Review article

Oral–facial–digital syndrome type 1: a review

Adyanthaya A[1], Adyanthaya S[2]

Abstract:
The oral–facial–digital syndromes result from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face and digits. Other organ systems can be involved, defining specific types of OFDS. To date, 13 types have been distinguished based on characteristic clinical manifestations. The oral–facial–digital syndrome type I is discussed in detail with emphasis on clinical features, molecular genetics and diagnosis.

Keywords: oral-facial-digital Syndrome; X-linked dominant inheritance

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Introduction

Oral-facial-Digital Syndrome (OFDS) is a general term for several apparently distinctive genetic diseases, which affects the face, oral structures and digits[1]. There are different OFD syndromes that are distinguished from each other based on the specific physical symptoms and the mode of inheritance and may have alternate names (Table 1)[2].

Orofaciodigital syndrome type I (OFD I) was first described by Papillon-Leage and Psaume in 1954[3] and further defined by Gorlin and Psaume in 1962[4]. OFD1 is transmitted as an X-linked dominant condition with lethality in males[5] and is characterized by malformations of the face, oral cavity, and digits, and by a highly variable expressivity even within the same family[6]. The incidence of OFD type I is estimated to be 1/50000to1/250000 in live births[7-8].

Type	Synonym
Type I	Gorlin syndrome I, Gorlin- Psaume
	syndrome, Papillon-Leage syndrome
Type II	Mohr syndrome, Mohr-Claussen syndrome
Type III	Sugarman syndrome
Type IV	Baraitser-Burn syndrome
Type V	Thurston syndrome
Type VI	Juberg-Hayward syndrome, Varadi
	syndrome, Varadi-Papp syndrome
Type VII	Whelan syndrome
Type VIII	Edwards syndrome
Type IX	Gurrieri syndrome
Type X	Figuera syndrome
Type XI	Gabrielli syndrome
Type XII	Moran-Barroso syndrome
Type XIII	Degner syndrome

Inheritance

Approximately 75% of cases of OFD1 are sporadic. The condition occurs almost exclusively in females. In familial cases, the most likely mode of inheritance is considered to be X-linked dominant with prenatal lethality in affected males[5,9].

Molecular Genetics

Feather et al. mapped the disorder to a region on the short arm of the X chromosome (Xp22.3-p22.2) spanning 19.8 cM and flanked by crossovers with the markers DXS996 and DX7S105 by performing linkage analysis[10]. Ferrante et al. analyzed several transcripts mapping to the critical region on Xp22 and found mutations in the *Cxorf5* gene, later named *OFD1* (MIM# 300170)[6]. It is widely expressed in metanephros, brain, tongue, and limb[11], which could be the cause for clinical expression of this syndrome.

Clinical Features

Dysmorphic features affecting the head include facial asymmetry, frontal bossing, nasal alar cartilage hypoplasia with flattening of nasal tip, broad nasal root, hypertelorism, and micrognathia with hypoplasia of the mandible ramus. Aberrant

1. Dr. Amith Adyanthaya, M.D.S, Reader, Dept of Pedodontics, KMCT Dental, College, Manaserry post, Calicut, Email: ady1473@yahoo.com

2. Dr. Soniya Adyanthaya, M.D.S, Reader, Dept of Oral Pathology & Microbiology, Yenepoya Dental College, Nithyananda Nagar, Derlakatte, Mangalore-575018, Karnataka State, India

Corresponds to: Dr. Amith Adyanthaya, M.D.S, Reader, Dept of Pedodontics, KMCT Dental, College, Manaserry post, Calicut, Email: ady1473@yahoo.com

hyperplastic frenulas (lingual, buccal, labial) and narrow upper lip are reported. The abnormal oral frenula appear to lead to the clefting of palate, tongue and median pseudoclefting of upper lip[1,6,12-15].. As a consequence of abnormalities in the frenula, the tongue appears bound down, lobular, or asymmetric, and the alveolar ridges may be cleft. Movement of the tongue is usually restricted[16]. Thickened alveolar ridges and abnormal dentition, both hyperdontia and hypodontia are additional characteristics of OFD1[6,13-15]. Supernumerary incisors have been identified in a case of oral-facial-digital syndrome type I in both primary and permanent dentition[16].

The digital abnormalities, which affect the hands (50%–70%) more often than the feet (25%), include brachydactyly (shortening), syndactly (fusion), clinodactyly (curvature) and rarely polydactyly (extra fingers). The CNS may also be involved in as many as 40% of cases. Involvement of the CNS includes mental retardation, hydrocephalus, cerebellar anomalies, porencephaly, and agenesis of the corpus callosum[6,13-15]. A patterned type of alopecia[17] and sparse, fine or coarse, dry lustreless hair have been observed[10,18], Feather SA et al 1997a). Multiple milia are most commonly observed on the face, scalp, auricles, and back of the hands. These lesions tend to be present in large numbers and generally have a prolonged persistence. They may resolve spontaneously after the first year of life leaving pitted scars. They are very important because of their usefulness in making an early diagnosis, allowing adequate genetic counselling[19-20].

Polycystic kidney disease is commonly associated with OFD1[14,21-22], and in some cases the renal involvement completely dominates the clinical course of the disease[13,18]. In a review of 35 OFD1 patients reported in the literature, Chetty-John et al. (2010) found that all had polycystic kidney disease, 9 (45%) of 20 evaluated had multiple liver macrocysts, and 5 (29%) of 17 evaluated had pancreatic macrocysts[23]. The ages of the patients with cysts ranged from 15 to 38 years. The findings were consistent with OFD1 being a ciliopathy, affecting the development and maintenance of bile ducts and renal tubules. They suggested that patients with OFD1 be routinely monitored for visceral involvement. Polycystic kidney, pancreatic cysts along with biliary cystadenomatous proliferation in the liver are also been reported[24].

Although the findings described for OFD1 overlap with those observed in other OFDS types, it has been suggested that OFD1 can be distinguished because of its X-linked dominant inheritance with male lethality and the presence of cystic kidneys[2].

Differential diagnosis

Autosomal dominant polycystic kidney disease (ADPKD) should be considered in the differential diagnosis of OFD1. The diagnosis of ADPKD has been made in some individuals who later were found to have OFD1[22]. The distinguishing features are mode of inheritance and the absence of oral, facial, digital, or brain abnormalities in ADPKD. The histopathology of OFD 1 polycystic kidneys differ from that of ADPKD is that OFD renal cysts are derived from both tubular and glomerular tissues whereas in ADPKD cysts are derived only from tubules[25]. The macroscopic and microscopic differences between cystic kidneys associated with OFD I and ADPKD have been discussed in other reports[26-27].

There is considerable overlap between the findings in OFD I and OFD II (Mohr syndrome). Hand abnormalities, lobulated tongues, and cleft abnormalities are observed in both the types. However, a broad nose with a biifd tip is seen in OFD II instead of the alar hypoplasia which characterizes OFD I. Conductive hearing loss, typically not seen in OFD I, has been reported in OFD II. Bilateral hallux syndactyly when present is strongly suggestive of OFD II. Polycystic kidneys have been reported in some patients with OFD I, but not in any patients with OFD II[25]. Radiologically, irregular mineralization of the hands and feet characteristic of OFD-I, but not of OFD-II, can be a distinguishing feature between these two syndromes. It is suggested that this finding is pathognomonic for the OFD-I syndrome[28].

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[29].

Genetic Counseling

Approximately 25% of females diagnosed with OFD1 have an affected mother[30]. A female proband with OFD1 may have the disorder as the result of a *de novo* gene mutation. Approximately 75% of affected females are simplex cases (i.e., occurrence of OFD1 in a single family member)[10,31]. When the mother of an affected female is also affected, the risk to sibs of inheriting the disease-causing *OFD1* allele at conception is 50%; however, most male conceptuses with the disease-causing *OFD1* allele miscarry[31].

If no family history of OFD1 exists, the risk that the unaffected mother of an affected female will give birth to another female with OFD1 is less than 1%. Two possibilities account for this small increased risk: (1) a new mutation in a second child or (2) germline mosaicism in a parent[32]. The risk to the offspring of females with OFD1 must take into consideration the presumed lethality to affected males during gestation. At conception, the risk that the disease-causing *OFD1* allele will be transmitted is 50%; however, most male conceptuses with the disease-causing *OFD1* allele miscarry[30]. A newborn male, born with clinical manifestations of OFD type I is exceptionally rare[26]. The risk to other family members depends on the status of the proband's mother. If the mother is affected, her family members could be at risk. The genetic counseling including discussion of potential risks to offspring and reproductive options should be provided to young adults who are affected or at risk of being carriers[30]. Often, mildly affected female relatives are diagnosed only after the identification of a severely affected individual[7].

Antenatal diagnosis

If the disease-causing mutation has been identified in the family, prenatal diagnosis for pregnancies at increased risk is possible by analysis of DNA extracted from fetal cells obtained by amniocentesis (usually performed at 15-18 weeks gestation) or chorionic villus sampling (usually performed at 10-12 weeks gestation)[30]. If the fetal karyotype is 46 XY, counselling should include discussion of the increased risk of miscarriage of affected males. If the foetus is found to be female, molecular genetic testing can be offered[33]. In pregnancies not known to be at increased risk for OFD1, the findings of structural brain anomalies and unilateral polydactyly of the great toe (duplicated hallux) should lead to consideration of OFD1. In such instances, it is appropriate to evaluate the mother for manifestations of OFD1[30]. In pregnancies of a female with OFD1, which are at 50% risk, prenatal ultrasound examination may detect structural brain malformations (e.g., porencephaly)[7,33].

Management

There is no specific therapy for OFDI syndrome. Treatment is directed at the problems encountered in an individual. To establish the extent of disease and to understand the needs in an individual diagnosed with oral-facial-digital syndrome type I (OFD1), examination of the face, especially the mouth, and the hands for characteristic anomalies, and age-appropriate assessment of development should be evaluated. Blood pressure analysis, serum creatinine concentration, urine analysis, and ultrasound evaluation of the kidneys, liver, and pancreas for cysts if the individual is age ten years or older and medical genetics consultation should be carried out[30]. The management of oro-facial-digital syndrome is multidisciplinary. Orthopedic surgery is often recommended to repair the defects of digits. Reconstructive surgery of auditory ossicles may be required to improve conductive deafness. Cosmetic or reconstructive surgery for cleft lip and palate, tongue nodule and accessory frenula is usually required. Removal of accessory teeth, orthodontic alignment and prosthetic rehabilitation can also be carried out if required. The degree of learning disabilities and other cognitive impairment should be evaluated along with speech therapy to provide appropriate support. The management of renal disease may require hemodialysis or peritoneal dialysis and renal transplantation. Special educational evaluation and input to address learning disabilities and other cognitive impairments are also required[30,34].

Regular follow-up for assessment of speech, periodic determination of blood pressure and serum creatinine concentration to monitor renal function is important. Annual assessment of renal function with follow-up by renal ultrasound evaluation to assess cyst development if abnormalities are detected and periodic screening for ovarian, pancreatic, and hepatic cystic disease should be considered (Toriello 2013).

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