Editorial Comment

Incidences of membranous nephropathy versus focal segmental glomerulosclerosis: increase in the former or decline in the latter?

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During the last three decades of the 20th century, a significant development in the field of glomerular diseases was an increased frequency of focal segmental glomerulosclerosis (FSGS) among patients presenting with proteinuria and a primary glomerular disease [1–10]. This increase in FSGS, initially noted in Chicago and other urban areas of the USA [1–7], was subsequently documented in rural areas of the USA and outside of North America [8–10]. The increase was reported in both adults and children and in different racial and ethnic groups, although the greatest overall incidence of FSGS was consistently found in individuals of African descent [1–5, 7, 11–13]. As a result, over a period of 20–30 years, FSGS overtook membranous nephropathy (MN) as the leading cause of nephrotic-range proteinuria in American adults when all races were considered [3, 4, 6] (Table 1). Furthermore, by the early 1990s, two independent studies from Chicago found FSGS to account for 50–70% of African-American adults with nephrotic-range proteinuria [3, 4].

The cause of this increased frequency of FSGS among proteinuric primary glomerular diseases remains unclear, although it does appear that this was most likely related to an increased incidence in FSGS rather than to a decline in other glomerulopathies, particularly MN. We found that the frequency of MN among all primary glomerular diseases diagnosed from the 1970s through the mid-1990s remained relatively constant [2]. Similarly, in an overwhelmingly white population from rural Minnesota, the overall incidence of MN increased modestly, albeit not significantly, during the period from 1974 to 2003, while that of FSGS increased 13-fold [8]. Part of the increase in FSGS during this interval appears to be related to the emergence of a severe histologic variant of FSGS, collapsing glomerulopathy (CG) [1, 2]. While a significant fraction of cases of CG are secondary to HIV infection (HIV-associated nephropathy) and to other environmental and genetic causes [14], the etiologie(s) of other cases remain unknown. Still, the emergence of CG can only account for a relatively small part of the overall increase in FSGS that occurred between the 1970s and 1990s. CG accounts for <20% of total FSGS in African-Americans [1, 2, 15], and it is rare in Caucasians and Hispanics who also experienced an increase in FSGS during this interval, albeit not to the levels seen in African-Americans [1, 2, 4, 6, 15]. We therefore speculated that the rise in FSGS across all races was likely due to one or more environmental factors, with a genetic predisposition accounting for the higher incidence of FSGS in African-Americans compared with persons of other races and ethnicities [2, 3].

In this issue of the Clinical Kidney Journal, Kraus et al. [15] report an apparent reversal of the trend of the late 20th century regarding the relative frequencies of FSGS and MN among primary glomerular diseases in a predominantly adult and primarily African-American and Hispanic population in Chicago. Among 204 primary glomerular diseases diagnosed from 2001 to 2011, MN accounted for 39% of cases in African-Americans and 32% in Hispanics, compared with 33 and 25%, respectively, for FSGS [15] (Table 1). Consistent with previous studies [16, 17], by far the most common histologic variant of FSGS in both African-Americans and Hispanics was FSGS (NOS); CG accounted for 15% of cases of FSGS in the former group and only 1 of 19 cases in the latter [15].

The surprising findings of this study leave us with a number of important questions. First, how widespread are these findings? Are similar trends being noted outside of Chicago, urban areas and North America? Has there been an increase in the relative frequency of MN compared with that of FSGS in Caucasians as well? Perhaps, a hint that this might be the case comes from a study by Northern Ireland [18], where it was observed that the yearly incidence of FSGS was three times higher during 1986–95 when compared with 1976–85, but did not increase further during 1996–05. Meanwhile, there was a slow, steady increase in the frequency of MN over the entire 30-year interval. Similar findings were observed by Swaminathan et al. [8] in their study of an overwhelmingly white population from rural Minnesota, with a marked increase in the frequency of FSGS from 1974–83 to 1984–93, but no further increase during 1994–2003. In contrast, however, Dragovic et al. [7] noted an increase in the frequency of FSGS among primary glomerulopathies even from 1992–97 to 1998–2002 among African-Americans, Hispanics and Caucasians in the New York City. Second, is this apparent reversal toward pre-1980 relative frequencies of MN and FSGS due to an increased incidence of the former,
a decrease in the latter or both? Recent studies have documented that ~70% of cases of primary MN have an autoimmune basis, due to autoantibodies directed against the type 1 phospholipase A2 receptor [19]. While not inconceivable, a relatively sudden and dramatic rise in the incidence of such autoantibodies in both the African-American and Hispanic-American populations would appear to be unlikely. This, combined with the dramatic rise in the frequency of FSGS among primary glomerular diseases between the 1970s and 1990s and the relatively constant frequency of MN during this same period [2, 8] suggests that a decline in the incidence of FSGS, rather than an increase in that of MN, would be more likely to account for the findings reported by Kraus et al. [15].

Assuming this to be true, two potential explanations for a decline in FSGS become apparent. First, since the publication of studies in the 1990s documenting the increased frequency of primary FSGS, a number of additional secondary and familial forms of FSGS have been described [e.g. 20–25]; these would have been considered as primary FSGS in the 1990s but not presently. Second, measures to reduce the spread of viral diseases, including HIV and hepatitis C, started during the early part of the AIDS epidemic in the USA in the early 1980s, continuing through the current era. Noting the possible association between certain non-HIV viruses and FSGS, including parvovirus B19 [26, 27], hepatitis B [28, 29] and others [30], these measures could potentially be contributing to a reduction in FSGS.

Finally, while both primary FSGS and MN are more often than not refractory to current immunosuppressive therapy, the finding of an autoantibody that is central to the pathogenesis of nearly three-quarters of cases of what is currently termed primary MN represents a unique opportunity for the development of specific treatment(s) for this disease. In this regard, the finding of Kraus et al. [15], particularly if found to be a more generalized phenomenon, might actually represent good news.

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