Oral-facio-digital syndrome type I: In the differential diagnosis of autosomic dominant polycystic kidney disease, about three cases

Síndrome orofaciodigital tipo i: en el diagnóstico diferencial de la poliquistosis renal autosómica dominante, a próposito de 3 casos

Dear Editor,

We present three patients with a clinical suspicion of autosomal dominant polycystic kidney disease (ADPKD),[1] but with collaboration from the UMERH-RM group, the correct diagnosis of oral-facial-digital syndrome type I (OFDSI) was obtained.

Case 1. Twenty-five-year-old woman with a personal history of cognitive deficit and surgical procedures for prognathism, anterior open bite malocclusion with extraction of two supernumerary canines and other teeth, fibromas, and tongue frenulae. She was referred to nephrology due to hypertension, glomerular filtration rate (GFR) of 61 ml/min and kidney ultrasound: right kidney 11 cm and left 12.4 cm, multiple corticomedullary cysts and liver with small cysts, compatible with ADPKD. There were no kidney cysts on an ultrasound performed five years prior and the kidneys measured 10.3 and 10.8 cm.

Physical examination: milia, slanted palpebral fissures, hypoplasia of the nasal wings, dental crowding, prognathism, clinodactyly and brachydactyly in hands and feet, and *hallux valgus*.

The head MRI identified agenesis of the corpus callosum and hypoplasia of the cerebellar vermis.

Genetic testing found a *de novo* pathogenic variant with deletion in exon 12: c.1193_1196delAATC (p.Q398LfsX1) on the *OFD1 gene,* giving rise to a truncated protein, previously reported as associated with OFDSI.

Case 2. Thirty-two-year-old woman with chronic kidney disease and GFR of 47 ml/min, in the context of non-steroidal anti-inflammatory drug abuse due to herniated disc. Treated surgically in childhood for accessory gingival frenulae and extraction of supernumerary teeth due to malocclusion.

After being referred to nephrology in 2015, polycystic kidneys were observed on ultrasound: right kidney 13 cm and left 13.4, with no changes in the liver, spleen, or pancreas.

Family history: mother with kidney transplant due to chronic consumption of non-steroidal anti-inflammatory drugs due to rheumatoid arthritis. The rest of the family (father, sister, son and daughter) have normal kidney function. All underwent ultrasound with kidneys normal in size with no cysts.

On physical examination: fissure of the upper lip, micrognathia, narrow palate and lobulated tongue, and brachydactyly-clinodactyly with marked difference in size between both hands.

During follow-up, onset of hypertension and rapid deterioration of GFR: 37 ml/min at six months and GFR: 30 ml/min at one year. On a new ultrasound, increase in kidney size (right 14.7 and left 15.1 cm). Clinically diagnosed with *de novo* rapidly progressing ADPKD and a candidate for tolvaptan. Head and face MRI ordered due to vertigo and headaches, with no abnormalities found. Currently 37 years old and GFR: 14 ml/min.

The *Next Generation Sequencing* (NGS) massive sequencing testing for cystic kidney diseases identified a pathogenic variant on exon 2 of the *OFD1 gene:* c.71dup, (p.Try24*), not previously reported, giving rise to a truncated protein changing the diagnosis from ADPKD to OFDSI. Family testing confirmed the same variant in her daughter, ruling it out in the rest of the family members.

Case 3. Twelve-year-old girl, daughter of case 2. With no history of interest, except the extraction of a supernumerary canine at six years old. On physical examination: accessory frenula and hands with brachydactyly and clinodactyly (like her mother, although affected to a lesser degree) (Fig. 1). On ultrasound, the kidneys were normal in size with no cysts.

OFDSI (OMIN #311200; ORPHA 2750) is a ciliopathy,[2] with a prevalence: 1/50,000–1/250,000 in live newborns.

In 1998, De Conciliis[3] identified the cause as the *OFD1* gene on the X chromosome, which codes for a protein with 1,011 amino acids, expressed in the centrosome and basal body of the primary cilia.[4] In the OFDSI, the embryogenesis process is altered, causing dysmorphias and kidney cysts. There are up to 18 types of oral-facial-digital syndrome, but type I is the most common.[5]

Up to 75% of the pathogenic variants of the *OFD1* gene are sporadic or *de novo*. In family cases, the inheritance pattern is X-linked dominant, being lethal in males affected during gestation,[6] therefore it would be transmitted from mothers to daughters.

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Table 1 – Main clinical characteristics and follow-up.

	Most common symptom	Follow-up
Facial features	Telecanthus (eyes widely spaced) Micrognathia Slanted palpebral fissures Hypoplasia of the nasal wings Median cleft lip	Detailed physical examination Reconstruction of facial dysmorphias by maxillofacial surgery
Oral cavity	Clefts in the soft and hard palate Lobulated tongue Lingual nodules Ankyloglossia (due to short lingual frenula) Accessory gingival frenulae Excess or Lack of teeth Dental malocclusion	Detailed physical examination In children with palate alteration, annually: - Hearing test - Speech exam - Odontologic follow-up (tooth extraction and orthodontia)
Digital alterations	Brachydactyly Syndactyly Clinodactyly of the fifth finger Thumb duplication *(hallux)* Preaxial or postaxial polydactyly	Detailed physical examination - Hand X-ray: rule out irregular mineralisation (fine reticular radiotransparencies and spicules on phalanges)
Renal	Polycystic kidney disease Chronic kidney disease Arterial hypertension	In those over 10 years, annually: - Blood test with GFR - Blood pressure check - Abdominal ultrasound
Central nervous system	Intellectual disability (usually associated with brain abnormalities) Intracerebral cysts Agenesis of the corpus callosum with or without Dandy-Walker malformation Agenesis of the cerebellum	Measure intellectual ability Developmental and behavioural assessment Head MRI Follow-up with neurology for seizures if they occur
Other	Milia on head and hands Hypoacusis due to repeated otitis Cysts in liver, pancreas, ovaries (only in case of polycystic kidney disease)	Assessment by dermatology (topical tretinoin for acne) Audiometry and speech therapy Annual abdominal ultrasound (along with search for kidney cysts)
Genetics	Inheritance: X-link dominant Lethal for males in gestation	If index case with pathogenic mutation: - Genetic testing for all female relatives (including asymptomatic)

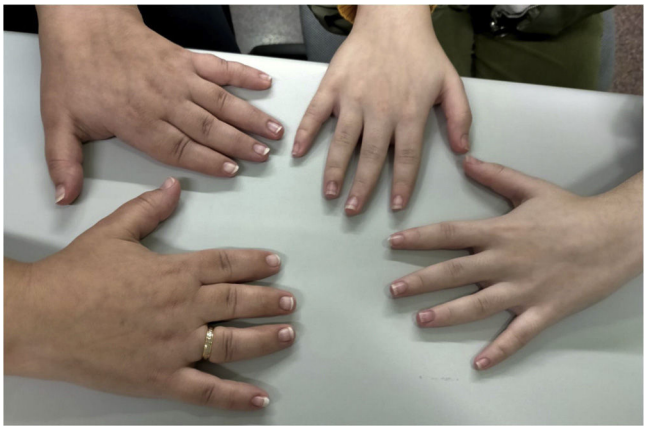

Figure 1 – Comparison of hands between case 2 (mother) and case 3 (daughter). In the mother (left), we observe brachydactyly and clinodactyly, while in the daughter (right), they are present to a lesser extent.

The clinical diagnosis for suspected OFDSI is established after birth via orofacial and digital dysmorphias; or in adults by being associated with polycystic kidneys (Table 1).[7] Annual blood pressure and kidney function checks and abdominal ultrasound are recommended because polycystic kidneys occur[8] in 50%, or even the majority of women according to other authors,[6] and may be the only manifestation.

Due to its great phenotype variability, genetic confirmation is required. NGS panels for cystic kidney disease, which identify the molecular cause in 80%, are the test of choice.[9]

In conclusion, all women with OFDSI must receive annual follow-up by nephrology, because they may develop polycystic kidneys and progressive chronic kidney disease, which determines their prognosis.[10] OFDSI brings up the differential diagnosis with ADPKD, with the search for orofacial and digital dysmorphias being key during the physical examination.

Conflicts of interest

The authors declare that there were no conflicts of interest.

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Portal hypertension and gastrointestinal bleeding in a kidney transplant patient with Alström syndrome

Hipertensión portal y hemorragia digestiva en un paciente trasplantado renal con síndrome de Alström

ARTICLE INFO

Dear Editor,

Alström syndrome (ALMS) is a very rare autosomal recessive genetic disease that may affect several organs, including the kidney, and be the cause of end-stage renal failure. It is considered a ciliopathy due to mutations in the LAMS1 gene (located on chromosome 2p13), and the first symptoms are observed in childhood.[1]

The life expectancy rarely exceeds 50 years. Photoreceptor dystrophy is present in 100% of cases, leading to early blindness. There may also be neurosensory hearing loss, truncal obesity, type 2 diabetes mellitus (DM2), acanthosis nigricans, hypertriglyceridaemia that may cause acute pancreatitis, hypogonadism, polycystic ovary syndrome, hypothyroidism, short stature, dilated cardiomyopathy, kidney failure, lung failure, etc.[1–3]

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[0] *Abbreviations:* portal hypertension, kidney transplantation; Alström syndrome, gastrointestinal bleeding.