Case Report

Oral-facial-digital syndrome type I: an unusual cause of hereditary cystic kidney disease

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Introduction

The term oral-facial-digital (OFD) syndrome designates a group of heterogeneous clinical patterns of which nine different types have been described [1]. A considerable overlap of the features of the various forms gives rise to difficulties in precise clinical differentiation. OFD-I is the most common pattern, first described by Papillon-Léage and Psaume in 1954 [2]. It is a rare X-linked dominant disorder with lethality in males, characterized by multiple congenital abnormalities, including oral frenulae and clefts, hamartomas of the tongue, hypoplasia of the nasal alae, asymmetrical shortening of the digits, and mental retardation in about half of affected subjects [1–3]. Its co-existence with PKD has been reported in a few patients [4–10].

Here we report on a two-generation family in which a mother and daughter had OFD-I co-existing with polycystic kidney disease (PKD).

Family report

The pedigree of the family is reproduced in Figure 1. The proband (subject III-2), a 26-year-old woman, had a perinatal diagnosis of OFD-I. The gestation and delivery of the patient were uneventful. However, a diagnosis of OFD-I was made at birth, due to the presence of intra-oral, facial and digital anomalies. There were facial asymmetry, cleft palate, cleft upper lip, clinodactyly of the fingers of the feet and syndactyly of the fingers of the hands requiring surgical correction. Patchy alopecia of the scalp and dry hair were also present. At 16 years of age, she was noted to have end-stage renal disease (ESRD). Renal ultrasonography revealed PKD. For a moderate mental retardation, a cranial computed tomography (CT) scan was performed, showing a mild degree of cerebral atrophy. Haemodialysis (HD) was started at the age of 17. At the age of 20 she underwent cadaveric kidney transplantation. Five years later, HD was started again for chronic allograft failure. A CT scan of the abdomen revealed enlarged polycystic kidneys. The parenchimal structure was diffusely altered by numerous lacunar, fluid, cystic lesions. Some larger cysts were located in the proximity of the iliac; numerous and smaller cysts were located on the periphery of the organ. The enlarged kidneys maintained a normal profile, with only minimal changes of the renal contour (Figure 2). Multiple liver and pancreatic cysts were also found (Figure 3A and 3B). Magnetic resonance angiography (MRA) of the circle of Willis did not reveal intracranial aneurysms. The proband's mother (subject II-2) also suffered from OFD-I of lesser severity. She had cleft palate, clinodactyly of the fingers of the hands and patchy alopecia of the scalp. She was of normal intelligence with no neurological dysfunction. At the ages of 23, 25 and 28, she had three successful pregnancies. However, at the age of 30 she did have a spontaneous abortion. The sex of the foetus was not known.

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At the age of 45 she was diagnosed with autosomal dominant polycystic kidney disease (ADPKD) after a renal ultrasonographic examination. At the age of 55, chronic renal failure was discovered: serum creatinine was 3.5 mg/dl; clearance creatinine 20 ml/min. A CT scan of the abdomen revealed PKD, with minimal changes of the renal contour. No hepatic cysts were found and no intracranial aneurysm was found by MRA of the circle of the Willis.

The other available family members (subjects I-1, II-1, II-3, III-1, III-3) were screened for both OFD-I and PKD with negative results. The maternal grandmother of the proband (I-2) died at age 68 from cardiac failure. She was reported phenotypically normal.

Discussion

In 1954, Papillon-Leage and Psaume [2] described eight girls with a syndrome characterized by oral, facial and digital malformations. The oral features included clefts of the tongue, hypertrophic buccal and lingual frenula, and an asymmetric cleft palate; the facial manifestations included a median cleft of the upper lip, hypoplasia of the alar cartilages, alopecia and granular skin; the digital features included various abnormalities, most notably syndactyly of the hands.

Gorlin and Psaume [3] further delineated this condition, suggesting a X-linked dominant inheritance, with the trait lethal in the hemizygous male.

In 1964, Doege et al. [4] first reported a mother and daughter, belonging to a larger kindred that contained 15 affected females, with OFD-I syndrome and PKD. The diagnosis was made at necropsy. However, both patients had evidence of renal impairment before death.

Since then, the combination of the OFD-I syndrome with PKD has been reported in a few other patients and is now considered a distinguishing feature of OFD-I syndrome [5–10].

In 1982, Stapleton et al. [7] gave a detailed description of the macroscopic and histological findings of the cystic kidneys associated with OFD-I syndrome in a personally studied case. He observed that, by contrast to ADPKD, renal cysts in OFD-I were smaller in size, inducing minimal changes of renal contour, and were of glomerular as well of tubular origin.

After examination of a new-born male with OFD-I and PKD who died 4 h after birth, Gillerot et al. [10] confirmed that PKD associated with OFD-I syndrome was different from ADPKD both macroscopically and microscopically.

In 1987, Donnai et al. [8] found five females, belonging to a three-generation family, with OFD-I syndrome presenting as adult polycystic kidney disease. Three family members were misdiagnosed as ADPKD and the accurate examination of the proband led to the correct unifying diagnosis.

The clinical findings and pattern of genetic inheritance of our patients are consistent with the diagnosis of OFD-I syndrome, with the proband demonstrating a more severe phenotypic expression of the disease than the mother. A CT scan of the abdomen revealed PKD in both patients. Renal cysts were numerous, smaller and more uniform in size compared with patients with ADPKD; thus the kidneys were less enlarged and the renal contour was not grossly deformed. In the proband, liver and pancreatic cysts were also found. Whereas the occurrence of hepatic cysts has been reported in one patient with OFD-I syndrome and PKD [5], the presence of pancreatic cysts has never been observed. In the proband, renal

Fig. 2. CT axial scan (following intravenous iodinated radiocontrast) of polycystic kidneys in the proband. The parenchimal structure is diffusely altered by lacunar, fluid and cystic lesions. Some larger cysts are located in the proximity of the ilus (arrow); numerous and smaller cysts are located to the periphery of the organ (arrowhead). Note that the kidneys, although enlarged, maintain a normal profile.
Fig. 3. (a) CT axial scan (following intravenous iodinated radiocontrast) of polycystic liver and kidneys in the proband. There are multiple small cysts in the liver (arrows) reproducing the dichotomous principal branches of the biliary tree, with a pattern of the density which is equal to that of the kidneys. (b) CT axial scan (following intravenous iodinated radiocontrast) of polycystic kidneys and pancreas in the proband. There is a bunch of small cysts (arrows) involving the head and the uncinate process of the pancreas.

disease clinically progressed to ESRD, which required HD at the age of 17. Conversely, the mother had a significantly later age of onset of chronic renal failure and she has not entered ESRD at the age of 55. Moreover, probably due to the presence of minor clinical features of the syndrome, she was misdiagnosed as ADPKD.

The implication of these findings for the nephrologist is that we need to be more aware of renal cystic diseases ‘other’ than ADPKD, including OFD-I syndrome. Genetic and clinical reasons support this view. A correct identification of the rare forms of hereditary cystic kidney disease ‘other’ than ADPKD may be important for genetic counselling. In a family with OFD-I syndrome, only the females with the clinical findings of OFD-I are at risk of developing PKD; normal males and phenotypically normal females are not at risk for PKD. Contrarywise, in a family with ADPKD, half of all first degree relatives are at risk of developing the same disorder.

From a clinical point of view, it is of note that the diagnosis of OFD-I syndrome is usually done in early childhood, when most patients with OFD-I come for medical observation. However, at the time of the initial diagnosis, the kidney involvement may not be apparent. Since the renal disease may be a delayed manifestation of the OFD-I syndrome, an appropriate patient follow-up can be provided for these patients.
To conclude, our data suggest that renal investigations for PKD should be performed in all females with OFD-I. Moreover, since a variable phenotypic expression is a well recognized feature of the syndrome, the presence of OFD-I syndrome should be looked for in a family where only females have PKD. Finally, the coexistence of OFD-I syndrome with PKD further emphasizes the complexity of the genetic background underlying cystogenesis. The existence of different inherited forms of cystic renal disease suggests that cyst formation and progression may depend on various molecular defects. In the OFD-I syndrome, nothing is known about the chromosome loci or defective gene, which appears to be lethal in hemizygous male and causes multiple abnormalities and epithelial cystic changes. Molecular biology studies are required to resolve this question.

References


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