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CASE REPORT

Oral-facial-digital syndrome with mesoaxial polysyndactyly, common AV canal, hirschsprung disease and sacral dysgenesis: Probably a transitional type between II, VI, variant of type VI or a new type

Rabah M. Shawky [a,*], Heba Salah Abd Elkhalek [a], Marwa M. Al-Fahham [b], Shaimaa Abdelsattar Mohammad [c], Shaimaa Gad [a]

[a] *Pediatric Department, Genetics Unit, Ain Shams University, Egypt*
[b] *Pediatric Department, Cardiology Unit, Ain-Shams University, Egypt*
[c] *Radio Diagnosis Department, Ain-Shams University, Egypt*

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KEYWORDS

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Polydactyly;
Y shaped metacarpal bone;
Syndactyly;
Common atrioventricular canal;
Hirschsprung disease;
Sacral dysgenesis

Abstract We report a 4 month old male infant, the first in order of birth of healthy first cousin consanguineous parents who has many typical features of oral-facial-digital syndrome type VI (OFDS VI) including hypertelorism, bilateral convergent squint, depressed nasal bridge, and wide upturned nares, low set posteriorly rotated ears, long philtrum, gum hyperplasia with notches of the alveolar borders, high arched palate, and hyperplastic oral frenula. He has mesoaxial and postaxial, polysyndactyly which is the specific feature of OFDS VI, however the cerebellum is normal on MRI brain. He has also some rare congenital anomalies including common atrioventricular canal, hirschsprung disease, and sacral dysgenesis. This patient may have a transitional type between II and VI, a variant of type VI or a new type.

1. Introduction

The Oral-facial-digital syndrome (OFDS) is a heterogeneous group of abnormalities that share anomalies of the oral cavity, face and digits of hands and feet. On the basis of other anomalies of the brain, kidneys, limbs, eyes and other organs, at least 13 subgroups have been described [1].

The various types of OFDS vary in modes of inheritance. Type I is X linked dominant, lethal prenatally in males. Type

* Corresponding author. Tel.: +20 2 22585577.
E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).
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VII is autosomal dominant or X linked dominant. Type VIII is X linked recessive. The other types are autosomal recessive [2].

The classification of OFDS into subtypes is complex as there are many overlapping features, and there are reports of individuals or family members with distinctive findings of more than one variant. This complexity in classification makes the process of discerning new types of OFDS demanding [3]. The finding that primary ciliary defects can cause multiple anomaly syndromes that phenotypically overlap with OFDS suggests that many if not all of OFDS could be caused by mutations in ciliary proteins [4].

Oral-facial-digital syndrome has an estimated incidence of 1 in 50,000–250,000 newborns. Type I accounts for the majority of cases of OFDS and it is rare, the other forms are very rare; most have been identified in only one or in few families [5].

We report an Egyptian patient who has many features of OFDS with cardiac, gastrointestinal and skeletal anomalies. We will try to include him into one of the subtypes of the syndrome.

2. Case report

We report a 5 month old male child, the first in order of birth of healthy first cousin consanguineous Egyptian parents. At the seventh month of pregnancy the mother noticed decreased fetal movements, 4D ultrasound was done for her which showed polyhydramnos. There was no maternal history of teratogenic drugs or radiation exposure. The patient was delivered at full term by cesarean section. His birth weight was 4 kg (at the 75 centile). The patient was referred to the Genetics Clinics, Pediatric Hospital, Ain Shams University because of craniofacial and musculoskeletal abnormalities. There was a past history of colostomy operation at the age of 2.5 months as a first step for correction of Hirschsprung's disease.

On examination, the skull circumference is 37.5 cm (< 5th centile), length is 56 cm (< 5th centile), weight is 3.8 kg (< 5th centile). The patient has an open anterior fontanel 4 × 3 cm, left facial hemihypertrophy. The eyes show hypertelorism, upward slant palpepral fissures, bilateral convergent squint. The patient has depressed nasal bridge, and wide upturned nares. The ears are low set and posteriorly rotated. The mouth shows thin upper and lower lips, long philtrum, gum hyperplasia with notches of the maxillary and mandibular alveolar ridges, high arched palate, and hyperplastic frenula between the upper lip and alveolar margin (Figs. 1–3).

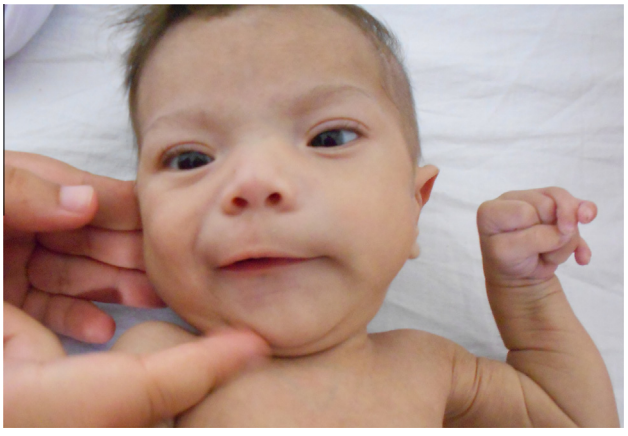

Figure 1 Facial features, and fisted hand of the patient.

Figure 2 Facial features of the patient.

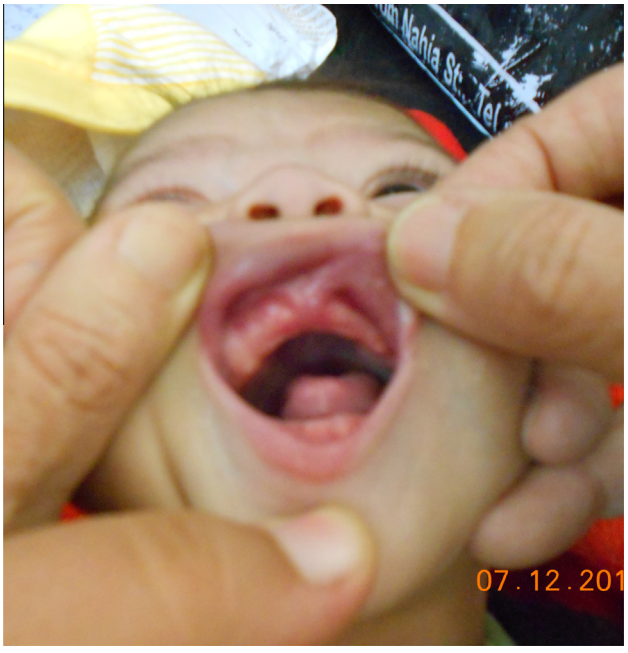

Figure 3 The mouth has gum hyperplasia, high arched palate, and thick bucco alveolar frenula.

The right hand shows postaxial hexadactyly (small extra finger), arachnodactyly, and wide space between 3rd, and 4th fingers, and between 4th, and 5th fingers (Fig. 4). The left hand shows postaxial, and central heptapolydactyly (7 fingers), arachnodactyly, and wide space between 2nd, and 3rd fingers, and between 3rd, and 4th fingers, partial syndactyly between the 4th, and 5th fingers. The 7th finger is short with soft tissue, and skin (no bone) attachment to the hand. There is prominent proximal interphalangeal joints and simian crease. The patient has tightly fisted hands with spastic finger flexors (Figs. 1 and 5). The right foot shows central hexapolydactyly (6 toes) the 4th and 5th toes are short. The extra toe (4th toe) has no nail. There is partial cutenous syndactyly between 3rd, 4th, and 5th toes. The 2nd toe is laterally curved, and the 6th toe is curved

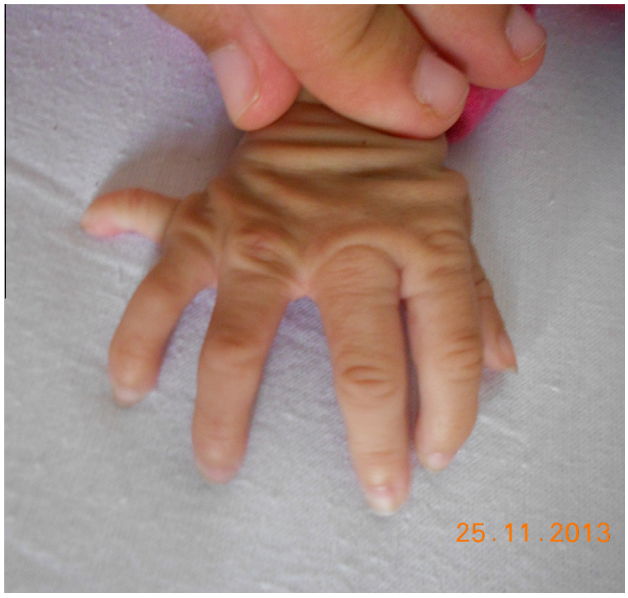

Figure 4 Postaxial polydactyly of the right hand.

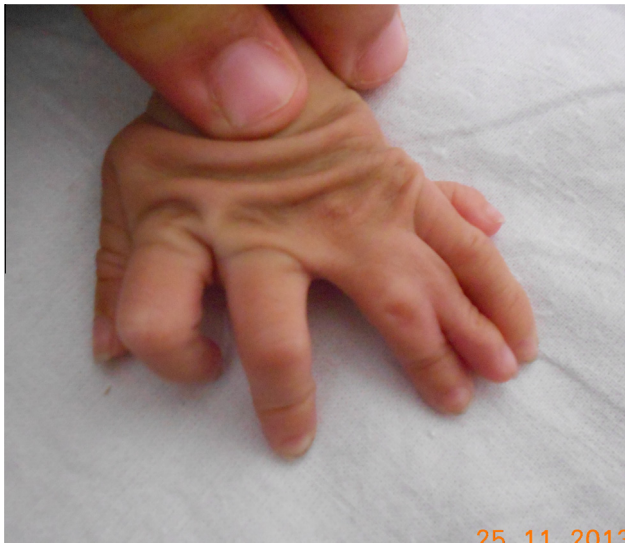

Figure 5 The left hand with postaxial, and central heptapolydactyly.

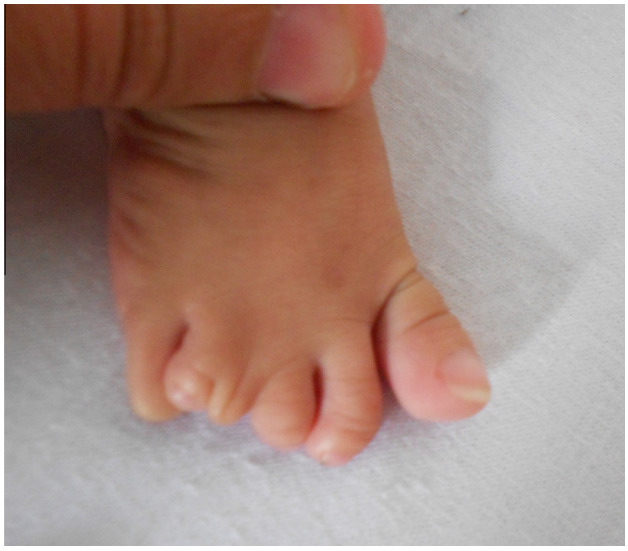

Figure 6 The right foot shows mesoaxial hexapolydactyly (6 toes).

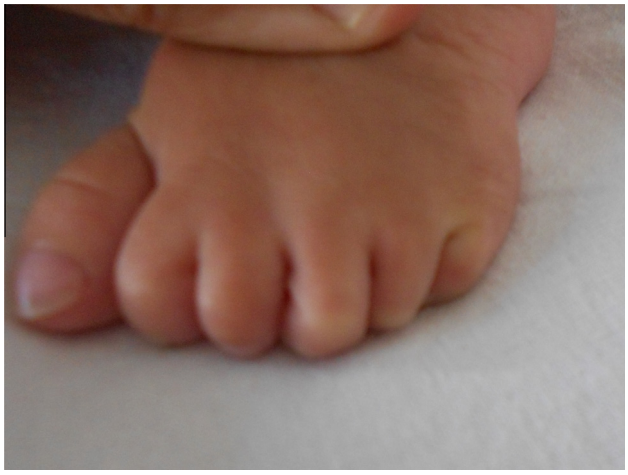

Figure 7 The left foot with post axial hexapolydactyly (6 toes).

medially. The big toe has low insertion (Fig. 6). The left foot shows post axial hexapolydactyly (6 toes), partial cutenous syndactyly between 2nd and 3rd toes. There is medial deviation of the 5th and 6th toes (Fig. 7).

The patient has normal mentality. Cardiac examination shows short harsh pansystolic murmur over the apex. Abdominal examination is normal apart from the opening of colostomy which is present in the left iliac quadrant. Neurological examination shows mild hypotonia.

Skeletal survey shows that the right hand has an extra digit at the ulnar side of the little finger, containing proximal and distal phalanges with no middle phalanx present. The proximal end of the third metacarpal bone shows eccentric expansion at its ulnar side abutting the proximal end of the second metacarpal bone with subsequent saucerization of its cortical outline and incomplete fusion of their cortical outline and medullary cavity. The left hand shows a small poorly formed extra digit seen at the ulnar side of the little finger, there is Y-shaped 3rd metacarpal bone (central and type B postaxial polydactyly). Abnormal small metacarpal is seen insinuated between the previously mentioned Y-shaped metacarpal and the 5th metacarpal. There is faint and small ossific center of the capitate which is small for patient's age with non visualization of the hamate bone (delayed bone age), in spite of the presence of small ossific centers of capitate and hamate on the right side (Figs. 8 and 9).

The right foot X-ray shows an abnormally extra-metatarsal bone insinuated between the 4th and 5th metatarsal bones. It shows distal subluxation. The associated duplicated toe is devoid of bony phalanges, the proximal phalanx of the 4th toe is abnormally elongated (meso-axial polydactyly) (Fig. 10). The left foot X-ray shows 6 metatarsal bones (Fig. 11).

X-ray of the ribs shows gracile appearance with abnormal horizontal orientation. The sacrum has only three sacral

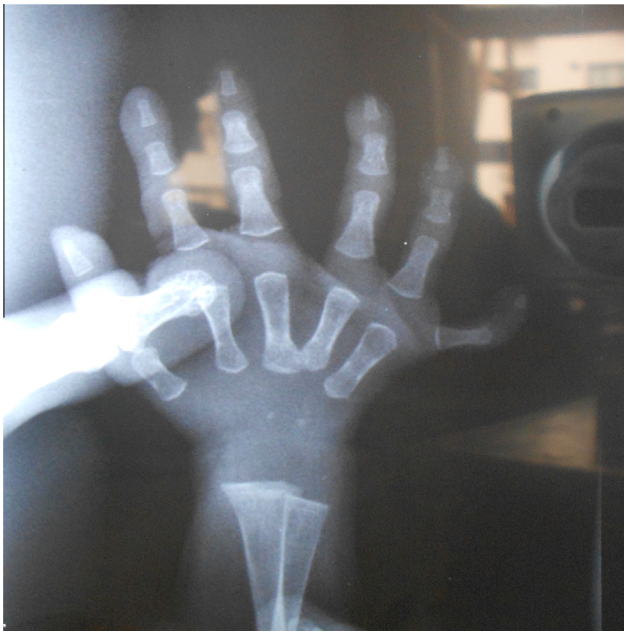

Figure 8 The X-ray of the right hand.

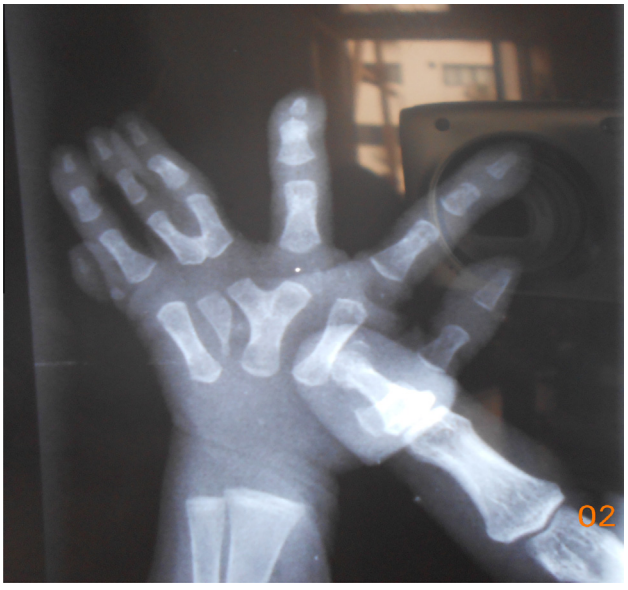

Figure 9 The X-ray of the left hand.

vertebrae, and the third sacral piece shows central notching signifying dysplastic sacrum.

ECHO cardiography showed common atrioventricular canal, dilated main pulmonary artery and its branches.

Pelviabdominal ultrasonography showed a mild increase in renal parenchymal echogenicity bilaterally suggesting mild degree of renal parenchymal disease. MRI brain was normal.

The family history is negative for congenital anomalies or mental retardation, and both parents are 1st cousins.

3. Discussion

Oral-facial-digital syndrome (OFDS) is the collective name of a group of rare inherited syndromes, characterized by

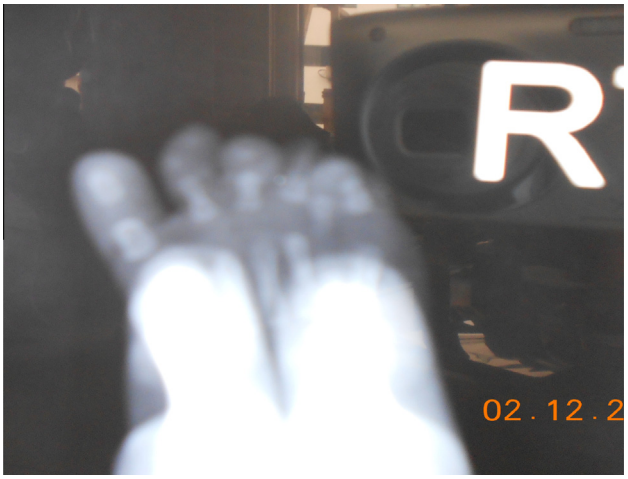

Figure 10 The X-ray of the right foot.

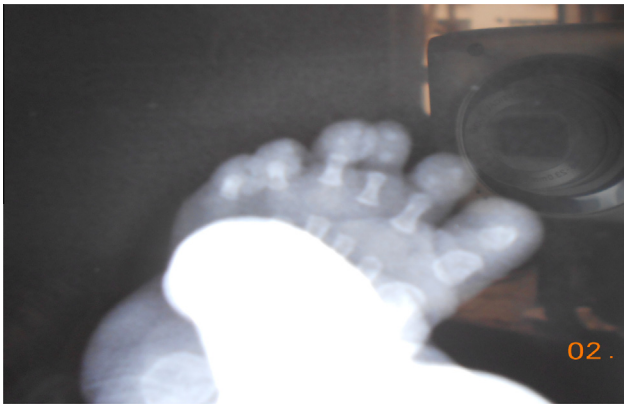

Figure 11 The X-ray of the left foot.

malformations of the face, oral cavity and lower parts of the limbs (hands, and feet) [6]. On the basis of other anomalies of the brain, kidneys, limbs, eyes and other organs at least thirteen subgroups have been described. Also overlapping features between types are common, and appearance of a new feature added to the syndrome is also common. Therefore classification of a specific patient is sometimes difficult [1].

Our patient has oral, facial and digital malformations. The facial features include mainly hypertelorism, bilateral convergent squint, depressed nasal bridge with broad nasal tip and low set ears. However there is absence of cleft lip and abnormal ocular movements. In addition our patient has upward slant palpebral fissures and hemihypertrophy of the face. The oral features in our patient included bucco-alveolar frenula, with high arched palate, gum hypertrophy with marginal grooves. However there are no lingual or sublingual nodules or hamartomas nor cleft palate.

As regards limb anomalies, our patient has six fingers in the right hand (post axial) and seven fingers in the left hand (mesoaxial and postaxial). The feet has six toes bilaterally, mesoaxial in right foot, and postaxial in left foot. Radiology disclosed a Y shaped third metacarpal in the left hand and an excess metatarsal in the left foot.

Polydactyly is present in all patients with OFDS, however mesoaxial polydactyly arising from a Y shaped third metacarpal is the cardinal and most specific feature of OFDS VI [7–10]. So the phenotypic features in our patient are suggestive of OFDS VI mainly because of the presence of bucco-alveolar frenula and central polydactyly of the left hand and the right foot with Y shaped third metacarpal. However some authors reported central polydactyly with forked metacarpals in OFDS II [8,11], or in a transitional type between OFDS II and OFDS VI [12].

Our patient has common atrioventricular canal, and dilated main pulmonary artery and its branches. Congenital heart disease is not common in OFDS, however it has been noted in OFDS II, IV, VI and transitional type between II and VI [13]. There is a report of three fetuses with combination of hydrolethalus, Pallister-Hall syndrome and OFDS VI who had endocardial cushion defect [14,15]. Hsieh and Hou [13] also reported a patient with OFDS with Y shaped fourth metacarpal and endocardial cushion defect with clinical resemblance to OFDS II or VI or an additional type. Also Shawky et al. [12] reported a common AV canal with pulmonary hypertension in a patient with a transitional type between II and VI.

Other congenital anomalies reported in OFDS VI and not detected in our patient include ocular findings particularly colobomas causing severe visual impairment (our patient has bilateral convergent squint). Renal involvement as dysplastic kidneys with preserved renal function is rarely associated with OFDS VI. Our patient has a mild parenchymal renal disease [16].

Absent motor development with ataxia, growth failure, hypogonadism and cryptorchidism, and cognitive impairment are usually reported in OFDS VI, however normal cognitive functions are possible but exceptional. Hypotonia with significant head lag and tightly fisted hands with spastic finger flexors, motor incoordination, delayed verbal skills and primitive fixation responses are also reported in OFDS VI [16]. Our patient has hypotonia and fisted hands with spastic fingers.

Our patient has dysplastic sacrum as well as gracile appearance of the ribs. Vertebral as well as craniofacial anomalies have been reported in patients with OFDS [17–19]. However there are no reports of anomalies of sacrum or ribs in OFDS.

Our patient has Hirschsprung's disease (HSCD) which has been previously described in one patient with pure Joubert syndrome [20], and in one patient with Bardet–Biedle syndrome, and in a patient with OFDS VI. This association does not seem to be accidental or by chance and cilia have been implicated in neural crest development [16].

The causative gene defects for OFDS are unknown except for many patients with type I (CXORF 5 or OFD1), some patients with type II (GL13), and type VI (TMEM216). Recent reviews however, suggest that OFDS are probably related to defects in ciliary structures and function [4,21–24].

Neuroimaging pattern in OFDS VI includes severe hypoplasia of the cerebellar vermis, hypoplastic and dysplastic cerebellar hemispheres, marked enlargement of the posterior fossa, and increased retrocerebellar collection of cerebrospinal fluid, abnormal brain stem and frequently supratentorial abnormalities that include hypothalamic hamartomas. Additionally ascending cerebellar peduncles and fused thalami have been reported. Molar tooth sign is also a mandatory diagnostic criterion of OFDS VI, and its presence allows its differentiation from other types [16]. Also Reuss et al. [25] estimated that one third to one half of patients with OFDS is mentally defective. The remainders have average or better intellectual development. However some individuals are reported with normal mentality. To our surprise MRI of the brain is normal in our patient, and his mentality is normal.

All the above mentioned findings make it difficult for us to delineate the subtype of OFDS as it does not conform to type VI due to the absence of MRI findings. Most probably our patient is a transitional type between II and VI, a variant of type VI or a new type.

To conclude, since differentiation between subtypes of OFDS is based mainly on clinical findings and neuroimaging and as significant phenotypic differences have been observed even within families, this classification should be viewed as tentative until more definitive methods are available. Although OFDS is rare in Egypt, an early diagnosis is necessary for genetic counseling and early symptomatic and supportive therapy as some patients present with episodic tachypnea [26].

Conflict of interest

The authors declare no conflict of interest.

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