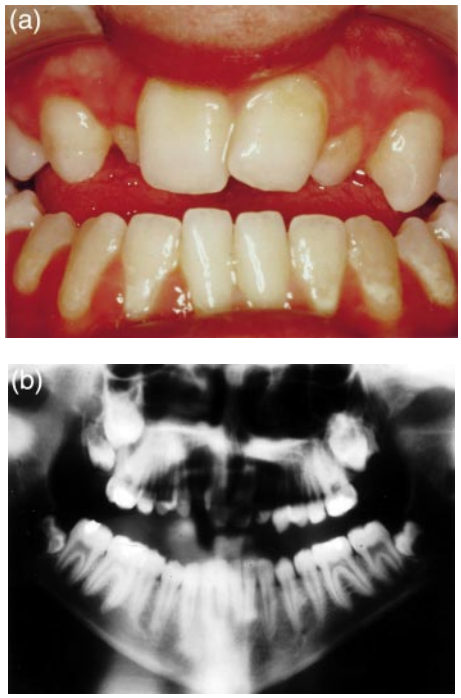

Figure 5 (a) Oral cavity of patient 3 at 14 years of age: the close spacing in the upper anterior arch and the maxillary retrognathia can be clearly seen. Teeth 21 and 11 have typical features of Kabuki syndrome: flattened coniform-shaped crowns with slight incisal inclination. (b) DPT at 15 years of age: of note are the hard tissue deposits in the large lumen of the pulp of the first molars, and the high position of the tooth buds of 17 and 27.

Assessment of the occlusion showed an uneven occlusion of the lateral teeth due to asymmetry of the arch to the right. Thus, there was a buccal occlusion on the right and a distal occlusion of half a premolar unit on the left. There was a crossbite from 15 to 25 and a normal overbite. The upper arch length was shortened. The lateral incisors were transposed.

The positions of teeth 11 and 21 diverged. The anterior lower arch was spaced. The lower primary canines had been resorbed as a result of the eruption of the lateral permanent incisors.

Due to the mental retardation, some compromises were made in treatment. From 1991 only removable orthodontic appliances were used. Initially, a fitted Y-plate was inserted to mould and expand the upper arch, which was adjusted weekly by the parents. During the course of treatment, the plate was repeatedly renewed in order to create space for the canines.

Patient 4

Neonatal features and physical/mental development. The patient, a boy, was born in 1979 following a normal term pregnancy. Birth weight was 3000 g and length was

50 cm. A submucous cleft palate and protuberances of the lower lips as a microform of fistula were diagnosed.

The patient was fed artificially for the first 8 weeks of life. During the first year a double hernia was surgically repaired. Because of chronic otitis media, he was under regular ENT care. A plastic columella was surgically produced in 1992. He had frequent kidney infections.

Motor development was delayed and he was only able to walk independently after 2 years of age. Speech development was delayed. The patient attended a school for the mentally handicapped. At age 16 years, height was below the 25th centile.

Chromosomal analysis showed the normal male karyotype 46,XY.

Clinical dental/oral features. The patient first presented at the Department of Pediatric Dentistry at 16 years of age. In addition to caries of some of the teeth, it was apparent that the upper lateral incisors and probably also the lower canines were unsupported. The crown of 11 was flattened and converged towards the incisors. No evaluation could be made of 21 due to carious destruction.

Radiographic findings. A DPT taken in 1995 showed that teeth 12 and 22 were not deformed. It was no longer possible to clearly establish which anterior teeth were missing. The roots of 11 and 21 were shortened, and were approximately the length of the crowns of the teeth. The pulp cavity of all teeth appeared to be very large. Deposits of hard tissue in the pulp chambers of the molars was identified. An unusual feature, as also described in patients 1 and 2, was the root development of the lower right first premolars: the pulp canal was split in the lower third indicating root division of a normally one-rooted tooth. Tooth 48 was elongated and 38 retained.

The development of a denticle in the pulp of the upper molars was still clearly evident on a DPT taken at 22 years of age. The pulp cavities of all teeth were also observed to be larger than average (Figure 6).

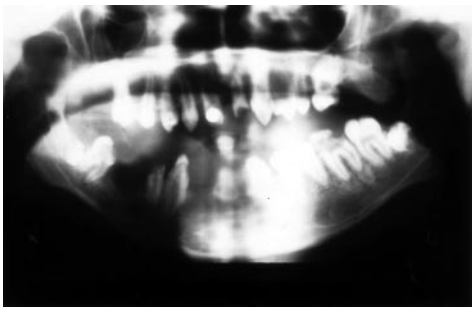

Figure 6 DPT of patient 4 at 16 years of age. The hard tissue deposits in the molar pulp can be seen. The chamber of the pulp in tooth 44 is divided in the lower third.

Orthodontic treatment was not indicated due to the poor status of the dentition.

Table 3 provides an overview of the dental/oral findings of the four patients.

Discussion

The purpose of this investigation was to identify anomalies of the oral cavity and teeth in these patients with Kabuki syndrome. The findings confirm the increased occurrence of a cleft palate, as described in the literature (Schrander-Stumpel *et al*., 1994; Burke and Jones, 1995; Peterson-Falzone *et al*., 1997; Wilson, 1998; Kawame *et al*., 1999). Patient 1 had a high palate also described by Chu *et al*. (1997) and Chrzanowska *et al*. (1998). Lower lip pits, the main feature of van der Woude syndrome, were present in subjects 2, 3, and 4. The occurrence of both Kabuki and van der Woude syndrome in the same patient has previously been described (Franceschini *et al*., 1993; Kokitsu-Nakata *et al*., 1999; Makita *et al*., 1999). Further features reported in the literature, the hypodontia and associated wide spacing between teeth, was found in patients 1 and 4. The tooth buds for the lateral upper and lower incisors were absent (Niikawa *et al*., 1981; Lerone *et al*., 1997; Mhanni *et al*., 1999). The finding of absent premolars or molars as described by Mhanni *et al*. (1999) and Chu *et al*. (1997) were not observed. The large spaces between the upper incisors in patients 2 and 3 led to extreme crowding of the canines.

All four patients had flat, screwdriver-like, crown-shaped upper incisors as described by Mhanni *et al*. (1999), the slight conical shape was not the pin-formed crown shape described by Lerone *et al*. (1997), and could better be described as barrel-shaped.

Radiographic assessment indicated several features not previously described in the literature. The pulp cavities of the molars were large and there were deposits of hard tissue in the form of a denticle. The pulp chambers of the incisors were very wide. In patients 1, 2, and 4 the form of the roots was worthy of note. External resorption was also diagnosed for tooth 21 in patient 2. In addition, even at 16 years of age, growth of the root of tooth 11 was incomplete. In patients 1, 2, and 4 the root forms were also notable. The same occurrence could be seen in tooth 53 in patient 2. A division in the lower third of tooth 44 was observed in patient 4.

These radiographic findings may extend the spectrum of symptoms associated with Kabuki syndrome. Further examination of subjects with this syndrome will show whether the features observed are characteristic. It can be assumed that the oral/dental features described will lead to prompt dental referral. When dental professionals are aware of the clinical features, it will contribute to diagnosis, allow referral to a clinical geneticist, investigation of oral/dental findings and support comprehensive care of the patient.

Table 3 Summary of oral/dental features of the four patients in the study.

Feature	Patient 1	Patient 2	Patient 3	Patient 4
Large spacing between incisors	+	+	+	+
Screwdriver-shaped crowns of the upper incisors	+	+	+	+
Hypodontia	+	–	–	+
Delay in eruption	+	+	+	
Upper arch retrognathia	+	+	+	+
Narrow spaces in the upper canine area	–	+	+	–
Large pulp lumina in the upper incisors and permanent molars	+	+	+	+
Deposition of hard tissue in the pulp of the permanent molars	+	+	+	+
Short roots in the upper arch	+	+	–	+
Root resorption of the upper central incisors	+	+	–	–
Division of the lower third of the root in normally single-rooted teeth	+	+	–	+
Tooth retention	–	–	+	+
Paramedian elevation on the lower lip	–	+	+	+
Cleft lip/palate	–	+	+	+
High palate	+	–	–	–

+, feature present; –, feature not present; blank space, no data.

Oral/dental findings seen in patients with the Kabuki syndrome could provide an important clue in the understanding of the pathogenesis of this syndrome. Based on the occurrence of findings consistent with van der Woude syndrome in some patients with Kabuki syndrome, a common aetiology has been postulated (Makita *et al*., 1999). Further molecular research is needed to clarify the genetic aetiology.

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