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Review Article

Genetic aspects of familial focal segmental glomerulosclerosis

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ABSTRACT

Focal Segmental Glomerulosclerosis (FSGS) participates in different clinical presentations therefore involved in underlying pathophysiological etiologies. Numerous reports have proposed that vulnerability to develop FSGS has an important genetic component. These studies comprise familial aggregation, differences in the incidence of FSGS between different ethnic groups, and segregation analysis. Genetic methods have been used to classify genes that contribute towards genetic predisposition. Various studies revealed the precise role of "candidate genes", which may cause FSGS with different pathogenesis. New studies to assess the role of associated genes have shown contradictory results. These results may be due to the fact that some of the previously reported genes may play only a moderate role. Presently genome wide studies have been carried out and these studies have contributed in finding out the location chromosomal positions. Interestingly novel, unrecognized genes to FSGS have been found. We have focused on different genetic studies including exact role and function of these genes on FSGS and have discussed the strength and weaknesses of these studies. Understanding of the development of FSGS may track future therapies and outcomes.

1. Introduction

Focal segmental glomerulosclerosis (FSGS) is a common form of kidney disease. Theodor Fahr in his book entitled, "Handbuch der speziellenpathologischen Anatomie und Histologie", has described the histologic features of idiopathic forms of FSGS.[1] Since then much focus has been emphasized on clinical characterization of the patients using histological techniques. These observations has led to the classification of FSGS into five morphological subtypes,[2] which may have various predictive and therapeutic inferences. FSGS has been classified into several light microscopic patterns namely cellular, perihilar, tip and collapsing variants as shown in Fig. 1.

FSGS shows an array of striking clinical features along with patho-physiological conditions.[3,4] Causes of FSGS are

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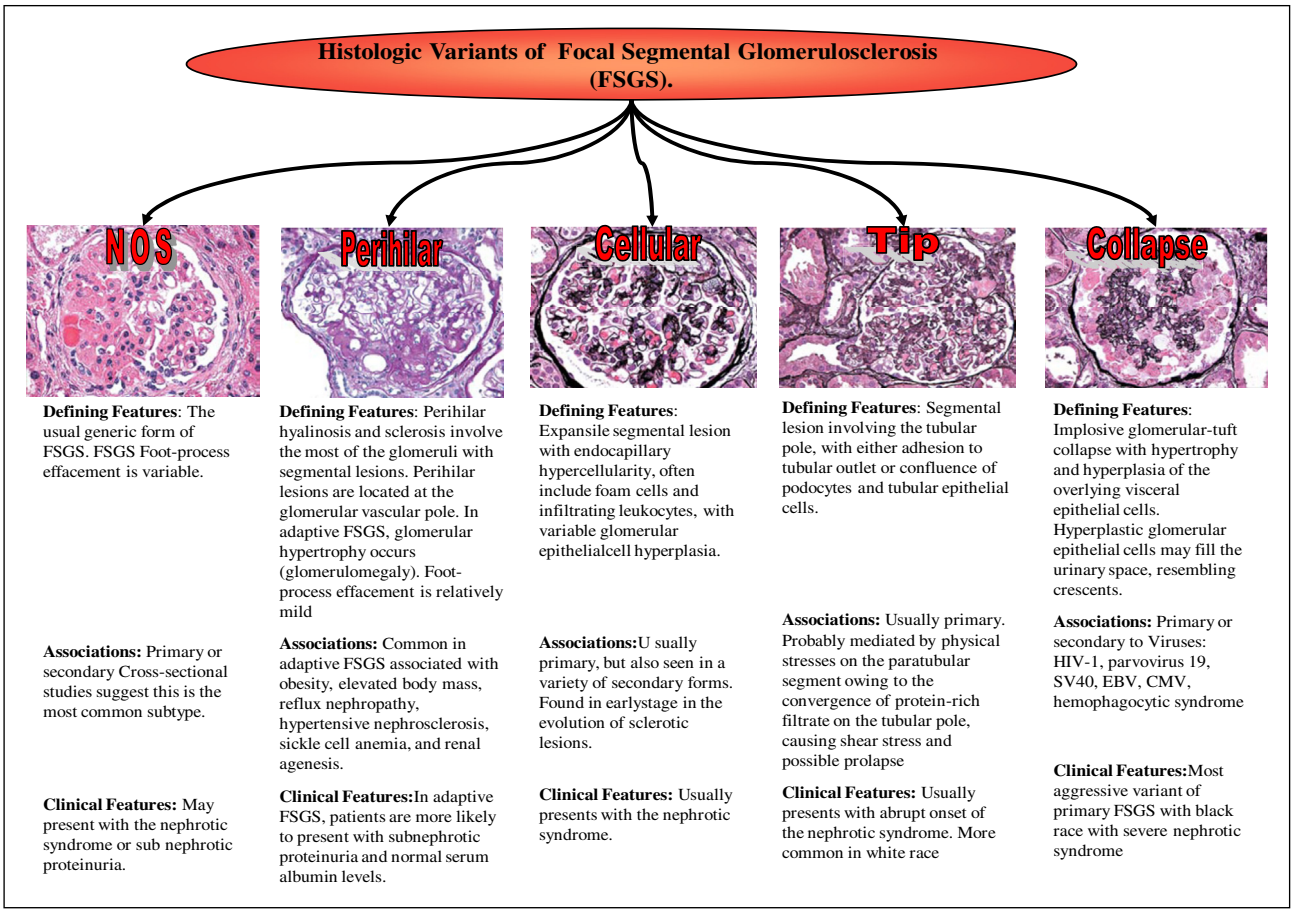

Fig. 1 – Light microscopic classification of FSGS.

classified into two forms i.e., primary (idiopathic form) and secondary based on etiological and functional aspect of the disease. The exact cause of idiopathic form is still not known. It has been proposed that FSGS may be mediated by circulating permeability factors. Secondary causes could be familial or genetic which are due to specific mutations, virus-associated, the viruses involved are, human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus and epstein barr virus.

FSGS can be drug induced involving heroin, interferon alfa, beta, and gamma, lithium, pamidronate, sirolimus, calcineurin-inhibitor nephrotoxicity and anabolic steroids. Another important cause is adaptive which is mediated by adaptive structural-functional responses to glomerular hypertension caused by elevated glomerular capillary pressures and flows. Main pathogenesis of FSGS is proteinuria due to the loss of glomerular filtration barrier which in turn is involved at the inner blood surface, outer urinary interface and center region as fenestrated glomerular endothelial cell, podocytes and glomerular basement membrane respectively (Fig. 2). The podocyte shows diverse functions including glomerular filtration, biosynthesis and maintenance of the glomerular capillary structure. Glomerular segmental scarring is observed when podocyte is lost in both human and animal models. Podocytes can be shed into the urine and can acts as a marker in FSGS. Podocytes have diverse membrane specializations and play a prominent role in glomerular function. Clinically podocyte dysfunction is limited to renal insufficiency and proteinuria.

2. Pathogenesis

Recurrent FSGS in renal transplants provides a unique opportunity to study the pathogenesis of FSGS. Pathologic studies have identified a proliferative lesion of the podocytes as the first sign of recurrent disease. The glomerular lesions evolve to form segmental glomerular scars with time. These findings and studies in experimental models of FSGS implicate podocyte injury in the pathogenesis of the recurrent disease. The cellular lesions have been seen early in the course of primary FSGS. In serum of advanced stages of FSGS cases, soluble circulating factor have been detected which increases glomerular permeability. This process leads to recurrence of FSGS. Morphologic changes have been noticed in podocytes that cause the permeability changes associated with proteinuria and destruction of glomerular filtration surface due to scarring which is associated with loss of glomerular function. Important contribution to understand how podocytes are affected was carried out by identifying the causative genes in hereditary forms of nephrotic syndrome.