Evolving Epidemiology of Pediatric Glomerular Disease

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Glomerular diseases are a common cause of kidney disease in children. These disorders account for 5%–14% of children with CKD and 15%–29% of children with ESKD worldwide (1). Nephrotic syndrome in particular is one of the most common manifestations of pediatric glomerular disease and affects between 2 and 7 per 100,000 children. Despite the ubiquity of glomerular disorders in pediatric nephrology practice, there remain a myriad of unanswered questions. Which children with hematuria and/or proteinuria need a kidney biopsy? What are the causes of pediatric glomerular disease? Why do some racial/ethnic groups develop glomerular disease at higher frequencies? Is the incidence of glomerular disease changing over time and what does this mean for the role of environment in the pathogenesis? An article by Nie *et al.* (2) in this issue of the *Clinical Journal of the American Society of Nephrology* provides much needed data about the frequency of biopsy-proven glomerular disease in children in China. This report is notable for the sheer volume of pediatric biopsies that were available for analysis. Almost 8000 pediatric kidney biopsies for indications including AKI, progressive CKD, isolated hematuria, proteinuria with or without nephrotic syndrome, and proteinuria and hematuria were included in this report. These numbers are almost unprecedented in pediatric nephrology glomerular disease research. So, what do they teach us?

Nie *et al.*'s study reported a remarkable ten-fold increase in kidney biopsies performed in China over the 11-year study period (2). There is still no consensus among pediatric nephrologists about which children with glomerular disease need a kidney biopsy, and there are no standard recommendations to guide this practice. The seminal International Study of Kidney Disease in Children performed kidney biopsies in over 500 children with incident nephrotic syndrome in the 1960s and 1970s. This study first confirmed that steroid responsiveness (*i.e.*, remission within 6 weeks of high-dose steroids) was seen in 78% of all children and was predictive of minimal change disease on histopathology (3). Results of this study led to a change of practice whereby most young children with an initial episode of nephrotic syndrome do not receive a biopsy and are treated empirically with steroids. After that agreement in approach to biopsy, there is wide variability in which children with nephrotic syndrome receive kidney biopsies thereafter and when. For example, a survey of North American pediatric nephrologists reported that 57% of nephrologists "always or sometimes" perform a kidney biopsy for frequently relapsing nephrotic syndrome, whereas 43% "rarely or never" biopsy for that indication (4). The approach to biopsy in children with isolated microscopic hematuria is also quite variable, with many nephrologists never performing a kidney biopsy and others considering it depending on family history or coexistence of albuminuria. Similarly, there is no consensus approach to which children with Henoch–Schönlein purpura nephritis (IgA vasculitis) should receive a kidney biopsy. The results of the study by Nie *et al.* (2) are somewhat difficult to interpret in the setting of the vast increase in kidney biopsies performed over the decade. Evolving biopsy practice patterns and expanding indications for biopsy may have significantly influenced the frequency of biopsies performed. The authors' adjustment for age, region, sex, indication, pathology, and hospital level is unlikely to account for the changing practice patterns for biopsy among Chinese pediatric nephrologists during the study period. A recent review of glomerular disease epidemiology included analysis of 1016 pediatric kidney biopsies from the University of North Carolina (5). This study also found changes in relative frequency of glomerular disease subtypes over three decades; however, the number of biopsies per decade were relatively constant in the pediatric population.

As expected, minimal change disease was the most common overall histopathologic diagnosis in the Chinese cohort, more common than IgA nephropathy. In contrast to results from biopsy series in other regions, minimal change disease was identified in a higher proportion (54%) of adolescents receiving a biopsy for nephrotic syndrome compared with younger children (47%). A recent publication from the Nephrotic Syndrome Study Network (NEPTUNE), a North American cohort of patients receiving their initial biopsy for proteinuria, described pathology in 150 enrolled children (6). They found minimal change disease in approximately 65% of children between the ages of 0–11 years and 35% of children aged 12–18 years. FSGS was the second most common diagnosis in both age groups. The proportion of children with FSGS increased in the adolescent age group compared with the younger children in the NEPTUNE study in contrast to the Chinese cohort, where FSGS was less common in adolescents. The proportion of children with minimal change disease in the study by Nie *et al.* increased over time (2), which might be explained by increased availability of electron microscopy data for biopsies over the study period or changing indications

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for kidney biopsy in this population. There is a chance that segmental glomerular scarring was missed in some children classified as "minimal change disease" because only five glomeruli were required for inclusion of the biopsy in this study. Other studies recommend at least 10–20 glomeruli to minimize the risk of missing focal sclerosis and also recommend sampling glomeruli at the corticomedullary junction to maximize sensitivity for a diagnosis of FSGS (7).

A more surprising finding was the declining proportion of FSGS in the Chinese cohort over the study period, from 14% to 4% of biopsies. This is in stark contrast to data from the United States showing an increasing frequency of FSGS in children over time (5,8). Studies of adults have also been consistent in showing increasing prevalence of FSGS over time, possibly because of rising obesity rates. Although pediatric obesity rates are lower in China than in other regions, this is unlikely to be responsible for a decreasing frequency of FSGS as obesity-related FSGS is unlikely to account for many children with FSGS in any series. Because the biopsy numbers in Nie *et al.*'s (2) study are reported as proportions, it is unclear if this reflects truly a decline in incidence of FSGS or an increase in biopsies for other indications. Because of the severe nature of the disease, classic FSGS with nephrotic syndrome, hypertension, and progressive CKD would likely have been one of the few children chosen to receive a kidney biopsy in the earliest years of the cohort, when fewer children were receiving biopsies overall.

Another notable finding in Nie *et al.*'s (2) report is the relatively high frequency of membranous nephropathy observed over the study period. Membranous nephropathy is rare in children in the United States and Europe, accounting for <2% of kidney biopsies for children in the NEPTUNE cohort (6). Remarkably, membranous nephropathy was more commonly observed in 13- to 18-year-old Chinese children with nephrotic syndrome than FSGS. The adjusted proportion of Chinese children with membranous nephropathy increased from 3% to 7% during the study period. The authors speculate that this finding may be because of long-term exposure to air pollution because similar increasing rates of membranous nephropathy were observed in Chinese adults and correlated with exposure to fine particulate matter in the air (9). If confirmed, these findings may have broad public health implications and highlight the importance of regional epidemiologic studies of glomerular disease.

Racial and ethnic differences have long been recognized in the prevalence of glomerular diseases in children; however, data from Chinese children have historically been missing from the literature. Across 29 large nephrology centers worldwide, substantial variation in the relative frequencies of glomerular disease diagnoses was noted across geographic regions (10). However, when comparing frequency distributions across regions, influences of race and ethnicity as well as geography were noted. Higher frequencies of FSGS and lower frequencies of IgA nephropathy and lupus nephritis were noted among Asians in North America compared with those in Asia (Japan and Thailand). This highlights the importance of environment as well as genetics in influencing glomerular disease frequency.

Nie *et al.* (2) have reported, for the first time, a large epidemiologic overview of glomerular disease in Chinese children. This study highlights the power of collaborative research networks for studying kidney disease in children, as well as the need to support epidemiologic studies in diverse geographic and ethnic populations. We are now at an important juncture in the field of pediatric glomerular disease research, where we need to move beyond describing our population and toward randomized trials of available therapies. This, of course, will require international cooperation because of the rare nature of these diseases in children. Studies such as Nie *et al.*'s (2), that help us understand the variability in prevalence of glomerular disorders by region, are important in planning for future studies and suggest that clinical trial enrollment should require kidney biopsy for inclusion.

Disclosures

None.

References

1. Ingelfinger JR, Kalantar-Zadeh K, Schaefer F: World kidney day 2016: Averting the legacy of kidney disease–focus on childhood. *Am J Kidney Dis* 67: 349–354, 2016
2. Nie S, He W, Huang T, Wang G, Geng J, Chen N, Xu G, Zhang P, Luo Y, Xu X, Hou F: The spectrum of biopsy proven glomerular diseases among children in China. *Clin J Am Soc Nephrol* 13: 1047–1054, 2018
3. The primary nephrotic syndrome in children. Identification of patients with minimal change nephrotic syndrome from initial response to prednisone. A report of the International Study of Kidney Disease in Children. *J Pediatr* 98: 561–564, 1981
4. Samuel S, Morgan CJ, Bitzan M, Mammen C, Dart AB, Manns BJ, Alexander RT, Erickson RL, Grisaru S, Wade AW, Blydt-Hansen T, Feber J, Arora S, Licht C, Zappitelli M: Substantial practice variation exists in the management of childhood nephrotic syndrome. *Pediatr Nephrol* 28: 2289–2298, 2013
5. O'Shaughnessy MM, Hogan SL, Poulton CJ, Falk RJ, Singh HK, Nickeleit V, Jennette JC: Temporal and demographic trends in glomerular disease epidemiology in the Southeastern United States, 1986-2015. *Clin J Am Soc Nephrol* 12: 614–623, 2017
6. Gipson DS, Troost JP, Lafayette RA, Hladunewich MA, Trachtman H, Gadegbeku CA, Sedor JR, Holzman LB, Moxey-Mims MM, Perumal K, Kaskel FJ, Nelson PJ, Tuttle KR, Bagnasco SM, Hogan MC, Dell KM, Appel GB, Lieske JC, Ilori TO, Sethna CB, Fervenza FC, Hogan SL, Nachman PH, Rosenberg AZ, Greenbaum LA, Meyers KE, Hewitt SM, Choi MJ, Kopp JB, Zhdanova O, Hodgin JB, Johnstone DB, Adler SG, Avila-Casado C, Neu AM, Hingorani SR, Lemley KV, Nast CC, Brady TM, Barisoni-Thomas L, Fornoni A, Jennette JC, Cattran DC, Palmer MB, Gibson KL, Reich HN, Mokrzycki MH, Sambandam KK, Zilleruelo GE, Licht C, Sampson MG, Song P, Mariani LH, Kretzler M: Complete remission in the nephrotic syndrome study network. *Clin J Am Soc Nephrol* 11: 81–89, 2016
7. Corwin HL, Schwartz MM, Lewis EJ: The importance of sample size in the interpretation of the renal biopsy. *Am J Nephrol* 8: 85–89, 1988
8. Srivastava T, Simon SD, Alon US: High incidence of focal segmental glomerulosclerosis in nephrotic syndrome of childhood. *Pediatr Nephrol* 13: 13–18, 1999
9. Xu X, Wang G, Chen N, Lu T, Nie S, Xu G, Zhang P, Luo Y, Wang Y, Wang X, Schwartz J, Geng J, Hou FF: Long-term exposure to air pollution and increased risk of membranous nephropathy in China. *J Am Soc Nephrol* 27: 3739–3746, 2016
10. O'Shaughnessy MM, Hogan SL, Thompson BD, Coppo R, Fogo AB, Jennette JC: Glomerular disease frequencies by race, sex and region: Results from the International Kidney Biopsy Survey. *Nephrol Dial Transplant* 4: 661–669, 2018

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