Focal Segmental Glomerulosclerosis and Chronic Kidney Disease in Pediatric Patients

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Focal segmental glomerulosclerosis (FSGS) is one of the most common forms of acquired glomerular disease leading to end-stage kidney disease. Its incidence is rising around the world. There is no proven therapy for those patients who do not respond to corticosteroids and it can recur in 20% to 25% of patients who receive a kidney transplant. The disease can be primary, or it can be secondary to various conditions including vesicoureteral reflux, obesity, medications, and infections. Recent advances have demonstrated the important role of genetic mutations in podocyte proteins as a cause of FSGS. There is an urgent need for randomized clinical trials to develop safe and effective therapy for FSGS that occurs in the native or transplanted kidney.

Key Words: FSGS

Focal segmental glomerulosclerosis (FSGS) is one of the most difficult and enigmatic diseases in nephrology. It can occur as a primary disorder without an identifiable cause, or as an illness secondary to a variety of problems. Over the last 20 to 30 years, the incidence of FSGS has been increasing in virtually all ethnic groups, across the entire age spectrum, and around the world. It is one of the most important causes of acquired chronic kidney disease (CKD) in children and adults and there is no proven therapy for steroid-resistant cases. Moreover, patients who progress to end-stage kidney disease (ESKD) and who receive a renal transplant cannot be reassured that the worst is behind them because FSGS can recur in the transplanted kidney in 20% to 25% of cases. Because of the profound renal morbidity associated with FSGS, it has been the subject of intensive basic science and clinical research since its initial identification in renal biopsy specimens obtained from patients with steroid-resistant nephrotic syndrome over 50 years ago. There has been considerable progress in understanding the pathogenesis of FSGS and renewed efforts have been made to conduct valid randomized clinical trials in this disease. The objectives of this review are: (1) to focus mainly on primary or idiopathic FSGS and on accomplishments in this area during the last 5 years; and (2) to highlight where future efforts should be directed in order to improve the clinical outcomes for patients with all forms of FSGS.

Definition and Histopathology

The diagnosis of FSGS is based on the detection of segmental sclerosis and hyalinization of a portion of the glomerular tuft. An effort has been made to create a histological classification so as to determine whether the renal pathology findings can predict response to treatment and long-term outcome. In the most widely used scheme, there are 4 categories of FSGS—not otherwise specified (NOS), tip, hypercellular, and collapsing.[1] The location of the scar can be at the vascular pole (NOS) or adjacent to the onset of the proximal tubule, the so-called tip lesion. The degree of mesangial cellularity can vary and there is ongoing controversy whether the severity of this finding has prognostic implications.[2,3] Finally, a severe subtype of FSGS, termed collapsing variant, has consistently been shown to be resistant to treatment and to follow a relatively aggressive downhill course. Immunofluorescence studies may show deposition of complement component 3 (C3) and immunoglobulin M (IgM) in sclerotic segments but this is considered a nonspecific finding. In contrast, the implication of isolated complement component 1q (C1q) staining in the mesangium is less clear, with some investigators interpreting this finding as suggestive of an underlying disease process such as systemic lupus erythematosus,[4] and others considering it within the spectrum of primary FSGS.[5] Electron microscopy shows fusion of the podocyte foot process, segmental scarring, and occasional deposits. Reticular inclusion bodies are seen on certain secondary forms of FSGS, for example HIV nephropathy. Foot process effacement is generally more widespread and severe in primary than in secondary FSGS.

Although the definition of FSGS appears straightforward, the literature and clinical experience suggest that misclassification of patients as having FSGS is fairly common. For example, over 10% of patients screened for enrollment in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded FSGS Clinical Trial were found not to have the disease after review of the biopsy material by a central committee of expert renal pathologists.[6] This may reflect the inaccurate classification of nonspecific scarring of glomeruli or misinterpretation of findings, such as glomerulomegaly, immature glomeruli, or foci of tubulointerstitial fibrosis, which are supportive but not diagnostic of FSGS. In a study of the difficulties in the histological assessment of glomerular sclerotic lesions

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1548-5595/$36.00

doi:10.1053/j.ackd.2011.03.005

such as FSGS, definite diagnosis required a representative renal biopsy specimen, a comprehensive evaluation with light microscopy, immunofluorescence, electron microscopy, and integration of morphological changes with relevant clinical data.[7] Histological examination of the renal tissue may not enable reliable differentiation of idiopathic and secondary forms of FSGS.[7] Differential immunohistochemical staining of the glomerulus for various podocyte markers, such as synaptopodin, dystroglycan, the cyclin kinase inhibitor p27, has been proposed as an alternative method to differentiate FSGS from minimal change nephrotic syndrome (MCNS) in specimens that may not show the classic histopathological lesion on light microscopy.[8-10] The accurate histopathological diagnosis of FSGS lesions requires collaboration between nephrologists and pathologists and, in the future, is likely to incorporate newer biomarkers in the kidney tissue. In addition, the urinary proteome may provide an additional tool to confirm the diagnosis of FSGS in questionable cases.[11]

CLINICAL SUMMARY

- The incidence of FSGS in pediatric patients is rising, and it is an important cause of CKD in this age group.
- FSGS has been linked to a growing list of genetic mutations in podocyte proteins which is shedding new light on the pathogenesis of the disease.
- Although calcineurin inhibitors are considered the standard of care, as indicated by the recently completed FSGS Clinical Trial, there are no proven treatments for patients with steroid-resistant disease.
- FSGS can recur in 20%-25% of patients who receive a kidney transplant. There is a pressing need to better identify patients at risk of this serious complication and to achieve remission in these circumstances.

Clinical Classification

In addition to the histopathology categories outlined earlier, FSGS is divided into 2 clinical categories—primary and secondary—on the basis of whether an underlying cause for the abnormality can be identified (Table 1). Primary or idiopathic FSGS represents cases in which there is no demonstrable etiology for the renal histopathological finding. Secondary causes include genetic mutations in podocyte proteins (see later in the text), obesity, medications (such as pamidronate, sunitinib, interferon),[12-14] infections (eg, HIV), vesicoureteral reflux, reduction in renal mass (eg, surgical resection of renal tumors, trauma), and systemic illness (such as plasma cell dyscrasias).[15] An interesting variant of disease related to decreased kidney mass is the observation that very low birth weight as a result of prematurity or intrauterine growth retardation is associated with reduced nephron number and an increased risk for secondary FSGS.[16] In general, patients with secondary causes of FSGS have lower levels of proteinuria and are less likely to present with clinically overt nephrotic syndrome, as compared with those with primary disease. It is important to maintain vigilance for emerging causes of secondary FSGS linked to changes in environmental factors, life style, and recreational practices. For example, a recent report documented the occurrence of FSGS in 10 body builders who were using anabolic steroids at a mean daily intake of 10 g. Most importantly, in 7 cases the proteinuria decreased with discontinuation of the anabolic steroids.[17]

Incidence

There has been a steady increase in the incidence of primary FSGS over the last 20 years. In most reports of adult patients that have appeared in recent years, there has been a 2- to 3-fold increase in the rate of diagnosis of this disease. Although this may reflect more selective reliance on kidney biopsies in patients with proteinuria and nephrotic syndrome, the increase is likely to be real because it is paralleled by an increase in the number of patients reaching ESKD secondary to FSGS. Similar trends have been observed in pediatric nephrology. For example, in an analysis of a computerized hospital database regarding children with primary nephrotic syndrome seen first between the years 1984 and 1995, 23% (95% CI: 16%-29%) of the kidney biopsies (n = 62) showed FSGS. A similar percentage was found in a survey of pediatricians to capture cases (n = 86) that were outside the database.[18] This rate of detection of FSGS was significantly higher than that described by the International Study of Kidney Disease in Children conducted in the mid-1960s and early 1970s, namely 6.9%. Again, it must be emphasized that the later figure is based on an unselected population of children with new-onset nephrotic syndrome. In contrast, most recent estimates of the incidence of FSGS are derived from single center reports describing renal biopsy findings in patients with a higher likelihood of steroid resistance and with clinical features indicating a non-MCNS lesion. The annual incidence rates of both primary nephrotic syndrome (3.6) and FSGS (1.6) were significantly higher in African Americans than Caucasians (1.8 and 0.3 cases/10^5 children per year, respectively).[18] In a similar survey from Children's Hospital of Eastern Ontario, there has been a three-fold increase in the incidence of FSGS over the 18-year period from 1985 to 2002.[19] However, although the traditional view is that African Americans have an increased risk of FSGS, it is the leading cause of the nephrotic syndrome in white adults living in Minnesota.[20]

Etiology

Dysfunction of the podocyte is a central feature in current working paradigm for the pathogenesis of FSGS.[21]