Distinction of Mohr`s Syndrome from OFD Type I: Case Report and Review of the Literature

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Abstract

The Oralfacialdigital Syndromes (OFD) results from the pleiotropic effect of a morphogenetic impairment affecting almost invariably the mouth, face and digits. In view of the different modes of inheritance and the different prognoses of the most common OFDs; OFD I, and II, it is important to establish a correct diagnosis in these patients. A case of type II OFD syndrome is being reported and the distinguishing clinico-radiological features with type I are compared. This case reports also reviews the various other types of OFD and their distinguishing characteristics and emphasizes the early diagnosis and treatment of the same.

Key Words: Oralfacialdigital Syndrome, Mohr Syndrome, OFD1 Protein- Humanm, Syndactyly, Brachydactyly, Genetics, X-Linked Disease, Gene CXORF5

Introduction

Oral-Facial-Digital Syndrome (OFD) is the collective name of a group of rare inherited syndromes characterized by malformations of the face, oral cavity, hands and feet [1]. Mohr is credited with the first description of patients with oral-facial-digital syndrome [2]. Although a case of apparent Mohr syndrome appears in the older literature (Case 460 of *Otto monstrorum sexcentorum descriptio anatomica*, 1841: Beckwith personal communication). Gorlin and Psaume published the first English report of the disorder with a detailed description [3]. Since then, several patients have been reported and at least 13 variants have been proposed. It is transmitted as an X-linked dominant/recessive trait. OFD VII, was withdrawn from the list because it was considered identical to OFD I [4].

Etiopathogenesis [5-8]

The cause of OFD I, a single mutation on gene *CXORF5*, the only one to have been identified to date. This gene is located on the short arm of the X chromosome (Xp22.3-22.2) and governs the codes for OFD syndrome protein I. This protein is essential for foetal survival and early development of all organs characteristically deformed in OFD [6]. The inheritance pattern of OFD I is X-linked dominant. Where most cases are caused by a new mutation in the gene, which occurs for the first time in the individual and is not inherited from either parent. The risk that parents of an affected child will have another child with the disease is therefore virtually non-existent. The new mutation, however, is hereditary and there is a risk that a woman with a new mutation will pass it down to the next generation through the X-linked dominant inheritance pattern. The gene responsible for OFD I: *CXORF5*, comprises of 23 exons encoding a 1011 amino acid protein (OFD1) that shares no sequence homologies with other proteins of known function [7]. Sub-cellular localization experiments showed that this protein is centrosomal and localized in the basal body of primary cilia. Interestingly, the OFD1 gene has been found to escape X-inactivation in humans, while the murine counterpart is subject to X-inactivation [7].

The inheritance pattern of OFD II is autosomal recessive, i.e. both parents are healthy carriers of the mutated gene (*Figure 1*). In each pregnancy involving the same partners, there is a 25% chance of the child inheriting the mutated gene from both parents. The child will then develop the disease. In 50% of cases the child will inherit only one copy of the mutated gene (from only one parent) and, like the parents, will become a healthy carrier of the mutated gene. In 25% of cases the child will inherit two normal genes and will neither develop the disease nor pass it on. If one parent is not a carrier, but the other has an inherited autosomal recessive disorder (and thus has two copies of the mutated gene), the children will all be carriers of the mutation but they will not have the disease. If an individual with an autosomal recessive disorder has a child with a partner who is a healthy carrier with one copy of the mutated gene, there is a 50% risk that the child will develop the condition, while in 50% of cases the child will be a healthy carrier of the mutated gene. OFD II is lethal for males. Most patients have been found to have normal chromosomal pattern [8].

Differential diagnosis

Acro–fronto–facio–nasal syndrome; Acrocallosal syndrome; Beemer-Langer syndrome; C syndrome; Carpenter syndrome; Craniofrontonasal dysplasia; Egger-Joubat syndrome; Ellis-Van creveld syndrome; Grix syndrome; Holoprosencephaly–polydactyly syndrome; Jeune syndrome; Lemli-Opitz syndrome; Majewski syndrome; Pallister–Hall syndrome; and Smith- Short rib-polydactyly syndromes. For the majority of these conditions, except for Ellis-van creveld syndrome, Jeune syndrome, Pallister–Hall syndrome, and Smith-Lemli-Opitz syndrome, the responsible genes have not been identified yet and it is therefore impossible to make predictions as to whether some of them will end-up being allelic forms of OFDs.

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Diagnosis

Once the clinician has ascertained a patient with OFD, any mode of inheritance or any positive family history should be ruled out. In patients with clear X-linked dominant transmission and in sporadic female patients, it is necessary to rule out mutations in the OFD1 gene. A brain MRI, an abdominal ultrasound, a skeletal survey, an ophthalmologic evaluation, and an audiometric test can differentiate different types of OFDs. A chromosome analysis should also be done to search for submicroscopic rearrangements by array-CGH analysis to obtain clues towards the identification of new candidate gene loci. OFD II is a rare autosomal recessive disease whose diagnosis is based only on clinical evidence. The molecular genetic basis is still unknown. And because of a variable clinical expression (even intra familial) the attribution of the correct diagnosis among the several forms of OFD is often difficult. OFD II appears to be much rarer than OFD I [9] and can be easily confused with OFD I. Therefore distinction between these two syndromes has important implications. Early accurate diagnosis is important for a genetic counseling point of view, since it implies a one in four risks of recurrence. Timely treatment and rectification is essential in providing the patient with a healthy lifestyle. We report a female patient with an amalgamation of anomalies similar to that observed by Mohr in 1941 suggestive of OFD type II.

Case Report

A 28 year old woman, the fourth child of a non- consanguineous 52 year-old mother and a late father (*Figure 2*) was referred to the Department of Periodontology, Dr. D.Y Patil Dental College & Hospital, Pune, India, for scaling of the teeth. With no history of OFD running in the family, this girl was born at full term, uneventful pregnancy, no prenatal and perinatal complications, weighed about 3200 gms. Past medical history revealed that she was admitted in the hospital one and a half years ago for swelling of lower limbs and face and was diagnosed with hypertrophic cardiomyopathy. Since then she has repeatedly complained of running nose. We compiled and reviewed all the clinical features of different Ofds (Table 1). As it is a case report and review of literature, no ethical clearance was required. However, the procedure of evaluation was explained, and written consent was obtained from the patient.

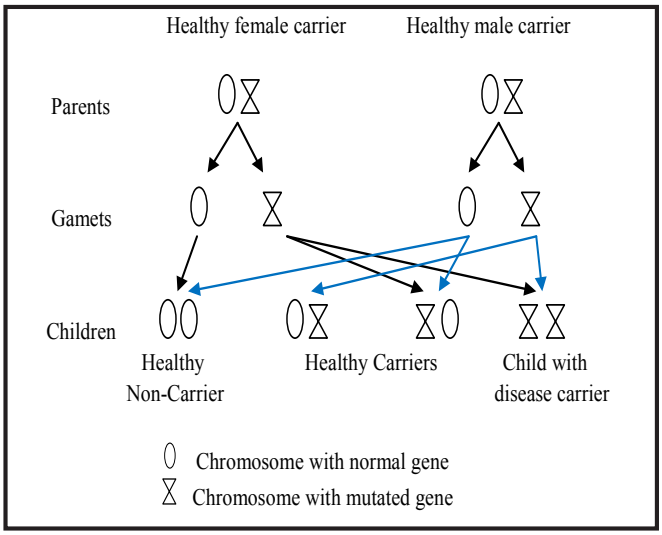

Figure 1. *Inheritance pattern of OFD II.*

Extraoral findings

Sloping head, frontal bossing, broad nasal bridge ocular hypertelorism (*Figure 2*), syndactyly, brachydactyly, polydactyly (*Figure 3*), shortened hands, metaphyseal irregularity (*Figure 3*) and flaring and bilateral polysyndactyly of hallux (*Figure 3*).

Intraoral findings

As restricted mouth opening, multiple enlarged oral frenii (*Figure 4*) median cleft lip (*Figure 2*), cleft high arched palate (*Figure 4*), poly lobed tongue showing multiple hamartomas on the tongue, (*Figure 5*), hypoplasia of mandible (*Figures 6* and *7*), narrow maxillary arch partial anodontia crowding of teeth and posterior cross bite (*Figure 5*).

Radiographic findings

Radiograph of feet showed polydactyly and bilateral reduplicated hallux and skeletal deformities (*Figure 7*). Radiograph of hands shows duplication of right 1st and 4th Phalanges and triplication left 1st phalange (*Figure 8*).

Investigations

Blood Investigations revealed the following information: Hb 9.8 gms%, total WBC count 7900/cu.mm, slightly raised ESR 33 mm/hr. Other laboratory investigations revealed blood urea 25 mg/dl. Microscopic examination of the tongue biopsy showed multiple fingerlike projections of stratified squamous epithelium, normal cartilaginous tissue and minor salivary glands, hyperkeratinization with a central core of fibrovascular

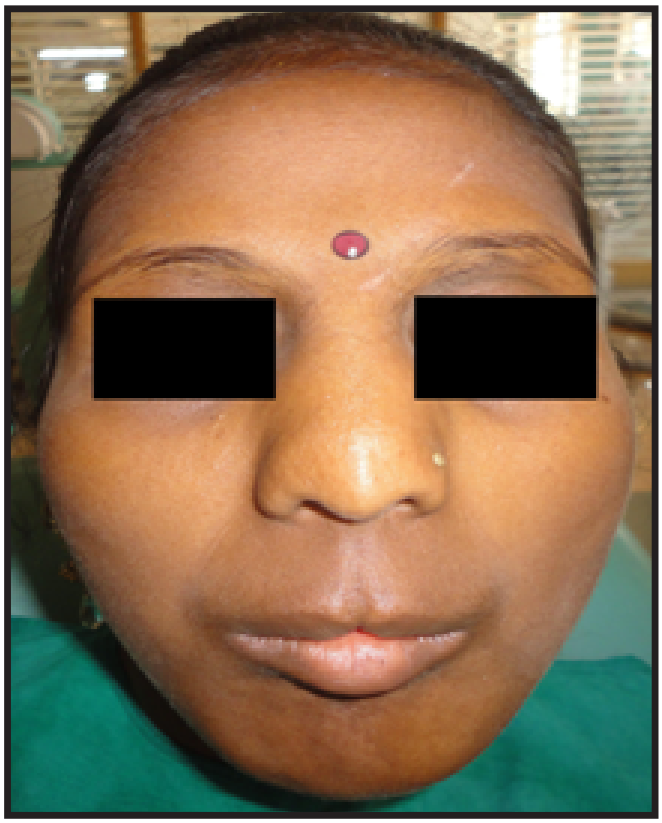

Figure 2. *A 28-year women, 4th child of a non-consanguineous. Note for median cleft lip, sloping head, frontal bossing and broad nasal bridge.*

Table 1. *Clinical features of different Ofds.*

OFD Subtype	Synonym	OMIM	Inheritance pattern/Cause	Distinguishing feature
OFD I	Papillon-Léage--Psaume syndrome [11]	311200	X linked dominant Mutations in OFD1 gene CXORF5	**Oral:** Micrognathia, median pseudo-clefting of upper lip & palate, hyperplastic frenula, lobulated/ bifid tongue, multiple hamartomas of the tongue [13,14] (in 70% cases of OFD [14]) thickened alveolar ridges and abnormal dentition, irregular margins of the lips. **Facilal:** Facial asymmetry, frontal bossing, hypertelorism, hypoplasia of the malar bones and nasal alar cartilages, broadened nasal ridge, and vanishing cutaneous milia of the face and ears, (usually disappear before 3rd year of life) dryness, brittleness, and/or alopecia of the scalp hair, hypotrichosis. **Digital malformations:** [14] syndactyly, brachydactyly, clinodactyly, unilateral duplication of the hallux, and more rarely, pre- or postaxial polydactyly. **CNS:** [15] microcephaly, agenesis of corpus callosum [16] porencephaly, intracerebral epithelial or arachnoid cysts, heterotopia of gray matter, abnormal gyrations and mild mental retardation. **Systemic:** Polycystic kidney disease [16], pancreatic, ovarian and liver cysts [17], Estimated incidence of 1:50,000–250,000 live births [6].
OFD II	Mohr/ Mohr-Claussen syndrome Syndrome [2]	252100	Autosomal recessive Mutations in unidentified gene.	**Oral:** Midline clefts of the lip, thick frenula, multiple lingual hamartomas [14], micrognathia. **Ocular:** Dystopia, canthorum, ocular hypertelorism, **Digital:** Clinobrachydactyly, syndactyly, and polysyndactyly of halluces [8]. Conductive hearing impairment [15]. **CNS:** Porencephaly and hydrocephaly, **CVS:** atrioventricular canal and endocardial cushion defects.
OFD III	Sugarman Syndrome [12]	258850	Autosomal recessive	Ceaseless seesaw winking of the eyes and/or myoclonic jerks. postaxial polydactyly, postaxial hexadactyly of hands and feet, profound intellectual disability, bulbous nose, low-set ears, lobulated hamartomatous of tongue, dental abnormalities, bifid uvula, pectus excavatum, short sternum, and kyphosis. Ceaseless seesaw winking of the eyes and/or myoclonic jerks. postaxial polydactyly, postaxial hexadactyly of hands and feet, profound intellectual disability, bulbous nose, low-set ears, lobulated hamartomatous of tongue, dental abnormalities, bifid uvula, pectus excavatum, short sternum, and kyphosis.
OFD IV	Baraitser-Burn Syndrome [18,19]	258860	Autosomal recessive	Skeletal dysplasia, tibial dysplasia and polydactyly, The phenotypic spectrum has been subsequently expanded to include occipitoschisis, brain malformation, ocular colobomas, intrahepatic cyst, renal cysts. Other findings include pectus excavatum, short stature anal atresia, and joint dislocations. (Severe tibial dysplasia differentiate type IV from type I)
OFD V	Thurston Syndrome [20]	174300	Autosomal recessive	Polydactyly, postaxial, with median cleft of upper lip, early dental loss. Only one affected individual has had hyperplastic frenulae reported. Exclusively in Indian ethnic background [18]
OFD VI	Varadi-Papp Syndrome [21]	277170	Autosomal recessive	Polydactyly, cleft lip/palate or lingual lump, and psychomotor retardation. cerebral and/ or cerebellar malformations in endogamic gypsies (vermis hypoplasia/aplasia, Dandy–Walker anomaly) [20]. Hypothalamic hamartoma, cerebellar dysgenesis, absent pituitary gland with precocious puberty, penile agenesis and abnormal clavicles [22]
OFD VII	Whelan Syndrome [4,23]	608518	X-linked dominant	Hydronephrosis, Oral (tongue nodules, bifid tongue, midline cleft of the lip), facial (hypertelorism, alar hypoplasia), and digital abnormalities (clinodactyly), hydronephrosis and facial asymmetry.
OFD VIII	Edwards Syndrome [24]	300484	X-linked recessive	Bilateral preaxial and postaxial polydactyly, tibial and radial defects (short), and epiglottal abnormalities Hypertelorism or telecanthus, broad, bifid nasal tip, median cleft lip, tongue lobulation and/or hamartomas, oral frenula, high-arched or cleft palate, bilateral polydactyly, and duplicated halluces
OFD IX	Gurrieri Syndrome [25]	258865	Autosomal recessive	Retinochoroidal colobomata, severe microcephaly, Dandy-Walker malformation, retrobulbar cysts and short stature. Digital anomalies: hallucal duplication detectable radiologically.
OFD X	Figuera Syndrome [26]	165590	Autosomal recessive	Fibular aplasia, mesomelic limb shortening due to radial hypoplasia. Digital anomalies: oligodactyly and preaxial polydactyly
OFD XI	Gabreilli Syndrome [27]	-	Autosomal recessive	Craniovertebral anomalies, ventriculomegaly, microcephaly, apophysis, fusion of vertebral arches in C1, C2, and C3, and clefts of vertebral bodies in a sporadic male patient, postaxial polydactyly, alar hypoplasia, duplicated vomer, midline cleft involving palate, vomer, ethmoid and crista galli
OFD XII	Moran Barroso Syndrome [28]	-	Autosomal recessive	Myelomeningocele, stenosis of the aqueduct of Sylvius, Dysplasia of AV valves
OFD XIII	Degner Syndrome [29]	-	Autosomal recessive	Psychiatric symptoms (major depression), epilepsy and leukoaraiosis (brain MRI) in association with core oral, facial, and digital findings.

connective tissue. Audiometry revealed bilateral conductive hearing loss. A 46% hearing loss was reported.

Treatment

As observed this patient had a normal intelligence and thus can be successfully treated by multidisciplinary approach involving various plastic & reconstructive surgeries for clefts of the lip and palate; correction of tongue nodules & partial reduplication of the hallux; speech and language therapy; physiotherapy; orthopedics surgery for syndactyly and orthodontic therapy for maxillary arch expansion and correction of crowding; extraction of supernumery teeth and frenectomies for correction of abnormal freni. A surgical attempt to reconstruct the auditory ossicles was advised to improve the conduction deafness.

A stepwise treatment was planned for this patient. Our treatment plan included initial phase-one therapy, (non-surgical periodontal therapy- scaling, root planning and polishing, oral hygiene instructions, 0.2% chlorexidine mouthwash and modified Bass brushing technique was advised). A recall visit was scheduled after 4 weeks. Carious lesions were excavated and restored with either glass ionomer

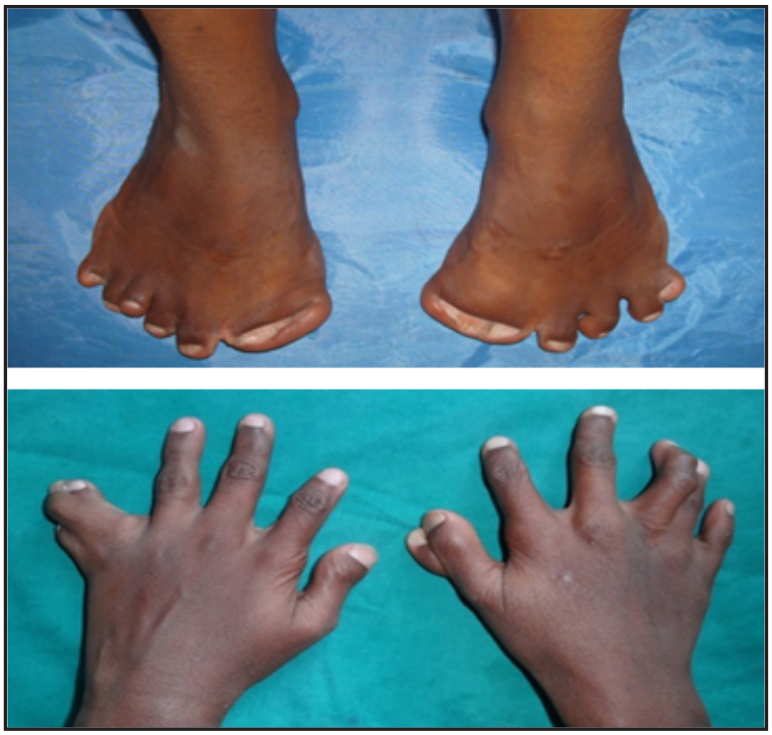

Figure 3. *Syndactyly, brachydactyly, polydactyly of hands & feet, shortened hands, bilateral polysyndactyly of hallux, and metaphyseal irregularity.*

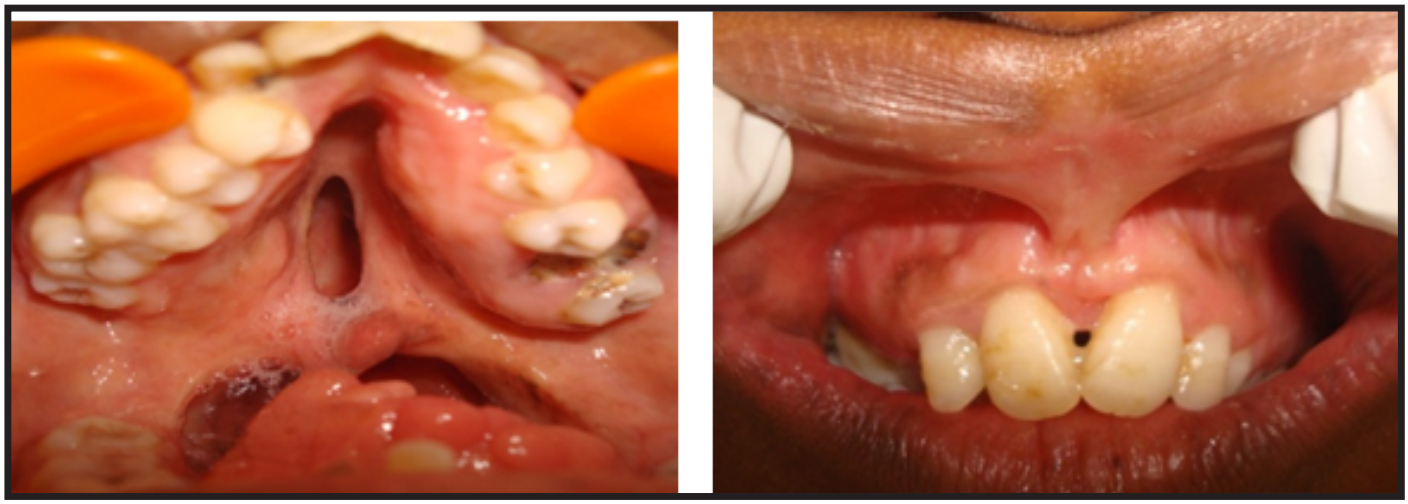

Figure 4. *High arched cleft palate and narrow maxillary arch, restricted mouth opening and multiple enlarged oral frenii.*

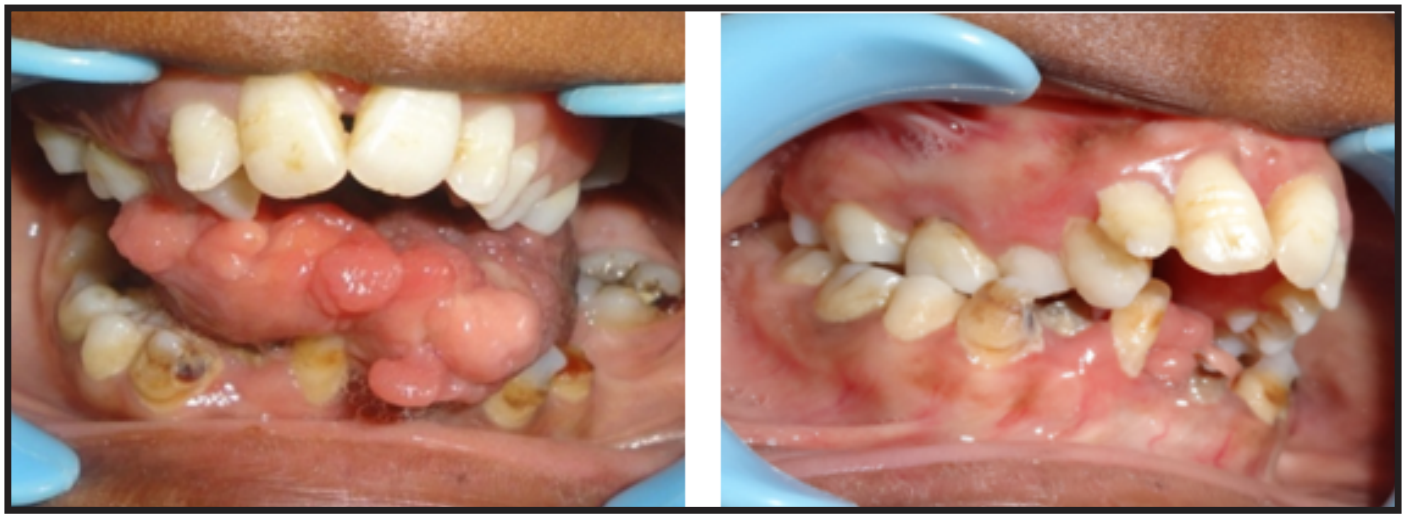

Figure 5. *Poly lobed tongue showing multiple hemartomas, narrow maxillary arch, partial anadontia, crowding of teeth and posterior crossbite.*

cement or composites. Grossly destructed teeth were extracted and endodontic therapy was rendered for restorable teeth with stainless steel crowns. As hyperactive mobility of the tongue was concerned, only fixed prosthesis were given. Frenectomy

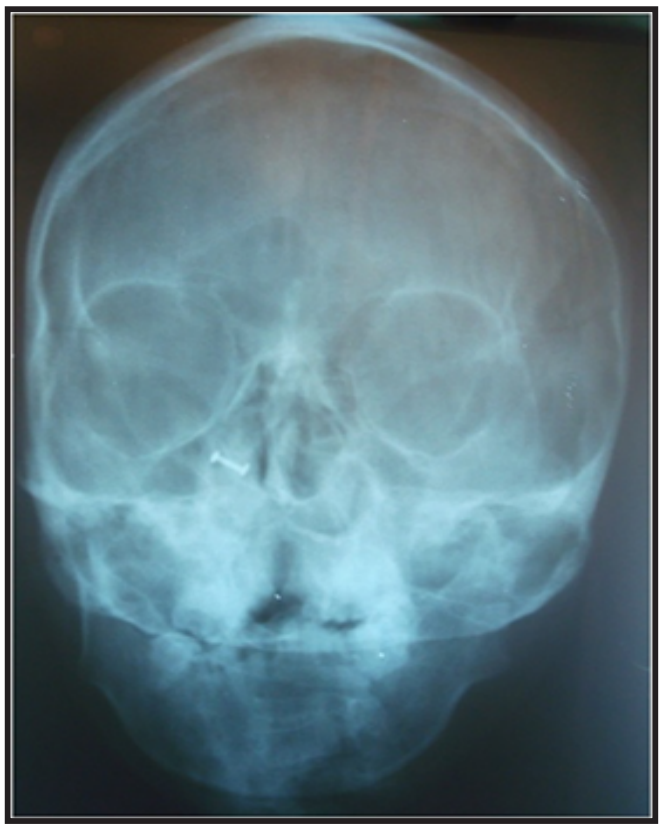

Figure 6: *Skeletal hypoplasia, note for complete hypoplasia of mandible.*

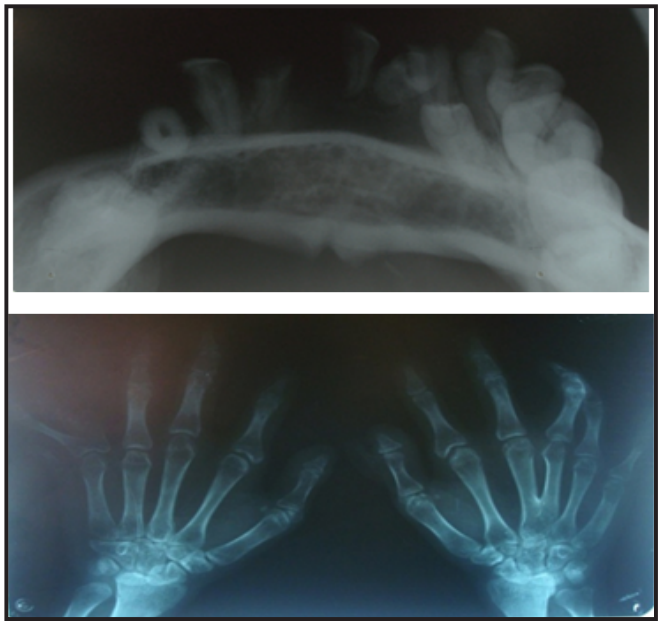

Figure 7: *Hypoplasia of mandible and partial anodontia, radiograph of feet showed polydactyly and bilateral reduplicated hallux.*

for maxillary and mandibular labial frenum was done with scalpel and electrocautery. Multiple hamartomas were treated by Nd:YAG laser and the patient is on regular follow up visits.

Interdisciplinary approach included correction of cleft lip and palate in the department of Oral and Maxillofacial surgery. Orthodontic expansion of the narrow arch and fixed orthodontic appliances for the correction of the mal-aligned teeth and posterior cross-bite are carried out simultaneously. Orthodontic therapy is still to be completed and the patient is on monthly recalls. Growth and development of face and

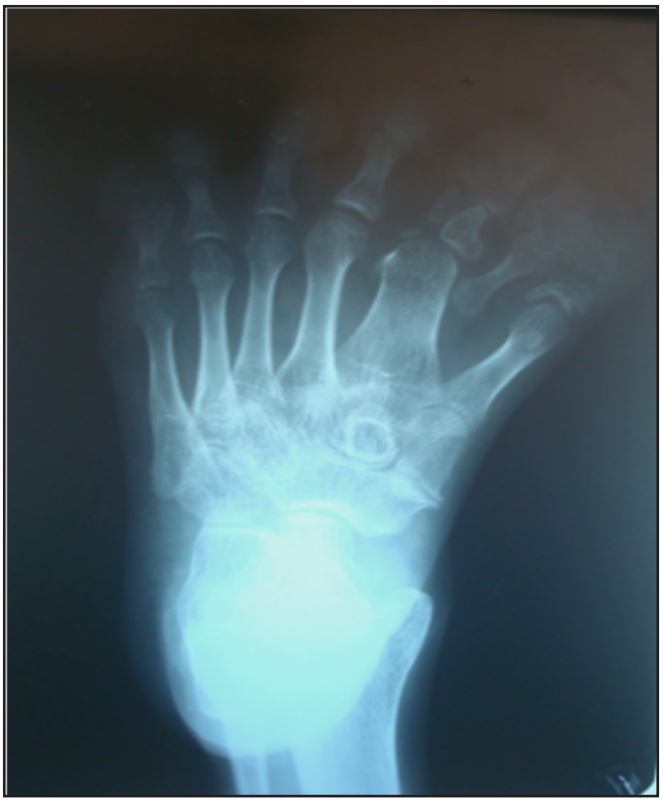

Figure 8. *Radiograph of hands shows duplication of right 1st and 4th Phalanges and triplication left 1st phalange.*

jaws are being monitored along with regular follow-up for assessment of speech. Management of this case was made according to the guidelines treatment and management of OFD 1 [1,5].

Discussion

Mohr [2] in 1941 described a family in which male proband had OFD malformation including a high arched palate, lobulate tongue, with papilliform outgrowths, a broad root of nose, ocular hypertelorism, syndactyly, brachydactyly and polydactyly of hands and feet. Important characteristic feature was polysyndactyly of the great toes. The reported child had three brothers who had more limited malformations of oral cavity and digits. Mohr concluded that this syndrome was due to a sex linked recessive sublethal gene [2]. Later Claussen [10] in 1946 reported a similarly affected child born to consanguineous parents of the same family reported by Mohr, thus leading to the conclusion that the syndrome was inherited as an autosomal recessive trait. A similar syndrome was described by Papillon-Leage and Psaume [11] who recognized that the condition was hereditary and affected exclusively females. Subsequent reports of only females with this OFD phenotype strengthened the hypothesis that it was inherited as an X-linked dominant trait. This hypothesis was confirmed almost 50 years later when Ferrante et al. unraveled the genetic basis in 2001 [7]. For some unknown reason, all subsequent literature reports referred to the X-linked dominant form (Papillon-Leage and Psaume) and not the X-linked recessive form (Mohr). Thus as a general consensus as X-linked dominant was excepted as OFD I, even though it

was described after the recessive form of Mohr and Claussen, which is now referred to as OFDS II. After the description of OFD I and II, the phenotypic spectrum was further expanded with extra-OFD manifestations [12] leading to the definition of new types, each being characterized either by distinctive clinical findings and/or by a specific mode of inheritance. Till date, about 13 variants have been proposed [13].

Conclusion

Mohr syndrome (OFD II) appears to be much rarer than OFD I. It can be easily confused with OFD I. Therefore early distinction between these two syndromes has important implications in genetic counseling.

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