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Re: NPHS2 Gene in Steroid-resistant Nephrotic Syndrome: Prevalence, Clinical Course, and Mutational Spectrum in South-West Iranian Children

Dear Editor,

The optimal treatment of a disease requires the knowledge of the etiology of the disease. However, in real life, this is largely elusive in the majority of diseases affecting the humans. The situation with regard to nephrotic syndrome (NS) in children is also no exception. The vast majority of cases of NS belong to the idiopathic category. Traditionally, immune pathogenesis has been thought to play the predominant role in the pathogenesis of the disorder.[1] This is the basis for the use of steroids and immunosuppressive drugs for the empirical treatment of this condition. Since steroids form the mainstay of treatment of idiopathic NS in children, the disease is often classified on the basis of response to this treatment into steroid sensitive (SSNS) and steroid resistant (SRNS) types. Among these, the later poses significant therapeutic challenges to the pediatric nephrologists.[2] Hence, much attention has been focused toward elucidating the causes and pathogenesis of this subset of idiopathic NS.[3] More recently, the attention has been directed toward identifying the genetic causes of idiopathic NS. Many studies have been conducted throughout the world on identifying the genetic mutations in a number of podocyte genes. There is a wide discrepancy in the reported results in these studies.[4,5] There are multiple reasons for the heterogeneous results in these studies, such as methodological differences, differences in enrolled cohorts, different definitions of SRNS, number of genes tested and so on. These factors may contribute to the real genetic differences in the different ethnic populations and geographic locations.

Basiratnia and colleagues[3] have analyzed the frequency of disease-causing mutations in *NPHS2* gene in 49 Iranian children with SRNS from the southwest Iran region. These authors have done a commendable job in describing the spectrum of genetic abnormalities in *NPHS2* gene in this condition in Iran. They found a high prevalence of *NPHS2* mutations (30.6%) in the studied cohort whose mean age was 6.8 years, although only one gene was analyzed in their study. The majority of these cases (n = 42) were sporadic, only 7 cases were familial in nature. The prevalence of mutations was very high in familial cases (57%) compared with the sporadic cases (26%). The observed histopathological lesions among the biopsied children in both mutation positive and mutation negative cases attest to the infidelity of the histological findings with regard to the etiology of the disease. Other clinicopathological parameters were also not help in differentiating mutation positive from mutation negative cases. The clinical response to pharmacotherapy was poor in the mutation positive cases. The results by Basiratnia and colleagues[3] more closely resemble the figures by European studies than studies from other parts of Asia.[4-6] Two recent studies from neighboring countries of Pakistan and Saudi Arabia found a markedly low rate of frequency, even while testing for three genes in each.[5,6] The reasons for these marked differences are not readily apparent, as almost similar methodology has been applied in these studies, ie, of direct gene sequencing. It seems that one important factor is the variation in the number of familial cases included in the study. True ethnic differences may also be at play

in these different results, as reported by Chernin and colleagues.[7]

There are a number of points in the study by Basiratnia and colleagues,[3] which have not been addressed, such as the timing of the genetic analysis of the patients. Should it be done before or after performing the biopsy? It seems that the genetic analysis was done late in the course of the disease, as eight of the 15 patients with *NPHS2* mutation were treated with immunosuppressive drugs, albeit with poor response. There is also no mention of number of cases in which DNA was obtained from paraffin blocks of tissue and the reason for it.

In summary, we congratulate the authors on the interesting findings of their study, which will add to the scarce data on the topic from this part of the world. There is a need for regional collaboration and multicenter studies to fully determine the role of genetics in SRNS children.

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