The Underestimated Burden of Monogenic Diseases in Adult-Onset ESRD

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The primary cause of ESRD remains unresolved in 15%–20% of adult patients, a percentage probably underestimated considering that the nonspecific diagnoses of hypertension- and renal vascular–related CKD represent 20%–25% of patients with ESRD.1,2 As genomic testing is more commonly used in nephrology, the importance of monogenic disease in these patients is becoming evident. In this issue of the Journal of the American Society of Nephrology, Snoek et al.3 examine the prevalence of the monogenic “childhood” disorder, nephrophthisis (NPHP), among patients with adult-onset ESRD. Their results suggest that it is more important than previously thought.

NPHP is recessively inherited, with a prevalence of approximately 1–2/100,000 individuals. The disease is characterized by the development of chronic interstitial fibrosis, resulting in ESRD usually before 30 years of age.4 Three subcategories on the basis of age at diagnosis have been defined: infantile (presenting either in utero with oligohydramnios-related symptoms or after birth with evolution to ESRD by 3 years of age); juvenile (associated with polyuria-polydipsia, growth retardation, and anemia); and more rarely, adolescent/adult, with just approximately 20 published cases (fewer than ten pedigrees) of NPHP-related ESRD in patients occurring after 18 years of age.5 Extrarenal manifestations, including retinal dystrophy (Senior–Løken syndrome) and neurologic features (Joubert syndrome), are identified in 10%–20% of affected individuals. NPHP is highly genetically heterogeneous (>20 described genes), but 25%–50% of resolved cases in patients are due to homozygous full deletion of the most common gene, NPHP1.5–7 Although NPHP represents approximately 15% of pediatric-onset ESRD, the disease is generally not on the radar of adult nephrologists.

Snoek et al.3 examined the prevalence of homozygous NPHP1 deletions by assessing copy number in genome-wide association study data generated from multiple cohorts of renal transplant recipients. A total of 5606 renal transplant recipients with first RRT at ≥18 years old were included, and 26 patients with homozygous NPHP1 deletions were identified (0.5% of the cohort). This study indisputably shows that NPHP is an under-recognized cause of adult-onset ESRD; however, questions remain about the exact contribution of NPHP to adult ESRD. In addition to the 26 patients with homozygous cases, heterozygous NPHP1 deletions were identified in 36 transplant recipients versus 10 donor controls (0.64% versus 0.30%, respectively; P<0.001). Complete analysis of NPHP1 point mutations in these patients may identify additional patients with NPHP, and full screening of all NPHP genes would be informative. In addition, adult transplant recipients do not reflect all patients with ESRD; some conditions, such as diabetic nephropathy, are under-represented in the transplant population. The primary renal diseases of the subjects included in the International Genetics and Translational Research in Transplantation Network (IGeneTRAiN) cohort would be informative in this regard.

Interestingly, just three of the 26 patients had already been diagnosed with NPHP. Five of the previously undiagnosed patients had a positive family history of renal disease, including four patients with renal insufficiency of unknown etiology and one patient with a diagnosis of autosomal dominant polycystic kidney disease. In NPHP, the kidneys are small to normal size, with increased echogenicity due to fibrosis and loss of corticomedullary differentiation; small cysts can develop late in the disease course. This contrasts with autosomal dominant polycystic kidney disease, where the development of bilateral multiple cysts ultimately results in significant kidney enlargement, and liver cysts are present in approximately 80% of patients.

Five patients were classified as either “tubular and interstitial nephropathy,” “medullary cystic disease,” or “urate nephropathy,” consistent with the final diagnosis of NPHP. Extrarenal features were present in two patients: either congenital blindness, suggesting Senior–Løken syndrome, or severe developmental delay, consistent with Joubert syndrome. Renal disease was discovered at an advanced stage in most of the patients; 11 of 15 patients started RRT within 3 years of discovery of renal disease. Of note, clinical information regarding extrarenal features was not available for nine of 26 patients. Performing “deep phenotyping” of this newly described population, including systematic evaluation of extrarenal features, abdominal imaging, and plotting the progression of renal insufficiency, will be important to better define disease variability in “adult” NPHP.

The development of modern genomics in the past decade has entirely changed molecular diagnostics, moving it from single-gene testing to next generation sequencing...
(NGS) of multiple genes, whole-exome sequencing, and even whole-genome sequencing. Among these options, gene panel–based NGS analysis provides a cost-effective and sensitive diagnostic approach. These broader NGS testing strategies allow unresolved patients with renal insufficiency to be screened even when the phenotype is poorly defined, with a high probability of detecting those associated with a monogenic etiology. Autosomal dominant tubulointerstitial kidneys diseases due to mutation to UMOD or MUC1 and rarely, REN or SEC61A1 have an NPHP-like renal phenotype, but this new study indicates the value of broader screening, including screening of the NPHP genes in patients with suspected autosomal dominant tubulointerstitial kidneys disease and a negative family history.

Systematic genetic screening to determine disease-causing (and even disease-modifying) variants will likely ultimately reframe kidney disease ontology. Obtaining a firm diagnosis of the primary renal disease, even when patients have already reached ESRD, is crucial in several aspects, including the evaluation of the risk of recurrent disease after transplantation and the selection of living related kidney donors. Familial studies can also lead to an earlier diagnosis in at-risk relatives, allowing for appropriate medical follow-up, BP monitoring, therapeutic education (including about nephrotoxic drugs), and genetic counseling for family planning.

Finally, the most important conclusion to draw from this study is that the frontier between adult and pediatric nephropathies is blurring. This calls for closer interactions between pediatric nephrologists, adult nephrologists, and clinical and molecular geneticists and more educational opportunities for all professionals willing to develop an expertise in nephrogenetics. Working hand in hand with full phenotypic characterization of patients, including careful analysis of the family history, will allow interpretation of the genetic information in light of the full clinical context. The hope is that the often-seen diagnosis of “renal insufficiency of unknown etiology” in adult patients reaching ESRD will diminish as molecular genomic screening becomes more widespread.

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DISCLOSURES

None.

REFERENCES
