Familial orofaciodigital syndrome type I presenting as adult polycystic kidney disease

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SUMMARY A three generation family with orofaciodigital syndrome type I is described. Several family members had been thought to suffer from autosomal dominant polycystic kidney disease but examination of the proband led to establishment of the correct diagnosis. The genetic implications for the offspring of the affected women and other family members were significantly altered.

Orofaciodigital syndrome type I (OFD I) was first described by Papillon-Léage and Psaume¹ in 1954 and further delineated by Gorlin and Psaume² in 1962. It is a multiple congenital anomaly syndrome consisting of oral frenulae and clefts, hamartomata of the tongue, hypoplasia of the nasal alae, asymmetrical shortening of the digits with occasional preaxial polydactyly of the feet, and retardation in about half of affected subjects. OFD I usually occurs in females and has been reported in several generations, consistent with an X linked dominant mode of inheritance with lethality in affected males. Doege *et al*³ reported polycystic kidneys at necropsy in a mother and daughter with this syndrome but considered it to be a separate genetic entity, and Majewski *et al*⁴ found polycystic anomalies of the kidneys in five of seven necropsied cases with OFD I. Harrod *et al*⁵ reported a patient who presented with polycystic kidney disease and was found to have the

classical features of OFD I but no family history. We report a family referred to the Genetic Clinic with a diagnosis of autosomal dominant polycystic kidney disease (ADPKD). History and examination revealed OFD I in five females in three generations (fig. 1).

Case reports

III.1

A 21 year old moderately mentally retarded female was referred for genetic counselling with a diagnosis

FIG 1 Family pedigree.

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FIG 2 Ultrasound scan of right kidney of III.1 showing cyst on anterior surface.

of ADPKD. Ultrasound scan of her kidneys performed because of family history revealed a small cyst 11 mm in diameter on the anterior surface of the right kidney (fig 2) and a 1 cm cyst on the left. On examination in the Genetic Clinic she was short (height 137 cm, <3rd centile). The occipitofrontal circumference was 61 cm (>97th centile), there was facial asymmetry, slight downward slant of the palpebral fissures, and deep pitted lesions over both cheeks with a few milia under the right eye (fig 3). There was a small cleft of the upper lip to the right of

the midline, multiple oral frenulae, and an irregular tongue border. There was brachydactyly of all fingers, the right fifth digit being extremely short with complete cutaneous syndactyly with the fourth fingers (fig 4). Both halluces were broad and there was a scar on the right where a preaxial digit had been removed. A history was obtained of convulsions from the age of two months, which were localised to the right side of the body. She was delayed in her motor and mental development and had required education in a special school.

FIG 3 III.1 at 21 years showing facial asymmetry, pitted lesions on cheeks, and small cleft of upper lip to the right of the midline.

III.4

The 21 year old cousin of the proband had a cleft palate which had been repaired at the age of two years and a hamartomatous lesion had been removed from the tongue at the age of 16 years. She had right conductive deafness for which a hearing aid was required. On examination she was short (height 142 cm, <3rd centile). She had a medial eyebrow flare, downward slanting palpebral fissures, and milia under both the lower eyelids. The lip margin was irregular, multiple oral frenulae were present between the lips and the gums, and there was a cleft in the right upper alveolar margin. The tongue was irregular and showed the scars of previous surgery (fig 5). There was brachydactyly of all fingers with clinodactyly of the fourth and fifth. The feet were short with a 1 cm difference between the two sides. The patient had a marked tremor accentuated by anxiety and tiredness. Ultrasound scan revealed cysts in one kidney.

II.2

The 54 year old mother of III.4 is currently attending hospital for management of declining renal function due to polycystic kidneys. On examination, her

FIG 4 Hands of III.1 showing asymmetrical brachydactyly, very short fifth finger of right hand, and cutaneous syndactyly with fourth finger.

FIG 5 III.4 at 21 years showing cleft in right upper alveolar margin and irregular tongue margin.

FIG 6 II.2 showing clefts in lower alveolar margin and multiple oral frenulae between gum and lower lip.

height was 157.5 cm (10th to 25th centile). The lower lip margin was irregular, there was a deep cleft in the alveolar margin in the bottom jaw on either side of the right lateral incisor, and multiple oral frenulae were present between the bottom lip and the gum margin (fig 6). The tongue had a bifid tip but was otherwise normal. The hands and feet were normal apart from mild brachydactyly.

II.1

The mother of III.1 died aged 64 years of uraemia secondary to chronic renal failure due to polycystic kidneys. At the age of 40 years she presented with a 12 month history of loin pain and IVP revealed deformed renal pelvises. Laparotomy was performed and showed multiple small cysts of the kidneys. Her

half sister (II.2) reported that she was deaf and had very short and 'curved in' fingers.

I.2

The maternal grandmother of the proband died at the age of 53 years from renal failure associated with polycystic kidneys. Her daughter reported that she had very short fingers and skin folds in her mouth which needed to be 'snipped' before dentures could be fitted.

III.2, III.3, II.3, and III.7 were examined and no evidence of OFD I found.

Discussion

Orofaciodigital syndrome type I affects many different parts of the body. The externally visible

anomalies are well described but internal anomalies including those of the kidney are less well documented. Polycystic kidneys have been found in patients with OFD I at necropsy^{3,4} and as a presenting feature in an apparently sporadic case.⁵ The family reported here further demonstrates that polycystic kidney is a feature of OFD I. The fact that only females were affected in three generations in this family lends support to the hypothesis that OFD I is an X linked dominant trait with lethality in affected males.³

The presence of mental retardation and oral and digital anomalies led to the unifying diagnosis in the proband and hence accurate genetic counselling could be given to family members. This was important both to the unaffected males (and their children) now shown not to be at risk for ADPKD and to the affected females whose daughters have a 1 in 2 risk of inheriting OFD I. We suggest that features of OFD I should be looked for in a family where only females have polycystic kidneys. Conversely, females diagnosed on external features as having OFD I should have renal investigations performed.

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