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Variations in expression of oral–facial–digital syndrome (type I): report of two cases

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Summary. Two case reports are presented, both clearly demonstrating the diagnosis of oral–facial–digital syndrome, type I, but widely different in the expression of the condition. The first patient showed only mild expression of the syndrome. On examination at the age of 4 years there were no obvious extra oral signs, intraoral findings included the presence of supernumeraries in the primary dentition, spacing in two areas and the presence of an extra frenum. The second can be considered as a more severe case. This patient had many of the typical manifestations, including frontal bossing, a degree of zygomatic hypoplasia and clinodactyly. Orally, the most striking finding was a bilateral cleft palate which had not been diagnosed prior to examination at the age of 6 years. Other findings included multiple frena and a bifid tongue.

Introduction

Oral–facial–digital syndrome (OFD) was first described as 'a hereditary malformation of the buccal mucous membrane and abnormal frena' in 1954 [1]. The same clinical entity was independently described as linguofacial dysplasia in 1957 [2] and as orodigitofacial dysostosis in 1962 [3], until the now widely accepted designation oral–facial–digital syndrome was introduced [4] the same year.

At its first description, the syndrome was reported to be inherited as an incomplete recessive [1], but later the condition was believed to be dominant [2]. OFD was finally classified into two different types; OFD I, inherited as an X-linked or sex-linked autosomal dominant and OFD II (Mohr syndrome), probably inherited as an autosomal recessive [4–6]. OFD type I was described as a dominant trait with variable penetrance, manifested only in females and lethal in males [5]. Paradoxically, several cases of male patients have been reported, however, some of them had XXY karyotype and it is possible that the others had Mohr syndrome (OFD type II) [6]. However, a case of a live born male infant who died 4 h after birth which was described recently could be described as OFD type I [7]. OFD type I has now been identifying as lying at Xp22·3-p22.2 with a variety of mutations giving rise to the phenotype in different pedigrees [8,9].

The prevalence of OFD type I varies in the literature. Originally it was reported to be present in 1 : 100 patients with cleft palate [3], changed later to 6·5% of female patients with cleft palate [10,11], but the prevalence reported more recently is significantly less and does not exceed 15 in every 1000 persons with cleft lip and/or palate or 0·0225 : 1000 [11,12] or 1 out of 50 000 live births [12,13].

Half of the patients with OFD type I show manifestations in all areas (oral, facial and digital) [4]. The oral and digital manifestations are presented in details in this paper and the other manifestations of OFD type I, as they have been described in the literature, are presented in Table 1.

Oral

The most commonly reported oral manifestation of the syndrome is midline cleft in the upper lip extending through the vermilion border (in 45% of

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Table 1. Non-oral clinical features of patients with OFD type I.

Facial	Digital	Others
Frontal bossing	Branchydactyly	Learning difficulties, speech impairment
Euryopia, dystopia canthorum, telecanthus	Syndactyly	Tremor
Hypoplastic alar cartilages, Thin nose	Clinodactyly	Hydrocephally, hydranencephally, porecencephally
flattening of nasal tip, asymmetrical nostrils		
Anomalous cranial vault	Camptodactyly	Partial agenesis of corpus callosum
Increased SNB angle	Extra digits	Granular skin appearance
Zygomatic hypoplasia (flattened midfacial region)	Toe malformations (unilateral hallucal polysyndactyly, syn-dactyly, brachydactyly)	Alopecia, dryness, brittleness of scalp hair
Seborrheic changes	Milia of face and ears	
Subdural hygroma	Thick short tubular bones of hands and feet	Irregular radiolucent reticulated areas
Congenital lip pits	Digital osteoporosis	Bilateral polycystic kidneys, polycystic liver

the patients), associated with hyperplasia of frena, which is seen in all patients [1–7,12,13–16]. Multiple, irregularly positioned hyperplastic fibrous bands extend to the alveolar process of the mandible, originating from the lower lip and cheeks [4,7,15]. Thick fibrous bands exist in the lower mucobuccal fold in 75% of the patients [13]. The hard palate may be highly arched [15] but is usually cleft; deep bilateral grooves starting from the maxillary buccal frenula and extending medially divide the palate into an anterior segment and two lateral palatal processes [1–5,7,12–14,16]. Most commonly the clefts are situated in the lateral incisor-canine regions [13,15]. The soft palate is completely and asymmetrically cleft in 80% of the cases [13]. Cleft tongue with two lobes is seen in 30% of the patients, and with three or four lobes in 45% [13,15]. A hamartomatous mass on the ventral surface of the tongue is seen in 70% of the cases [4,12,13]. This could be a misplaced tuberculum impar, a structure that normally develops between the first and second branchial arches [3]. Supernumerary maxillary primary canines and premolars are seen in 20% [6,15]. Malposition of teeth is also frequent [1,2,6,12,13,16] and can be accompanied by crowding [15]. Apart from these, a number of other manifestations have been described; microglossia, ankyloglossia or tongue-tie, T-shaped canine crown form, tooth fusion, infraoclussion of teeth, absence of mandibular lateral incisors, enamel hypoplasia, high caries susceptibility, small or hypoplastic mandible with a short ramus, and an extended bony ridge from the alveolar crest medially to the midline in the canine premolar area [3,7,12–16].

Digital

The most commonly described digital manifestations of the syndrome affect the hands and have been described as branchydactyly, syndactyly, clinodactyly, camptodactyly and extra digits [7]. However, toe malformations have also been reported and less commonly thick and short tubular bones and digital osteoporosis, as well as limb deformity, which can be expressed as short limbs [7,15].

Case report 1

The first patient reported here was a Caucasian girl who first presented to the dental hospital clinic at the age of 4 years 3 months – referred by a general practitioner for observation of the long-term

development of her dentition. The patient had already been diagnosed with oral–facial–digital syndrome type I. When she was 1-year-old she had surgery to remove fibrous bands that were tethering the cheek to the alveolus and the tongue. At the same time, a cleft tip of the tongue was repaired. The medical history contained no other significant details and there was no family history of congenital anomalies. No other member of the family exhibited the condition.

On clinical examination at 4 years 3 months the patient did not show many typical manifestations of the OFD syndrome. Her face showed no asymmetry of any kind, there was no cleft of either of the lips, and there was no obvious abnormalities in the dimension of the facial bones. The child's fingers and toes and other bones appeared to be normal and neither the hair nor the skin appeared to be affected.

On her initial oral examination, the patient was in the primary dentition stage of development. She had two supernumeraries, one between the lateral incisor and the canine in each upper quadrant. Space was obvious between the upper right primary canine and the supernumerary primary canine. In the mandible there was space between the two lower right primary incisors. An extra frenum was present on the right side of the mandible. The oral hygiene was reasonable, the patient was caries free and an anterior open bite was noticed which was attributed to the use of a dummy.

Radiographic examination revealed a maxillary supernumerary primary canine on the left side but no supernumerary teeth were evident in the permanent dentition [Fig. 1]. The normal development of all permanent teeth except the third permanent molars, which were missing, was confirmed by the dental orthopantomogram.

The patient has been reviewed every 6 months since first attendance. Her primary teeth started to exfoliate early and by the age of five, she had lost all primary incisors and the supernumeraries. All permanent central incisors, as well as the lower permanent left lateral incisor had erupted at this age. There was no sign of the permanent first molars, but these were close to eruption when the patient was seen again at the age of 6 years and 10 months. Her parents reported that abscesses often accompanied the exfoliation of her primary teeth. One year after her first visit to the hospital, she had caries in the upper right primary molars.

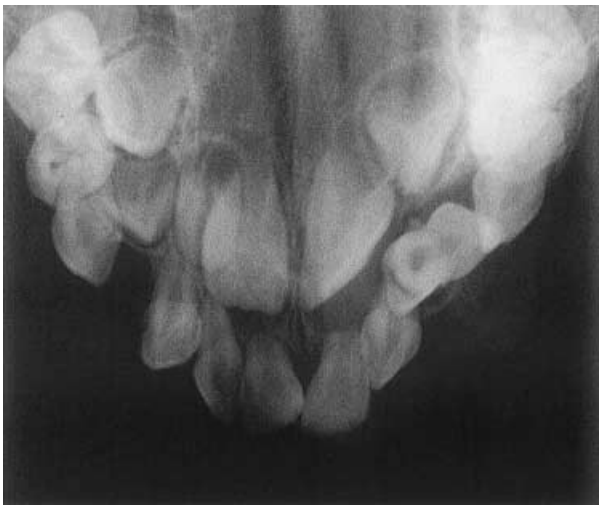

Fig. 1. Patient 1, occlusal maxillary radiograph showing a supernumerary primary canine at the left and the space left by the exfoliation of the supernumerary primary canine at the right.

Case report 2

The second patient was a Caucasian girl who first attended the dental hospital at the age of 6 years 10 months old, referred by a general dental practitioner for observation of her dental condition. The medical records showed the diagnosis of oral–facial–digital syndrome, but the type was not noted. A history of previous operation at a younger age for the removal of a tissue mass from the tongue was noted. The medical history was otherwise non-contributory and there was no family history of OFD or other congenital anomalies. All other children of the family were phenotypically normal.

On clinical examination the patient had many of the typical manifestations of OFD syndrome. Frontal bossing was apparent and also some degree of zygomatic hypoplasia that made the middle face look flattened [Fig. 2.]. The patient showed an inclination of both middle fingers of her hands to the right (clinodactyly) [Fig. 3]. The parents reported her toes to be normal. There were no apparent skin problems but the scalp hair was brittle.

On oral examination, the patient was in the mixed dentition stage, showing multiple frena buccally, at the right side of the mandible. The tip of the tongue was bifid into two lobes [Fig. 4]. Hyperplastic fibrous bands were present bucally in the maxilla. The most striking manifestation was a bilateral cleft palate, which had not previously been diagnosed [Fig. 5].

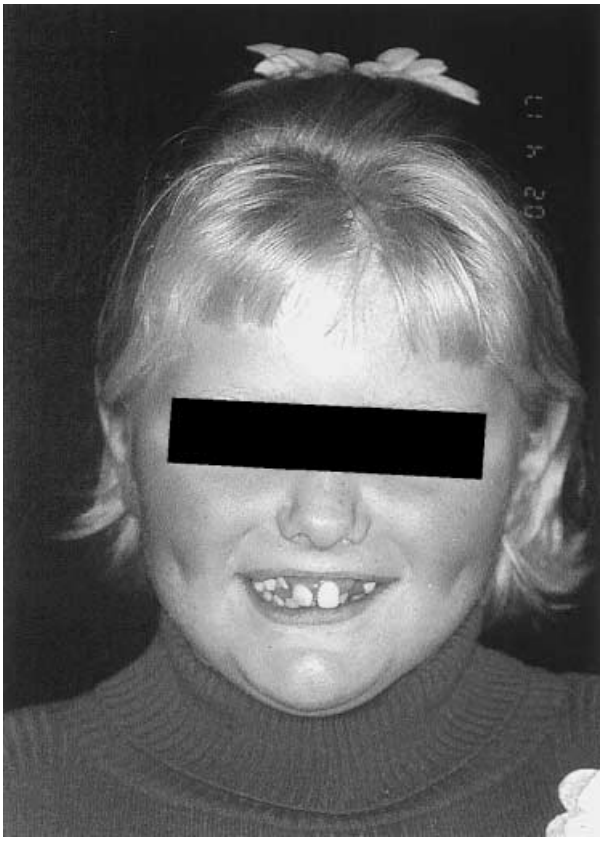

Fig. 2. Patient 2, facial appearance showing frontal bossing and flattened middle face.

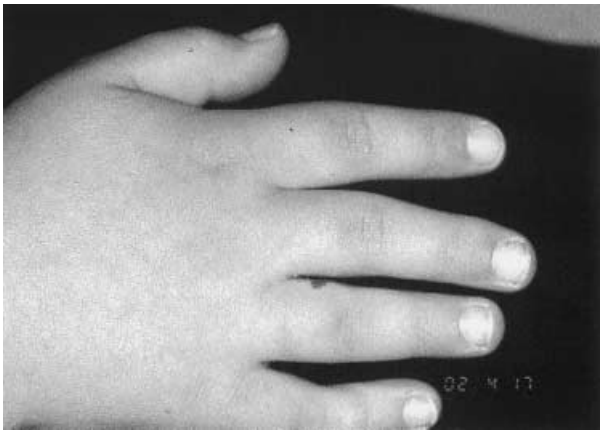

Fig. 3. Patient 2, clinodactyly of middle finger.

On radiographic examination, the orthopantomogram revealed two supernumerary permanent canines in the maxilla, one in each quadrant. The upper right lateral permanent incisor was absent and so was the lower left permanent lateral incisor. The third permanent molars were all missing [Fig. 6].

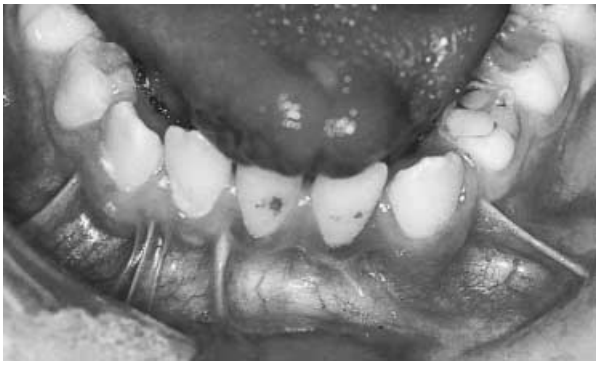

Fig. 4. Patient 2, intraoral view of the mandible showing multiple frenula at the right side. Note the two lobes at the tip of the tongue.

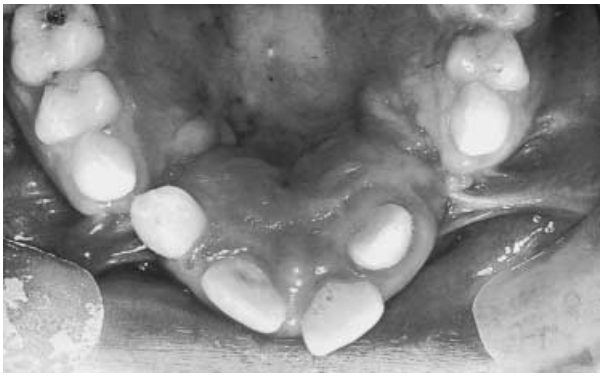

Fig. 5. Patient 2, intraoral view of the maxilla showing bilateral cleft sides between the lateral incisors and the canines. Note the hyperplastic fibrous bands in the upper mucobuccal folds.

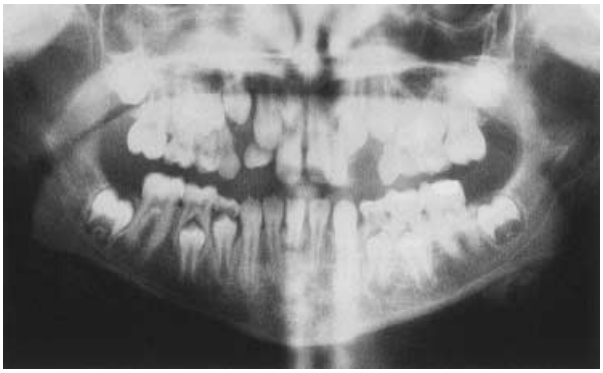

Fig. 6. Patient 2, orthopantomogram showing in the maxilla a supernumerary canine at the left side and possible canine-formed lateral or supernumerary lateral at the right side. A retained primary tooth lies in the line of the cleft on the upper right. There is absence of the lower left lateral and all third permanent molars.

A preventive program was followed and surgery to include grafts to repair the bilateral clefts was scheduled for the age of $9^{1}/_{2}$ years.

Discussion

The cases of OFD presented previously in the literature have demonstrated the common manifestations of the oral–facial–digital syndrome. However, the spectrum of the OFD syndrome has not yet been fully revealed, since each patient shows variations in the expression of the syndrome. As a result, in many reports, one or more specific features are added arising from the clinical examination and leading to the description of a 'new type' of the same clinical entity. Recently, up to eight types of the OFD syndrome were described and even then a few cases were classified as miscellaneous [7,13].

It is not certain that each group of patients truly constitutes a new type of the OFD syndrome and such a claim is not the purpose of this paper. Nevertheless, the two patients described here illustrate the variations in expression of the type I of the OFD syndrome. In Table 2, the oral clinical features of OFD type I presented in the literature are compared with the clinical features that the two patients described in this report show.

Both patients were born to unrelated healthy parents after uneventful full term pregnancies. According to the literature, approximately 75% of cases with OFD type I are sporadic [9]. It has also been reported that the syndrome may be expressed with great variability and may not be detected in every member of an affected family, or may even skip generations before recurring [3]. That could be the case in the two patients described in this paper, or they may alternatively have occured as a result of a spontaneous mutation.

The first patient is perhaps the least affected OFD patient presented in the literature to date although the oral manifestations of the patient include many that have been described in patients reported in the past [1–22]. More specifically, she had hyperplastic frenula and fibrous bands in the mucosa that had been surgically removed, a cleft palate and tongue, both operated on in the first year of her life, and supernumerary primary teeth that had already exfoliated. The patient had a perfectly normal appearance and, apart from an extra frenum at the right side of the mandible, nothing else to suggest the syndrome, since her face, digits, hair and the rest of her body

Table 2. Comparison between the oral manifestations of OFD I, as described in the literature and the manifestations in the present patients.

Oral – literature		Patient 1	Patient 2
Frenula	Hyperplasia, thick fibrous bands in lower muccobuccal fold	Extra frenum buccally in the mandible between lateral incisor and canine	Multiple frena buccally in the mandible
Lips	Midline cleft upper lip	Normal	Normal
Hard palate	Cleft	Cleft	Cleft
Soft palate	Cleft	Normal	Normal
Tongue	Cleft, hamartomatous mass, ankyloglossia/tongue-tie	Cleft, multiple lobes	Cleft, bifid, hamartomatous mass
Teeth	Supernumerary maxillary primary and permanent caines and premolars, malposition, T-shape canine crown form, missing mandibular lateral incisors, enamel hypoplasia, high caries	Supernumerary maxillary primary canines, absence of third permanent molars	Supernumerary maxillary primary and permanent canines, canine formed type lateral, absent lower lateral, absence of third permanent molars
Jaws	Small/hypoplastic mandible, short ramus infraocclusion, extended bony ridge from alveolar crest medially to the midline in canine-premolar area	Normal	Normal

were apparently unaffected. In the literature, it has been reported that the presence of multilobulated tongue and hyperplastic frenula may be considered as the minimum diagnostic criteria for OFD syndrome, type I. Brachydactyly is also considered a common finding but it does not always occur [22]. The first patient described in this paper had only two essential features and additionally primary supernumerary teeth, which supports what has been reported previously.

The first patient also presented with an open bite, which was not considered to be a manifestation of the syndrome and was attributed to the use of a dummy. However, recently a further case has presented, where an open bite was also present, which makes the original simplification of this finding questionable [15]. The crowding, which has been described as a rather common finding compared with the presence of clefts, could help to explain the orthodontic anomalies, such as the open bite.

The clinical picture in the case of the second patient was rather more complicated. Orally, there had been hyperplastic fibrous bands extending to the vermillion border from the cheeks and a mass which had been surgically removed from the ventral surface of the tongue. Unfortunately, no detailed description of the condition was given and no pathological assesment was available, although it is likely that this was a hamartomatous mass at the ventral surface of the tongue, a feature seen in 70% of patients with OFD type I [13]. In addition, in this patient, supernumerary permanent canines were present in the maxilla and two of the permanent lateral incisors were missing. The identity of the teeth present in the upper right quadrant was unclear; possibly a supernumerary canine was present with a missing lateral, or perhaps the crown of the lateral incisor was canine-formed. Recently, another case was described, where supernumerary primary canines were also reported and where the mandibular incisors appeared to be fused with the canines, whereas in the permanent dentition a supernumerary maxillary permanent canine and premolar were present and a mandibular canine and lateral incisor were missing [15]. The most commonly missing teeth reported in the literature have been the mandibular lateral incisors and the most commonly reported supplementary teeth the maxillary canines. More recently, variations have been reported in the teeth that may be missing or supernumerary in OFD cases [3,12]. The third permanent molars are also often missing, as in patient 1. When patient 2 was first seen in the hospital, multiple frena were present at the right side of the mandible and a cleft palate was diagnosed.

The second patient also showed facial and digital manifestations. The middle face was flattened and basal fronting was obvious, as well as clinodactyly of the middle fingers in both hands. The first patient, who has a milder expression of the syndrome, did not exhibit any digital manifestations, as opposed to the second patient, who was a more severe case and who presented with digital and facial manifestations. It may be concluded that, in patients with OFD, even though congenital anomalies seem to be invariably present in the oral region, those of the face and digits are not always be found.

Manifestations of the syndrome reported in other papers such as learning difficulties, speech delay, familial tremor, findings concerning the short tubular bones and the cranial vault, as well as cysts in kidneys and liver, toe malformations and osteoporosis [1–3,12–14,16–21] were not present in either of the patients described in this paper.

In both of our patients, delayed eruption of some permanent teeth was reported. The first permanent molars in the first patient had not erupted by the age of seven when she was last examined although they were close to eruption. Whilst that could hardly be considered as a delay, combined with the fact that the primary teeth exfoliated very early, it could be regarded as a manifestation of the syndrome. In the second patient, the primary incisors had not yet exfoliated by the age of seven. This could be attributed to the presence of the supernumerary teeth or to the clefting of the alveolar bone and it is again not certain if it is a manifestation of the syndrome.

Currently, neither of our patients appears to face any problems concerning their every day activities and each appears well adjusted, both socially and medically.

In conclusion, two female children are presented, both clearly demonstrating the diagnosis of OFD syndrome, but differing widely in the expression of the condition. This throws into question the previous practice of subdividing the condition. Genomic information will help in the resolution of this dilemma.

Résumé. Cet article décrit deux cas cliniques clairement établis de syndrome oro-digito-facial type I dont les expressions cliniques sont très différentes. Le premier patient montrait une expression mineure

du syndrome. Lors de l'examen à l'âge de 4 ans, aucun signe extra-buccal n'était présent, les manifestations intra-buccales comprenaient la présence de dents surnuméraires en denture temporaire, deux zones d'espacement et la présence d'un frein supplémentaire. Le second cas peut être considéré comme plus sévère. Le patient avait de nombreuses manifestations typiques, dont une bosse frontale, une certaine hypoplasie zygomatique et clinodactylie. Dans la bouche, le fait le plus notable était une fente palatine bilatérale qui n'avait pas été diagnostiquée avant l'examen à l'âge de 6 ans. Les autres caractéristiques comprenaient des freins multiples et une langue bifide.

Zusammenfassung. Zwei Fälle werden vorgestellt, beide mit der eindeutigen Diagnose eines Oral-Facial-Digitalen Syndroms Typ I, aber mit großen Unterschieden hinsichtlich der Ausprägung. Der erste Patient zeigte eine nur milde Ausprägung des Syndroms. Bei einer Untersuchung im Alter von 4 Jahren waren keine extraoralen Zeichen erkennbar, intraoral fanden sich überzählige Zähne, Lückenbildung und ein zusätzliches Frenulum. Der zweite Fall kann als schwerere Ausprägungsform betrachtet werden. Dieser Patient wies zahlreiche typische Manifestationen auf, einschließlich vorgewölbter Stirn, Jochbeinhypoplasie und Clinodaktylie. Intraoral war das hervorstechendste Merkmal eine beidseitige Gaumenspalte, welche erst im Alter von 6 Jahren diagnostiziert worden war. Weiterhin zeigten sich multiple Frenula und eine lingua bifida.

Resumen. Se presentan los informes de dos casos, ambos demuestran claramente el diagnóstico de síndrome Oral-Facial-Digital, tipo I, pero que son muy diferentes en la expresión de la condición. El primer paciente, mostró sólo una ligera expresión del síndrome. En un examen a los 4 años no había signos extraorales obvios, los hallazgos intra-orales incluyeron la presencia de supernumerarios en la dentición primaria, espaciamiento en dos áreas y la presencia de un frenillo extra. El segundo puede considerarse un caso más severo. Este paciente tenía muchas de las manifestaciones típicas, que incluía protuberancia frontal, un grado de hipoplasia zigomática y clinodactilia. En boca, el hallazgo más llamativo fue un paladar hendido bilateral que no había sido diagnosticado antes del examen a la edad de 6 años. Otros hallazgos incluyeron múltiples frenillos y lengua bífida.

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