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Brief review

Animal models of pediatric chronic kidney disease. Is adenine intake an appropriate model?

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ABSTRACT

Pediatric chronic kidney disease (CKD) has peculiar features. In particular, growth impairment is a major clinical manifestation of CKD that debuts in pediatric age because it presents in a large proportion of infants and children with CKD and has a profound impact on the self-esteem and social integration of the stunted patients. Several factors associated with CKD may lead to growth retardation by interfering with the normal physiology of growth plate, the organ where longitudinal growth rate takes place. The study of growth plate is hardly possible in humans and justifies the use of animal models. Young rats made uremic by 5/6 nephrectomy have been widely used as a model to investigate growth retardation in CKD. This article examines the characteristics of this model and analyzes the utilization of CKD induced by high adenine diet as an alternative research protocol.

Modelos animales de la enfermedad renal crónica en edad pediátrica. ¿La ingesta de adenina es un modelo apropiado?

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RESUMEN

La enfermedad renal crónica (ERC) tiene características específicas. De manera especial, el retraso del crecimiento es una manifestación clínica importante de la ERC que se inicia en la infancia ya que se presenta en un gran número de lactantes y niños con ERC, y repercute profundamente en la autoestima e integración social de los pacientes afectados. Varios factores asociados con la ERC pueden provocar retraso del crecimiento por interferencia con la fisiología normal de la placa de crecimiento, el órgano donde se produce el ritmo de crecimiento longitudinal. Apenas es posible estudiar la placa de crecimiento en seres humanos y ello justifica el uso de modelos animales. El modelo más utilizado para investigar el retraso del

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crecimiento en la ERC son ratas jóvenes que se convierten en urémicas por nefrectomía 5/6. Este artículo revisa las características de este modelo y analiza el uso de la ERC inducida por una dieta con elevado contenido de adenina como protocolo de investigación alternativo.

Impact of chronic kidney disease

Chronic kidney disease (CKD) is a global public health problem because of its associated adverse health outcomes and high healthcare costs. The Disease Fact Sheet 2014 published by the Centers for Disease Control and Prevention (CDC), estimates that more than 10% of adults in USA, which accounts for more than 20 million people only in this country, have CKD with variable disease seriousness. Diabetes and hypertension are responsible for 7 out of 10 new cases of end stage renal disease (ESRD) in USA. From 1990 to 2010, deaths from CKD raised by about 82% worldwide accounting for the third largest increase among the top 25 causes of death, after acquired immunodeficiency syndrome (396%) and diabetes (93%).[1] Cardiovascular complications are the leading cause of mortality in adults with CKD so that these patients are more prone to die from cardiovascular events than to reach ESRD.

Peculiarities of pediatric chronic kidney disease

As adults represent the vast majority of CKD patients, most publications on CKD focus on adult population. However, CKD that presents at pediatric age, although less prevalent in absolute terms, has important and distinct peculiarities, as briefly commented below.

Demography

Whereas the prevalence of CKD in adults is well known, there are scarce reliable data in children. In North America, 11 cases per million of diagnosed CKD in children between 0 and 19 years have been reported, the prevalence being higher in males and blacks. In the European Union the incidence stands around 11–12 cases per million of the age-related population and the prevalence 56–75 cases per million of the age-related population, according to several national registries.[2,3]

Causes

The causes of CKD in pediatric population also differ from those of adults. Congenital anomalies of the kidney and urinary tract (CAKUT) are the leading cause and account for approximately 50% of cases. By contrast, acquired glomerulonephritis are the cause of CKD only in 5–14% of children although this percentage is higher in adolescents and ESRD cases.[4] In European registries, the proportion of CAKUT (58–59%) was slightly higher, while the proportion of glomerulonephritis was lower (5–7%) than in the NAPRTCS database.[5,6]

Clinical manifestations

The key role of interstitial nephropathies as responsible for pediatric CKD explains that the majority of children who have CKD, and even ESRD, are polyuric or have preserved diuresis, unlike adults. This facilitates the management of these patients but also entails peculiar therapeutic implications because of the poorly regulated loss of water and electrolytes, sodium in particular.It is also of note that CKD is often present since the first months of life and lasts until adulthood.

Although the final height of CKD patients has improved over the last decades,[7] the North American Pediatric Trials and Collaborative Studies (NAPRTCS) 2008 Annual Report showed that the mean height of 7037 pediatric CKD patients was −1.44 SD score (SDS) and 35% of children had a height below −2 SD.[4] Similar data shows the Spanish national registry of children with CKD (REPIR II), where the mean height of 605 patients was −1.03 SD and 25% of the children had a height below −1.88 SD[8].

On the other hand, a variety of neurocognitive deficits occur in children with CKD.[9] Thus, pediatric CKD has a profound impact on somatic growth, bone metabolism, and neurocognitive development.[10] The CKD-related effects and its long-term sequelae are to a large extent different from those found in adult patients.

Treatment

An adequate metabolic control, optimal nutritional management, appropriate hormonal therapy, intensive dialysis and early renal transplantation are the best remedies to improve growth and neurological development of children with CKD.[11]

Animal models

Animal models have long been used as a research strategy to increase the knowledge of diseases that affect humans, particularly to better understand pathophysiological mechanisms and to test new therapies. There is wide agreement that the best experimental models for the study of human disease should mimic the entity under consideration in terms of anatomy, physiology, and course of the disease. Thus, useful experimental models should facilitate studies both as the disease evolves and in stable chronic disease. Further, a useful animal model must adhere to current animal welfare regulations and needs to be technically feasible and financially sustainable. Therefore, it should be reproducible, simple, with brief experimental time and easy interpretation of the results. Even if the animal model meets these criteria, it is of note that findings derived from animal models must be taken with