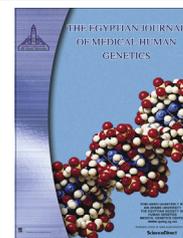




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CASE REPORT

Oral–Facial–Digital Syndrome type VI with self mutilations



Rabah M. Shawky ^{a,*}, Heba Salah Abd-Elkhalek Elabd ^a, Shaimaa Gad ^a,
Radwa Gamal ^a, Shaimaa Abdelsattar Mohammad ^b

^a Pediatric Department, Genetics Unit, Ain Shams University, Egypt

^b Radio Diagnosis Department, Ain Shams University, Egypt

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Molar tooth sign;
Peudocleft lip

Abstract We report the case of a 2.5 year old female, 2nd in order of birth of 1st cousin consanguineous marriage, with the typical features of Oral–Facial–Digital Syndrome type VI (OFDS VI) including midline pseudo cleft upper lip, sublingual nodule, molar tooth sign by MRI brain, bilateral mesoaxial polydactyly (hexadactyly), and developmental delay. The patient had self mutilations which was not reported before in OFDS VI except once.

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1. Introduction

Oral–Facial–Digital Syndrome type VI (OFDS VI) or Varadi–Papp syndrome (OMIM 277170) is a rare autosomal recessive syndrome [1], belonging to Joubert Syndrome and Related Disorders (JSRD) [2]. The first description of the Oral–Facial–Digital Syndrome (OFDS) was published six decades ago [3]. So far, 13 subtypes have been described according to the mode of inheritance and the involvement of the other organs and systems (eye, brain, tibia, skeletal changes, and presence of millia) [4]. However, classification into the subtypes is not always easy or clear, and additional subgroups have been proposed [5–7].

Joubert Syndrome (JS) is a rare midbrain–hindbrain malformation with an estimated prevalence between 1:80,000

and 1:100,000 live births [2]. The characteristic neurological signs of JS include muscular hypotonia (most prominent during infancy), cerebellar ataxia (typically developing later), ocular motor apraxia, and an irregular breathing pattern in the neonatal period [8]. Additionally, cognitive functions are impaired in almost all patients [9]. The so-called molar tooth sign (MTS) is a consistent and pathognomonic neuroanatomical feature of JS [10].

At present, causative mutations in 13 genes have been associated with Joubert Syndrome and related disorders (JSRD) (JBTS1/INPP5E, JBTS2/TMEM216, JBTS3/AHI1, JBTS4/ NPHP1, JBTS5/CEP290, JBTS6/TMEM67, JBTS7/RPGRI1L, JBTS8/ARL13B, JBTS9/CC2D2A, JBTS10/OFD1, JBTS12/KIF7, JBTS13/TCTN1 and the TCTN2 gene) [11]. Additionally, heterozygous, not causative mutations have been found in the JBTS11/TTC21B gene [12]. All JSRD genes encode for proteins of the primary cilium [13].

Based on the extent of multiorgan involvement, six phenotypes of the JSRD spectrum have been recently defined: (1)

* Corresponding author. Tel.: +20 2 22585577.

E-mail address: shawkyrabah@yahoo.com (R.M. Shawky).

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“pure” JS (purely neurological without retinal, renal, or liver involvement); (2) JS with ocular defect (neurological features associated with retinal dystrophy); (3) JS with renal defect (neurological features with renal involvement, mostly nephronophthisis); (4) JS with oculorenal defects (association of neurological signs with both retinal dystrophy and nephronophthisis); (5) JS with hepatic defect (neurological features with congenital liver fibrosis); and (6) JS with Oral–Facial–Digital defects [14]. The sixth JSRD phenotype represents the Oral–Facial–Digital Syndrome type VI (OFDS VI). This characteristic multiple malformation syndrome was first identified in 1978 by Váradi and Papp in a male gypsy child, and published in 1980. Subsequently, the syndrome has been quoted as Váradi–Papp Syndrome [15].

Oral–Facial–Digital Syndrome type VI (OFD6) is a rare autosomal recessive disorder distinguished from other Oral–Facial–Digital Syndromes by metacarpal abnormalities with central polydactyly and by cerebellar abnormalities [16].

Here we report the case of a female child with OFDS most probably type VI with self mutilations after taking consent of the parents.

2. Case report

A 2.5 year old female, 2nd in order of birth of 1st cousin consanguineous marriage. Her father was 36 years old, and her mother 26 years. Her birth weight was 3 kg after simple vaginal delivery for full term pregnancy which was complicated by meconium aspiration. There was no history of drug intake by the mother. The patient was referred to the Genetics Clinic, Pediatric Hospital, Ain Shams University complaining of global developmental delay since birth and self mutilations in the form of lip and tongue biting.

Since the age of 6 months, the mother noticed that her daughter was delayed in both motor and mental development. At the age of 1 year, the patient developed one attack of tonic clonic convulsions associated with oculogyric crisis upon which she was admitted to the hospital for 5 days. At the age of 1.5 years she developed self mutilation behavior in the form of lip and tongue biting. At the age of 2 years she was admitted to the hospital for tonic clonic convulsions with oculogyric crisis and then discharged on anti-epileptic oral treatment. At the age of 2.5 years she was admitted again to hospital for convulsions in the form of fixed eye gaze, and abnormal movements in the form of lip biting and respiratory distress. Our patient had delayed motor, mental and speech development. She had a previous sib who died at the age of 4 days with congenital heart, absent lower jaw and hepatosplenomegaly with no definite diagnosis. Both parents were normal.

On examination, her weight was 11 kg (5th percentile), her length was 85 cm (25th percentile), her span was 71 cm and her skull circumference was 48 cm (50th percentile). The patient had hairy broad forehead, partial synophrys, narrow palpebral fissures, hypertelorism, bilateral low set ears, central pseudo-cleft upper lip, self injury in lower lip due to continuous biting (Fig. 1), decayed malformed teeth with brownish discoloration, and sublingual nodule on the right side of the tongue measuring 1 cm × 1 cm (Fig. 2). There was bilateral mesoaxial polydactyly (hexadactyly) (Fig. 3) in both hands, and left complete simian crease. The back, abdominal, genital and cardiac

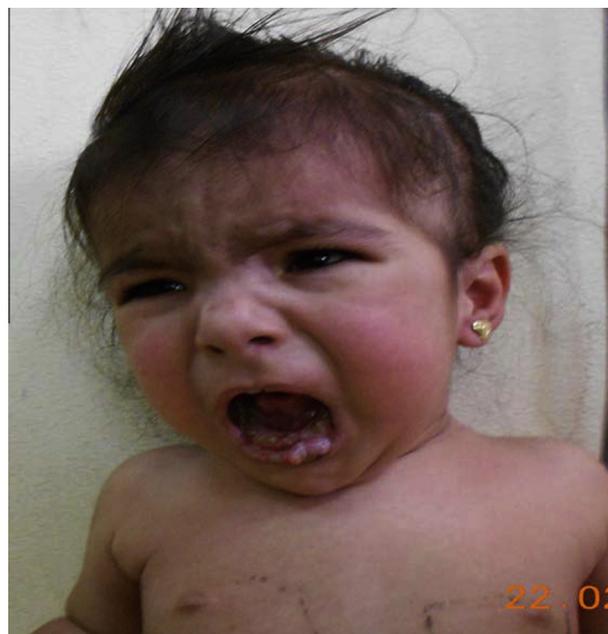


Figure 1 Facial features of the patient with evidence of self mutilations of lower lip and tip of the tongue.

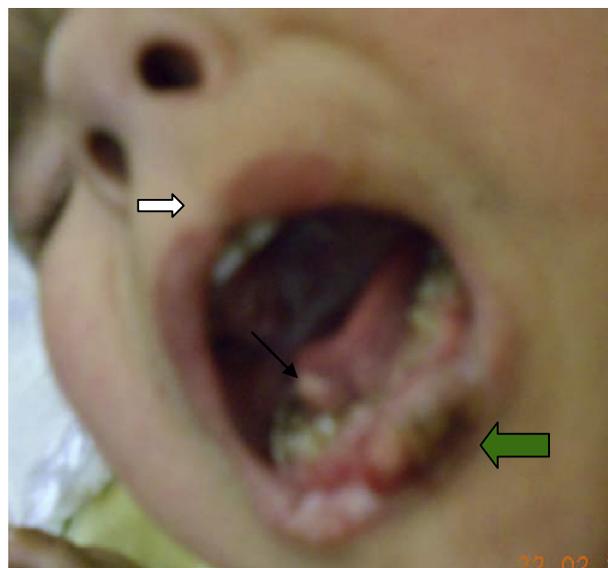


Figure 2 Sublingual nodule on the right side of the undersurface of the tongue (black arrow), self biting of lower lip (green arrow), and pseudo cleft upper lip (white arrow).

examinations were normal. Neurologic examination demonstrated hypotonia.

Abdomino-pelvic ultrasonography, ECHO cardiography, and chest X ray were normal. Extended metabolic screen was normal. Plain X-ray of both hands demonstrated mesoaxial polydactyly with soft tissue fusion seen at the proximal aspect of the third and fourth fingers on the right side (incomplete simple syndactyly) (Fig. 4). MRI brain showed molar tooth sign (MTS) (Fig. 5).



Figure 3 Mesoaxial hexadactyly of left hand.

3. Discussion

We report the case of a 2.5 year old female patient with features of OFDS type VI. Common facial features usually reported in these patients include cleft lip, broad nasal tip/bridge, hypertelorism, epicanthic folds, abnormal eye movements, strabismus [1], and low set ears [17]. Oral findings commonly include lingual or sublingual nodules [18], oral frenula [1] and highly arched and/or cleft palate [18,19].

Our patient had sublingual nodules, high arched palate, decayed malformed teeth, midline pseudo cleft upper lip, hypertelorism and low set ears. In addition, she had a broad forehead, partial synophrys, and narrow palpebral fissures. What is striking in our patient is the evidence of self mutilations in lower lip and tip of the tongue due to continuous biting of these parts by the patient which started at the age of 1 year to one and half year.

Wey et al. [20], reported a patient with OFDS VI with characteristic multiple midline defects including, median cleft lip and palate, lingual cleft with nodules and midline brain anomalies. In addition the case is uniquely associated with the presence of midline craniosynostoses. Self mutilations have not been reported in OFDS. However some Joubert Syndrome patients develop self-injurious behavior such as self mutilation, head banging and self biting [21], and OFDS VI is currently classified as one of the Joubert Syndrome related disorders [2].

In our patient, there is absence of cleft palate, oral frenula, epicanthic folds, strabismus and abnormal eye movements usually reported in OFDS VI [1]. As regards limb anomalies, our patient had mesoaxial polysyndactyly in both hands with normal feet. In OFDVI polydactyly is present in almost all patients and its most characteristic forms are a mesoaxial hand polydactyly arising from an additional central metacarpal bone or from a bifid or Y-shaped third metacarpal bone [20], and a preaxial foot polysyndactyly with bifid hallux [1]. In our patient there was absence of metacarpal and foot abnormalities. Mesoaxial hand polydactyly is extremely rare and specific for OFD VI among the JSRD phenotypes, but not consistent in OFD VI because different forms of polydactyly have been previously reported [18,22,23].

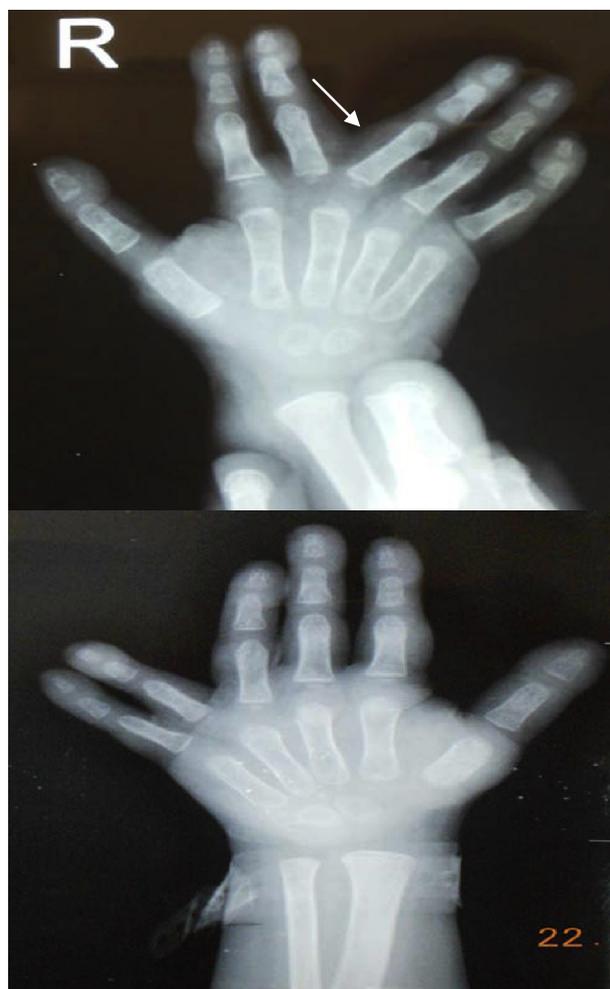


Figure 4 Plain X-ray of both hands: Mesoaxial polydactyly is noted bilaterally with soft tissue fusion seen at the proximal aspect of the third and fourth fingers on the right side (arrow) (incomplete simple syndactyly), and short phalanges.

Our patient had normal ECHO cardiography and abdomino-pelvic ultrasonography. Congenital heart disease is not common in OFDS, however it has been noted in OFDS VI [24]. There is a report of three fetuses with combination of hydroletharus, Pallister-Hall syndrome and OFDS VI who had endocardial cushion defect [25,26]. Hsieh and Hou [24] 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. [27] reported a common AV canal with pulmonary hypertension in a patient with OFDS transitional type between II and VI and reported another patient [7] with hirschsprung disease, sacral dysgenesis, common atrioventricular canal, dilated main pulmonary artery and its branches probably a transitional type between II, VI, variant of type VI or a new type.

In previous reports, involvement of eyes and kidneys had only been reported in four OFDVI patients [23,28]. Other congenital anomalies reported in OFDS VI and not detected in our patient include ocular findings particularly colobomas causing severe visual impairment [29].

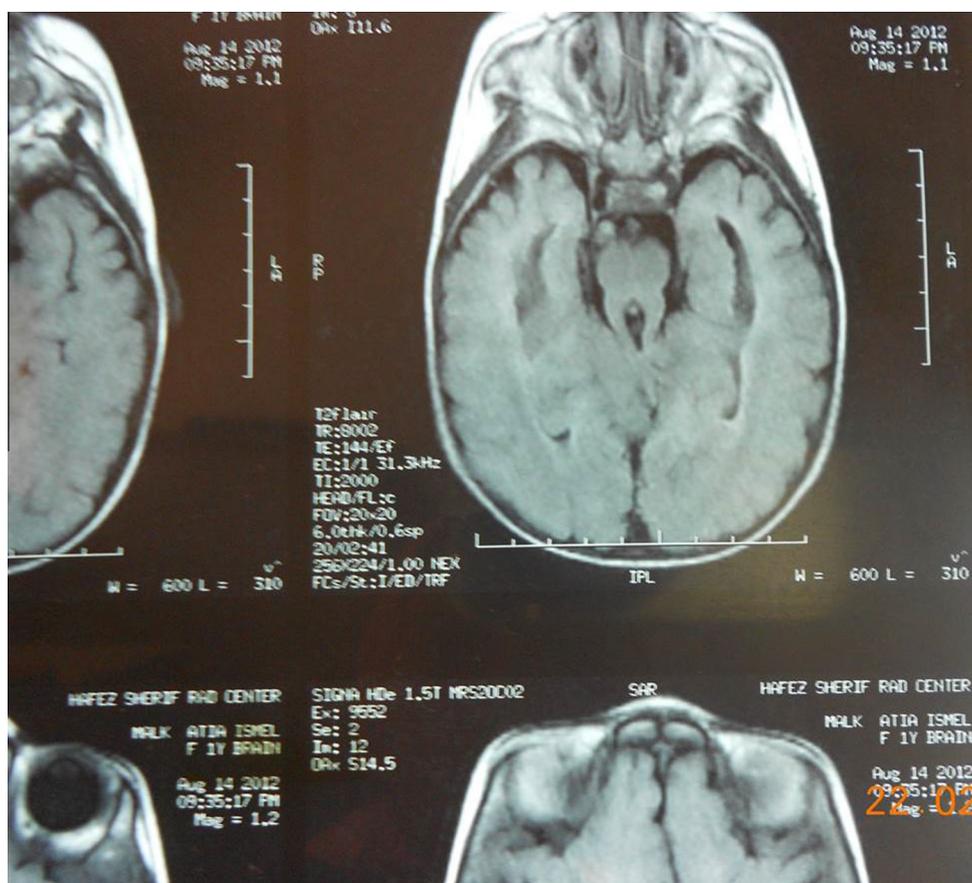


Figure 5 MRI brain showing molar tooth sign.

Our patient had delayed motor, mental and speech development. Developmental delay and/or cognitive impairment of variable degrees are present in almost all patients with JSRD [9,30]. In OFDS VI, developmental delay and/or cognitive impairment were considered to be key features in the original report [31]. Normal cognitive functions have occasionally been reported [1]. Our patient suffered tonic clonic convulsions, and neurologic examination demonstrated hypotonia. Episodic tachypnea, hypotonia and/or ataxia, growth failure, and deafness were often reported [1]. Our patient had also a history of episodic respiratory distress. Our patient had normal genitalia although hypogonadism and/or cryptorchidism with micropenis were also noticed in OFD VI [1].

The presence of MTS in MRI, which is present in our patient, is mandatory to diagnose OFD VI. MTS has not been described in any other type of Oral-Facial-Digital Syndrome and its presence allows the differentiation of OFD VI from other types [32].

Our patient presented with all features consistent with the diagnosis of OFDS VI. Based on the literature there is diagnostic criteria in OFDS VI: (1) tongue hamartoma(s) and/or additional frenula and/or upper lip notch. (2) Mesoaxial polydactyly of one or more hands or feet. (3) Hypothalamic hamartoma [32].

Early accurate diagnosis of OFD VI is necessary for proper genetic counseling and prognosis. Prenatal diagnosis of pregnancy at risk is possible [33]. With the advent of MR imaging,

the diagnosis of JSRD can be made prenatally before 24 weeks' gestation [34].

There is consanguinity between the parents but there is no family history of a similar condition. However, our patient had sib death with absent lower jaw and congenital heart. Because of the variable clinical expression, even intrafamilial, the attribution of the correct diagnosis among the several forms of OFDS is often difficult [35]. Considering the broad spectrum of anomalies of various organs, it has been proposed that OFD syndromes belong to the group of ciliopathies [4].

To date no major gene has been consistently associated with OFD VI and the mutations in the TMEM216 gene remain occasional [32]. The diagnosis of OFD VI is still currently based on clinical findings and neuroimaging [36]. Neuroimaging pattern in OFDS VI includes, in addition to the molar tooth sign, 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 [32].

To conclude: Although OFDS is a rare disorder, we reported in addition to the child in this case report, two previous children with OFDS [7,27], in about 6 months in our hospital. It is evident that features of various types overlap significantly and new subtypes need to be added. Also molecular diagnosis will help in delineating various types of OFDS.

Conflict of interest

The authors declare no conflict of interest.

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