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Clinical Report

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Cowden disease and multicystic dysplastic kidney: increased risk of renal cancer?

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Abstract
Unilateral multicystic dysplastic kidney is one of the most frequently identified urinary tract abnormalities in children. Although it can be an isolated finding, it is often associated with other anomalies of the kidney and urinary tract. It has also been described in association with other multisystemic disorders of known genetic aetiologies. Cowden disease (CD) is a rare autosomal-dominant disorder with age-related penetrance characterized by benign and malignant hamartomatous lesions affecting derivatives of all three germ cell layers. Hamartomas can emerge in virtually every organ, but are mostly found in the skin and gastrointestinal tract. We report a 7-year-old patient presenting with unilateral multicystic dysplastic kidney and CD, a hitherto unknown association in paediatrics, which raises the question of an increased risk of renal cancer.

Keywords: Cowden disease; hamartoma; multicystic dysplastic kidney; *PTEN* tumour suppressor gene

Background

Multicystic dysplastic kidney (MCDK), a variant of renal dysplasia, is one of the most frequently identified congenital urinary tract abnormalities (CAKUT). Its incidence varies, depending on the study and country, but ranges from 1 in 3640 to 1 in 4300 live births [1, 2]. Renal dysplasia is characterized by structural disorganization of the renal tissue, involving undifferentiated epithelium and primitive ducts surrounded by fibromuscular connective tissue [3]. Although MCDK can be an isolated finding, it is often associated with other CAKUT. Additionally, this condition has also been described in association with other multisystemic disorders of known genetic etiologies [4]. Most MCDKs undergo involution within the first years of life; nevertheless, a continuous follow-up should be performed not only to identify other urologic abnormalities, but also because hypertension and abnormal renal function have been reported [5–7].

Cowden disease (CD, MIM 158350) is an autosomal-dominant condition with variable expression that results most commonly (80%) from a mutation in the *PTEN* gene on chromosome 10q [8]. It is characterized by multiple hamartomatous neoplasms of the skin and mucosa, gastrointestinal tract, bones, central nervous system, eyes and genitourinary tract. This disease is associated with the development of several types of malignancies during the adult life, making recognition of individuals with this condition important [9].

We report a 7-year-old male patient with antenatal diagnosis of unilateral MCDK and recently identified CD—an unknown association—and discuss its approach as well as the obligatory multidisciplinary follow-up in the future.

Case report

A 7-year-old male patient with no relevant family history had a prenatal diagnosis of probable unilateral MCDK and macrocephaly. Renal ultrasound examination at 30 weeks gestation showed a small right kidney (24 mm), globally hyperechogenic with multiple cysts of variable size.

He was born at 39 weeks gestation by Cesarean section. After birth, isolated macrocephaly (95th percentile) was confirmed without other abnormalities at physical examination. Renal ultrasound at 2 and 15 days of life confirmed a small right dysplastic kidney (35 mm) together with a normal, non-dilated and well-differentiated left kidney (52 mm). A voiding cystourethrography showed bilateral vesicoureteric reflux (right grade 4 and left grade 3). The rest of the neonatal period was uneventful.

During infancy, the patient had normal weight and stature growth (50th percentile) but notable macrocephaly (>97th percentile) with prominent forehead and small jaw. Psychomotor development was slightly delayed (walking at 20 months) and mild mental retardation was established.

Both karyotype analysis and cerebral magnetic resonance imaging were normal. Other etiological investigations were inconclusive.

At follow-up, normal blood pressure, urinalysis and renal function were observed. A renal ultrasound showed progressive right dysplastic kidney involution but still detectable by 7 years of age.

Macrocephaly and psychomotor delay were suggestive of CD and prompted us to perform mutation screening of the *PTEN* gene. The emergence of a nodular lesion (6 mm) above the right eyebrow (histological analysis confirmed a leiomyoma) and a slightly squamous appearance of the lower lip were convincing additional evidence for CD. A single nucleotide substitution (c.210-14A > G) within intron 3 of the *PTEN* gene created a new acceptor-splicing site 13 nucleotides upstream of exon 4. This frameshift variant creates a premature stop codon, predicted to result in the synthesis of a truncated PTEN protein, therefore probably not functional. This mutation occurred *de novo* since it was absent in both parents' DNA extracted from blood leucocytes.

Discussion

Multicystic dysplastic kidney is characterized by the presence of multiple, non-communicating cysts of various sizes separated by dysplastic parenchyma and the absence of a normal pelvicaliceal system [1]. It usually develops as a sporadic condition, although familial occurrence has been reported. Mutations in genes, such as *EYA*1, *SIX*1, *TCF*2 and *PAX*2, which are known to have important roles in ureteric bud development, have been identified in multiple syndromes with renal dysplasia, including MCDK. Indeed both branchio-oto-renal syndrome (mutations in *EYA*1 or *SIX*1) and renal-coloboma syndrome (mutations in *PAX*2 gene) result in dysplastic kidneys—including MCDK—and vesicoureteric reflux. MCDK has also been reported in other syndromes, including Alagille syndrome (mutations in the *JAG*1 gene), Beckwith–Wiedemann syndrome (imprinting disorder at 11p15.5), hypoparathyroidism-deafness-renal dysplasia syndrome (mutations in the *GATA*3 transcription factor), maturity-onset diabetes of the young type 5 (MODY5, mutations in the *TCF*2 gene), trisomy 18, VACTERL association, Waardenburg syndrome type 1 and Williams syndrome [1, 4, 10]. To our knowledge, MCDK has not been reported in association with CD.

Originally described in 1963 by Lloyd and Dennis, CD (or multiple hamartoma syndrome) was named after the family in which it was first reported [11]. PTEN (phosphatase and tensin homologue) hamartoma tumour syndrome refers to a broader category, which includes CD, Bannayan–Riley–Ruvalcaba syndrome, and possibly Proteus-like syndromes. Rare cases of CD are due to a germline mutation in the *BMPR*1A (bone morphogenetic proteins) gene [9]. The members of the bone morphogenetic protein family, namely *BMP4* and *BMP7* genes, have already been shown to encode important signalling molecules throughout kidney development in mice, and deletions/mutations in these genes have been associated with segmental multicystic dysplasia [12, 13].

The *PTEN* tumour-suppressor gene, located on chromosome 10q23.3, encodes a lipid and protein phosphatase, which exerts its lipid phosphatase activity through dephosphorylation of phosphoinositide-3-kinase (PI3K) products, which in turn decreases the activity of kinases downstream of PI3K such as Akt and mTOR and its protein phosphatase activity on proteins of the mitogen-activated protein kinase pathway [14]. Thus, a loss or reduction in *PTEN* activity leads to increased phosphorylation of key cellular proteins involved in cell-cycle progression, metabolism, migration, survival and spreading [15, 16]. PTEN also plays a role in maintaining chromosomal integrity [17].

CD is an inherited autosomal-dominant trait with incomplete and age-related penetrance and a wide range of expressivity. It is characterized by multiple hamartomas and neoplasms of ectodermic, endodermic and mesodermic origin affecting skin, oral mucosa, gastrointestinal tract, bones, central nervous system, eyes and genitourinary tract. Mucocutaneous features include trichilemmomas, oral mucosal papillomatosis, acral keratosis and palmoplantar keratosis. This disease is associated with the development of several types of malignancies, especially breast and thyroid carcinoma. Morbidity and mortality from CD are primarily due to increased frequency of malignant tumours; benign tumours also cause significant morbidity [18, 19].

CD is a rare condition with around 300 published cases internationally. Since the identification of the susceptibility *PTEN* gene, the estimated incidence of CD has increased from 1 in 1 000 000 to 1 in 200 000 individuals. This most likely remains an underestimation as CD is associated with a high degree of phenotypic variability and hallmark features are under-recognized within the medical community. The diagnosis of CD is typically considered between 13 and 64 years of age, with an average of 22 years; a slight female preeminence is noted [9, 18].

The 'pathognomonic' criteria of CD (facial trichilemmomas, acral keratoses, papillomatous papules and mucosal lesions), unfortunately, are not specific enough. The National Comprehensive Cancer Network 2008 has proposed operational criteria for the diagnosis of this condition [20] (Table 1).

In our patient, supraorbital leiomyoma and squamous appearance of the lower lip were very suggestive of CD. He also had congenital macrocephaly (major criterion), genitourinary malformation and mental retardation (two minor criteria). Molecular analysis confirmed the presence of a mutation in the *PTEN* tumour-suppressor gene.

The overall prognosis of patients with unilateral MCDK and normal contralateral kidney is usually considered to be excellent. Morbidity and mortality may result from other urological malformations, urinary tract infections, arterial hypertension and chronic kidney disease. Despite the dysplastic structure of the renal parenchyma, there is no epidemiological evidence for an increased risk of cancer in the standard forms of MCDK [6, 7]. However, concerns about such complications have resulted in historical nephrectomies [21, 22]. Nowadays, a more conservative approach is universally recommended [5]. In our patient, the voiding cystourethrography showed bilateral vesicoureteric reflux, but no urinary tract infection has occurred, and both blood pressure and renal function were normal. However, the presence of such vesicoureteric reflux in a single kidney is a risk factor for further parenchymal scarring, so that periodic assessment of glomerular filtration rate, proteinuria and blood pressure should be emphasized.

Table 1. International Cowden consortium diagnostic criteria

Pathognomonic criteria
Mucocutaneous lesions: facial trichilemmomas and acral keratoses
Papillomatous lesions
Major criteria
Breast cancer
Thyroid carcinoma (especially follicular)
Macrocephaly
Lhermitte–Duclos disease
Endometrial cancer
Minor criteria
Other thyroid lesions (adenoma, multinodular goiter)
Mental retardation (intelligence quotient <75)
Gastrointestinal hamartomas
Fibrocystic disease of the breast
Lipomas
Fibromas
Genitourinary tumours (uterine fibroids and renal cell carcinoma) or malformations
Operational diagnosis in an individual
Mucocutaneous lesions alone meet the criteria if (i) six or more facial papules are present, of which three or more must be trichilemmomas; (ii) cutaneous facial papules and oral mucosal papillomatosus are present; (iii) oral mucosal papillomatosus and acral keratoses are present or (iv) six or more palmoplantar keratoses are present.
Two major criteria, but one must include either macrocephaly or Lhermitte–Duclos disease
One major and three minor criteria
Four minor criteria
Operational diagnosis in a family in which one individual is diagnostic for CD
One pathognomonic criterion
Any single major criterion with or without minor criteria
Two minor criteria
History of Bannayan–Riley–Ruvalcaba syndrome

According to recent studies, the risk of malignant transformation of MCKD to Wilms' tumour and renal or transitional cell carcinoma appears to be minimal [5].

To our knowledge, there is little, if any, consensus recommendation about the management of paediatric patients with CD, particularly with regard to the risk of tumours, although different supervision protocols are established for patients >18 years [18–20, 23].

In the patient presented here, the association of MCDK with CD raises the problem of an increased risk of renal malignancy, thus a periodic imaging follow-up must be recommended. In the case of any doubt from ultrasonography, a magnetic resonance imaging should be performed and nephrectomy should be considered.

In addition, a periodic multidisciplinary surveillance should be maintained including psychomotor development, dermatology consultation, evaluation of thyroid morphology and function, assessment of any potential sign that could be related to gastrointestinal involvement as well as any sign potentially related to a growing intracerebral mass.

CD is an almost unknown condition in paediatrics. Although signs or 'pathognomonic' features of this syndrome are not often observed in early childhood, it is important to inform paediatricians about this disease, mainly with regard to the increased risk of cancers.

Conflict of interest statement. None declared.

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