Autosomal Dominant Medullary Cystic Kidney Disease (ADMCKD)

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Abstract
Autosomal dominant medullary cystic kidney disease (ADMCKD) belongs, together with nephronophthisis (NPH), to a heterogeneous group of inherited tubulo-interstitial nephritis, termed NPH-MCKD complex. The disorder, usually first seen clinically at an average age of 28 years, is characterized by structural defects in the renal tubules, leading to a reduction of the urine–concentrating ability and decreased sodium conservation. Clinical onset and course of ADMCKD are insidious. The first sign is reduced urine–concentrating ability. Clinical symptoms appear when the urinary concentrating ability is markedly reduced, producing polyuria. Later in the course, the clinical findings reflect the progressive renal insufficiency (anemia, metabolic acidosis and uremic symptoms). End-stage renal disease typically occurs in the third-fifth decade of life or even later. The pathogenesis of ADMCKD is still obscure and how the underlying genetic abnormality leads to renal disease is unknown. ADMCKD is considered to be a rare disease. Until 2000, 55 affected families had been described. There is no specific therapy for ADMCKD other than correction of water and electrolyte imbalances that may occur. Dialysis followed by renal transplantation is the preferred approach for end-stage renal failure.

Keywords
Autosomal dominant medullary cystic disease, medullary cysts, nephronophthisis, tubulo-interstitial nephritis

Disease name
Autosomal dominant medullary cystic kidney disease (ADMCKD)

Synonyms
- Nephronophthisis, autosomal dominant
- Polycystic kidneys, medullary type

Diagnostic criteria
The renal presentation of MCKD is relatively non-specific. Urinalysis is not helpful, generally revealing few cells or casts. The diagnosis is made by inference from the family history, polyuria due to decreased concentrating ability, the relatively normal urinalysis and the presence of hyperechogenic kidneys of slightly reduced or normal size on renal ultrasonography. Multiple

small and occasionally larger cysts at the corticomedullary junction may be found. Although computed tomography (CT) imaging is the most sensitive technique, to detect cysts as small as 5 mm in diameter, ultrasound is reliable and non-invasive. Traditionally, finding medullary cysts has been regarded as the hallmark of the condition. However, the high frequency of macroscopic cysts in older reports may be considered the natural consequence of the original definition of the disorder: in many cases, the diagnosis has depended on the presence of grossly visible cysts. On the basis of this initial emphasis on medullary cysts, the misconception has arisen that MCKD is a true cystic disorder. However, careful review of the literature shows that medullary cysts have not been found in all patients for whom this diagnosis was made. The error of this tenet was clearly shown by reports of large families in which some but not all affected family members had medullary and cortico-medullary cysts sufficient to justify the diagnosis. Moreover, the introduction of ultrasonography clearly revealed that medullary cysts mainly developed during the later phases of the disease and that longer-surviving patients were more likely to show the changes of medullary cystic disease. However, these late cystic changes may not be unique to this disease, as they have been observed in patients with end-stage renal disease due to other etiologies. For this reason, some authors think it is not appropriate to consider MCKD a cystic disease. In conclusion, although the finding of medullary cysts may be helpful for the diagnosis of MCKD, medullary cysts bear no major diagnostic importance and are not required for diagnosis of MCKD, despite the name of the disease. The diagnosis can be confirmed histologically, with the most important criteria being the tubulo-interstitial changes, such as areas of tubular atrophy, thickening of tubular basement membrane with periodic acid Schiff-positive material, interstitial fibrosis, and interstitial infiltrates. However, it is noteworthy that MCKD cannot be diagnosed exclusively based on a specific histological image, and the clinical and familial history must be taken in consideration.
In conclusion, the presence of a positive family history consistent with ADMCKD, the classical findings of long-standing polyuria and renal insufficiency in an adult patient aged from 30 to 50 years old make the diagnosis of ADMCKD likely.

Differential diagnosis
The differential diagnosis of ADMCKD should include a variety of diseases causing chronic progressive tubulointerstitial disease with minimal or no glomerular abnormalities. These disorders include chronic pyelonephritis, urinary tract obstruction, polycystic kidney disease and medullary sponge kidney. These diseases should be excluded on the basis of intravenous urography, D-mercaptosuccinic acid (DMSA) scintigraphy or renal ultrasonography findings, showing focal parenchymal scarring, hydronephrosis, multiple bilateral cysts with enlarged kidneys, or malformation of the terminal collecting ducts in the pericaliceal region of the renal pyramids, respectively.

Prevalence
The prevalence of the disease is unknown. ADMCKD has been considered rare, based on the reports of isolated kindreds in different countries worldwide, mainly in Europe and North America. Until 1996, only 30 affected families had been described. Since then, 25 additional families have been reported in the English literature.

Clinical description
ADMCKD belongs together with nephronophthisis (NPH), to a heterogeneous group of inherited tubulo-interstitial nephritis, termed NPH-MCKD complex, which share some histopathological lesions and clinical similarities. The most common variant is juvenile NPH, a disease with autosomal recessive inheritance. Clinical signs of NPH typically are present in early childhood and invariably leads to end-stage renal failure within the second decade of life. MCKD is a less common dominant condition; it is generally recognized later in life, leading to end-stage renal failure at the age of 40-50 years. Because of the inability to clearly distinguish clinically and pathologically between these two processes, the compromise appellation of NPH-MCKD complex has been used. In the literature, however, the description of the NPH-MCKD complex is confusing, since it includes diseases with different modes of inheritance and associations with various disorders. Thus, the clinical and genetic heterogeneity of the NPH-MCKD complex has become a matter of controversy. Originally, the two conditions represented by NPH and MCKD were considered to be separate entities, with NPH being thought to affect young siblings and to be associated with medullary cysts only sporadically. Subsequently, since the clinico-pathological identity of MCKD and familial NPH appeared to be solid, several authors have suggested that NPH and MCKD are in fact a single disorder. This unifying concept concerning the relationship between NPH and MCKD, however, was later refuted based on the identification of several affected families which

suggested a dominant pattern of inheritance. Thus, in spite of the similaritus of the phenotypes (except for age of onset), some authors found, it is preferable to return to the recognition of MCKD and NPH as distinct clinical entities and proposed the term MCKD for the disease with dominant inheritance occurring in adults and the term NPH for the juvenile forms recessive with transmission.

In recent years, the distinctness of the autosomal recessive familial juvenile NPH and the autosomal dominant MCKD has been definitively indicated by the fact that the disorders map to different chromosomal sites. In 1992, linkage analysis and positional cloning approaches to recessive juvenile NPH contributed to the identification of a candidate gene mapping to chromosome 2q13. In 1998, an autosomal dominant form of MCKD associated with hyperuricemia and gout was mapped to chromosome 1q21 *(MCKD1*) in two large Cypriot families (8). Moreover, in 1999, the genome-wide linkage mapping of a second locus for MCKD was described (*MCKD2*) on chromosome 16p12 in a four-generation Italian pedigree with ADMCKD associated with hyperuricemia and gout.

Clinical onset and course of ADMCKD, characterized by structural defects in the renal tubules, are insidious and involve such a paucity of signs and symptoms that diagnosis in the pre-azotemic stage is very uncommon. ADMCKD is a condition which presents relatively late in life, with an average age at onset of 28 years. Some reported cases of ADMCKD, however, are young adults or children. In addition, juvenile and adult forms of the disease coexist in some families suggesting that an age limit is difficult to establish.

The first sign of the disease is reduced urine concentrating ability, which may be the only renal dysfunction found during early investigations, preceding the decline of the glomerular filtration rate; proteinuria is mild or absent, and few formed elements can be seen in the urine sediment. Clinical symptoms appear when the urine concentrating ability is markedly reduced, thereby producing polyuria. The natural history of MCKD is characterized by slow progression to chronic renal failure leading to end stage renal disease, which typically occurs in the third-fifth decade of life. Thus, later in the course, the clinical findings reflect to the progressive renal insufficiency: anemia, metabolic acidosis and uremic symptoms, such as nausea, anorexia and weakness. Many patients with the disease are hypertensive at later stages; however, hypertension may be absent in a minority of patients, who present a salt-losing syndrome as a prominent part of the clinical picture.

The main association described is gout and/or hyperuricalcemia, which has been reported in some families with ADMCKD. However, the significance of the association of familial chronic interstitial nephropathy and medullary cysts with hyperuricemia and gout is not well established. In particular, it is not clear whether this association identifies a single nosological entity. Moreover, it is noteworthy that remarkable similarities in phenotypic expression can been observed between ADMCKD associated with hyperuricemia and gout, and familial juvenile hyperuricemic nephropathy (FJHN), another dominant tubulointerstitial renal disease with comparable penetrance progressing towards renal failure. In FJHN, the biochemical hallmark is hyperuricemia resulting from grossly reduced fractional uric acid clearance, with gout being a variable finding. The most important traditional differences between ADMCKD with hyperuricemia, and gout and FJHN are represented by the presence of medullary cysts in ADMCKD patients and the juvenile onset of renal failure in FJHN. There are, however, remarkable overlaps between the characteristics of both diseases, and cases of ADMCKD without medullary cysts and early onset of renal failure are frequently observed. Moreover, medullary cysts have recently been described also in FJHN as well and reduced fractional uric acid clearance may also be present in ADMCKD. In addition to these remarkable similarities in phenotypic expression between ADMCKD with hyperuricemia, and gout and FJHN, it is noteworthy that two recent studies separately mapped the locus of FJHN to chromosome 16p12, close to the MCKD2 locus, raising the question as to whether MCKD2 and FJHN are allelic variants of the same disease entity.

Management

There is no specific therapy for ADMCKD other than correction of water and electrolyte imbalances that may occur. Dialysis followed by renal transplantation is the preferred approach for end-stage renal failure. The tubular injury does not occur in the transplanted kidney.

Etiology

The etiopathogenesis of ADMCKD is still obscure. The renal lesion of this genetic disorder is functionally and morphologically a tubular defect with progressive interstitial inflammation and fibrosis. These changes emphasize a central role of altered tubular structure in the pathogenesis. Originally, it was postulated that the disease resulted from the action of a nephrotoxic substance on the kidney. However,

that hypothesis lacked supportive evidence. That the disease has never been shown to develop in transplanted kidneys argues against a systemic effect, but how the underlying genetic abnormality leads to renal disease is unknown. Further advances in molecular genetics of MCKD, through identification of the genes responsible for the disease, might enable us to understand the pathogenesis of MCKD. By analogy with NPH, a disease sharing many clinical and pathological features with MCKD, it has been hypothesized that the products of the *MCKD* gene(s) might be part, through their interaction with renal cystine crystal and other binding partners, of focal adhesion-signaling complexes.

Genetic counseling

MCKD displays an autosomal dominant pattern of inheritance with age-dependent penetrance. This means that the offspring of an affected individual are at 50% risk of having the disease. Most individuals with MCKD have a family history of the disease. In a minority of patients, the family history may be negative, due to an incomplete penetrance of the disease or a new mutation. No candidate gene has been identified; however, two chromosome areas, 1q21 and 16p12, may harbor disease-causing gene(s). Other families have been reported which did not show linkage to *MCKD1* nor to *MCKD2*. Thus, the disease is genetically heterogeneous.

In a sufficiently large family, it might be possible to demonstrate linkage to *MCKD1* or *MCKD2*, allowing for linkage-based diagnosis. In this setting, asymptomatic individuals at 50% risk may request testing to determine whether they have inherited the mutation from an affected parent. Affected individuals also might request antenatal testing, with such techniques as chorionic villus sampling, amniocentesis, percutaneous umbilical blood sampling, or fetal skin or muscle sampling. However, these approaches require an accurate clinical diagnosis of the proband. Moreover, it should be remembered that many disorders display incomplete penetrance (meaning that not all carriers will express the disorder at any given age) and that, since the expression of the disease can vary within a given family, genetic testing does not predict the natural history (age of onset and overall severity) of the disease.

Finally, genetic testing may have a promising role in renal transplantation from living related kidney donors, in order to ascertain the genetic status of at-risk family members of affected individuals.

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