

## Focal segmental glomerulosclerosis: what are the risks of recurrence after renal transplantation?

Laure-Hélène Noël

Hôpital Necker – Université René Descartes Paris V. Paris, France.

Received for publication: 11/05/2010

Accepted in revised form: 26/05/2010

### Key-Words:

Circulating Factor; Columbia classification; Focal Segmental Glomerulosclerosis; Hereditary podocytopathies; Recurrence.

### INTRODUCTION

Focal and segmental glomerulosclerosis (FSGS) is a glomerulonephritis which tends to recur. The incidence of recurrence is known to be rather high and some nephrologists consider the disease a contraindication to renal transplantation. But when we speak of focal segmental glomerulosclerosis we refer to several diseases. Not all focal segmental glomerulosclerosis are at risk of recurrence and when renal transplantation is proposed, it is necessary to know what type of focal segmental glomerulosclerosis is responsible for end-stage renal disease<sup>1</sup>.

In this paper we discuss the aetiology of FSGS, the most useful genetic studies to perform before renal transplantation, the value of the Columbia classification for predicting recurrence and the frequency of recurrence when the patients are well classified.

### DEFINITION

FSGS is a lesion rather than a disease. Irreversible podocyte injury which can be multifactorial leads to

this type of lesion. A mature podocyte is a nondividing cell with a complex structure which is contractile and covers several capillaries. Its function is to synthesise glomerular basement membrane mediators and it is also capable of endocytosis and peptide degradation. On the surface there are numerous molecules including receptors and adhesion molecules and this complex cell is very important in filtration<sup>2</sup>.

The podocyte is very susceptible to injury, unable to proliferate and unable to affect repair following damage. Experimental models help us to understand the chronology of the events leading to FSGS<sup>3</sup>.

### SEQUENCE OF EVENTS IN THE DEVELOPMENT OF FSGS

Stereotypical responses to injury include progressive morphologic evidence of podocyte injury beginning with foot process effacement and progressing through cell body attenuation and pseudocyst formation to detachment of the podocyte from the glomerular basement membrane (GBM) and loss of the urinary space. When the denuded area of GBM created by podocyte loss meets the parietal epithelium, these cells attach to the capillary basement membrane. This begins a sequence of events leading to the formation of an adhesion. This part is invaded by fibroblast, organisation, enlargement of the lesion and progression to global glomerular sclerosis<sup>4</sup>.

## ■ REVIEW OF THE DIFFERENT FSGS AETIOLOGIES

Three groups of FSGS can be distinguished: secondary forms, hereditary podocytopathies and FSGS related to a circulating factor.

### ■ 1. Secondary forms

In evaluating risk of recurrence in renal transplantation, the secondary forms must be recognised as they do not recur.

#### ***Glomerular hypertension***

Compensatory hyperfiltration following reduction in renal mass is accomplished in part by elevation of the transcapillary pressure gradient and this implies glomerular hypertension, podocyte injury and the development of FSGS<sup>5</sup>.

#### ***Hyperlipidaemia and obesity***

The excess excretory load seen with obesity is associated with adaptative change in glomerular filtration (hyperfiltration, afferent arteriolar dilatation and glomerular capillary hypertension) typical of reduced nephron number accompanying chronic kidney disease. The effect of these factors on the glomeruli is expected to be exaggerated in individuals with reduced nephron number resulting from intrauterine growth retardation.

Adverse adaptation to excess renal sodium retention in obesity (mediated by angiotensin II and sympathetic activation) induces hyperfiltration and afferent vasodilatation which leads to glomerular injury. Hyperinsulinaemia/insulin resistance, seen early in obesity-initiated metabolic syndrome and which precedes hyperglycaemia, causes adverse renal structural modification. These include glomerular hypertrophy and pathologic effects on glomerular cells. The excess intracellular lipids may have a direct toxic effect on renal cells by promoting the synthesis of lipid products capable of causing cell injury<sup>6</sup>.

#### ***Chronic pyelonephritis and reflux nephropathy***

In this field the presence of FSGS supports the hypothesis that adaptative changes following nephron

loss due to atrophic pyelonephritis and reflux nephropathy place stress on podocytes and lead to progressive loss of renal function<sup>7</sup>.

#### ***Oligomeganephronia***

This is a rare congenital form of renal hypoplasia that occurs without dysplasia or other urinary tract abnormalities. Morphological studies show enlargement of glomeruli, juxtaglomerular apparatus and tubules. The glomeruli show no other changes until late in the course when they develop segmental glomerular scars with adhesion and epithelial cell hyperplasia. It is usually a sporadic malformation with no family history. It can be associated to other abnormalities and constitutes branchio-oro-renal syndrome, acro-renal syndrome and renal-coloboma syndrome. PAX2, a nuclear transcription factor, is critical in the development of the kidney, eye and ear. Mutant forms of PAX2 have been reported in patients with renal-coloboma syndrome and in sporadic forms of oligomeganephronia<sup>8</sup>. HNF1 $\beta$  gene mutations have also been described<sup>9</sup>.

#### ***Unilateral renal agenesis***

FSGS can appear because of an insufficient number of nephrons and is secondary to focal glomerular hypertension as previously described<sup>10</sup>.

#### ***Cholesterol atheroembolisation***

Renal atheroembolisation is a common complication of atherosclerosis and the risk factors include male sex, peripheral vascular disease, hypercholesterolemia and hypertension. The mobilisation of cholesterol crystals in the circulation is responsible for vascular obstruction, ischaemic phenomena and loss of nephrons. Other factors such as hyperfiltration and hyperlipidaemia can be involved<sup>11</sup>.

#### ***Viral aetiology***

It is important to eliminate any viral aetiology to FSGS. HIV in black patients is the most commonly implicated virus in FSGS<sup>12</sup>.

Viral infection has been linked to FSGS and parvovirus B19 infection in some series, but needs to be confirmed<sup>13</sup>.

## Therapy

An association between pamidronate, a bisphosphonate inhibitor of bone reabsorption used in the treatment of malignancy, and osteolytic metastases has been reported. Patients who develop nephrotic syndrome all received prolonged courses of the drug at a higher than recommended dosage. The pronounced podocyte pathology seen in this syndrome supports a cytotoxic effect of pamidronate and in analogy with the metabolic effects of bisphosphonate on osteoclasts, the drug has several potential mechanisms of interfering with podocyte metabolism and function<sup>14</sup>.

## ■ 2. Genetic diseases

It is very important to propose genetic investigation in patients with FSGS when secondary forms have been excluded. This is now available and must be used when podocytopathies are observed, particularly in the cases which are cortico-resistant.

The age of appearance of nephrotic syndrome, terminal renal insufficiency is very important to consider.

### Slit diaphragm proteins

#### *Congenital nephrotic syndrome (Finnish-Type NPHS1 mutations)*

Any nephrotic syndrome developing within a year of birth could be the manifestation of Congenital Nephrotic Syndrome (Finnish-Type-CNS) with a mutation concerning the gene coding for nephrin (NPHS1 mutation). CNS has an autosomal recessive mode of inheritance and it occurs in various ethnic groups and races. The gene responsible (NPHS1) was identified by genome-wide screening of affected Finnish families and was mapped on the long arm of chromosome 19(19q13)<sup>15</sup>. Nephrin is the protein product of NPHS1, which is a major component of podocytic slit diaphragm. It gives normal function of the glomerular filter. The most common pathological finding is tubular dilatation. Few glomerular abnormalities may be present at birth, but foetal glomeruli, mesangial sclerosis are seen in varying proportions as the disease develops. Electron

microscopy shows wide-spread effacement of the glomerular epithelial foot processes. Slit diaphragm is not seen between the adjacent pedicels and nephrin is not usually expressed. Immunoglobulin and complement are concentrated in scars. Death usually occurs within the first year from complications of nephrotic syndrome.

Among genetic podocytopathies, it is the one form where recurrence was observed. Patralka *et al.* observed nephrotic syndrome after transplantation<sup>16</sup>. The nephrotic grafts showed foot process effacement and decreased slit diaphragms. The presence of anti-nephrin without nephrin antibodies was discovered in these patients, supporting an immune pathogenesis. Thus, recurrent nephrotic syndrome appears to have a different pathogenesis from the original disease and cannot be considered as a true recurrence.

#### *Autosomal Recessive FSGS and steroid-resistant Nephrotic Syndrome*

This form is observed in children. It is a familial form of steroid-resistant nephrotic syndrome with recessive transmission, early onset and lack of recurrence of the disease after transplantation. The gene is mapped on chromosome 1q25-1q31. The gene, NPHS2, encodes podocin, a membrane protein that is exclusively expressed in podocytes of foetal and mature kidney<sup>17</sup>. Podocin plays a role in the functional organization of the slit diaphragm. It interacts with CD2AP and nephrin. Individuals with homozygous or compound heterozygous NPHS2 mutations uniformly present with nephrotic syndrome or heavy proteinuria that does not respond to steroid therapy. The course of rapid progression to end-stage renal disease is almost universal. This genetic defect is observed in children but has been described in young adults. In families with this type of genetic podocytopathies, the affected individuals were compound heterozygotes for R229Q<sup>18</sup>. No patients are homozygous for R229Q. It was postulated that this mutation by itself does not cause FSGS but its association with the disease in that it enhances susceptibility to FSGS in the presence of a second mutated NPHS2 allele. Testing R229Q should be part of the work-up to a renal transplantation in patients with FSGS. The discovery of this mutation suggests the absence of recurrence

risk. Some cases of recurrent proteinuria after transplantation but without anti-podocin antibodies has been described.

### **Autosomal dominant forms**

#### *CD2AP Mutations*

CD2-associated protein (CD2AP) is associated to nephrin and podocin and is related to cytoskeleton. The mutations were studied in knock-out mice which develop glomerular sclerosis, massive proteinuria and die shortly after birth. An African-American series with primary FSGS and HIV-associated FSGS and changes concerning CD2AP protein has been demonstrated and it was found mutations that deleted more than 80% of CD2AP protein. The gene is mapped on chromosome 6p12. It was postulated that as in heterozygous CD2AP mice, decreased levels of CD2AP associated with the heterozygous state in human beings confer disease susceptibility<sup>19</sup>. The transmission of the disease is autosomal dominant. These forms develop disease phenotype in adulthood.

#### *Transient receptor potential cation 6 (TRPC6)*

TRPC6, encoding a member of transient receptor potential superfamily of ion channels, is a calcium-permeable cation channel, which mediates capacitive calcium entry into the cell. Several different mutations have been identified as a cause of autosomal-dominant FSGS. This form of nephrotic syndrome is with adult onset but it exists also in children. Sporadic forms have been described. The gene is mapped on chromosome 11q21-22<sup>20</sup>. Because of the role in the control of cationic channels, new therapeutic approaches can be proposed.

#### *Formin gene INF2*

Another gene identified in a region of chromosome 14q was recently described<sup>21</sup>. By sequencing multiple genes in this region, nine independent nonconservative missense mutations in INF2 were detected, which encode a member of the formin family of actin-regulating family. Formin is co-expressed with nephrin in the slit diaphragm and seems to play a role in the regulation of actin polymerisation in podocyte function. The transmission

of this form is autosomal dominant and affects children and also young adults.

### **Cytosolic proteins**

#### *Alpha-Actinin 4*

This is associated to the foot process of podocytes. The gene coding for this protein is mapping on chromosome 19q13<sup>22</sup>. When mutations concerning this gene are observed, mutant alpha-actinin strongly binds to filamentous actin and this abnormal interaction may affect podocyte function by a variety of mechanisms, including the interaction of actin with the slit-diaphragm and with the glomerular basement membrane via integrins.

Phenotypic presentation is variable with some patients developing nephrotic syndrome, end-stage renal failure at an early age and some having only microalbuminuria,

The transmission of the disease is autosomal dominant.

#### *Phospholipase C epsilon*

PLCE-1/NPHS3 gene mapping on chromosome 10q23-24 encodes phospholipase C epsilon, present in podocyte cytoplasm and which has indirect interaction with nephrin. Mutations concerning this gene have recently been implicated in nephrotic syndrome beginning in childhood with FSGS by renal biopsy<sup>23</sup>. The transmission is an autosomal recessive form.

### **Nuclear proteins. WT1**

WT1 was first considered as a transcriptional factor that plays a major role in kidney and gonad development and maintenance of podocyte function. Immunohistochemistry shows a nuclear staining. This gene is mapped on chromosome 11p13. The nephrotic develop early and may be confused with Finnish type congenital nephrotic syndrome. However, the course to end-stage renal disease is rapid, usually within four years and the histological form is more a Diffuse Mesangial Sclerosis than a typical FSGS<sup>24</sup>. Patients with Denys Drash syndrome and Frasier syndrome (associated or not to Wilms tumor but with gonad abnormalities) have Diffuse Mesangial Sclerosis when they have nephrotic syndrome<sup>25</sup>. When mutations

concerning WT1 are found, it is necessary to explore if there are renal tumour and gonad abnormalities.

### **Mitochondrial products**

The MELAS syndrome (mitochondrial myopathy, encephalopathy, lactic acidosis and stroke) may have renal manifestations as nephrotic syndrome. The renal biopsy can show FSGS<sup>26</sup>. The discovery of diabetes mellitus, neuromuscular symptoms, hypertrophic cardiomyopathy, macular dystrophy associated must propose the exploration of A3243 mutation in the mitochondrial gene MITL1.

### ■ 3. Circulating factors

The fact that FSGS is reputed to recur is the base for proposing the role of a circulating factor to explain the podocytopathy.

Recurrent FSGS following renal transplantation is a unique model of FSGS in human beings as the same process that causes glomerular pathology in the native kidney is presumably acting in the graft. In a typical case, nephrotic syndrome recurs soon after renal transplantation, often within 24 hours. Despite the presence of massive proteinuria, the biopsies show no evidence of FSGS and electron microscopy demonstrates variable foot process effacement. In the presence of continuing proteinuria, the same patients developed segmental glomerular pathology in serial renal biopsies.

Savin *et al.* demonstrated that serum or plasma from patients with recurrent FSGS increased glomerular permeability of glomeruli isolated from normal rats and that plasmapheresis decreased the serum activity on glomerular permeability<sup>27</sup>. It was also demonstrated that when whole serum from patients with collapsing glomerulonephritis was injected into mice, they developed glomerular enlargement, focal, segmental and global collapse, podocyte swelling and diffuse foot process effacement. Removal of IgG from the serum did not eliminate the pathogenic effect and the authors concluded that there might be more than one circulating factors. It was proposed that the plasma of these patients caused redistribution of slit diaphragm proteins, nephrin, podocin, CD2AP and actin from cell membrane in a diffuse cytoplasmic distribution<sup>28</sup>.

Preliminary characterisation of the permeability factor has shown that it is larger than known lymphokines, with special chemical properties as it is weakly anionic and hydrophobic<sup>27</sup>. It consists of highly glycosylated proteins or peptides. Musanne *et al.* used proteomic techniques to identify six proteins that maintained their permeability characteristics after purification and renaturation: fibulin, apolipoprotein 1, vitronectin, albumin isoforms, gammachain fibrinogen and mannan-binding lectin-associated serine protease<sup>29</sup>. Finally, the characteristics of the circulating factor are not totally defined and its presence cannot be evaluated before transplantation.

### ■ HISTOLOGICAL CLASSIFICATION OR COLUMBIA CLASSIFICATION<sup>30</sup>

Usual histological classification identifies five mutually exclusive variants: perihilar variant, cellular variant, tip variant, collapsing variant and if these four variants are eliminated, the fifth variant is nonotherwise specified (NOS). Evolution varies in relation with variant but it is known that terminal renal insufficiency is observed in all variants and the variant determination cannot predict an unfavourable evolution. It is also very difficult with the histological variant to predict response to steroids.

### ■ COLUMBIA CLASSIFICATION AND TRANSPLANTATION

The variant type observed in the native kidney is not predictive of either recurrence or type of FSGS seen on the allograft. The Columbia classification is of no help in predicting recurrence after renal transplantation or histological lesions in the case of proteinuria recurrence<sup>31</sup>.

### ■ FREQUENCY OF RECURRENCE

In evaluating the risk of FSGS recurrence, it must be known that secondary FSGS and genetic FSGS do not recur. These forms must be recognised before the proposition of a transplantation.

In so-called idiopathic forms, but probably with circulating factor, a 30 to 50% recurrence is observed in first renal transplantation. After a graft is lost to recurrence, the probability of a recurrence in a second transplant can increase to up to 80%<sup>27,32</sup>.

## CONCLUSION

Transplantation in patients with FSGS is not contraindicated despite being the form of glomerulonephritis which recurs frequently with a nonnegligible risk of transplant lost. Transplantation from a living donor increases the risk of recurrence. Aggressive plasmapheresis for about two weeks early in the recurrence leads to a long-lasting remission.

**Conflict of interest statement.** None declared.

## References

- Schwartz MM. Focal Segmental glomerulosclerosis. In Jennette JC, Olson JL; Schwartz MM, Silva FG, eds *Heptinstall's Pathology of the kidney*, 6th ed Philadelphia: Lippincott-Raven, 2007:155-95
- Mundel P, Shankland SJ. Podocyte biology and response to injury. *J Am Soc Nephrol* 2002;13:3005-15
- Kriz W. The pathogenesis of 'classic' focal segmental glomerulosclerosis-lessons from rat models. *Nephrol Dial Transplant* 2003;18:vi39-44
- Rennke HG. How does glomerular epithelial cell injury contribute to progressive glomerular damage? *Kidney Int* 1994;45:558-63
- Korbet SM. Angiotensin antagonists and steroids in the treatment of focal segmental glomerulosclerosis. *Sem Nephrol* 2003;23:219-28
- Bagby SP. Obesity-initiated metabolic syndrome and the kidney: A recipe for chronic kidney disease? *J Am Soc Nephrol* 2004;140:2775-91
- Tada M, Jimi S, Hisano S, *et al*. Histopathological evidence of poor prognosis in patients with vesicoureteral reflux. *Pediatr Nephrol* 2001;16:482-7
- Salomon R, Tellier AL, Attie-Bitach T, *et al*. PAX2 mutations in oligomeganephronia. *Kidney Int* 2001;59:457-62
- Bellané-Chantelot C, Chauveau D, Gautier JF, *et al*. Clinical Spectrum associated with hepatocyte factor-1beta mutations. *Ann Int Med* 2004;140:510-7
- Kiproff DD, Colvin RB, Mc Cluskey RT. Focal and Segmental Glomerulosclerosis and proteinuria associated with unilateral renal agenesis. *Lab Invest* 1982;46:275-81
- Greenberg A, Bastacky SI, Iqbal A, *et al*. Focal Segmental Glomerulosclerosis associated with nephrotic syndrome in cholesterol atheroembolism. *Clinicopathological correlations*. *Am J Kidney Dis* 1997;29:334-344
- Rao TK, Filippone EJ, Nicastro AD, *et al*. Associated focal and segmental glomerulosclerosis in the acquired immunodeficiency syndrome. *N Engl J Med* 1984;310:669-73
- Moudgil A, Shidban H, Nast CC, *et al*. Association of Parvovirus B19 infection with idiopathic collapsing glomerulopathy. *Kidney Int* 2001;59:2126-33
- Markowitz GS, Appel GN, Fine PL, *et al*. Collapsing focal segmental glomerulosclerosis following treatment with high dose pamidronate. *J Am Soc Nephrol* 2001;12:1164-72
- Kestila M, Lenkkeri U, Mannikko M, *et al*. Positionally cloned gene for a novel glomerular protein is mutated in congenital nephrotic syndrome. *Mol Cell* 1998;1:1-20
- Patrakka J, Ruotsalainen V, Reponen P, *et al*. Recurrence of nephrotic syndrome in kidney grafts of patients with congenital syndrome of Finnish type role of nephrin. *Transplantation* 2002;73:394-403
- Boute N, Gribouval O, Roselli S, *et al*. NPHS2 encoding the glomerular protein podocin is mutated in autosomal recessive steroid-resistant nephrotic syndrome. *Nat Genet* 2000;24:349-54
- Machuca E, Hummel A, Nevo F, *et al*. Clinical and epidemiological assessment of steroid resistant nephrotic syndrome associated with the NPHS2 R229Q variant. *Kidney Int* 2009;75:727-35
- Kim JM, Wu H, Green G, *et al*. CD2-associated protein haploinsufficiency is linked to glomerular disease susceptibility. *Science* 2003;300:1298-300
- Winn MP, Dastalakis N, Spumey RF, Middleton JP. Unexpected role of TRPC6 channel in familial nephrotic syndrome: does it have clinical implication? *J Am Soc Nephrol* 2006;17:378-87
- Brown EJ, Schlanderoff JS, Becker DJ, *et al*. Mutations in the formin gene INF2 cause focal segmental glomerulosclerosis. *Nat Genet* 2010;42:72-6
- Kaplan JM, Kim SH, North KN, *et al*. Mutations in ACTN4 encoding alpha-actinin-4, cause familial focal segmental glomerulosclerosis. *Nat Genet* 2000;24:251-6
- Gbadegesin R, Hinkes BG, Hoskins BE, *et al*. Mutations in PLCE1 are a major cause of isolated diffuse mesangial sclerosis (IDMS). *Nephrol Dial Transplant* 2008;23:291-297
- Jeanpierre C, Denamur E, Henry I, *et al*. Identification of constitutional WT1 mutations in patients with isolated mesangial sclerosis and analysis of genotype/phenotype correlations by use of a computerized mutation database. *Am J Hum Gen* 1998;62:824-33
- McTaggart SI, Algar E, Chow CW, *et al*. Clinical Spectrum of Denys-Drash and Frasier syndrome. *Pediatr Nephrol* 2001;16:335
- Moulonguet-Doleris L, Hill GS, Chedin P, *et al*. Focal segmental glomerulosclerosis associated with mitochondrial cytopathy. *Kidney Int* 2000;58:1851-8
- Savin VJ, Shara R, Sharma M, *et al*. Circulating factor associated with increased glomerular permeability to albumin in recurrent focal segmental glomerulosclerosis. *New Engl J Med* 1996;334:879-83
- Coward RJ, Foster RR, Patton D, *et al*. Nephrotic plasma alters slit diaphragm-dependent signaling and translocates nephrin, podocin and CD2 associated protein in cultured human podocytes. *J Am Soc Nephrol* 2005;16:629-37
- Musante L, Candiano G, Bruschi M, *et al*. Characterization of plasma factors that alter the permeability to albumin within isolated glomeruli. *Proteomics* 2002;2:197-205
- D'Agati VD, Fogo AB, Bruijn JA, Jennette JC. Pathologic classification of focal segmental glomerulosclerosis: a working proposal. *Am J Kidney Dis* 2004;43:368-82
- Canaud G, Dion D, Zuber J, *et al*. Recurrence of nephrotic syndrome after transplantation in a mixed population of children and adults: course of glomerular lesions and value of the Columbia classification of histological variants of focal and segmental glomerulosclerosis (FSGS). *Nephrol Dial Transplant* 2010;25:1321-8
- Dantal J, Bigot E, Bogers W, *et al*. Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *New Engl J Med* 1994;330:9-25

## Correspondence to:

Prof. Laure-Hélène Noël  
INSERM U 1016  
Necker Hospital  
161 rue de Sèvres  
75015 Paris  
FRANCE  
E-mail: laure-helene.noel@inserm.fr