

Case report

Otolaryngologic aspects of oral–facial–digital syndrome

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Abstract

The oral–facial–digital (OFD) syndromes are a heterogeneous group of hereditary disorders which have in common the findings of oral abnormalities, facial dysmorphism, and hand/feet malformations. We report the case history of an 18-month-old male with cerebellar cysts, hydrocephalus, tongue hamartomas, and polydactyly. These findings are most consistent with OFD VI. The clinical features of eight different types of OFD are discussed, with particular attention to the characteristics of the most interest to the otolaryngologist. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

The oral–facial–digital (OFD) syndromes share the common findings of cleft lip and/or palate, tongue clefts or hamartomas, hypertelorism, hand and/or foot malformations, and central abnormalities. These general characteristics were first described in OFD I by Papillon–League and Psaume in 1954 [1]. Since then, an additional seven types of OFD have been identified, with each type either featuring additional or fewer anomalies than those seen in OFD I [2]. Since many of the hallmarks of this syndrome manifest in the head and neck, we report a case

history of a child with oral–facial–digital syndrome and discuss the varying features seen in the different OFD types.

2. Case report

The case subject is an 18-month-old male diagnosed by prenatal ultrasound evaluation with a large cerebellar cyst (Dandy–Walker malformation), hydrocephalus and polydactyly. Since an older brother who died shortly after birth had been diagnosed with Meckel–Gruber syndrome (similar findings plus encephalocele), it was initially thought that the patient had the same syndrome.

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Fig. 1. Infant with oral–facial–digital syndrome type VI. Note severe macrocephaly and occipital protrusion.



Fig. 2. Tongue hamartomas associated with OFD.



Fig. 3. Postaxial polydactyly due to Y shaped metacarpals associated with OFD VI.

After an uneventful labor and delivery, it was confirmed that the infant had hydrocephalus, severe macrocephaly (Fig. 1), Dandy–Walker cysts and a large skin covered occipital skull defect. He had bilateral microtia and vertical creasing of the lobules. Distinct lobulation of the tongue was noted (Fig. 2). Postaxial (fifth digit) polydactyly due to Y-shaped metacarpals was present in both hands and in his right foot (Fig. 3). No eye abnormalities were detected. Besides from a slightly high arched palate, no cleft abnormalities were found. A renal ultrasound showed normal kidneys bilaterally. Given the findings of tongue nodules and the absence of cystic kidneys and encephalocele, the diagnosis was changed from Meckel–Gruber syndrome to OFD. This prompted a review of his brother's records which showed that an encephalocele in fact had not been present. Moreover, his parents remembered that his brother had 'flesh-colored lumps' on his tongue. These additional discoveries indicate that the patient's brother also had OFD. Although the patient does not fit exactly into any one of the known OFD syndromes, it was felt that he probably had OFD type VI because of the presence of cerebellar Dandy–Walker cysts in addition to postaxial polydactyly and a lobulated tongue. A ventriculoperitoneal shunt was placed shortly at 6 weeks of age to relieve hydrocephalus.

In the following 2 years, he has had numerous plastic surgical procedures that have chiefly addressed his polydactyly, severe occipital protrusion and macrocephaly. At the age of 2 years, the otolaryngology service was asked to evaluate this patient's tongue nodules prior to a hand surgical procedure. At that time, the nodules were thought to be hamartomas characteristic of the OFD syndromes. The tongue lobules were excised concomitantly with his next hand operation without complications. Histopathologic evaluation confirmed that the tongue lesions were hamartomas (Fig. 4). Although he has severe speech and cognitive impairment, the patient continues to grow and thrive. Limited oral intake is supplemented by gastric tube feedings, and his motor development, although delayed, continues to improve.

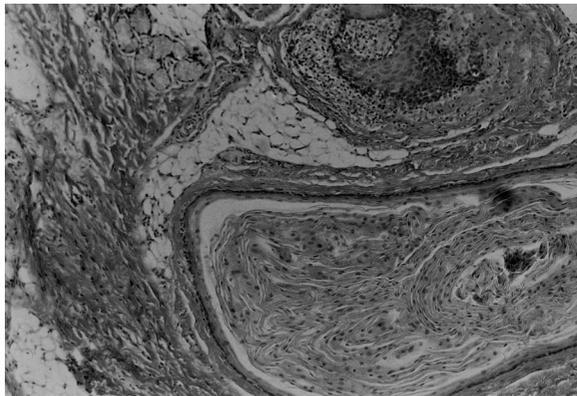


Fig. 4. Histologic appearance of tongue hamartomas. Oral mucosa covers lobules of ectopic fat, salivary gland tissue and skeletal muscle.

3. Discussion

Since its first description in 1954 by Papillon–Leage and Psaume [1], a number of similar syndromes with features of oral abnormalities, facial dysmorphism and digital abnormalities have been described. Eight to ten different variants of OFD have been described to date, and it is unclear which of these truly should be classified together. The following synopses of the eight most commonly accepted OFD syndromes are described to serve as a starting point for the differential diagnosis when a patient presents with these abnormalities and to illustrate the often confusing overlaps within the OFD spectrum (Table 1).

In OFD I (Papillon–Leage–Psaume syndrome) affected individuals typically have clefts of the jaw and tongue, missing teeth, face and skull malformations and hand abnormalities. Hyperplastic oral frenulae cause clefting of the jaw and tongue. Hypoplasia of the nasal ala is a common facial abnormality in OFD I. Digital abnormalities commonly found include brachydactyly (shortened digits), syndactyly (fusion of two or more digits) or polydactyly (bifurcated digits). Polydactyly is further subdivided into preaxial (first digit bifurcation), central (third digit bifurcation), or postaxial (fifth digit bifurcation) patterns. Preaxial polydactyly of the feet is the most common pattern seen in OFD I. Mental retardation and renal abnormalities are often present. It is the

only OFD thought to be X-linked dominant, and it is almost invariably fatal in males. This was demonstrated further when Wahrman et al. described OFD type I in an XXY male [3]. OFD type I is the only type commonly associated with corpus callosum agenesis, and porencephaly. Intracerebral and arachnoid cysts have also been described in individuals with OFD I [4]. There is a 50% incidence of mental retardation. It is also the only OFD type in which renal cysts occur which grossly resemble adult polycystic kidney disease, although types VI and VII also may manifest with renal abnormalities [5]. The histopathology of OFD type I polycystic kidneys differ from that of classic adult polycystic kidney disease in that OFD renal cysts are derived from both tubular and glomerular tissues whereas typical adult polycystic kidneys are cysts only derived from tubules [6]. Genetic linkage analysis has mapped the locus for OFD type I to a region spanning 19.8 centiMorgans (cM) on the short arm of the X chromosome (Xp22.2–p22.3) [7].

OFD II (Mohr syndrome) is similar to OFD I in that affected individuals usually have hand abnormalities, lobulated tongues, and cleft abnormalities. However, a broad nose with a bifid tip is seen in OFD II instead of the alar hypoplasia which characterizes OFD I [8]. Bilateral hallux polysyndactyly when present is strongly suggestive of OFD II. OFD II is characterized by distinct tongue nodules, rather than the bifid tongue more commonly seen in OFD I. Although both OFD I and OFD II may present with porencephaly, corpus callosum agenesis is not seen in OFD II. Conductive hearing loss, typically not seen in OFD I, has been reported in OFD II [8]. Laryngeal hypoplasia and tracheal stenosis have also been described in a small subset of individuals with OFD II [9]. Most OFD II kindreds exhibit autosomal recessive inheritance.

OFD III (Sugarman syndrome) is similar to OFD I and OFD II with a few exceptions. OFD III is characterized by small and irregularly shaped dentition, a bulbous nose, and strictly postaxial polydactyly [10]. Hypertelorism, exophthalmos, pectus excavatum and mental retardation are regular findings in this form of OFD. An unusual finding only seen in some patients with

Table 1
Outline of the different features of the eight main OFD syndromes

	OFD I	OFD II	OFD III	OFD IV	OFD V	OFD VI	OFD VII	OFD VIII
Oral	Tongue and jaw clefts, hyperplastic oral frenulae, arched/ cleft palate	Tongue nodules/clefts, hyperplastic oral frenulae, arched/cleft palate	Tongue nodules/clefts, arched/cleft palate, extranumerary teeth	Tongue nodules/clefts, arched/cleft palate, micrognathia		Tongue nodules/clefts, hyperplastic oral frenulae, arched/cleft palate	Tongue nodules/clefts, hyperplastic oral frenulae, arched/cleft palate	Tongue nodules/clefts, hyperplastic oral frenulae, arched/cleft palate
Facial	Hypertelorism, alar hypoplasia, median cleft lip	Bifid nasal tip, median cleft lip	Hypertelorism, low set ears, bulbous nasal tip	Epicanthal folds, low set ears	Median cleft lip	Hypertelorism, median cleft hypertelorism, cleft lip, broad nasal tip, cleft palate	Hypertelorism, preauricular skin tags, cleft lip, facial asymmetry or weakness,	Hypertelorism, median cleft lip, bifid nasal tip
Auditory		Conductive hearing loss		Sensorineural hearing loss				
Laryngotracheal		Laryngeal hypoplasia, tracheal stenosis		Laryngeal hypoplasia		Tracheomalacia		Epiglottic hypoplasia
Skeletal	Brachydactyly, syndactyly; preaxial polydactyly of feet	Brachydactyly, syndactyly, hallux duplication	Postaxial polydactyly	Pre- and/or postaxial polydactyly, tibial hypoplasia	Postaxial polydactyly	Central polydactyly (hands), postaxial polydactyly of fingers, preaxial polydactyly of toes	Brachydactyly, syndactyly	Bilateral polydactyly of hands, abnormal tibiae, duplicated hallux
Renal	Polycystic kidneys				Renal agenesis/hypoplasia		Congenital hydronephrosis	
Neurologic	Corpus callosum agenesis, porencephaly,	Porencephaly, hydrocephalus	See-saw winking, myoclonic jerks		Cerebellar atrophy, porencephaly	Cerebral abnormalities		
Inheritance	X-linked dominant	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal recessive	Autosomal dominant	X-linked recessive

OFD III is alternating eye movements (seesaw winking) and myoclonic jerks and spasticity. Families with OFD III seem to follow an autosomal recessive pattern of inheritance.

OFD IV (Bum–Baraitser syndrome) is typified by the presence of epicanthal folds, micrognathia, and low set ears in addition to other features seen in OFD I (facial abnormalities, tongue hamartomas, and pre- or postaxial polydactyly [11]. Severe tibial hypoplasia is the hallmark of OFD IV. Bilateral sensorineural hearing loss and laryngeal hypoplasia have been described in some affected individuals, but are not common findings [2]. Autosomal recessive inheritance is suspected.

OFD V (Thurston syndrome) is characterized by a midline cleft lip and postaxial polydactyly of the hands and feet [12]. It is the mildest form of OFD, and the mode of inheritance is autosomal recessive.

OFD VI (Varadi–Papp syndrome) is distinguished from the other OFDs by metacarpal abnormalities with postaxial polydactyly, and cerebellar abnormalities [13]. The postaxial polydactyly found in OFD VI is typically caused by a Y-shaped metacarpal bone. Cerebellar abnormalities have been described in every patient with OFD VI. These range from cerebellar cysts (Dandy–Walker malformations) to findings as severe as absence or hypoplasia of the cerebellum. A common central abnormality in OFD types I and VI are hypothalamic hamartomas [14]. Feeding abnormalities, tracheomalacia and short stature have been seen in some children. Most affected individuals have severe mental retardation and developmental delay, although rare individuals have been described with normal intelligence. Its pattern of inheritance is considered to be autosomal recessive [15].

OFD VII (Whelan syndrome) has been described in only one mother–daughter pair to date. These individuals had facial asymmetry with associated facial weakness, congenital hydronephrosis, coarse hair, brachysyndactyly and preauricular skin tags. The mode of inheritance is thought to be possibly autosomal dominant [16].

OFD VIII (Edwards syndrome) is characterized by mild mental retardation, bilateral polydactyly of the hands, abnormal tibiae, short stature, hy-

poplasia of the epiglottis, and a duplicated hallux [17]. It is the only OFD which exhibits X-linked recessive inheritance.

Other syndromes have been described as possible forms of OFD. Gurrieri et al. have described two brothers with cleft lip, lobulated tongue and digital abnormalities consistent with the OFD syndromes; the main distinguishing feature seen in this variant are retinal abnormalities [18]. Fibular aplasia in association with oral and digital abnormalities has been described by Figuera et al. as a possible new variant [19]. In addition, a number of other well characterized syndromes featuring orofacial and skeletal abnormalities need to be considered in the differential diagnosis of OFD. Pallister–Hall syndrome, Ellis–van Creveld syndrome, Smith–Lemli–Opitz syndrome are only a few of the syndromes which overlap with the OFD syndromes. As seen in the history of the patient described in this report, Meckel–Gruber syndrome is yet another syndrome with similar features. No universally accepted classification system for OFD exists, and it remains to be seen which OFD syndromes are truly genetically distinct. A true understanding of the developmental pathways of these syndromes awaits identification by molecular biologists of the genes and the mutated alleles responsible for OFD.

For the otolaryngologist, if a patient has the facial abnormalities described above in conjunction with oral abnormalities and digital abnormalities, the diagnosis of OFD needs to be considered. The specific finding of multiple tongue hamartomas should be considered to be highly suggestive of OFD. Literature searches of the Medline and Online Mendelian Inheritance in Man (OMIM) databases revealed that Cowden syndrome is the only other syndrome in which multiple tongue hamartomas are present. However, Cowden syndrome is characterized by multi-organ hamartomas, [20] whereas in OFD the hamartomas are limited to the tongue alone. A thorough evaluation by a dysmorphologist is essential to determine possible associated anomalies and which form of OFD an affected individual may have. The preliminary workup should include a head CT scan, a skeletal X-ray survey and renal ultrasound. An audiogram should be con-

sidered if any auricular abnormalities exist and if the individual has features consistent with OFD II or OFD IV. Karyotyping should be performed to detect any possible chromosomal rearrangements or deletions which can be used to track a mutation within a family as well as identify possible locations for responsible genetic mutations. Determination of the OFD type can indicate the mode of inheritance and prognosis for affected individuals, which are the critical elements necessary for genetic counselling.

4. Summary

In summary, the oral–facial–digital syndromes are a widely varying group of hereditary disorders which are characterized by oral (tongue hamartomas, cleftlip/palate), facial (hypertelorism,

nasal malformations), and digital (syndactyly, polydactyly etc.) abnormalities. Tongue hamartomas should be considered as highly indicative of the presence of an OFD syndrome. Individual OFD syndromes may also include central, skeletal and renal pathology. Given the specific otolaryngologic findings seen in the OFD syndromes described, we hope this report will increase the recognition of this group of syndromes among otolaryngologists and lead to earlier diagnosis and treatment.

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