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The Case of Oral-Facial-Digital Syndrome Type I

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ABSTRACT

Oral-facial-digital syndrome type I (OFDS1) is a genetic disorder that is lethal before birth in males and affects females. It is a complex condition impacting the oral-facial-maxillary region, as well as the central nervous system (CNS) and kidneys. Oral features include a lobulated tongue, tongue nodules, cleft palate, accessory gingival frenula, and hypodontia. Facial characteristics often involve underdeveloped alae nasi, median cleft or pseudocleft of the upper lip, and micrognathia. Brain MRI is crucial for diagnosis, revealing intracerebral cysts, agenesis of the corpus callosum, cerebellar agenesis, and Dandy-Walker malformation. About 50% of individuals with OFDS1 experience intellectual disability. We have presented the case of OFDS1 with intellectual disability and multiple defects of the oral cavity and face, but not presenting with agenesis of the corpus callosum and normal kidneys. Maxillofacial surgeons performed two surgeries, with the next one scheduled for 3 months.

Keywords: Accessory gingival frenula; central nervous system (CNS); cleft palate; hypodontia; kidneys; lobulated tongue; oral-facial-maxillary region.

INTRODUCTION

Oral-facial-digital syndrome type I (OFDS1) is a genetic disorder that is lethal before birth in males and affects females. It is a complex condition impacting the oral-facial-maxillary region, as well as the central nervous system (CNS) and kidneys. Oral features include a lobulated tongue, tongue nodules, cleft palate, accessory gingival frenula, and hypodontia. Facial characteristics often involve underdeveloped alae nasi, median cleft or pseudocleft of the upper lip, and micrognathia. Brain MRI is crucial for diagnosis, revealing intracerebral cysts, agenesis of the corpus callosum, cerebellar agenesis, and Dandy-Walker malformation. About 50% of individuals with OFDS1 experience intellectual disability.

While these clinical features resemble those seen in other OFDS types, OFDS1 is distinguishable by its X-linked dominant inheritance pattern and the unique presence of polycystic kidney disease.

The incidence of OFDS is estimated at 1 in 50,000 to 1 in 250,000 live births. Among individuals with cleft lip or palate, the frequency is significantly higher, at 8–16 per 1000.[1] Due to the lethality in males, the overall incidence in females is greater than in males, at a ratio of 2:1.

There are 14 different OFDS types, although some lack clear definitions (Tab.1).[2] Signs and symptoms can vary widely, making diagnosis challenging. OFDS type I is the most common, but generally, all OFDS types are scarce. The condition may also include other features depending on the specific type, such as polycystic kidney disease, seizures, heart defects, and distinctive skeletal traits.[3]

TABLE 1. Types of Oral-facial-digital syndrome (OFDS). Courtesy of Robin Godshalk, MS, MHA

OFDS Type 1 (Papillon-Leage-Psaume syndrome) • Distinctive features include hyperplastic frenula, a lobulated tongue, nasal cartilage hypoplasia, cleft lip and palate, digital malformations, cutaneous milia, hypotrichosis, porencephaly, agenesis of the corpus callosum, and sparse, brittle hair; • Inheritance: X-linked dominant, fatal before birth in males.	**OFDS Type 2 (Mohr syndrome)** • Key features include ocular hypertelorism, micrognathia, and hydrocephalus; • Inheritance: autosomal recessive.
OFDS Type 3 (Sugarman syndrome) • Unique characteristic: “see-saw” wink; • Inheritance: autosomal recessive.	**OFDS type 4 (Baraitser-Burn syndrome)** • Key characteristic: skeletal dysplasia; • Inheritance pattern: Autosomal recessive.
OFDS Type 5 (Thurston syndrome) • Distinctive features include a cleft lip, postaxial polydactyly, and early tooth loss; • Inheritance: autosomal recessive.	**OFDS Type 6 (Varadi Syndrome)** • Key features include syndactyly and/or bifid toes, preaxial or mesoaxial polydactyly, lingual and sublingual hamartomas, hypothalamic hamartoma, cerebellar dysgenesis with the molar tooth sign, and a rare optochiasmatic pilocytic astrocytoma; • Inheritance: autosomal recessive.
OFDS Type 7 (Whelan syndrome) • Distinctive features: facial asymmetry and hydronephrosis; • Inheritance: autosomal dominant or X-linked dominant.	**OFDS type 8, also known as Edwards syndrome** • Key features include short tibiae or radii, along with bilateral preaxial and postaxial polydactyly; • Inheritance: X-linked recessive, not lethal prenatally in either sex.

TABLE 1. Types of Oral-facial-digital syndrome (OFDS). Courtesy of Robin Godshalk, MS, MHA (Continued)

OFDS type 9 (Gurrieri syndrome) • Key features comprise retinochoroidal coloboma, severe microcephaly, Dandy-Walker malformation, retrobulbar cysts, and short stature; • Inheritance: autosomal recessive.	**OFDS type 10 (Figuera syndrome)** • A feature that distinguishes fibular aplasia; • Inheritance: autosomal recessive.
OFDS type 11 (Gabrielli syndrome) • Key features include postaxial polydactyly, ventriculomegaly, microcephaly, alar hypoplasia, a duplicated vomer, cleft ethmoid, and cleft vertebral bodies; • Inheritance: autosomal recessive.	**OFDS type 12 (Moran-Barroso syndrome)** • Key features include myelomeningocele, aqueductal stenosis of the Sylvius aqueduct, and atrioventricular valve dysplasia; • Inheritance: autosomal recessive.
OFDS type 13 (Degener syndrome) • Distinctive features include brachyclinosyndactyly and leukoaraiosis; • Inheritance: autosomal recessive.	

Genetic counselling is essential for diagnosing OFDS1, which follows an X-linked inheritance pattern. Male individuals often face lethality, and the complete OFDS1 phenotype has not been seen in males beyond the perinatal stage. Around 75% of affected females are isolated cases, meaning the condition appears in only one family member, often due to a new (de novo) pathogenic variant. About 25% of females with OFDS1 have a mother who is also affected, since mild cases might only be diagnosed after identifying a severely affected relative. If the proband's mother carries the pathogenic variant, there is a 50% chance of transmitting it with each pregnancy.[3]

Diagnosis is challenging due to the lack of a consensus on diagnostic criteria for OFDS1.

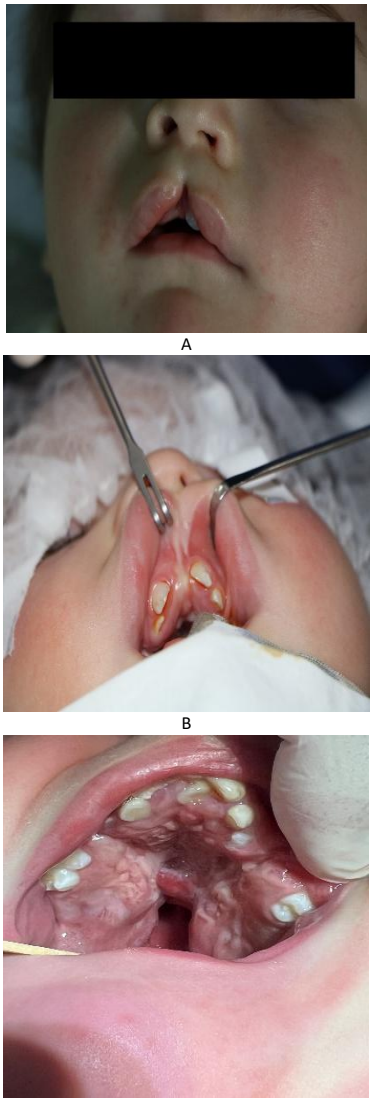
The treatment primarily focuses on symptom management, involving surgery for conditions such as cleft lip/palate, tongue nodules, accessory frenulae, syndactyly, and polydactyly. It also includes speech therapy and intensive care for otitis media when necessary. Additional procedures encompass removing accessory teeth and orthodontic interventions to correct malocclusion. Routine care addresses conditions like seizure disorders, kidney problems, and ADHD.

Surveillance includes yearly audiology assessments and speech development evaluations for children with cleft lip and/or palate. Annual dental check-ups are also recommended. Additionally, ultrasounds of the kidneys, liver, pancreas, and ovaries should be performed regularly.

CASE

The patient is a 1-year, 10-month-old girl born to an uncomplicated fourth pregnancy at 38 weeks via vaginal delivery. Her Apgar score was eight at birth. Immediately after birth, she exhibited an oral cavity defect and swallowing difficulties. A children's maxillofacial surgeon identified several anomalies: a bifurcated upper lip on the philtrum, excess of the skin on the mucosa of the upper lip, and a deformation of the left nasal alae (Fig.1A and 1B). She can open her mouth easily. The oral and nasal cavities are fused due to a gap involving both the soft and hard palates. A 10 mm soft neoplasm is visible inside this gap. The gaps in the palate and upper lip are unusual (Fig.1C). Additionally, bilateral latent gaps are present where the deciduous canines and first molars project onto the hard palate.

FIGURE 1. Case of the 1-year, 10-month-old girl with a bifurcated upper lip on the philtrum, excess of the skin on the mucosa of the upper lip, and a deformation of the left nasal alae



A

B

C

Explanations: A and B. Median cleft of the upper lip before surgery. C. Cleft palate and neoplasm.

The tongue exhibits five large visible neoplasms (Fig.2A). A small tumor is located on the duct of the left submandibular salivary gland. A notch at the tip of the tongue causes a bifurcation of this area. The frenulum of the tongue is broad and dense, attaching from the bifid tip of the tongue to the anterior part of the alveolar mandible. Atypical frenula are also observed in the sublingual area and bilaterally in the upper vestibular fold.

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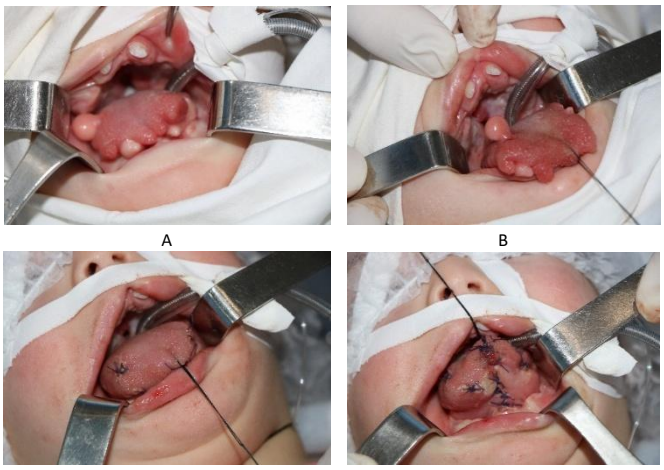
During the initial phase, procedures involved plastic surgery on the lingual frenulum, removal of tongue tumors, and reconstruction of the tongue tip (Fig.2B, 2C, and 2D). Ultrasound scissors were employed to excise five large tumors. The bifid edges of the tongue were smoothed out, greatly enhancing its shape. A small neoplasm on the submandibular salivary duct was not resected. All tissues removed were sent for histopathological analysis, which confirmed the presence of fibroepithelial polyps on the tongue surface.

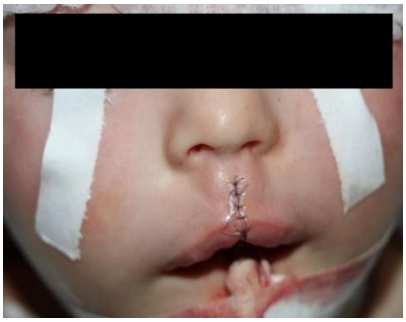
FIGURE 2. Case of the 1-year, 10-month-old girl with the lobulated tongue before, during, and after surgery



Explanations: A. Lobulated tongue before surgery. B and C. Lobulated tongue during surgery. D. Lobulated tongue and tongue frenulum at the end of surgery.

Four months later, a second surgery was carried out to reconstruct the upper lip. A skin segment from the lip frenulum to the mucosal area of the upper lip was excised. The perioral muscle was carefully separated from the skin and mucosa, and the wound was closed in three layers. This procedure successfully restored the anatomical structure of the upper lip (Fig.3).

FIGURE 3. Median cleft of the upper lip after surgery



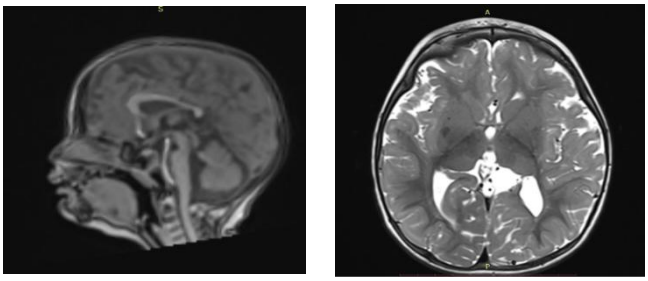
Neurological examination reveals delayed speech, with only 8-10 simple words produced, and no advanced speech skills. Social interactions are minimal. Muscle tone is slightly reduced across all limbs. Deep reflexes are symmetrical and regular. The gait is unsteady, accompanied by mild nystagmus and dysmetria. The IQ, as measured by the Raven test, falls within the 40-59 range.

Abdominal ultrasound results were expected. Ultrasounds of the kidneys and urinary tract also showed normal findings. Syndactyly was noted between the 4th and 5th fingers of the left hand (Fig.4). Hypertelorism was clearly observed. Additionally, a patent foramen ovale was identified.

FIGURE 4. Syndactyly

The brain MRI reveals several abnormalities, including subcortical heterotopia in the right frontal lobe, subependymal heterotopia in the right lateral ventricle, left-sided parahippocampal schizencephaly, a left arachnoidal cyst, and a Dandy-Walker malformation (Fig.5).

FIGURE 5. Brain MRI



Genetic testing was performed using the WES method, revealing a heterozygous likely pathogenic variant in the OFD1 gene. These findings support a diagnosis of X-linked dominant OFDS1. The result was confirmed through an alternative method, specifically Sanger sequencing.

It is advisable to conduct targeted parental testing to determine whether the variant is inherited or de novo, which is essential for effective family genetic counseling. Furthermore, targeted testing should be performed on all affected and at-risk family members when applicable. Genetic counselling, including reproductive options such as prenatal and preimplantation diagnosis if relevant, is also recommended.

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DISCUSSION

OFDS1 is a rare genetic disorder primarily affecting females. Sometimes, OFDS1 is suspected at birth due to characteristic oral, facial, and digital anomalies. In other cases, diagnosis occurs later in childhood or adulthood after polycystic kidney disease is detected.[3] Nearly all individuals with OFDS1 are female, though a few affected males have been reported. Most affected males are described as malformed fetuses born to females with OFDS1. As of now, 234 individuals with pathogenic variants in OFDS1 have been identified.[4]

The clinical features are very distinctive, with oral manifestations appearing in 97-100% of cases. Over 80% of patients exhibit facial abnormalities and digit anomalies, and brain abnormalities are present in more than 65%. Additionally, more than half of the cases show polycystic kidneys.

Our case is quite rare, primarily presenting characteristic oral abnormalities and neurological symptoms. The only significant finding is the absence of kidney problems, while a cardiac defect with a patent foramen ovale has been identified.

Our case also displayed intellectual disability, which is often observed in children with OFDS1. However, MRI results revealed some differences from the typical radiological features of OFDS1.[5,6] While the characteristic Dandy-Walker malformation and intracerebral cysts associated with OFDS1 were present, the corpus callosum appeared normal, unlike in other OFDS1 cases. Additionally, rare features such as heterotopias and schizencephalic porencephaly were identified. Due to these unusual radiological findings, a follow-up MRI is scheduled within a year to monitor disease progression. The facial characteristics commonly associated with OFDS1, including frontal bossing and cleft or pseudocleft of the upper lip, were observed. However, ocular hypertelorism, which is atypical for OFDS1 and more common in OFDS type 2, was also noted in our patient.

Our case management involves neuropsychological support and speech therapy. We also have a planned reconstructive surgery to enhance the palate.

Our plan involves evaluating the patient's speech abilities and IQ, as well as conducting a follow-up MRI to monitor disease progression.

CONCLUSIONS

In all cases of multiple maxillofacial defects, clinicians should consider assessing neurological status and conducting genetic tests to initiate treatment promptly and enhance neurodevelopmental outcomes.

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