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Case Report

Cystic renal disease presenting in pregnancy: a novel presentation of oral-facial-digital syndrome type 1

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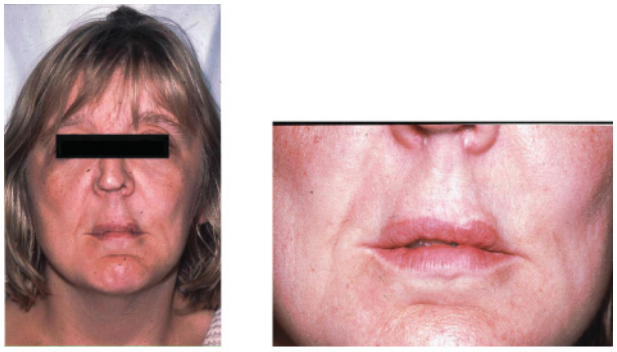
Introduction

Oral-facial-digital (OFD) syndrome type 1 is a rare X-linked dominant condition caused by mutations in the *OFD1* gene on Xp22, which is lethal in affected males [1]. Females display a highly variable expressivity of polycystic kidneys, oral, facial and digital abnormalities. Structural central nervous system anomalies may occur and some affected females have intellectual disability. The diagnosis is usually made in childhood, although occasionally the condition may not be identified until later adulthood. We describe an unusual presentation of cystic renal disease in a 34-year-old pregnant woman, who was subsequently found to have OFD syndrome type 1.

Case report

A 34-year-old lady was referred at 16-week gestation to the combined renal obstetrics service, with deteriorating renal function, urea 7.8 mmol/l and creatinine 174 μmol/l. She was hypertensive (158/98 mmHg), 24-h urine protein excretion was 0.23 g/24 h and creatinine clearance 36 ml/min. She was taking no regular medications. She had been normotensive at booking (126/85 mmHg), urinalysis had been normal and serum creatinine was 120 μmol/l. This was her second pregnancy; her first pregnancy 2 years back had been complicated by the development at 35-week gestation of hypertension (167/102 mmHg), proteinuria (unquantified), renal impairment (creatinine 123 μmol/l) and intrauterine growth retardation. She had an emergency caesarean section at 35 weeks following prolonged spontaneous rupture of membranes and delivered a healthy male child. The patient was discharged home with a presumptive diagnosis of self-limited pre-eclampsia on atenolol but with no arrangements for nephrology follow-up. On discharge, serum creatinine was 190 μmol/l; this fell to 118 μmol/l during follow-up and urine dipstick showed 1+ protein. No renal imaging or further investigations were performed at that time.



1a 1b

Fig. 1. Craniofacial anomalies of oral-facial-digital syndrome type 1. The patient had scars from previous corrective surgery for a cleft lip and palate and hypoplastic alae nasi.

The patient had undergone several corrective operations in childhood for congenital cleft lip and palate. Four years back, she had been diagnosed with infiltrating ductal carcinoma grade III and high-grade ductal carcinoma *in situ* of the right breast. She had a right mastectomy with adjunctive radiotherapy and chemotherapy. She remained in complete remission. Her parents, two sisters, brother and her son had no oral abnormalities and there was no family history of renal disease. Her parents were non-consanguineous. She worked as a hospital social worker.

On examination, she exhibited hypernasal speech and there were scars from previous corrective surgery to the cleft lip and palate. Facial features included a pinched nose with broad prominent nasal root and hypoplastic alae nasi. Intraoral examination revealed a lobulated tongue, multiple intraoral frenulae and repaired clefts (Figure 1a–c). Examination of the hands and feet revealed clinodactyly of the

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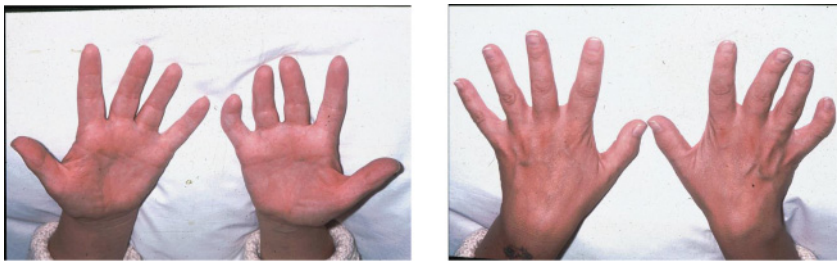

2a 2b

Fig. 2. Limb anomalies of oral-facial-digital syndrome type 1. The patient had brachydactyly, variable skin syndactyly and clinodactyly of the right little finger.

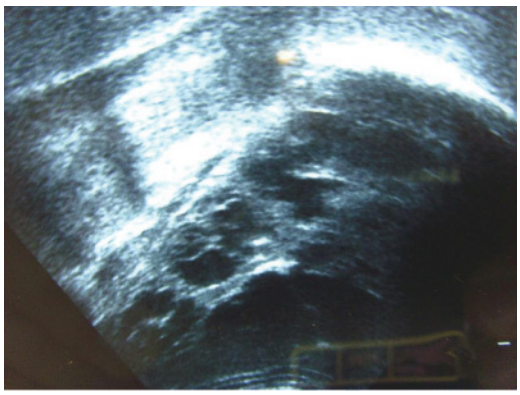

Fig. 3. Renal ultrasound scan demonstrated multiple renal cysts.

left fifth finger, brachydactyly and soft tissue syndactyly of the fingers and toes (Figure 2a and b).

Abdominal ultrasound scan demonstrated bilateral renal enlargement, with each kidney measuring 17 cm pole to pole and containing multiple cysts (Figure 3). There were no cysts in the liver or pancreas. Due to the constellation of clinical features the patient was referred to the clinical geneticists, who confirmed a diagnosis of OFD syndrome type 1. The absence of any relevant family history suggests that the condition had arisen through spontaneous mutation in the *OFD1* gene.

Following presentation she was started on methyldopa and her blood pressure remained under satisfactory control up until 35-week gestation, when she developed worsening hypertension (150/91 mmHg), progressive renal impairment (creatinine 200 μmol/l) and increasing proteinuria (0.6 g/24 h). Fetal growth had remained within normal limits. An elective caesarean section was performed at 35 weeks of gestation and a healthy baby boy was delivered.

Over the proceeding 5 years, there was a progressive decline in renal function despite tight blood pressure control and she is now planning a pre-emptive living donor renal transplant.

OFD syndromes are a heterogeneous group of developmental syndromes characterised by limb malformations and craniofacial anomalies [2]. The features in the hands (and feet) include brachydactyly, soft tissue syndactyly, clinodactyly, pre- or postaxial polydactyly and bifid halluces. Craniofacial anomalies include facial asymmetry, hypertelorism, midline cleft or notch of the upper lip, cleft palate, lobulated tongue, tongue cysts and excess oral frenulae. Characteristic radiological features include irregular patterns of radiolucency and/or spicule-like formation in metacarpals and phalanges.

The classification of OFD syndromes is based on the phenotype and mode of inheritance, and 11 different types have been described. In addition to the limb and craniofacial malformations, additional anomalies may segregate with specific OFD syndromes. For instance, OFD types Mohr (II) and Varadi (VI) are associated with cerebellar anomalies, while OFD type 1 is associated with the development of cystic renal disease [3–6]. The pattern of inheritance of OFD syndromes also varies; OFD types 2, Mohr (II) and Varadi (VI) are autosomal recessive malformation syndromes, while OFD type 1 is inherited as an X-linked dominant disease.

The patient we describe had a combination of limb and craniofacial anomalies, along with cystic kidney disease, consistent with a diagnosis of OFD type 1. OFD type 1 (MIM#311200) is the commonest OFD syndrome and was first described by Papillon-Léage and Psaume in 1954 [7]. It has an estimated incidence of 1 in 50 000 to 1 in 250 000 live births and occurs in diverse racial backgrounds [8]. OFD type 1 can be easily distinguished from other OFD syndromes by its X-linked dominant inheritance and the development of polycystic kidneys, which seem to be specific to OFD type 1 [9–11]. The reported incidence of cystic kidney disease in OFD type 1 varies between 15 and 50% [4,8,12,13]. Renal failure necessitating dialysis or transplantation either in childhood or early adulthood can, however, dominate the clinical course of the disease. Phenotypic differences in OFD type 1 are not limited to the expression of cystic kidney disease. Differences have also been described in the expression of cleft palate and CNS abnormalities [8]. Such differences in the level of expressivity are seen both across and within affected families and might be explained by different degrees of somatic mosaicism resulting from non-random X-chromosome inactivation [14].

Approximately 75% of OFD type 1 cases are sporadic arising from spontaneous mutation in the *OFD1* (formerly *Cxorf5*) gene (as in this case). Twenty-nine different mutations in *OFD1* have been described, eleven of these by a collaborative French and Belgian study of sixteen families [15]. Most of these mutations lead to a premature truncation of the protein in its N-terminal region and are, therefore,

predicted to act with a loss of function mechanism. Slight phenotype–genotype correlations have been reported, with renal cysts associated with splice mutations compared with other mutations [15]. It has been suggested that *OFD1* exons 3, 8, 9, 13 and 16 are mutational hotspots and that the study of these regions could lead to tangible benefits for families, when trying to distinguish between clinically 'blurred' types of OFD syndromes.

The *OFD1* gene encodes a 1011-amino-acid protein, OFD1, which shares no sequence homologies with proteins having known function [16]. Prenatal lethality in affected males suggests OFD1 has a widespread importance in organogenesis and is essential for fetal survival. The expression of OFD1 is ubiquitous in human adult organs, and *OFD1* mRNA has been identified in embryonic organs known to be affected in OFD type 1 (metanephros, brain, tongue and limb) and is developmentally regulated [14,17]. While the precise function of OFD1 is unknown, it has been detected in the centrosome and the basal body of primary cilia, including primary cilia in fully differentiated renal epithelial cells [18]. Consistent with this tissue distribution, knockout mice lacking OFD1 display defective primary cilia formation and left–right axis specification [19].

Cilia dysfunction has been associated with a wide range of developmental and adult phenotypes, with mutations in ciliary proteins associated with nephronophthisis, polycystic kidney disease, Bardet-Biedl and Joubert syndromes, all of which are associated with the development of cystic kidney disease [20]. Recent work has shown that OFD1 can associate with RuvBl1, a protein belonging to the AAA^+ family of ATPases [21]. RuvBl1 has been shown to be important in a number of different biochemical processes including transcriptional regulation and cell division. Mutation of the *RuvBl1* gene is associated with the development of cystic kidneys and there is provisional data suggesting RuvBl1 has a functional role in cilia formation and function [22]. The relationship of OFD1 with other primary cilium proteins including polycystin-1, polycystin-2, nephrocystin and inversin, which are responsible for the common genetic forms of cystic kidney disease, remains to be established.

Conflict of interest statement. None declared.

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