OCULODENTODIGITAL DYSPLASIA- AN INTERESTING CASE

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ABSTRACT:
Oculodentodigital dysplasia (ODDD) is a rare, autosomal dominant disorder with high penetrance and variable expressivity, caused by mutations in the Connexin 43 (Cx43) or gap junction protein alpha-1 (GJA1) gene. It has been diagnosed in fewer than 300 people worldwide. It affects many parts of the body particularly eyes (oculo), teeth (dento), and fingers (digital). The common clinical features include facial dysmorphism with thin nose, conductive deafness, microphthalmia, syndactyly, and tooth anomalies like enamel hypoplasia, anodontia, microdontia and early tooth loss. Other less common features are abnormalities of the skin and its appendages, such as brittle nails and sparse hair. To prevent this syndrome from being overlooked, awareness of possible symptoms is necessary. Early recognition can prevent blindness, dental problems and learning disabilities. Described here is the case of a 29 year male. Careful clinical re-evaluation revealed ODDD, characterised by the predominance of facial and ophthalmological involvement with congenitally missing teeth.

Key Words: Oculo-dento-digital dysplasia, syndactyly, microphthalmia, camptodactyly.

INTRODUCTION:
Oculo-dento-digital dysplasia (ODDD) [MIM *164200], is an extremely rare autosomal dominant disorder with high penetrance, variability expressivity, and advanced paternal age in sporadic cases. It is also known as oculodento-osseous syndrome or Meyer-Schwickerath syndrome. This rare developmental multisystemic disorder was first described by Lohmann in 1920. Meyer-Schwickerath introduced the term “dysplasia oculodentodigitalis” in 1957. Gorlin established the acronym of ODDD syndrome in 1963. Approximately 300 such patients have been reported so far, the majority of them being white.

Ophthalmic findings include microphthalmia, microcornea, fine porous spongy iris abnormalities, cataracts, glaucoma, and optic atrophy. Dental abnormalities include microdontia, anodontia, multiple caries, early tooth loss and mandibular overgrowth with wide alveolar ridge and skeletal anomalies include syndactyly, camptodactyly and clinodactyly due to hypoplasia or aplasia of the middle phalanges. The typical craniofacial anomalies include a thin nose with hypoplastic alae nasi, small antverted nares, prominent columnella, hyper- or hypotelorism, cranial hyperostosis and microcephaly. ODDD patients also have abnormalities of the skin and its appendages, such as brittle nails, slowly growing hair, sparse, curly or kinky hair and, very rarely, palmoplantar keratoderma. Some cases have dysplastic ears and conductive hearing loss.

Neurological symptoms, such as mental delay, ataxia, spasticity, neurogenic bladder disturbances and as slowly progressive leukodystrophy may also be present. Brain magnetic resonance imaging studies of patients with ODDD have shown diffuse bilateral abnormalities in the subcortical cerebral white matter, which can define a slowly progressive leukodystrophy. Mutations in the connexin 43 gene or gap junction protein alpha-1 gene (GJA1) located on chromosome 6q22-q24 leads to disruption of Cx43-mediated cell to cell communication resulting in disrupted morphological patterning during development and altered functioning of cells in mature tissue. The gap junction protein Cx43 is almost ubiquitously expressed in various tissues of ectodermal and mesodermal origin, which might explain the complex phenotype and widespread organ involvement in ODDD.3

CASE REPORT:
A 29 year old male but with senile appearance reported to Department of Oral Medicine and Radiology with a chief complaint of loose denture since 2 years. Patient gave history of denture wearing since 24 years with no history of eruption of teeth. The first denture was made when patient was 5 years old and the dentures were remade on different occasions according to the growth. He is the third child of non-consanguineous healthy parents with no contributing family history.

On General physical examination- The gait was ataxic with moderate built & nourishment and other vital signs were found to be in the normal range.
Examination of skin & its appendages revealed ichthyosis, dry, scaly skin, hypotrichosis (figure-1, A), dystrophic and brittle nails (figure-1, B).

Examination of skeletal system: The hands revealed camptodactyly of 4th and 5th fingers & syndactyly of thumb, 2nd and 3rd fingers (figure-2, A). The feet revealed syndactyly of 2nd to 5th toe and clinodactyly of great toe (figure-2, B).

**Figure 1:** (A) showing dry scaly skin and hypotrichosis and
(B) showing dystrophic brittle nails.

**Figure 2:** (A) camptodactyly of 4th and 5th fingers & syndactyly of thumb, 2nd and 3rd fingers.
(B) syndactyly of 2nd to 5th toe & clinodactyly of great toe.

**Figure-4:** The oral cavity showing (A) diffuse bluish pigmentation of oral mucous membrane.
(B) Total anodontia and diffuse areas of inflammation pertaining to the denture bearing surface.

**Figure-5:** Orthopantamograph showing completely edentulous upper & lower arches with flattening of alveolar ridges

Examination of face revealed dry lips, angular cheilitis (figure-3, A), eyes appearing small & shrunken with sparse eyebrows, short palpebral fissures (figure-3, B), trichiasis and pale blue irids, nose showed prominent columella (figure-3, C).

Examination of oral cavity showed diffuse bluish pigmentation of oral mucous membrane (figure-4, A). Patient was also found to have total anodontia and diffuse areas of inflammation pertaining to the denture bearing surface on palate, suggestive of denture induced stomatitis (figure-4 B).

Combining all these features, a provisional diagnosis of hypohidrotic anhidrotic Ectodermal dysplasia with denture induced stomatitis was made.


Patient was further screened with orthopantamograph, which confirmed completely edentulous upper & lower arches with flattening of alveolar ridges (figure-5).

Considering our differential diagnosis patient was further referred for ophthalmological examination which revealed additional significant findings like mild hypertelorism, entropian, micro-cornea, symblepharon, diminished visual acuity and reduced tear secretion.
The patient was also being evaluated for hearing loss in the department of ENT, where he was advised an audiogram which revealed conductive hearing loss of left ear.

Taking into consideration, the clinical features of patient, combining the valuable opinion of the concerned specialities and having a retrospective look on literature a clinical diagnosis of Oculo-dento-digital dysplasia with denture induced stomatitis was made.

Patient was prescribed antifungal agents for denture stomatitis and occlusal rehabilitation was done.

**DISCUSSION:**

Oculodentodigital dysplasia (ODDD) is a disorder with distinct clinical features affecting both ectodermal and mesodermal cell lineages. The developmental abnormalities in ODDD appear to be caused by impaired Cx43 function during embryogenesis and epithelial differentiation.3

Gap junctions are clusters of intercellular channels that permit the diffusional exchange of ions, small metabolites, nutrients, and signaling molecules between adjoining cells. Gap junction intercellular communication controls and coordinates an abundance of cellular activities. It is crucial for tissue morphogenesis and homeostasis, cell growth, differentiation, response to stimuli, and fulfils many other tissue-specific functions. In humans, the gap junction system is formed by a polygenic family of more than 20 different connexin proteins named by their predicted molecular mass. All connexins are integral membrane protein. Six connexin molecules are assembled into oligomers called connexon, which are transported to the cell membrane and aggregate into gap junction plaques.9

Cx43 is expressed in various tissues such as brain, heart, gonads, lens, cornea, skin and bone. Reduction of Cx43 expression in animal models resulted in microphthalmia and a smaller retina.9 These data correspond well with the ocular abnormalities in ODDD like microcornea, as well as microphthalmia seen in our patient. In the postnatal tooth development of rats, Cx43 channels have been demonstrated between the odontoblasts and appeared to be necessary for the secretion of the dentin matrix.10

The demonstration of a genetic linkage of the oculodentodigital dysplasia (ODDD) to the GJA1 locus offers the strongest evidence for a critical role of Cx43 in skeletal development. To date, at least 24 distinct point mutations of GJA1 have been identified in subjects with this disease.11

GJA1 missense mutations found in ODDD have a dominant negative effect. The complex combinatorial interactions among the connexins suggest that additional mutational analysis of connexins other than connexin 43 in ODDD patients may give us insights into which specific connexions may modify the functional consequences of the GJA1 missense mutations.1

There are many conditions mentioned in literature with overlapping features as in ODDD. These include: EEC syndrome, Hallermann–Streiff syndrome, Orofacial digital syndrome Type II, KID syndrome etc. The EEC syndrome is characterised by ectodactyly or lobster-claw deformity, ectodermal dysplasia, and cleft lip and palate. It is a rare disorder with autosomal dominant inheritance, variable expression, and in some families lack of penetrance.12 Cleft lip/palate is present in most patients, and in those without cleft lip/palate the philtrum or uvula or both are often abnormal.13 The cleft lip/palate was not present in our patient and significant eye changes and facial features favouring ODDD were present.

Hallermann-Streiff Syndrome (HSS) is a rare disorder characterized primarily by head and face abnormalities, with dental abnormalities also present in 50-80 percent of cases. Seven essential signs were described by Francois as diagnostic criteria for HSS these include-dyscephalia and bird-like facies, abnormal dentition, hypotrichosis, atrophy of skin especially on the nose, Congenital cataracts, Bilateral microphthalmia and Proportionate dwarfism.hss2. The digital changes like syndactyly or camptodactyly like ODDD is not present in this syndrome.14

The Mohr-Clausen syndrome or oro-facial-digital syndrome type II (OFD-II)] is transmitted as an autosomal recessive and is characterized by malformation of face, oral cavity and digits. Facial and oral features include frontoral bossing, facial asymmetry, broad nasal bridge, cleft upper lip and cleft palate, lobulated tongue. Digital features include clinodactyly, syndactyly, brachydactyly, pre- and post-axial polydactyly and duplication of the first toe. Other systemic features include conductive deafness, congenital heart defects and renal abnormalities, in variable combination. Diagnosis is mainly clinical.15 There are usually no eye manifestations and skin changes as seen in ODDD.

Keratitis-ichthyosis-deafness (KID) syndrome is the most severe cutaneous connexin disorder because of the involvement of several epithelia of ectodermal origin, including skin, appendages, nail, teeth, inner ear, and cornea. Most of the cases are sporadic (N90%), but examples of autosomal dominant or potentially recessive transmission have been reported. The majority develops symmetrical, well-
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circumscribed hyperkeratotic plaques with underlying erythema on the extremities and face (erythrokeratoderma). In others, the skin is thickened and has a coarse-grained appearance or shows filiform follicular hyperkeratoses without erythema. With very few exceptions, palms and soles are hyperkeratotic with a rough, stippled, or grainy-appearing surface. Chronic cheilitis and perle`che are common, whereas hair and nail dystrophy, scarring alopecia, dental anomalies, and heat intolerance are less frequent. Roughly 96% of patients with KID syndrome also develop during childhood ophthalmologic problems, such as corneal neovascularization, chronic blepharitis, and conjunctivitis, which may cause progressive visual decline and blindness. Most consistent is the finding of sensorineural hearing loss, which is often congenital, bilateral, and severe to profound whereas in ODDD hearing loss is conductive. In KID syndrome there are no digital manifestations as seen in ODDD.

The broad clinical overlap between these genetic disorders likely stems from the shared tissue expression and function of cutaneous connexins. Molecular diagnostic and prenatal testing for these connexin disorders has become available and certainly aids in establishing a correct diagnosis.

CONCLUSION:
This rarest entity poses a diagnostic challenge for the clinician and the awareness of possible symptoms is necessary to arrive at one. Early recognition can prevent significant co-morbidities in the form of blindness, deafness and learning disabilities which can severely affect the quality of life in this condition. We as an oral physician can significantly contribute in bringing the smile on the face of these patients.

REFERENCES:

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