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Childhood Kidney Disease: A Troubling Prognosis?

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The 11th annual World Kidney Day was celebrated on March 10, 2016, across the globe in an effort to better inform the general public, policymakers, and the medical community about the importance of childhood kidney disease and the growing recognition that the antecedents of adult kidney disease can begin in childhood. A recent study by Calderon-Margalit et al[1] in the *New England Journal of Medicine* provides further insight into the long-term outcomes of children with a history of kidney disorders that were assessed as having resolved by late adolescence. Specifically, the study assessed the risk for end-stage renal disease (ESRD) in the long-term follow-up of 17-year-olds who had normal kidney function and no hypertension, but a history of congenital anomalies of the kidney and urinary tract, pyelonephritis, or "resolved" glomerular disease.

Commentary on Calderon-Margalit R, Golan E, Twig G, et al. History of childhood kidney disease and risk of adult end-stage renal disease. N Engl J Med. 2018;378(5):428-438.

What Does This Important Study Show?

Investigators performed a retrospective population-based historical cohort study of 1,521,501 Israeli adolescents who underwent full medical examinations before mandatory military service in 1967 to 1997 and linked the database to the Israel ESRD registry. The cohort included 3,198 recruits with a history of congenital anomalies of the kidney and urinary tract, 1,465 of whom had undergone complete or partial nephrectomy, pyelostomy or pyeloplasty, or ureterostomy or other operations involving the ureters and kidney; 7,231 participants with either a single or recurrent episodes of pyelonephritis, with or without additional malformations of the kidney; and 8,611 participants with a history of glomerulonephritis or nephrotic syndrome and free from the disease for at least 1 year before entry into the military service. All had serum creatinine values within the normal range, and none had hypertension or proteinuria. The frequency of ESRD in this cohort was compared with recruits with no history of kidney disease in childhood. Individuals with medical conditions known to confer an increased future risk for ESRD (diabetes, hypertension, proteinuria, or evidence of ongoing kidney disease) were excluded from the analysis. Cox proportional hazard models were used to estimate the risk for ESRD associated with a history of resolved childhood kidney disease. Remarkably, the authors concluded that a history of any of these diagnoses, despite physician-determined resolution by young adulthood, conferred a substantial increased risk for ESRD over 30 years of follow-up, with a multivariable-adjusted hazard ratio (HR) of 4.19 (95% confidence interval [CI], 3.52-4.99) and earlier onset of ESRD by 7 years (mean age, 41.6 ± 10.7 vs 48.6 ± 10.0 years). The magnitude of risk was similar among kidney disease diagnoses: congenital anomalies of the kidney and urinary tract 5.19 (95% CI, 3.41-7.9), pyelonephritis 4.03 (95% CI, 3.16-5.14), and glomerular disease 3.85 (95% CI, 2.77-5.36).

This study is unique for a variety of reasons. All recruits were documented to have normal kidney function, as determined by clinical and laboratory evaluations at the time of entry into military service. All conscripts received a comprehensive health history, medical record review, physical examination with anthropometric measurements, blood pressure assessment, and dipstick urinalysis. Those for whom the presence of kidney disease could not be ruled out were referred to a board-certified nephrologist for confirmatory diagnosis, which was subsequently verified by 2 additional military physicians, with kidney function ultimately documented as "normal" or "abnormal." Unfortunately, details of the presentation of kidney disease during childhood, treatments, specific disease entities, and age at diagnosis are not reported. In addition, actual values for serum creatinine and therefore estimated glomerular filtration rate were not provided because this was dichotomized as normal or abnormal. It is possible that creatinine values in the normal range reported for adults may be insensitive as an assessment of kidney function in individuals with low muscle mass.[2] The authors also acknowledge the potential for misclassification among diagnoses based on the observation that pyelonephritis was more prevalent in the earlier conscription cohorts from the 1960s to 1970s, perhaps due to undiagnosed underlying congenital anomalies of the kidney and urinary tract because prenatal diagnostic imaging was not as widely available at that time.

How Does This Study Compare With Prior Studies?

This study is one of the first to quantify the long-term risks associated with structural anomalies of the kidneys and urinary tract, as well as transient and seemingly self-limited kidney disease in childhood such as pyelonephritis and glomerulonephritis. These may have a more ominous prognosis than initially suspected. In the last decade, several observational studies have identified an association between mild cases of acute kidney injury and the subsequent development of chronic kidney disease (CKD).[3,4] One prospective cohort study of tertiary-care pediatric intensive care unit patients noted the development of CKD in ~10% of children aged 1 to 3 years after a single episode of acute kidney injury, with nearly half the rest of the cohort identified as "at risk" for CKD.[5] A

registry of children with congenital anomalies of the kidney and urinary tract reported the development of ESRD in 19% of the cohort by age 30 years, with significantly higher HRs in patients with posterior urethral valves (HR, 5.1; 95% CI, 1.89-13.8).[6] One of the more surprising findings from this study revealed that participants with a solitary kidney who were diagnosed at a mean age of 15 years with normal mean serum creatinine levels of 0.68 mg/dL and low prevalence of hypertension or proteinuria at diagnosis also had an increased risk for ESRD by age 30 years (HR, 2.43; 95% CI, 1.09-5.4), with an almost 50% probability of requiring dialysis by age 30 years in this subgroup. Similar findings have been reported in cohorts of children with diarrhea-associated hemolytic uremic syndrome[7] and Henoch-Schönlein purpura[8] even if they experienced resolution of symptoms in childhood.

The authors speculate that the underlying reason for their findings may be the hyperfiltration hypothesis, which was described by Hostetter et al[9] more than 3 decades ago. This pioneering work proved in animal models that a reduced functional nephron number leads to compensatory glomerular hypertrophy and enlargement of remnant nephrons. Although this adaptation offers an advantageous response in the short term, the long-term outcome is characterized by glomerulosclerosis and a resulting vicious cycle of additional reduction in nephron number. There is a growing evidence basis, both experimentally and in epidemiologic studies, that supports this conceptual model, particularly the significantly increased risk for kidney disease, hypertension, and cardiovascular disease seen in premature and/or low-birth-weight infants for whom nephron endowment is limited.[10] These results are also consistent with more recent data indicating a small but increased risk for kidney failure in living kidney donors.[11]

What Are the Implications for Nephrologists?

The findings from Calderon-Margalit et al suggest that we need to have heightened vigilance in long-term surveillance of kidney function in patients who experienced kidney disease during childhood, even those with resolution of the acute condition. This risk and the necessity for long-term follow-up need to be communicated to primary care physicians and to the families of affected children because follow-up of these individuals by nephrologists could prove difficult in clinical practice, with an already burdened global nephrology workforce.[12] Heightened efforts by primary care providers in the early detection and treatment of risk factors for CKD progression, such as hypertension or proteinuria, will be crucial. Progressive care models[13] that emphasize the integration of primary care and subspecialists across the continuum of CKD care will facilitate this long-term care and still achieve improved health outcomes. Expanded education efforts are vital given the current state of low awareness of KDOQI (Kidney Disease Outcomes Quality Initiative) and KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. Finally, further research elucidating molecular mechanisms of cell-cycle pathways of cell repair, inflammation, and fibrosis that contribute to CKD progression is necessary. Novel biomarkers capable of detecting early impairments in glomerular filtration rate and that one day may serve as potential therapeutic targets for interventions designed to halt the progression of CKD early in its course will be of great interest to the nephrology community. Innovative and multidisciplinary efforts are imperative if we are to intervene on behalf of the millions of at-risk children who may not manifest the adverse outcomes of their presumed benign childhood kidney disease until young adulthood.

Article Information

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