Orocardiodigital syndrome: an oral-facial-digital type II variant associated with atrioventricular canal

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Abstract

We report on a patient with a constellation of anomalies including hamartomas of the tongue, polysyndactyly, and atrioventricular canal. A similar association has been previously described by Orstavik *et al* in two sibs. The clinical spectrum of the oral-facial-digital syndrome (OFDS) type II includes all these features. In particular, congenital heart defect, mainly atrioventricular canal, has been described in a few cases. It has been previously suggested that these latter patients may be affected by a variant of OFDS type II. We propose to distinguish this orocardiodigital variant and point out the association of the syndrome with atrioventricular canal.

(J Med Genet 1996;33:416-418)

Key words: oral-facial-digital syndrome; congenital heart defect; atrioventricular canal.

The oral-facial-digital syndromes (OFDS) are heterogeneous conditions with overlapping phenotypic manifestations and difficult clinical classification.¹ OFDS type II (Mohr syndrome) is an autosomal recessive condition characterised by midline cleft of the upper lip, hamartomas of the tongue, hallucal polysyndactyly, and postaxial polydactyly of the hands.² Congenital heart defect (CHD) has been described in a few patients with OFDS II.^{3,4} It has been suggested that this association of anomalies may represent a distinct OFDS.⁵ In addition, Orstavik *et al*⁶ reported two sibs with CHD, hamartoma of the tongue, and polysyndactyly without the facial dysmorphism characteristic of OFDS.

We report a female patient with a constellation of anomalies similar to that observed by Orstavik *et al*.⁶ This observation, together with other known patients, suggests a striking association of OFDS II and atrioventricular canal.

Case report

The proband, a girl, is the first child of healthy, non-consanguineous parents. At the time of delivery the mother was 26 years old and the father 30 years. The family history was unremarkable. The mother's second pregnancy resulted in a healthy boy.

The baby was born vaginally at term after an uncomplicated pregnancy. Birth weight was 3350 g, length 50 cm, and OFC 35 cm. Apgar scores were 8 and 9 at one and five minutes.

A CHD was diagnosed in the first months of life and echocardiography showed a partial atrioventricular canal (AVC) with a cleft of the mitral valve, and a common atrium with a septum between the pulmonary veins and the mitral valve (cor triatriatum type). Oral examination showed three polyps located on the dorsum and lateral rims of the tongue. There was no tongue lobulation or oral cleft. In addition, the baby had postaxial polydactyly and cutaneous syndactyly of fingers 2 and 3 on the left hand and bilateral hallucal polysyndactyly. An imperforate hymen was also noted.

The girl was re-evaluated at 6 years of age. Her weight was 22.4 kg (75th centile), height 129 cm (>97th centile), and OFC 53 cm (75th

Figure 1 Front (A) and lateral (B) facial appearance of the patient at 6 years of age.

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Received 19 October 1995
Revised version accepted for
publication 8 January 1996

Figure 2 Clinical (A) and x ray (B) appearance of hallucal duplication.

Table 1 Clinical features of patients with specific association of hamartoma of the tongue, polydactyly, and congenital heart defect

Clinical feature	Orstavik et al ⁶		Present case
	Case 1	Case 2	
Oral			
Tongue hamartoma	+	+	+
Cleft tongue	–	–	–
Oral frenula	–	–	–
Median cleft lip	–	+	–
Cardiac			
Atrioventricular canal	+	–	+
Common atrium	–	–	+
Aortic coarctation	+	+	–
Digital			
Hand polydactyly	+	+	+
Hand syndactyly	+	–	+
Hallucal duplication	+	–	+

centile). The facial appearance was mildly dysmorphic including hypertelorism (inner canthal distance 3.5 cm =>97th centile) and retrognathia (fig 1A and B). The oral polyps were removed at 7 months of age. On histological examination they were hamartomas. Dental malposition was noted. The extra finger had also been operated on. The feet showed hallucal duplication, more evident on the left where a varus deformity of the big toe (fig 2A) was also present. Intellectual development was normal. Language performance was also considered normal, but speech therapy had been

Table 2 Congenital heart defects in the OFDS

Genetic condition	Congenital heart defect	Reference
OFDS II	AVC, common atrium, truncus arteriosus	3
	VSD, mitral atresia	4
	AVC	4
	AVC, aortic coarctation	6
	Aortic coarctation	6
OFDS II/VI	AVC, common atrium	Present case
	AVC	13
OFDS IV	Common atrium, VSD	22
	Cor triloculare	10
	Tetralogy of Fallot	23
	ASD, mitral valve stenosis	24
OFDS VI	AVC, aortic coarctation	9
	Aortic stenosis	8

carried out because of velopharyngeal incompetence. CHD was successfully repaired at 4 years of age.

X ray examination showed a postaxial extra finger on the left and hexodactyly of both feet caused by hallucal duplication. The phalanges of the big toe were duplicated and deviated on the left, while only the distal phalanx was duplicated on the right (fig 2B). No additional skeletal anomalies were seen. Ophthalmological and audiometric evaluations were unremarkable. Cerebral, abdominal, and pelvic ultrasound examinations indicated no abnormalities. Standard chromosome analysis of blood lymphocytes disclosed a normal female karyotype.

Discussion

Clinical manifestations in our patient strikingly overlap those of case 1 of Orstavik et al,⁶ while case 2 had a less severe phenotype. Interestingly, an AVC was present in our patient and in the first sib of Orstavik et al.⁶ The features of these three cases are summarised in table 1.

Hamartoma of the tongue and polysyndactyly of the hands and feet are clinical features of OFDS II, IV, VI, and VIII,⁵ while CHDs have been reported in OFDS II, IV, and VI.^{3 4 7–9} A diagnosis of OFDS IV or VI can be excluded in our patient. The anomalies found in OFDS IV include mesomelic short limbs with tibial dysplasia, cleft palate, and cerebral anomalies,¹⁰ while patients with OFDS VI have cerebellar malformation and central polydactyly of the hands.^{8 9} Another genetic condition with oral and digital involvement, the so-called “postaxial polydactyly-dental-vertebral syndrome”,¹¹ has been excluded in our girl as neither dental nor vertebral anomalies were present. However, the clinical features found in our patient and in those reported by Orstavik et al⁶ resemble the oral and digital malformations characteristic of OFDS II, although the facial component is not obvious and CHD is present as an additional abnormality. Clinical heterogeneity of OFDS II has supported the existence of different subtypes,^{12 13} including a variant with central nervous system involvement and a transitional type with overlapping features of types II and VI. Cardiac malformations can be associated with OFDS,^{3 4 7–9 13} although it appears that AVC occurs predominantly in OFDS II (table 2). In fact, four out of the six patients labelled as OFDS II with CHD have in effect AVC (present case).^{3 4 6} Detailed clinical features of these patients are

Table 3 Clinical features of patients with oral-facial-digital syndrome II and congenital heart defect

Clinical features	Cordero and Holmes ³	Iaccarino et al ⁴	
		Case 1	Case 2
Tongue hamartoma	–	–	–
Cleft tongue	+	–	–
Median cleft lip	+	+	–
Epiglottis anomaly	+	–	–
Congenital heart defect	+	+	+
Hand polydactyly	+	+	+
Hallucal duplication	+	+	+

shown in table 3. None of them was reported to have hamartomas of the tongue. Interestingly, AVC was also present in a fetus with transitional OFDS II/VI.¹³

Based on our results, we propose that OFDS II can be further split to include an orocardiodigital syndrome with hamartoma of the tongue, polysyndactyly of the hands and feet, and CHD, namely AVC. It is well known that AVC occurs as an isolated malformation, but can be associated with non-cardiac anomalies. Although it is occasionally found in children with various aneuploidies and mendelian syndromes, a non-random association of AVC has been noted with specific genetic conditions, including trisomy 21,¹⁴ deletion 8p,¹⁵ 3C syndrome,¹⁶ and Noonan syndrome.¹⁷ In addition, AVC is commonly observed in patients with heterotaxia¹⁸ and Ellis-van Creveld syndrome.^{19,20} In particular, children with Ellis-van Creveld syndrome present a type of AVC consisting of a single atrium and partial AVC similar to that reported in the present case and in patients with OFDS II (table 2). Interestingly, AVC is also found in another syndrome with polydactyly of the hands and feet, the Kaufman-McKusick syndrome.²¹

In conclusion, although CHD is not common in OFDS, the existence of a subtype with cardiac involvement is emerging from personal observation and previously reported patients. This orocardiodigital syndrome showing a high frequency of AVC suggests a non-random association of this pattern of malformations. In addition, a specific link between AVC and genetic syndromes with polydactyly is suspected.

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