DISSERTAÇÃO – ARTIGO DE REVISÃO BIBLIOGRÁFICA
Mestrado Integrado em Medicina

RECURRENCE OF FOCAL SEGMENTAL GLOMERULOSCLEROSIS AFTER KIDNEY TRANSPLANTATION

Nuno Moreira Fonseca

Orientador
Dra. La Salete Martins

Porto, Junho 2012

U.PORTO
INSTITUTO DE CIÊNCIAS BIOMÉDICAS ABEL SALAZAR
UNIVERSIDADE DO PORTO

REVIEW ARTICLE
Master in Medicine

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Nuno Moreira Fonseca[1]

Supervisor
La Salete Martins, M.D.[2]

[1]Sixth year medical student
Address: Rua Júlio Lourenço Pinto, nº170, 9ºHab2, 4150-004, Porto, Portugal
Email: moreirafonseca@live.com
Affiliation: Institute of Biomedical Sciences Abel Salazar – University of Porto
Address: Rua de Jorge Viterbo Ferreira, nº228, 4050-313, Porto, Portugal

[2]Nephrologist
Affiliation: Centro Hospitalar do Porto, Nephrology Department
Address: Largo Prof. Abel Salazar, 4099-001, Porto, Portugal

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ABBREVIATIONS

BK	BK virus
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CSA	Cyclosporine A
DD	Diseased donor
EBV	Epstein-Barr virus
FP	Fator de permeabilidade
FSGS	Focal segmental glomerulosclerosis
GBM	Glomerular basement membrane
GESF	Glomerulosclerose segmentar e focal
HCV	Hepatitis C virus
i.e.	isto é / *id est*
LD	Living donor
MCD	Minimal change disease
MeSH	Medical Subject Headings
NOS	Not otherwise specified
PCR	Polymerase chain reaction
PF	Permeability factor
PP	Plasmapheresis

INTRODUCTION

Focal segmental glomerulosclerosis is a major cause of nephrotic syndrome. Recurrence after transplantation is an important cause of graft loss. Treatments currently available for this condition have unsatisfactory results and much still remains unknown about its pathophysiology.

The purpose of this article is to review current medical literature on the recurrence of focal segmental glomerulosclerosis, its risk factors and its optimal management. Search criteria for literature included all relevant English-language studies published between January 1995 and January 2012 to be found in Medline, PubMed and UpToDate, including retrospective, prospective, and cohort studies, case reports, and randomized controlled trials.

MeSH terms included in searches were “focal segmental glomerulosclerosis”, “recurrence”, “allograft”, “kidney transplant”, “kidney transplantation”, “renal transplant”, “renal transplantation”, “immunosuppression” and “plasmapheresis”.

RESUMO

A glomerulosclerose segmentar e focal é uma entidade clinicohistológica. Clinicamente, é caracterizada por uma proteinúria geralmente nefrótica e, histologicamente, é definida como um conjunto de lesões escleróticas glomerulares de padrão segmentar (atinge apenas uma parte do tufo glomerular) e focal (apenas uma parte dos glomérulos renais estão envolvidos).

A GESF é a causa mais comum de síndrome nefrótico idiopático, totalizando 35% de todos os casos. A sua evolução cursa com perda progressiva da função renal. 50-70% dos doentes com GESF atingem no prazo de 10 anos o estadio 5 da doença renal crónica, necessitando de uma terapia de substituição renal.[1]

Após o transplante a taxa de recorrência da doença primária é de 30%. Num período de 10 anos, cerca de 80% dos enxertos poderão tornar-se não funcionantes devido à recorrência da doença.[2, 3]

A GESF pode ser classificada quanto à sua etiologia e quanto ao seu padrão histológico. Etiologicamente a GESF é dividida em primária (idiopática) e secundária. A GESF é considerada primária quando não é possível determinar nenhuma causa subjacente. A GESF pode ser secundária a infecções víricas, toxicidade medicamentosa, massa renal reduzida, obesidade e/ou a alterações genéticas.

A classificação histológica divide a GESF em 5 variantes observadas à microscopia óptica: variante perihilar, variante celular, variante colapsante, variante "tip lesion" e GESF não especificada. Apesar das particularidades histológicas de cada variante, todas têm em comum alterações ultraestruturais dos podócitos. Para além do plano histológico, as variantes apresentam diferenças nas suas características clínicas, na resposta ao tratamento e no prognóstico.

O processo patogénico da GESF primária é desconhecido. O mecanismo de lesão podocitária não está esclarecido. Atualmente, a hipótese que reúne maior consenso é a da existência de um factor circulante, apelidado de factor de permeabilidade. Em 1974, Shaloub sugeriu tratar-se de uma proteína de peso molecular de 30-50KD que circula no sangue e é produzida por células T.[4] Até à data a identificação bioquímica desta molécula permanece incompleta. O fator de permeabilidade foi isolado a partir do soro de doentes com GESF e quando testado *in vitro* mostrou aumentar a permeabilidade glomerular, através de alterações da ultraestrutura podocitária.

Complementarmente a esta teoria, foi desenvolvida a hipótese do fator ausente. Esta hipótese postula a existência de fatores inibidores do fator de permeabilidade. Numa situação patológica, a ausência destes inibidores permitiria a ação do fator de permeabilidade levando ao desenvolvimento de GESF.[5] Mais recentemente foi destacado o papel das integrinas α3β1. Estas são responsáveis pela adesão dos podócitos à membrana basal e encontram-se em número reduzido nos doentes com GESF.[6]

A recorrência de GESF no pós transplante renal foi descrita pela primeira vez por Hoyer nos anos de 1970. Presentemente, a GESF é a doença renal que apresenta maior recorrência após o transplante. O diagnóstico de recorrência é estabelecido através de uma biópsia renal realizada no contexto do aparecimento de proteinúria superior a 1g/dia. [7]

É importante ter presente a noção de que nestes doentes nem toda a proteinúria do pós-transplante renal significa o ressurgimento de GESF. O tempo de instalação, a duração e a magnitude da proteinúria, juntamente com a biópsia do enxerto renal, permitem estabelecer ou excluir a presença de GESF.

O diagnóstico de recorrência de GESF implica a exclusão das etiologias da forma secundária da doença, uma vez que a presença de uma etiologia secundária aponta para um caso de GESF *de novo* ao invés de uma recorrência da doença primária. Para tal são também empreendidos outros estudos, incluindo pesquisas víricas no sentido de eliminar uma causa infecciosa. O tempo de instalação da proteinúria bem como os dados da microscopia (a espessura do processo podocitário e a quantificação do seu apagamento) são úteis à diferenciação entre a recorrência da doença primária e a GESF *de novo*.[8, 9]

A importância da recorrência no pós-transplante e a implicação que esta tem na viabilidade do enxerto levou à análise de fatores que pudessem estar associados a um risco aumentado de recorrência da doença. Apesar de alguns estudos terem encontrado uma taxa de recorrência maior no sexo feminino assim como em indivíduos de raça caucasiana ou hispânica, estes achados não são consensuais e não constituem factores de risco.[10] O grau de atividade do fator de permeabilidade, o padrão histológico da GESF prévio ao transplante e a idade do dador do enxerto renal, também foram estudados como potenciais fatores de risco mas não foi encontrada evidência nesse sentido. [10-12]

Atualmente, os doentes considerados de alto risco para recorrência da GESF são aqueles cuja GESF se iniciou antes dos 15 anos de idade, em que a GESF progrediu até ao estadio 5 da doença crónica renal em 3-5 anos após o seu início; os que apresentem um episódio de

proteinúria maciça no prazo de 4 semanas após o transplante e aqueles que já perderam um enxerto renal devido à recorrência da doença.[8, 11, 13-15]

Apesar de hoje existir melhor informação sobre o processo patogénico da GESF e da sua recorrência, a morbilidade associada e a perda da função do enxerto renal continuam notoriamente elevadas. De uma perspectiva epidemiológica global, os doentes transplantados que sofrem uma recorrência de GESF são um grupo restrito. Este facto limita a possibilidade de se empreenderem estudos randomizados de larga escala com objectivo de estabelecer uma abordagem terapêutica ideal para estes doentes. Consequentemente, o tratamento da recorrência da GESF no pós-transplante renal permanece controverso.

Tanto a terapêutica da GESF como a da sua recorrência se baseiam nos seguintes objectivos: minimização da lesão renal provocada pelo fator de permeabilidade, supressão das células B e T e a nefroproteção a longo prazo. Foi verificado que a remissão sustentada do síndrome nefrótico protege contra a perda de função do enxerto e a progressão da doença renal crónica. Menos de 15% dos doentes que entram em remissão completa progridem para o estadio 5 da doença renal crónica.[16] Mesmo uma remissão parcial, definida como a redução da proteinúria em 50%, associa-se a uma sobrevida superior do enxerto renal. Infelizmente as remissões espontâneas do síndrome nefrótico nestes doentes são raras, ocorrendo em menos de 6% dos casos. [16, 17]

A abordagem imunossupressora é consideravelmente mais eficaz no tratamento da GESF do que no tratamento da recorrência. A plasmaferese é a técnica de eleição para o tratamento dos casos de recorrência, apresentando pouco ou nenhum benefício quando aplicada na GESF prévia ao transplante.

Os doentes com GESF são tratados inicialmente com um regime de corticóides em monoterapia. O esquema terapêutico para adultos deve consistir na toma de 1 mg/kg/dia de prednisolona (até 80 mg) durante 3-4 meses. Este esquema conduz a uma taxa de remissão de 30-40% em adultos e de 50% em crianças, nas doses preconizadas.[16] O estabelecimento da remissão depende de vários factores: a extensão da fibrose intersticial estabelecida antes do início do tratamento, i.e. a cronicidade da lesão renal antes de se iniciar o tratamento; a variante histológica de GESF (a variante "tip lesion" tem a resposta mais favorável e a variante colapsante apresenta os resultados menos favoráveis); a dose e a duração da corticoterapia.

Se as recidivas de síndrome nefrótico forem frequentes ou se o doente for

corticodependente então deve ser iniciado um esquema terapêutico com ciclofosfamida ou com ciclosporina A.

Os doentes são considerados corticoresistentes quando o síndrome nefrótico persiste após 4 meses de terapia com prednisolona na dose de 1 mg/kg/dia. Nestes doentes o uso de ciclosfosfamida entre 2-3 meses até 18 meses, conduz a uma taxa de remissão completa inferior a 20%.[16] Em alternativa, os doentes corticoresistentes podem ser tratados com ciclosporina A numa dose de 3.5-6mg/kg/dia, durante 6 meses, ajustada de forma a manter um nível sérico estável de 100-200ng/mL. Este esquema resulta em taxas de remissão completa inferiores a 25%.[16, 18]

Os doentes que apresentam uma recorrência no pós-transplante são tratados com plasmaferese. Esta técnica permite reduzir a concentração sanguínea do fator de permeabilidade e consequentemente reduzir o nível de proteinúria. A plasmaferese consiste na substituição do plasma por uma solução de albumina a 5%. O número de sessões necessárias para alcançar a remissão do síndrome nefrótico é variável. O esquema típico do tratamento consiste em 1 a 2 trocas de volume plasmático com uma frequência de 3 a 4 vezes por semana, até que a remissão seja alcançada. A maioria dos pacientes necessita aproximadamente de 10 a 20 sessões. Se a ciclofosfamida for usada durante 2 meses como agente adjuvante, poderá ser possível reduzir o número de sessões necessário para alcançar a remissão. A eficácia da plasmaferese é variável. Os melhores resultados verificam-se em crianças, nas quais a taxa de remissão completa pode atingir os 60 a 80%.[1, 10, 19] As recidivas podem surgir em 20 a 30% dos doentes e a plasmaferese poderá ser necessária em esquema crónico num terço dos doentes. [15]

A variabilidade de resposta dos doentes a este tratamento poderá ser explicada pelas especificidades de cada população, pela magnitude e pelo tempo desde o início da proteinúria. Os doentes podem apresentar diferentes níveis de atividade do fator plasmático, ou mesmo uma sensibilidade renal diferente para esta molécula. Foi comprovado que o momento de início da plasmaferese é crucial. Quanto mais cedo for começada após a verificação da proteinúria, melhores são os resultados.[1] No entanto, na maioria dos estudos sobre a utilização da plasmaferese verificou-se que, apesar do tratamento, a sobrevida do enxerto é fraca. Durante este tratamento, 25 a 35% dos enxertos tornam-se não–funcionantes no prazo de 32-41 meses.[10] Apesar da plasmaferese ter sido extensivamente testada no tratamento de doentes com recorrência de GESF, nunca um estudo randomizado testou a sua eficácia.

A imunoadsorção com coluna de proteína A é outro método que permite reduzir a concentração plasmática do fator de permeabilidade em doentes com recorrência da GESF, dada a sua grande afinidade molecular para com este fator. No entanto, não é utilizada em monoterapia mas sim como um meio adjuvante da plasmaferese. A combinação destas técnicas produz uma redução da proteinúria em 82% dos doentes.[1, 20]

Recentemente, o rituximab mostrou resultados promissores quando associado à plasmaferese no tratamento da recorrência da GESF, especialmente em doentes resistentes à plasmaferese. Esta combinação permitiu induzir remissão parcial ou completa em até 71,4% dos casos.[21]

Uma outra aposta interessante no tratamento destes doentes é a galactose oral, uma vez que este fármaco não tem os efeitos tóxicos característicos dos imunossupressores geralmente empregues. Esta molécula apresenta uma grande afinidade para com o fator plasmático e, quando administrada, diminui a interação deste fator com a galactose do glicocálice glomerular.[22] Mais estudos são necessários para o apuramento dos benefícios do uso da galactose nestes doentes.

Tanto os doentes com GESF como aqueles com recorrência de GESF devem ser tratados com inibidores da enzima de conversão da angiotensina ou com bloqueadores dos receptores da angiotensina II. Estes fármacos são nefroprotetores dado que diminuem a proteinúria e retardam a progressão da doença renal crónica.

A hiperlipidemia é uma característica comum nos doentes com síndrome nefrótico e deve ser tratada. As estatinas são geralmente empregues e permitem baixar o risco de mortalidade cardiovascular destes doentes.

Considerando que a plasmaferese, em qualquer das suas combinações enquanto tratamento da recorrência da GESF, é a técnica que demonstra os melhores resultados na remissão do síndrome nefrótico, foi postulada a hipótese do seu efeito benéfico na prevenção da recorrência, se iniciada no período do pós-transplante imediato, antes do surgimento de proteinúria. No entanto, o uso profilático da plasmaferese em doentes com alto risco de recorrência demostrou não existir modificação nem na taxa de recorrência da GESF após o transplante nem na sobrevida do enxerto.[10, 23] Até à data, nenhum meio dito profilático demonstrou prevenir a recorrência da GESF.

Perante a elevada taxa de recorrência no pós-transplante e perda da função do enxerto a que esta leva, as considerações sobre a opção de transplantar um doente em estadio 5 da doença renal crónica tornam-se delicadas. Para além de serem considerados os riscos

envolvidos no procedimento cirúrgico, a discussão da transplantação tem uma dimensão ética que deriva da escassez de órgãos existentes. Tal facto levou a uma avaliação exaustiva dos resultados obtidos na transplantação, de forma a apurar a estratégia que apresenta os melhores resultados. Uma das áreas mais estudadas foi a proveniência do enxerto. Inicialmente, verificou-se que os rins de dador vivo teriam uma maior taxa de recorrência e como tal a sua utilização foi desaconselhada. Mais tarde, avaliando a sobrevida deste tipo de enxerto no pós-transplante verificou-se que estes podem ser utilizados, e que apesar da taxa de recidiva ser elevada, esta não é superior à verificada nos rins de dador cadáver. [23]

Atualmente o transplante com rim de dador vivo não está aconselhado em doentes que tenham tido uma GESF de evolução fulminante, nem em doentes que já tenham perdido um enxerto devido à recorrência da doença. Contudo, esta modalidade de transplantação, ainda que muito controversa, pode ser realizada nestas situações desde que, doente e dador, tenham sido devidamente informados sobre os riscos envolvidos.

A GESF permanece uma entidade misteriosa. Para que no futuro seja possível dar uma melhor resposta a estes doentes, é necessário investigar mais aprofundadamente o processo patogénico subjacente. Só desta forma será possível elaborar novas estratégias que permitam prevenir a sua recorrência ou a indução da sua remissão.

Recurrence of Focal Segmental Glomerulosclerosis After Kidney Transplantation

Focal segmental glomerulosclerosis is a clinicopathologic entity defined as proteinuria associated with focal and segmental sclerotic glomerular lesions. Podocyte injury is the main pathophysiologic process. It is thought to be caused by a circulating plasma protein, known as permeability factor. Although its nature remains uncertain, it is known to alter glomerular permeability to proteins. The disease courses with progressive loss of renal function and patients often undergo kidney transplantation, determined by end-stage renal disease. Primary disease frequently recurs in the allograft kidney, at rates of 30-50%. Disease recurrence leads to allograft loss in 80% of patients within the first 10 years. Several risk factors for recurrence have been established but to this day no strategy has shown to prevent recurrence. Treatment is based on plasmapheresis and immunosuppressant drugs, but results are unsatisfactory. The success of transplantation as a treatment option is hampered by the high risk of recurrence on allografts and by the poor graft survival rate. FSGS recurrence is considered a major challenge for transplant physicians and has prompted concerns over the transplantation of kidneys from living donors. This review aims to provide a comprehensive overview of the recurrence of focal segmental glomerulosclerosis through a critical analysis of the relevant English-language literature.

Definition of FSGS

Focal segmental glomerulosclerosis is a clinicopathological entity clinically characterized by proteinuria, commonly in the nephrotic range, with high incidence of progression to chronic kidney disease stage 5.[9] Pathologically, it is characterized by sclerotic glomerular lesions which are simultaneously focal, involving only a subset of glomeruli, and segmental, affecting only a portion of the glomerular tuft.[24] Other features include the obliteration of glomerular capillaries with hyalinosis, the formation of adhesions between the glomerular tuft and Bowman's capsule, and podocyte hypertrophy.[25]

Epidemiology

FSGS is the most common cause of idiopathic nephrotic syndrome, accounting for 35% of all cases and over 50% of cases among blacks.[26] Within 10 years of initial presentation, 50–70% of patients with FSGS will progress to CKD stage 5 requiring renal replacement therapy.[1] In the United States, the annual incidence of CKD stage 5 cases due to FSGS is 7 per million for the general population, 20 per million for black individuals, and 5 per million for white individuals.[27] It is currently the underlying cause in 3.3% of all CKD stage 5 patients.[27] Its incidence has increased more than eleven-fold over the past 20 years.[27] FSGS is also the disease most frequently responsible for CKD stage 5 in children.[4]

Recurrence following transplantation develops in approximately 30% (range 15%–50%) of patients and is associated with poor graft survival.[4, 9] More than half of kidney recipients with recurrent disease will lose grafts as a consequence.[2, 9, 10]

Classification

FSGS can be classified according to etiology and histopathology.[9] The etiological classification divides FSGS into primary (idiopathic) or secondary.[9] FSGS is considered primary when no underlying cause is found. FSGS can be secondary to other disease processes such as viral infections (e.g., HIV, Parvovirus 19), drug toxicity (e.g., captopril, pamidronate, heroin and lithium), reduced renal mass (e.g., reflux nephropathy, sickle cell disease), or obesity and genetic abnormalities (table 1).[1]

The histopathologic classification divides FSGS into five main light microscopy patterns: perihilar variant, cellular variant, tip variant, collapsing variant and FSGS not otherwise specified (NOS). The morphologic criteria of this classification are summarized in table 2. Despite the particular histological features of each variant, the existence of ultrastructural podocyte alterations is a common element.[9] Besides light microscopy features, immunofluorescence and electron microscopy prove necessary to exclude other causes of glomerular sclerotic scarring. Imunofluorescence microscopy usually reveals an absence of immune

Primary (idiopathic) FSGS
Secondary FSGS
Infections
HIV, Parvovirus B19
Drug toxicity
Pamidronate, Lithium, Interferon-α,
Heroin, Captopril
Reduced renal mass
Unilateral renal agenesis
Reflux nephropathy
Surgical renal ablation
Renal dysplasia
Chronic allograft nephropathy
Obesity
Renal scarring
Focal proliferative glomerulonephritis
Diabetic nephropathy
Hypertensive arterionephrosclerosis
Membranous glomerulopathy
Thrombotic microangiopathies
Genetic abnormalities
Mutations in nephrin (NPHS1)
Mutations in podocin (NPHS2)

Table 1 - Etiologic Classification of FSGS

deposits, with the exception of certain unspecific deposits thought to be the result of the nonspecific binding of IgM and complement (C3 and variably C1 in sclerotic lesions). Mild mesangial deposition of IgM may also be found.[25] Electron microscopy examination reveals ultrastructural alterations in podocytes including hypertrophy, foot process effacement, microvillous transformation, and detachment from glomerular basement membrane.[9]

Variants of FSGS may be etiologically and pathogenetically distinct and therefore give rise to different clinical characteristics.[9] Nevertheless, it is currently unclear whether these morphologic variants reflect different pathogenesis or are the expression of varying severities of podocyte injury or different stages of the same pathologic process.[25]

The collapsing variant is defined by the presence of at least one glomerulus displaying segmental or global obliteration of the glomerular capillary lumina, with wrinkling and collapse of the glomerular basement membrane associated with podocyte hypertrophy and hyperplasia.[9, 25] This variant has the most aggressive course. The disease often presents with renal dysfunction, undergoes rapid progression to CKD stage 5 and exhibits low sensitivity to steroids.[9, 25] Besides occurring in primary FSGS, it also presents in many secondary etiologies, mainly HIV-associated FSGS.[9, 25] It is most commonly seen among blacks which may explain the worse prognosis in this group.[28] Given its unique histopathology and clinical course, some argue that this variant should be named collapsing glomerulopathy and not be considered a form of FSGS.[28] Nonetheless, consensus has not yet been reached on this matter.

The tip variant of FSGS is defined by the presence of at least one glomerulus with a segmental lesion involving the tip domain (i.e., the peripheral 25% of the glomerular tuft next to the origin of the proximal tubule). It presents as a steroid sensitive nephrotic syndrome and has the best rate of full remission of all FSGS variants.[9, 25]

The cellular variant is defined by the presence of at least one glomerulus with segmental endocapillary hypercellularity involving at least 25% of the tuft and causing occlusion of the capillary lumen. It is thought that this variant of FSGS represents an early developmental stage in the evolution of segmental sclerosis.[9, 25] Moreover, some patients may undergo spontaneous remission without immunosuppressive therapy.[28]

The perihilar variant of FSGS is defined by the presence of perihilar sclerosis and hyalinosis involving more than 50% of segmentally sclerotic glomeruli.[9, 25] It is frequently observed in FSGS secondary to increased glomerular capillary pressure, such as renal agenesis, obesity or reduced functional mass.[9, 25, 28]

The NOS variant is defined as a discrete segmental consolidation of the glomerular tuft by increased extracellular matrix, causing obliteration of the glomerular capillary lumen. It is the most common form of FSGS and is generally considered the classic form of this disease. The diagnosis of this variant requires the exclusion of all other morphologic categories.[9, 25]

FSGS variants appear to be substantially different in terms of clinical features, optimal therapy, response to treatment, and renal prognosis.[9] However, further studies involving large cohorts of patients with FSGS are required in order to determine if this classification is useful for the management of FSGS.[9]

Pathogenesis

The pathogenesis of primary FSGS is unclear but its key process appears to be injury to glomerular visceral epithelial cells (podocytes). Podocytes have several functions including glomerular filtration, biosynthesis, and maintenance of glomerular capillary architecture.[9] Thus, structural and functional abnormalities of podocytes cause permeability changes associated with proteinuria.[9]
In FSGS, damage to podocytes is followed by proliferation of mesangial, epithelial and endothelial cells, with subsequent collapse of glo merular capillary loops and eventual sclerosis.[4] The most popular pathogenetic hypothesis suggests the contribution of a circulating plasma factor.[4]

Variant	Positive Criteria	Negative Criteria
Collapsing variant	At least one glomerulus with segmental or global collapse and podocyte hypertrophy/hyperplasia	None
Tip variant	At least one segmental lesion involving the tip domain (outer 25% of tuft next to origin of proximal tubule) The tubular pole must be identified in the defining lesion The lesion must have either an adhesion or confluence of podocytes with parietal or tubular cells at the tubular lumen or neck	Exclude collapsing variant Exclude any perihilar sclerosis
Cellular variant	At least one glomerulus with segmental endocapillary hypercellularity occluding lumina, with or without foam cells and karyorrhexis	Exclude tip and collapsing variants
Perihilar variant	Perihilar sclerosis and hyalinosis involving >50% of segmentally sclerotic glomeruli	Exclude cellular, tip, and collapsing Variants
FSGS (NOS)	At least one glomerulus with segmental increase in matrix obliterating the capillary lumina	Exclude perihilar, cellular, tip and collapsing variants

Table 2 - Morphologic Variants of FSGS

Shalhoub was the first to suggest the existence of a T Cell secreted circulating mediator– named permeability factor – with an anionic charge and affinity for protein A and galactose.[22, 29]

Although several other studies have supported the importance of this T cell PF, its complete biochemical identification has not yet been achieved, nor has it been shown to be FSGS specific.[30] A putative PF with a molecular weight between 30-50 kDa has been isolated from the sera of patients with FSGS and shown to increase glomerular permeability to albumin in *in vitro* experiments.[4]

PF may alter the podocyte structure through its effects on nephrin and podocin or by interfering with the phosphorylation of cellular proteins in the podocyte. It may also influence the activity of serine proteases or induce integrin-like kinase activity leading to detachment of podocytes from GBM.[29, 31, 32] PF also inhibits the synthesis of nitric oxide, possibly by up-regulating asymmetric dimethylarginine (an endogenous inhibitor of all nitric oxide synthases), leading to the loss of its anti-fibrotic effect within the mesangium.[33]

Amongst the molecules proposed to be PF is cardiotrophin-like cytokine 1, but doubts remain about this assumption.[34]

Studies have shown that almost 100% of patients with high levels of PF develop recurrence of the disease. This, allied with the often rapid onset of proteinuria, sometimes within hours to days after transplant, supports the hypothesis of PF as an etiological factor.[4] Moreover, serum from patients with recurrent FSGS has been shown to produce proteinuria when injected intravenously into rats.[4]

Complementary to the PF theory another hypothesis, the "missing factor theory", has been postulated.[5, 35-38] Normal serum components such as apolipoproteins E and J have been proposed to be inhibitory factors of serum PF.[5] It is thought that their absence triggers PF activity.[5] One study has shown that the urine of patients with FSGS neutralizes PF activity, suggesting the loss of an inhibitor in the urine.[39] In another study, while plasma from FSGS patients altered the distribution of slit diaphragm proteins, coincubation of non-nephrotic plasma with the nephrotic plasma prevented these alterations.[40]

Modifications in α3β1 integrins, responsible for the attachment of podocytes to the glomerular basement membrane, may be important in the pathogenesis of primary FSGS. Studies have shown that reductions in α3β1-integrin subunits on podocytes found in patients with primary FSGS can be associated with the degree of podocyte loss.[6] The amount of podocyte loss and the reduction in α3β1 integrins were correlated with the degree of proteinuria and established glomerular sclerosis.[6] Extensive podocyte loss is considered to play a role in FSGS pathogenesis and the level of urinary podocytes has been found to correlate with disease progression in FSGS and in many other renal diseases.[41, 42]

The pathogenic process of secondary FSGS and the familial forms will not be discussed in detail since, unlike primary FSGS, these forms do not recur after transplantation. The familial forms involve gene mutations for molecules like nephrin (NPHS1) or podocin (NPHS2) which control slit diaphragm assembly.[1, 10] In these cases there will be no recurrence of disease once an allograft is in place, since FSGS pathogenesis is due to mutations in the kidney and not to PF.[1, 10] If clinical entities of secondary etiologies appear after transplantation, the new episode of FSGS is classified as *de novo* and not as a recurrence.[1, 10]

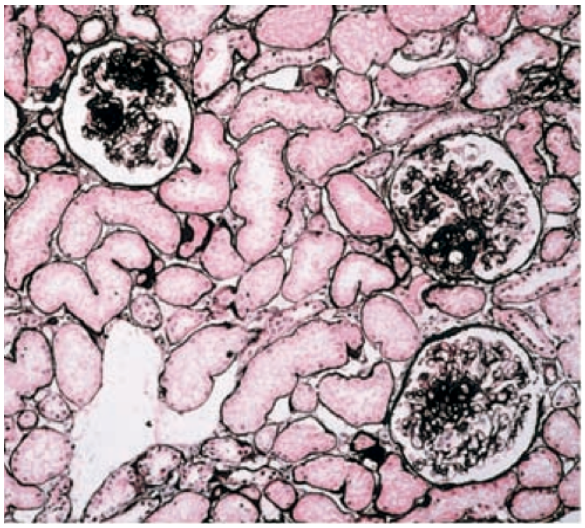

Figure 1 – segmental sclerosis involving many glomeruli

Recurrence

The recurrence rate of FSGS is 30% in adults and 50% in children for the first allograft.[1] There is an exponential increment of risk up to 80%, for the second allograft and approximately 100% for the third and fourth allografts.[43, 44]

The recurrence of FSGS after renal transplantation was first described by Hoyer in the 1970's. Nowadays, FSGS is the kidney disease which most commonly recurs after kidney transplantation and its diagnosis is best made based upon renal allograft biopsy findings in the setting of significant proteinuria (greater than 1 g/day).[7] Some authors purport to only evaluate the hypothesis of recurrence when a serum albumin level of <3.0 g/L is present.[20]

It should be kept in mind that not every proteinuria seen in a post-transplantation period is necessarily a recurrence of primary FSGS or a *de novo* episode caused by a secondary form of FSGS.[29, 45, 46] In patients whose primary disease is FSGS, it is often difficult to differentiate between proteinuria secondary to FSGS recurrence and that normally seen in the immediate post-transplant period.[29, 45] Early proteinuria may result from numerous causes, comprising proteinuria from native kidneys or secondary to ischemia–reperfusion injury to the graft. Thus, during the early post-transplant period, a diagnosis of FSGS recurrence, whilst often supposed, is difficult to establish in the absence of a renal biopsy. Non-FSGS proteinuria should decrease over a 3-week period but can persist up to 9 weeks after transplantation.[29, 46] Nephrectomy of native kidneys in order to enable early diagnosis and intervention in recurrent FSGS is not recommended.[10] Myslak has reported persistent proteinuria >1.5 g/day and/or increases in proteinuria >0.5 g/day beyond 3 weeks post-transplant, together with falling serum albumin, as being highly suggestive of FSGS recurrence.[46] Other tests, such as monitoring PF, have not been proven to be of clinical value.[47] Proteinuria developing 2 years after renal transplant is usually considered a manifestation of chronic allograft nephropathy, since FSGS recurrence rarely occurs after this stage.[10] An allograft biopsy should provide important information and enlighten the cause of post-transplantation proteinuria. In case of FSGS, the disease's characteristic lesions will be found.

A diagnosis of recurrence requires accurate classification of the original disease and exclusion of de *novo* FSGS.[9] *De novo* FSGS develops as a secondary form of FSGS. It is important to distinguish between recurrence of the primary disease and the presence of its secondary form because the treatment of these entities is significantly different.[9]

In order to confirm recurrence, it is necessary to exclude all etiologies of secondary FSGS; evidence of infection should be assessed, preferably via PCR or direct immunostaining. PCR for Parvovirus B19, CMV, EBV, BK, and HCV should be carried out.[9]

Primary FSGS is more likely to present with early and sudden onset nephrotic syndrome, while secondary FSGS presents more insidiously, with subnephrotic range proteinuria and renal insufficiency.[8] Exceptions are, for example, FSGS secondary to pamidronate toxicity which typically presents with full nephrotic syndrome and acute or subacute renal failure, showing collapsing lesions on microscopy.[8] Microscopy provides others clues that may help to distinguish primary and secondary processes. The amount of foot process effacement in secondary FSGS is usually much less than that seen in primary FSGS (usually >30%).[8] The quantitative analysis of foot process' width also allows differentiation. One study reported a median width for podocyte foot processes of 3236 nm in patients with idiopathic FSGS and 1098 nm in patients with secondary FSGS (compared with 562 nm in control patients).[9]

In case of recurrence, the main histological feature revealed by electron microscopy is widespread foot process effacement, also compatible with minimal change disease.[48] Serial biopsies taken 2 to 6 months after recurrence show reduced incidence of MCD features over time, along with increased incidence of characteristic FSGS segmental lesions, accumulation of intracapillary foam cells, podocyte detachment and epithelial hypercellularity, as seen with light microscopy.[9]

Accordingly to IJpelaar, these later biopsies reveal the same histological variant seen in the native kidney in 81% of cases.[48] Diagnostic biopsies of FSGS have been reported as soon as 4 to 6 weeks after the transplantation.[48] Recurrence may

appear evident within days after transplant (as early as the first 48-72 h), particularly in children.[49] The average time of diagnosis is 2 weeks after surgery in children and 7.5 months in adults.[50]

It has been demonstrated that the recurrence of FSGS leads to a lower graft survival rate in recipients with this disease when compared to recipients with other primary renal diseases.[51] Recurrence will lead to graft loss in 30-50% of patients during the first 5 years of follow-up and up to 80% over a 10-year period.[2, 3]

Risk factors for recurrence

Age

It has been largely documented that children have a higher incidence of recurrence. It has been established that disease onset under the age of 15 is a risk factor for the development of FSGS in the post-transplantation period. Disease onset under the age of 6 is linked with recurrence rates as high as 50-80%.[8, 13, 14]

Race and ethnicity

The recurrence rate in whites (23%) and Hispanics (20%) is significantly greater than in blacks (9%).[10] A United States Renal Data System analysis also found that the rate of graft loss caused by recurrent FSGS was significantly greater for both living donor (LD) and diseased donor (DD) transplants in white recipients (LD, 4.2%; DD, 2.8%) than in nonwhite recipients (LD, 3.2%; DD, 1.1%).[10] Although FSGS incidence is higher amongst African-Americans, the post-transplant recurrence rate for this group is lower.[10, 17]

Sex

A single center study has identified a higher recurrence rate among women. Other studies have not found any such difference.[14]

Clinical course of native kidney FSGS

An aggressive course of primary FSGS prior to transplant is a risk factor for recurrence. Disease course is considered aggressive when CKD stage 5 is reached within 3-5 years of disease onset.[8, 11, 13]

Permeability Factor

A study by Savin measured and correlated PF activity with the risk of recurrence. The study found that high PF activity (≥0.50) was associated with a recurrence rate of 86% whereas low activity (<0.50) was associated with a recurrence rate of 17%.[11] The study also states that plasmapheresis can be associated with reductions in both proteinuria and in PF.[11] However, pre-transplant activity of PF has yet to be shown to predict recurrence. Research on PF continues, with no consensus for the time being. The lack of standardized bioassays and their inability to consistently predict recurrence preclude routine testing at the present time.[20]

Histological features of native kidney FSGS

It has been stated that histological findings of mesangial hypercellularity in the majority of glomeruli can be linked with increased incidence of recurrence.[1] However, other studies fail to show any significant correlation: mesangial hypercellularity was seen in 25% of kidney recipients with recurrence and in 20% of those without recurrence.[10] Therefore, taking existing studies into consideration, native kidney histology does not appear to be a significant risk factor for recurrent FSGS.[10] In much the same way, the importance of histologically classifying the primary disease into variants has also been disputed regarding its usefulness in predicting both risk of recurrence and the histological variant in which disease will recur. It appears that all variants of FSGS recur at comparable frequencies, regardless of the FSGS variant.[52] Contrary to IJpelaar, Canaud has stated that there is no correlation between the histological variants in native kidneys and those later found in allografts. The histological classification has been acknowledged to predict renal outcomes and responses to treatment of native kidneys, but doubts remain over its usefulness in estimating the risk of recurrence.[9]

Early onset of post-transplant proteinuria

There is consensus among most studies that early recurrent heavy proteinuria, usually 2 to 4 weeks after the allograft is in place, is associated with a higher incidence of recurrence.[8, 14, 15]

Donor source

According to one study, recipients of kidneys from older donors are more likely to suffer recurrence and so the use of renal grafts from younger donors in adults with FSGS was advised.[12]

Previous graft loss due to FSGS recurrence

Prior graft loss due to recurrence is linked with a very high risk of recurrence in subsequent allografts.[1, 8, 13] The rates of recurrence are as high as 80% for the second transplant and >90% for the third and subsequent transplants.[44]

- Onset of primary FSGS before the age of 15
- Aggressive course of primary disease (CKD stage 5 in 3-5years)
- Onset of heavy proteinuria within 4 weeks of transplantation
- Recurrence of FSGS on a previous graft

Table 3 – Risk factors for the recurrence of FSGS

Management

Despite the advances attained in understanding the pathogenic process of recurrent FSGS, the associated morbidity and rate of graft loss remains notably high. Owing to the lack of randomized, large case series and double-blinded studies, the ideal management of this disease remains controversial. Still, the most important therapeutic aims have been established. These are, first of all, to minimize the initial injury to allograft by circulating factor, then, to achieve T cell and B cell suppression to prevent immunological injury and finally to provide long-term nephroprotection. The achievement of sustained remission protects against early graft loss and progression of CKD in the allograft kidney.[1] Less than 15% of patients achieving complete remission progress to CKD stage 5 whereas up to 50% of persistently nephrotic patients progress to CKD stage 5 within 5 years.[16] Even partial remission, defined as a decline in proteinuria of more than 50%, is associated with an improved renal survival. Unfortunately, spontaneous remissions are rare in nephrotic FSGS patients, occurring in less than 6% of patients.[16 17]

Immunosuppression has proven considerably more effective in the treatment of the primary disease than in the recurrent form. Conversely, plasmapheresis is considered to be the therapy currently presenting the best results for treating recurrent FSGS, but has little or no use in primary disease.

The following section summarizes current advances in the management of FSGS and recurrent FSGS.

Management of FSGS

The immunosuppressive approach to the treatment of primary FSGS includes the use of steroids, alone or in combination with cytotoxic agents or cyclosporine A.

In the initial treatment of FSGS, steroids are most commonly used alone. An initial course of treatment for adults should consist of prednisone given at a dose of 1 mg/kg/day (up to 80 mg) for 3-4 months.[16] In patients responding to treatment (complete or partial remission), the dose of prednisone may be reduced to 0.5 mg/kg/day with treatment maintained for 6-8 weeks and then tapered off over 4-6 weeks.[16] A course of up to 6 months of prednisone therapy has achieved remission rates of 50% in children and has shown less encouraging rates of 30-40% in adults.[16] Remission depends on the initial renal function, the pathological variant of FSGS (with the tip variant carrying the most favorable prognosis, and the collapsing variant the worst prognosis), the extent of interstitial fibrosis on renal biopsy, and dose and duration of the steroid treatment.[17]

If relapse occurs after a prolonged period of steroid-induced remission, a second course of steroid therapy should be undertaken. If relapses are frequent or if patients are steroid-dependent then treatment with cyclophosphamide or cyclosporine A should be initiated.[16] The pathways through which high-dose cyclosporine may induce remission are divided into those with a direct effect on podocytes and those with an indirect effect. CSA's direct action on podocytes is a blockade of calcineurin-mediated dephosphorylation of synaptopodin and stabilization of the actin cytoskeleton.[19] The indirect effect comprises the inhibition of both T helper cell activation and cytokine release.[1, 4]

A combination of cyclophosphamide and prednisolone during a 2 to 3 month period, reestablishes remission in 70% of children and adults who relapse. Relapsed patients treated with Cyclosporine A usually undergo remission within the first month of therapy.[16] However, maintenance of remission in these patients implies continuous CSA therapy, since over 75% of patients relapse once CSA is tapered or stopped.[16]

The median time of remission for corticosensitive patients is 3 months in adults and 8 months in children.[17] Adults are considered to have steroid-resistant FSGS when nephrotic syndrome persists in spite of a 4 month trial with prednisone at a dose of 1 mg/kg/day.[16] In steroid-resistant adults, courses of cyclophosphamide, typically for 2-3 months but with durations up to 18 months, have resulted in complete remission rates of <20%.[16] A course of 3.5-6mg/kg/day of cyclosporin A, taken in two daily doses for 6 months, with adjustments to maintain a blood level of 100-200ng/mL, has resulted in complete remission rates of less than 25% in patients with steroid resistant FSGS.[1, 16, 18]

It has been suggested that patients who achieve remission under the use of CSA may be slowly tapered-off medication without subsequent relapse if remission has been established for over a year.[16] Thus, an attempt should be made to taper CSA in patients with prolonged remissions in order to minimize potential complications such as nephrotoxicity.[16, 17]

Management of recurrent FSGS

Strategies such as plasmapheresis and protein A column immunoadsorptive therapy decrease the serum concentration of circulating permeability factor, thus lowering proteinuria and inducing remission of nephrotic syndromes.[1] Over the past decade numerous studies of these methods have been carried out, with variable degrees of success reported.

Plasmapheresis treatment consists in the removal of plasma which is replaced by a 5%

albumin fluid.[1] The number of treatment sessions required to achieve remission is inconstant. The typical PP schema consists of: 1 to 2 plasma volume exchanges with a frequency of 3 to 4 treatments per week, until remission. Most patients require approximately 10-20 sessions.[1] Adjuvant treatment with a 2-month course of cyclophosphamide lowers the number of PP sessions required to induce remission.[15]

The effectiveness of PP treatment is variable. The best outcomes for PP are seen amongst children, with complete remission attained in 60 to 80% of cases.[1, 10, 19] Relapse rates vary from 20% to 30% and maintenance PP is necessary in a third of those responding to treatment.[15]

The variability in patients' responses may be explained by variations between specific population studies or in time of onset and magnitude of proteinuria.[53] Additionally, there may be differences in the level or pathogenicity of the permeability factor, or even in the kidney's sensitivity to this molecule.[53] There is evidence that treatment starting time is very important. Best results are obtained when PP is started early after the onset of proteinuria and when renal biopsies show no abnormalities other than foot process fusion on electronic microscopy (usually during the first month).[1, 20, 53, 54] In contrast, if PP is delayed or if FSGS sclerotic lesions are well established, typically a month after onset, the treatment's effectiveness will be lower.[20, 53, 54]

Nevertheless, most studies using PP state that the overall graft survival rate for recipients with recurrent FSGS is still considered poor. Graft failure rates at 32 to 41 months after transplant were found to be 25% to 35%.[10] Even though PP has been extensively used in the management of recurrent FSGS, no randomized trials have addressed its efficacy.[10]

Protein A column adsorption has been used in combination with PP because it has been shown to have affinity with the putative PF.[1] This combination reduced proteinuria in 82% of cases. Data is available only on the efficacy of the combination treatment since protein A column adsorption has never been tested on its own.[1, 20]

Rituximab is a monoclonal antibody derived from the combination of both human and mouse genetic material. It causes B cell depletion by targeting the CD-20 surface marker.[1] Rituximab's role in the management of FSGS was discovered by chance while being used to treat other conditions in patients with FSGS.[21] Rituximab has shown promising results in the treatment of recurrent FSGS when used conjointly with PP, especially in PP-resistant patients.[55] This combination leads to complete or partial remission in as many as 71.4% of cases.[21] The rituximab therapeutic schema consists of 2 to 6 doses of 375 mg/m^2 given once every 1 to 2 weeks. Remission is generally achieved after 9 months of therapy.[1] A case of hepatitis B reactivation has been reported after treatment with rituximab in this setting.[56]

Galactose presents a high affinity for PF, and experimental data suggest that it could reduce PF activity to undetectable levels in just 48 hours.[4, 53, 57] One of the mechanisms by which PF might induce proteinuria is by interacting with the galactose in the glomerular glycocalyx.[22] Administration of galactose might induce the formation of circulating complexes of free galactose and PF, thus preventing PF from interacting with the glycocalyx.[22] One study reports a case of long-standing remission of a PF-associated nephrotic syndrome on oral galactose therapy.[57] This treatment was used only as a last resort after the disease had proved resistant to corticosteroids, immunosuppression and PP. Due to its non-toxic features, galactose may represent a highly desirable therapeutic tool in the management of recurrent FSGS. However, reports of its use in this setting are scarce and more studies are needed to thoroughly confirm its beneficial effect.[4, 53, 57]

Other therapeutic approaches may be recommended. Both patients with FSGS or recurrent FSGS should be given angiotensin-converting-enzyme inhibitors or angiotensin II receptor blockers. They diminish the degree of proteinuria and slow the rate of progression to CKD stage 5.[11] Along with its antiproteinuric effect, losartan also decreases the production of transforming growth factor β, the central cytokine of fibrotic processes.[54] African-Americans appear to particularly benefit from angiotensin-converting enzyme inhibitors.[17] The major concern with the use of these therapeutic agents is that early usage may result in graft dysfunction.[1]

Hyperlipidemia is a common finding in patients with nephrotic syndrome, and may reach alarming levels. Statins are indicated for these patients, who will benefit from lower cardiovascular mortality. Moreover, statins have been shown to have a nephroprotective effect independent of the lipid metabolism.[1] Close attention should be payed to the association of statins and cyclosporine due to the higher risk of rhabdomyolysis.[1]

Prophylaxis of recurrent FSGS

Considering that treatment with PP, in its several combinations, has shown the best rates of partial and complete remission, it has been postulated that its use might also be beneficial in preventing the establishment of recurrence, when used before the detection of proteinuria in the post-transplant period. However, an approach involving prophylactic PP in patients with high risks of recurrence showed that recurrence of FSGS

after renal transplantation was the same whether or not patients received preemptive PP and long-term outcomes were not improved.[10, 23]

To date, no prophylactic method has been documented to prevent the recurrence of FSGS.

Transplantation

Patients with history of prior transplant loss secondary to FSGS recurrence have a very high risk of recurrence in their current allograft. In this setting the rate of recurrence is as high as 80% in the second transplant and > 90% in the third and subsequent transplants.[43, 44] Recurrence in these patients will lead to graft loss in 10% to 80 % of the cases. [43, 44]

In the face of this discouraging reality of extremely high rates of recurrence and graft loss due to recurrence, the option of whether or not to undergo additional transplants should be carefully considered. Besides taking into account the risks involved in the procedure itself, the discussion of transplantation as a treatment option in this scenario raises far more ethical concerns than other treatments, given the scarcity of available resources. An extensive evaluation of transplantation outcomes has been carried out in order to understand which strategies offer the best results, in order to avoid procedures being undertaken in vain.

One of the most commonly assessed issues is that of the outcomes of transplants using living donor and deceased donor kidneys. Several studies have found a higher rate of recurrence in recipients of LD related grafts; probably due to closer HLA matching between living versus DD.[58] On the basis of this finding, recommendations have been made towards avoiding LD transplantation in recipients with FSGS as their original disease.[59] Other studies have shown 5-year graft survival rates for LD recipients of 82% in patients with non-FSGS, compared with only 71% in FSGS patients; on the other hand, in DD recipients, the graft survival rate was 64% in those with FSGS vs. 68.5% in those with no FSGS.[23] Thus, the outcome appears to be worse for patients with FSGS regardless of the type of donor. LD is not an inappropriate choice for transplantation in FSGS patients since when comparing the results of LD transplant in FSGS patients (71%) to the graft survival rate in non-FSGS DD patients (68.5%), the results are quite similar.[23, 59-61] In any case, appropriate counseling should be provided to the family, patient and donor since the failure of a related-LD transplant may have a devastating effect.

Patients whose first graft showed no signs of early dysfunction and patients not at high risk for recurrence, can be considered for a transplant with a LD kidney.[23] In general, due to less encouraging outcomes, children or adults who presented with fulminant FSGS, or patients who lost their previous graft due to recurrent disease should avoid LD kidney transplantation, but can proceed with this measure as long as all risks have been previously disclosed to both donor and recipient.[62]

Conclusion

Primary focal segmental glomerulosclerosis remains a mysterious entity with a poorly understood pathogenesis. Its recurrence after kidney transplantation is frequent and is associated with poor graft survival. Proteinuria should be promptly and routinely assessed after transplantation to check for recurrence. Before establishing the diagnosis of recurrence, secondary etiologies should be excluded.

The established risk factors for recurrence are: onset of primary disease before the age of 15, aggressive course of primary disease, early onset of heavy proteinuria after transplantation and recurrence on a previous graft. Even though it is possible to ascertain a patient's risk profile, strategies to prevent recurrence have not proved efficient.

Recognition of recurrence should prompt the immediate use of plasmapheresis. Immunosuppressive therapy has an adjuvant role. Despite the various therapeutic schemes employed, results are still unsatisfactory. There is a shortage of multicenter controlled studies aimed at delineating optimal therapeutic approaches. Drugs such as rituximab and galactose may show promising results in the future.

In spite of the risk of recurrence, patients with FSGS should not be excluded from transplantation. Kidneys from living donors should be avoided in patients with high-risk of recurrence, although it is not an absolute contraindication. The loss of a graft has a significant impact on the patient, even more so if donated by a living relative, and so careful consideration should be taken.

In order to improve the care we provide to patients, a deeper knowledge of the pathogenesis that underlines this disease is needed. Only then will it be possible to understand how to prevent its recurrence, and how to induce its remission.

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ACKNOWLEDGMENT

I would like to thank Dr. La Salete Martins for her scientific guidance and generosity in accepting the supervision of this work.