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Review

A review on autosomal dominant tubulointerstitial kidney disease☆

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ABSTRACT

In recent years there has been a reclassification of hereditary tubulointerstitial renal diseases. The old concepts of nephronoptisis or medullary cystic disease have been reordered based on the discovery of new genes. The 2015 KDIGO guidelines proposed a unification of terminology, diagnostic criteria and monitoring. So far 4 genes causing autosomal dominant tubulointerstitial kidney disease have been described: *MUC1*, *UMOD*, *HNF1B* and *REN*. Although the mutation in each of them causes distinctive features in how they present, all have in common the progressive tubulointerstitial damage and renal fibrosis. In this article, we present a review of the guidelines and the literature, and some practical recommendations for dealing with this disease.

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Revisión de la nefropatía tubulointersticial autosómica dominante

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RESUMEN

En los últimos años ha habido una reclasificación de las nefropatías tubulointersticiales de base genética. Los antiguos conceptos de nefronoptisis o enfermedad quística medular han sido reordenados con base en el hallazgo de nuevos genes. Las guías KDIGO del 2015 proponen una unificación de terminología, unos criterios diagnósticos y de seguimiento. Hasta el momento se han descrito 4 genes causantes de la nefropatía tubulointersticial autosómica dominante: *MUC1*, *UMOD*, *HNF1B* y *REN*. Aunque la mutación en cada uno de los genes produce unos rasgos diferenciales en la forma de presentación, todas las formas tienen en común el progresivo daño túbulo-intersticial y la fibrosis renal. En este artículo, se pretende una revisión de las guías, de la literatura y ofrecer unas recomendaciones prácticas para el manejo de esta enfermedad.

Introduction

The term interstitial nephropathies includes diseases that predominantly affect the renal interstitium; although, to various degree all elements of the renal parenquima (glomeruli, tubules and vessels) may also be involved. Since renal tubular cells are often damaged, some authors rather use the term tubulointerstitial nephropathies.[1] The progression of renal disease is clearly related to the tubulointertitial damage.[2]

Within tubulointerstitial nephropathies, the are familiar forms with a very heterogeneous clinical profile even within the same family.[3] Corticomedullary cysts are present in several families and were clearly differentiated by the age of onset, then the concept of "nephronoptisis complex – cystic medullary disease" was coined.[4,5] Nephronoptisis defines childhood forms with autosomal recessive inheritance, and the genes initially described were NPHP1 (nephrocystin protein) and INVS (inversin protein)[6,7]; up to 19 genes causing different forms of nephronoptisis have been described to date.[7] The term medullary cystic disease was applied to adult forms with autosomal dominant inheritance, and the first gene identified was *UMOD* (uromodulin).[8,9]

More knowledge about the genes involved and the very inconstant presence of cysts requires changes in these concepts. Hopefully the clinical profile of this entity, with anodyne presentation and variable evolution, will be better defined.[10]

Terminology

The term autosomal dominant tubulointerstitial kidney disease (KD) has recently been established by the KDIGO guidelines using the acronym ADTKD.[11] Prior to this consensus, the nomenclature was non uniform being a source of confusion (Table 1).

The working group of the KDIGO guidelines decided to unify the terminologies and the clinical features of these rare inherited renal diseases,[11] which have in common the tubulointerstitial fibrosis and slow progression to chronic end-stage renal disease (ESRD).[1,12] The advantages of the new terminology are:

- Reveals the genetic origin of these diseases with an autosomal dominant inheritance pattern. It separates these diseases of the rest of the acquired chronic tubulointerstitial nephropathies, and nephronoptisis (of autosomal recessive inheritance).
- Summarizes the clinical characteristics of the disease caused by mutations in four different genes.
- Allows for clinical suspicion before histological or genetic diagnosis.
- Allows to differentiate these diseases from other dominant autosomal diseases of tubular origin (such as autosomal dominant polycystic kidney disease or distal tubular acidosis).
- It avoids some of the previous terminologies that could cause confusion, especially those that include the terms "cystic diseases" or "medullary cysts".
- The terminology is simple and easy to use.

General clinical features

The penetrance of the disease is very high, close to 100% if patient lives long enough; however, severity and age of onset vary considerably among families and also within a family.[11,13]

The disease progresses slowly. The age of onset of ESRD is highly variable, from 25 to 70 years in patients with a mutation in the *UMOD* gene.[3,14,15] The rate of decline in glomerular filtration is variable, and it depends on the mutated gene, but in general the decline in renal function is slow.[3,13,16]

Signs and symptoms are not specific:

- Proteinuria is negative or present in small amount (<1 g/day).[3,13,16]
- Urinary sediment is usually normal or, exceptionally, with microhematuria.[3,13,16]
- The size of the kidneys is normal and decreases as the disease progresses. Renal cysts, which are usually located