Clinical Study

Recurrent Focal Segmental Glomerulosclerosis in Renal Allograft Recipients: Role of Human Leukocyte Antigen Mismatching and Other Clinical Variables

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1. Introduction

Primary Focal Segmental Glomerulosclerosis (FSGS) is the pathologic description of multiple histopathologic variants [1] of a disease process that results in fibrosis of segments of multiple renal glomeruli. Recent discovery of genetic mutations affecting podocyte structure and function has lead to understanding of a minority of the FSGS pathophysiology [2–5]. However, the underlying mechanism of the disease process itself is still largely unknown, and the presence of a circulating permeability factor has been implicated in its etiology [6]. In patients with defined podocyte mutations FSGS only rarely recurs [7, 8] unless associated with that same permeability factor as shown by Carraro et al. [9].

Primary FSGS without a clear etiology has a high risk of recurrence of about 30% in the first allograft [10]. Furthermore, recurrence rate in the second allograft is even higher [11]. The episodes of recurrence are managed by modalities such as plasmapheresis, indicating that humoral factor is involved in the pathogenesis [12].

The presence of high levels of HLA-specific antibodies reduces access to transplantation, increases the risk of rejection, and impacts long-term graft survival. This is only partially overcome by improved immunosuppressive or desensitizing regimens. Whereas risk of acute rejection in recent years has substantially decreased [13, 14], chronic rejection remains the most common cause of allograft failure for which the mechanism is still poorly understood and may be mediated by a variety of factors including low levels of immune responses to alloantigens, previous early episodes of acute rejection, and other variables [15]. HLA donor/recipient mismatching has been associated with...
| No. | LM/IF                                                                 | EM                                                                 |
|-----|----------------------------------------------------------------------|----------------------------------------------------------------------|
| 1   | 8 G: no global or segmental sclerotic/proliferative lesions, no pub | 1 G focal FP effacement, focally swollen endothelial cells, normal GBM |
|     | LM; 2 G trace IgM mesangial                                          |                                                                      |
| 2   | 12 G: 1 globally sclerosed, no segmental sclerotic/proliferative    | 2 G diffusely effaced FP, normal GBM                                 |
|     | lesions, scant protein reabsorption droplets                         |                                                                      |
|     | IF; 1 G negative                                                     |                                                                      |
| 3   | 5 G: tubules with mild atrophy with extensive dilatation/thyroidization with sparse protein reabsorption droplets and mild ATN, with absent inflammation or fibrosis | 1 G with mesangial expansion and diffusely effaced FP, normal GBM |
|     | IF; 0 G                                                              |                                                                      |
| 4   | 16 G: no segmental sclerotic/proliferative lesions, focal interstitial chronic inflammation | 3 G focal FP effacement, normal GBM                                   |
|     | IF; 0 G                                                              |                                                                      |
| 5   | 5 G: no global or segmental sclerotic/proliferative lesions, focal mild interstitial fibrosis | 1 G focal FP effacement, normal GBM                                 |
|     | IF; 1 G negative                                                     |                                                                      |
| 6   | 1 G: no global or segmental sclerotic/proliferative lesions, focal mild interstitial fibrosis | 1 G focally effaced FP with microvillous change, focal loss of fenestrations, focal areas of prominence of the lamina rara interna of GBM |
|     | IF; 0 G                                                              |                                                                      |
| 7   | 2 G: no global or segmental sclerotic/proliferative lesions, tubules 100% intact, no fibrosis | 1 G with focally effaced FP, normal GBM                              |
|     | IF; 1 G trace mesangial IgM                                           |                                                                      |
| 8   | 25 G: 2 globally sclerosed, with remaining G exhibiting mesangial expansion with increased matrix | 2 G with mesangial expansion and diffusely effaced FP, normal GBM |
|     | IF; 1 G with 1+ IgM                                                   |                                                                      |
| 9   | 12 G: no global or segmental sclerotic/proliferative lesions, tubules 100% intact | 2 G with focally effaced FP, normal GBM                              |
|     | IF; 2 G weak IgG mesangial staining                                   |                                                                      |
| 10  | 7 G: 1 globally sclerosed, one nodule of mesangial matrix, mild tubular atrophy with mild interstitial inflammation | 1 G with patchy effacement of FP and focal areas of prominence of the lamina rara interna with mild mesangial expansion and no electron dense deposits |
|     | IF; 1 G 1+ IgM mesangial                                             |                                                                      |
| 11  | 20 G: majority of normal size and cellularity, but few with mild mesangial expansion with focal thickening of the glomerular basement membrane without “spikes” or “splitting”. 1 G with a central area of hyalinosis | 2 G with focal effacement of FP and mild mesangial expansion, normal GBM |
|     | IF; 2 G negative                                                     |                                                                      |
| 12  | 29 G: no global or segmental sclerotic/proliferative lesions, tubules 70% intact with mild atrophy, mild ATN, and mild interstitial fibrosis | 1 G with focal effacement of FP and mild mesangial expansion, normal GBM |
|     | IF; 2 G with 1+ punctuate mesangial deposits and trace IgM mesangial deposits |                                                                      |
| 13  | 12 G: 1 globally sclerotic G, no segmental sclerotic/proliferative lesions, tubules 100% intact, no fibrosis, IF; 2 G with trace + mesangial IgA and + c1q deposits | 1 G partial effacement of FP and focally collapsed GBM               |
| 14  | 15 G: no global or segmental sclerotic/proliferative lesions, IF; 3 G negative | 1 G with focal areas of effacement of FP with microvillous transformation and normal GBM |
| 15  | 20 G: 2 G with segmental sclerotic lesions with focal epithelial cell prominence with glomerular capsular adhesions IF; 5 G with 1+ IgM and trace IgA and c1q | 1 G with extensively obliterated FP and normal GBM with focally ischemic pleating |
| 16  | 6 G: no global or segmental sclerotic/proliferative lesions IF; 1 G negative | 2 G with focal effacement of FP and normal GBM                        |
increased incidence of humoral rejection brought about by production of donor specific antibodies to HLA antigens [15, 16]. In addition, increased HLA-DR4 frequency has been reported in adult patients with idiopathic FSGS [17], and the donor HLA-B8 may be associated with risk of recurrent FSGS [18].

Considering that there are documented associations (i) between primary FSGS and increased HLA-DR4 frequency [17], (ii) between recurrent FSGS and donor HLA haplotypes [18], (iii) between recurrent FSGS and acute humoral rejection episodes post-transplant [19], and the implication of a humoral factor in the etiology of FSGS and acute rejection episodes, we hypothesized that HLA donor/recipient mismatching may be used as a surrogate marker to predict the risk of recurrence of FSGS in renal allograft patients. No such analysis has been attempted before to identify unique markers of recurrent FSGS, as evidenced by nephrotic range proteinuria or by renal biopsy, in both children and adults.

2. Materials and Methods

2.1. Data Collection. We conducted a retrospective review of the medical records of 119 transplant patients, 42 pediatric and 77 adult, with the primary diagnosis of FSGS, who received a total of 131 transplants (49 in the pediatric population, aged 8–21, and 82 in the adults, between the ages of 22 and 80) at the transplant service of the Montefiore Medical Center in the Bronx, NY, from February 1990 to July 2007. This study was approved by the Institutional Review Board of the Montefiore Medical Center. Demographic information such as the patients’ date of birth and date and age at transplantation, race, gender, and presence or absence of current hypertension was obtained from patient medical records.

Tissue typing data such as HLA typing data of the HLA A, B, and DR subtypes for each patient and donor was available for all but two patients. Finally, data indicating the use of pre- and posttransplant plasmapheresis was obtained from patient medical records.

### 2.2. Treatments and Definitions

Diagnosis of primary FSGS was based on renal biopsy report review by the study investigators.

Diagnosis of FSGS recurrence in our patient population was defined as the presence of both nephrotic range proteinuria of >40 milligrams per m² per day or urinary protein to creatinine ratio (\( U_{P/CR} \)) greater than 3.5 and the report of histological evidence of FSGS on allograft biopsy.

In our center, patients with recurrent FSGS underwent post-transplant plasmapheresis also known as Therapeutic Plasma Exchange (TPE). In addition, patients with high pre-transplant plasma reactive antibodies (PRAs) levels undergo prophylactic plasmapheresis prior to transplantation to reduce the likelihood of immediate antibody-mediated allograft rejection.

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**Table 1: Continued.**

| No. | LM/IF | EM |
|-----|-------|----|
| (17) | 19 G: 1 globally sclerotic glomerulus, no segmental sclerotic/proliferative lesions, tubules 100% intact, no fibrosis, IF; 1 G with trace IgM mesangial deposits | 1 G with focal areas of effacement of FP with mild mesangial expansion, no electron dense deposit and normal GBM |
| (18) | 7 G: 1 globally sclerotic G, no segmental sclerotic/proliferative lesions, focally increased mesangial matrix, tubules 80% intact, mild tubular atrophy without ATN but with focal protein reabsorption droplets and mild fibrosis, IF; 0 G | 1 G with scant mesangial electron dense deposits, extensive effacement of FP, focal swelling of endothelial cells, variably thickened and pleated GBM with apparent expansion of mesangial matrix possibly by collapsing capillary basement membranes |
| (19) | 20 G: 2 globally sclerotic G and 4 segmental lesions with minimal mesangial cells and matrix increase, minimal tubular atrophy, fibrosis, and inflammation, IF; 4 G with 2+ focal IgM, trace IgA, and 1+ κ and λ light chains | 2 G with rare mesangial and subendothelial electron dense deposits, mild thickening of GBM and intact FP |
| (20) | 7 G: with no segmental sclerotic/proliferative lesions, mildly increased mesangial matrix, tubules 90% intact, with mild fibrosis with focal protein reabsorption droplets IF; 2 G with trace IgM | 1 G with focal areas of effacement of FP with mild mesangial expansion, no electron dense deposit and normal GBM |
| (21) | 16 G: 2 segmental sclerotic lesions, patchy mild inflammation predominantly mononuclear IF; 6 G, 1+ mesangial IgM and focal trace c1q | 1 G with focally obliterated FP and normal GBM |
| (22) | 10 G: no segmental sclerotic/proliferative lesions, tubules 80% intact with mild focal atrophy and dilatation with scant protein reabsorption droplets, IF; 2 G with trace c1q | 1 G with partially effaced FP, GBM with focal subendothelial lucencies and focally present inflammatory cells in capillary lumens |

**Table Legend:**

LM: light microscopy; IF: immunofluorescence for IgG, IgM, IgA, c3, c1q, κ and λ light chains, Fibrinogen; EM: electron microscopy; G: glomeruli; GBM: glomerular basement membrane; IgA: immunoglobulin A; IgM: immunoglobulin M; IgG: immunoglobulin G; FP: foot processes of glomerular epithelial cells.
Table 2: Demographics of recurrent Focal Segmental Glomerulosclerosis in renal allograft recipients from 1990 to 2007 at Montefiore Medical Center.

| Data of all transplant recipients | All transplants for primary FSGS (n = 131) | FSGS recurrence (n = 22) | No recurrence (n = 109) | P value |
|-----------------------------------|---------------------------------------------|--------------------------|-------------------------|---------|
| Age at transplantation (years)    | 29.28 ± 1.26                                | 18.64 ± 2.86             | 31.43 ± 1.31            | <.001   |
| Male                              | 71 (54%)                                    | 11 (50%)                 | 60 (55%)                | .82     |
| Malec                             | 49 (37%)                                    | 7 (32%)                  | 42 (39%)                | .59     |
| African American                  | 52 (40%)                                    | 11 (50%)                 | 41 (38%)                |         |
| White                             | 66 (50%)                                    | 8 (37%)                  | 58 (53%)                | .32     |
| Other                             | 13 (10%)                                    | 3 (14%)                  | 10 (9%)                 |         |
| African Americanc                 | 31 (24%)                                    | 6 (27%)                  | 25 (23%)                |         |
| Whitec                            | 51 (39%)                                    | 7 (32%)                  | 44 (40%)                | .65     |
| Otherc                            | 10 (8%)                                     | 2 (9%)                   | 8 (7%)                  |         |
| Live Donor                        | 50 (38%)                                    | 10 (45%)                 | 40 (27%)                | .63     |
| Cadaveric Donor                   | 78 (60%)                                    | 12 (55%)                 | 66 (61%)                |         |
| Prednisone                        | 117 (89%)                                   | 18 (82%)                 | 99 (91%)                |         |
| Calcineurin Inhibitors            | 103 (79%)                                   | 16 (73%)                 | 87 (80%)                | .75     |
| Purine inhibitors                 | 28 (21%)                                    | 6 (27%)                  | 22 (20%)                |         |
| Rapamycin                         | 30 (23%)                                    | 4 (18%)                  | 26 (24%)                |         |

| Data for subgroup of pediatric patients | All transplants for primary FSGS (n = 49) | FSGS recurrence (n = 19) | No recurrence (n = 30) | P value |
|-----------------------------------------|---------------------------------------------|--------------------------|-------------------------|---------|
| Age at transplantation (years)          | 15.08 ± 0.62                                | 13.79 ± 1.02             | 15.9 ± 0.76             | .085    |
| Male                                    | 27 (55%)                                    | 9 (47%)                  | 18 (60%)                | .56     |
| Malec                                   | 15 (31%)                                    | 6 (32%)                  | 9 (30%)                 | .71     |
| African American                        | 23 (47%)                                    | 10 (53%)                 | 13 (43%)                | .80     |
| White                                   | 17 (35%)                                    | 6 (32%)                  | 11 (37%)                |         |
| Other                                   | 9 (18%)                                     | 3 (16%)                  | 6 (20%)                 |         |
| African Americanc                       | 11 (22%)                                    | 6 (32%)                  | 5 (17%)                 | .63     |
| Whitec                                  | 10 (20%)                                    | 5 (26%)                  | 5 (17%)                 |         |
| Otherc                                  | 7 (14%)                                     | 2 (11%)                  | 5 (17%)                 |         |
| Live Donor                              | 21 (43%)                                    | 8 (42%)                  | 13 (43%)                | .99     |
| Cadaveric Donor                         | 28 (57%)                                    | 11 (58%)                 | 17 (57%)                |         |
| Prednisone                              | 38 (78%)                                    | 16 (84%)                 | 22 (73%)                | .061    |
| Calcineurin Inhibitors                  | 35 (71%)                                    | 13 (68%)                 | 22 (73%)                |         |
| Purine inhibitors                       | 16 (33%)                                    | 6 (32%)                  | 10 (33%)                |         |
| Rapamycin                               | 8 (16%)                                     | 3 (16%)                  | 5 (17%)                 |         |

* number of subjects, corrected to exclude acute rejection.
Table 3: Recurrent Focal Segmental Glomerulosclerosis in renal allograft recipients from 1990 to 2007 at Montefiore Medical Center.

| Data of all transplant recipients | All transplants for primary FSGS ($n = 131$) | FSGS recurrence ($n = 22$) | No recurrence ($n = 109$) | $P$ value |
|---------------------------------|-----------------------------------------------|---------------------------|--------------------------|----------|
| HLA, mean                       | $1.83 \pm 0.14$                               | $1.85 \pm 0.16$           | $1.73 \pm 0.33$          | .83      |
| HLA$^c$                         | $1.89 \pm 0.17$                               | $1.91 \pm 0.19$           | $1.80 \pm 0.45$          | .81      |

| Number of HLA matches           | All transplants for primary FSGS ($n = 131$) | FSGS recurrence ($n = 22$) | No recurrence ($n = 109$) | $P$ value |
|---------------------------------|-----------------------------------------------|---------------------------|--------------------------|----------|
| 0                               | 37 (28%)                                      | 30 (28%)                  | 7 (32%)                  | .99      |
| 1                               | 23 (18%)                                      | 20 (18%)                  | 3 (14%)                  | .99      |
| 2                               | 27 (21%)                                      | 22 (20%)                  | 5 (23%)                  | .99      |
| 3                               | 21 (16%)                                      | 17 (16%)                  | 4 (18%)                  | .99      |
| 4                               | 13 (10%)                                      | 11 (10%)                  | 2 (9%)                   | .99      |
| 5                               | 4 (3%)                                        | 3 (3%)                    | 1 (5%)                   | .99      |
| 6                               | 4 (3%)                                        | 4 (4%)                    | 0 (0%)                   | .99      |
| HLA < 3                         | 42 (32%)                                      | 27 (25%)                  | 15 (68%)                 | .99      |
| HLA ≥ 3                         | 10 (8%)                                       | 6 (6%)                    | 4 (18%)                  | .99      |
| PRA$^m$                         | $26.83 \pm 3.04$                              | $30.19 \pm 3.65$          | $14.89 \pm 3.76$         | .036     |
| PRA < 30                        | 32 (24%)                                      | 20 (18%)                  | 12 (55%)                 | .72      |
| PRA ≥ 30                        | 11 (84%)                                      | 8 (7%)                    | 3 (14%)                  | .15      |
| PRA$^c$                         | $23.76 \pm 3.67$                              | $26.73 \pm 4.52$          | $14.38 \pm 4.79$         | .15      |
| PRA$^c$ < 30                    | 22 (17%)                                      | 13 (16%)                  | 9 (41%)                  | .99      |
| PRA$^c$ ≥ 30                    | 4 (3%)                                        | 2 (2%)                    | 2 (9%)                   | .99      |
| PreTx pp                        | 8 (6%)                                        | 5 (5%)                    | 3 (14%)                  | .13      |
| PostTx pp                       | 25 (19%)                                      | 8 (7%)                    | 17 (77%)                 | <.001    |
| Acute Rejection                 | 39 (30%)                                      | 32 (29%)                  | 7 (32%)                  | .80      |
| Humoral                         | 6 (5%)                                        | 6 (6%)                    | 0 (0%)                   | .29      |
| Cellular                        | 22 (17%)                                      | 15 (14%)                  | 7 (32%)                  | .14      |
| Chronic Rejection               | 46 (35%)                                      | 35 (32%)                  | 11 (50%)                 | .16      |
| Hypertension                    | 63 (48%)                                      | 49 (45%)                  | 14 (64%)                 | .16      |

| Data for subgroup of pediatric patients | All transplants for primary FSGS ($n = 49$) | FSGS recurrence ($n = 19$) | No recurrence ($n = 30$) | $P$ value |
|----------------------------------------|-----------------------------------------------|---------------------------|--------------------------|----------|
| HLA, mean                              | $1.43 \pm 0.19$                               | $1.42 \pm 0.32$           | $1.43 \pm 0.23$          | .92      |
| HLA$^c$                                | $1.39 \pm 0.24$                               | $1.46 \pm 0.43$           | $1.33 \pm 0.27$          | .98      |

| Number of HLA matches                 | All transplants for primary FSGS ($n = 49$) | FSGS recurrence ($n = 19$) | No recurrence ($n = 30$) | $P$ value |
|----------------------------------------|-----------------------------------------------|---------------------------|--------------------------|----------|
| 0                                      | 16 (33%)                                      | 7 (37%)                   | 9 (30%)                  | .95      |
| 1                                      | 10 (20%)                                      | 3 (16%)                   | 7 (23%)                  | .95      |
| 2                                      | 14 (29%)                                      | 5 (26%)                   | 9 (30%)                  | .95      |
| 3                                      | 4 (8%)                                        | 2 (11%)                   | 2 (7%)                   | .95      |
| 4                                      | 5 (10%)                                       | 2 (11%)                   | 3 (10%)                  | .95      |
| 5                                      | 0 (0%)                                        | 0 (0%)                    | 0 (0%)                   | .95      |
| 6                                      | 0 (0%)                                        | 0 (0%)                    | 0 (0%)                   | .95      |
| HLA < 3                                | 40 (82%)                                      | 15 (79%)                  | 25 (83%)                 | .72      |
| HLA ≥ 3                                | 9 (18%)                                       | 4 (21%)                   | 5 (17%)                  | .72      |
| PRA$^m$                                | $16.68 \pm 3.52$                              | $13.56 \pm 4.12$          | $18.68 \pm 5.17$         | .88      |
| PRA < 30                               | 30 (61%)                                      | 12 (63%)                  | 18 (60%)                 | .72      |
| PRA ≥ 30                               | 10 (20%)                                      | 3 (16%)                   | 7 (23%)                  | .72      |
| PRA$^c$                                | $10.24 \pm 3.27$                              | $12.63 \pm 5.46$          | $8.57 \pm 4.08$          | .52      |
We analyzed our data using STATA (Stata Corporation, College Station, TX, USA) and Microsoft Office Excel (Microsoft Corporation, Redmond, WA, USA). Variables of interest included number of HLA matches, age at transplantation, time to recurrence, and PRA levels recorded as absolute values. Variables that were coded as binaries include the presence or absence of treatment with plasmapheresis, occurrence or absence of recurrent disease, donor allograft type (deceased versus live), and race (white, black, Hispanic or other).

Statistical analysis was performed using Fischer’s exact test for categorical data and the Mann-Whitney test for nonparametric variables with a *P*-value of <.05 being statistically significant.

3. Results

3.1. Demographics of Recurrent Disease. We analyzed 119 patients (42 children and 77 adults) who received 131 allografts for primary FSGS. Forty-two pediatric patients underwent 49 transplants and 77 adult patients underwent 82 transplants in the period from February of 1990 to July of 2007. There were total of 131 allografts for primary FSGS (11 subjects were transplanted twice, and one had a third allograft) with 20 cases of FSGS recurrence (17 children) in the primary allograft, and two children who had FSGS recurrence in the secondary allograft. All cases of recurrent FSGS (*n* = 22) in the allograft had a pathologic report of this diagnosis (Table 1). Recurrence of FSGS post transplantation occurred in 63.6% of cases within one month; less than 14 days in 7 out of 22 recurrences (31.8%), between 15 and 30 days in another 7 (31.8%), and 36.4% recurrences occurred beyond 31 days post transplant. Of the 77 adult patients, only 3 developed recurrences in the allograft, all of them being in the primary graft. All patients with FSGS recurrence in a second allograft (*n* = 2) were pediatric (13 years and 18 years at the age of last transplantation), and in all cases the first allograft was lost due to histopathologic diagnosis of recurrent FSGS in addition to nephrotic range proteinuria.

Majority of our transplant patients were Caucasians but 40% were African American, and 10% other races (Hispanic, Asian, and Middle Eastern). Demographic information is presented in Table 2. There is a statistically significant association between age at transplantation and recurrence as explained by the higher rate of recurrence in the pediatric population. This observation has been noted in a previous report published by NAPRTCS data [20].

There was no significant association noted between FSGS recurrence and acute rejection, chronic rejection, number of HLA matches, or pretransplant plasmapheresis (Table 3). There was an expected association between posttransplant plasmapheresis and recurrence of FSGS in the allograft that is explained by the fact that one of the core treatment modalities to deal with recurrence is TPE.

There were higher levels of PRA that were statistically significant in the control group as compared to recurrent disease (Table 3). However, when corrected for acute rejection which is a confounder because it is independently associated with elevated PRA levels, this apparent relationship becomes insignificant. This lack of significant association persists when the PRA levels are divided into two groups of higher than or lower than 30 (Table 3). Kaplan-Meier analysis showed that recurrent FSGS-free survival time was similar in subjects with PRA < 30 and PRA ≥ 30, *P* = .47.

In the pediatric subset, 43% of the recipients received organs from live donors and 57% from deceased donors. There were 19 cases of recurrence in the pediatric age group, 3 of them being in the second allograft. There was no increased risk of recurrence associated with ethnicity, male gender, deceased versus live donor organ transplantation, or the modality of immunosuppression used (Table 2).

Independently, we found that acute rejection is not associated with HLA mismatching or TPE and there is no baseline difference in hypertension between the two
Table 4: (a) Acute Rejection in renal allograft recipients from 1990 to 2007 at Montefiore Medical Center. (b) Subgroup of subjects with acute rejection adjusted for FSGS recurrence in renal allograft recipients from 1990 to 2007 at Montefiore Medical Center.

(a) Data of adult and pediatric patients combined

| Number of HLA matches | All transplants for primary FSGS (n = 131) | Acute Rejection (n = 39) | No-rejection (n = 92) | P value |
|-----------------------|-------------------------------------------|--------------------------|----------------------|--------|
| 0                     | 37 (28%)                                  | 10 (26%)                 | 27 (29%)             |        |
| 1                     | 23 (18%)                                  | 12 (31%)                 | 11 (12%)             |        |
| 2                     | 27 (21%)                                  | 6 (15%)                  | 21 (23%)             |        |
| 3                     | 21 (16%)                                  | 5 (13%)                  | 16 (17%)             | .36    |
| 4                     | 13 (10%)                                  | 4 (10%)                  | 9 (10%)              |        |
| 5                     | 4 (3%)                                    | 1 (3%)                   | 3 (3%)               |        |
| 6                     | 4 (3%)                                    | 1 (3%)                   | 3 (3%)               |        |
| HLA < 3               | 42 (32%)                                  | 18 (46%)                 | 24 (26%)             | .73    |
| HLA ≥ 3               | 10 (8%)                                   | 5 (13%)                  | 5 (5%)               |        |
| PRAm                  | 26.83 ± 3.04                              | 32.75 ± 5.28             | 23.76 ± 3.67         | .054   |
| PRAc                  | 30.19 ± 3.65                              | 36.35 ± 6.08             | 26.73 ± 4.52         | .068   |
| PRA < 30              | 32 (24%)                                  | 10 (26%)                 | 22 (24%)             | .080   |
| PRA ≥ 30              | 11 (84%)                                  | 7 (38%)                  | 4 (4%)               |        |
| Hypertension          | 63 (48%)                                  | 15 (38%)                 | 48 (52%)             | .25    |
| HTNc                  | 38 (29%)                                  | 8 (21%)                  | 30 (33%)             | .032   |

Data for subgroup of pediatric patients

| Number of HLA matches | All transplants for primary FSGS (n = 49) | Acute Rejection (n = 21) | No-rejection (n = 28) | P value |
|-----------------------|-------------------------------------------|--------------------------|----------------------|--------|
| 0                     | 16 (33%)                                  | 6 (29%)                  | 10 (36%)             |        |
| 1                     | 10 (20%)                                  | 6 (29%)                  | 4 (14%)              |        |
| 2                     | 14 (29%)                                  | 5 (24%)                  | 9 (32%)              |        |
| 3                     | 4 (8%)                                    | 1 (5%)                   | 3 (11%)              | .59    |
| 4                     | 5 (10%)                                   | 3 (14%)                  | 2 (7%)               |        |
| 5                     | 0 (0%)                                    | 0 (0%)                   | 0 (0%)               |        |
| 6                     | 0 (0%)                                    | 0 (0%)                   | 0 (0%)               |        |
| HLA < 3               | 40 (81%)                                  | 17 (81%)                 | 23 (82%)             | .99    |
| HLA ≥ 3               | 9 (18%)                                   | 4 (19%)                  | 5 (18%)             |        |
| PRAm                  | 16.68 ± 3.52                              | 26.75 ± 6.86             | 10.24 ± 3.27         | .024   |
| PRAc                  | 18.68 ± 5.17                              | 31.55 ± 9.41             | 8.57 ± 4.08          | .026   |
| PRA < 30              | 30 (61%)                                  | 9 (29%)                  | 21 (75%)             | .14    |
| PRA ≥ 30              | 10 (20%)                                  | 6 (29%)                  | 5 (18%)             |        |
| Hypertension          | 28 (57%)                                  | 11 (52%)                 | 17 (61%)             | .77    |
| HTNc                  | 15 (31%)                                  | 5 (24%)                  | 10 (36%)             | .13    |

PRAc: PRA peak, mean corrected to exclude FSGS recurrence cases.
HTNc: for cadaveric donors.

(b) Adult and pediatric patients with acute rejection and recurrence of FSGS

|                      | All acute rejection and no recurrence (n = 21) | PostTx pp (n = 5) | No PostTx pp (n = 16) | P Value |
|----------------------|-----------------------------------------------|-------------------|-----------------------|--------|
| Cellular rejection   | 15 (71%)                                      | 2 (40%)           | 13 (81%)              | .12    |
| Humoral rejection    | 6 (29%)                                       | 3 (60%)           | 3 (19%)               |        |
groups (acute rejectors versus controls). There is however an expected association between hypertension and the presence of a deceased donor allograft (Table 4).

4. Discussion

In our study we present single-center experience with recurrent FSGS. Recurrent FSGS has been explained by the existence of a circulating humoral factor called the FSGS permeability factor as seen in the report of Sharma et al. [6]. This has been supported by the effectiveness of postrecurrence plasmapheresis as treatment of recurrent FSGS in the allograft. In our study we hypothesized that HLA donor/recipient mismatching may create immunologic milieu that may enhance production of this factor, and as such may be used as a surrogate marker to predict the risk of recurrence of FSGS in renal allograft patients even before transplantation is performed.

Our study confirmed that there is a positive association between recurrence of FSGS and younger age at transplantation. The 1997 report of NAPRTCS supports this finding as well [20]. This is partially explained by the fact that pediatric FSGS is more aggressively treated by transplantation than with years of dialysis that is seen with adult disease before a transplant is considered. The hypothesis is that dialysis removes, over time, whatever humoral circulating permeability factor that is responsible for recurrent disease.

Our hypothesis of a link between HLA donor/recipient mismatches, a surrogate marker of increased risk of rejection, and FSGS recurrence was founded in these proposed humoral mechanisms of recurrent FSGS [17–19]. The results we obtained definitely support the association between PRA levels and acute rejection with a significance level of \( P < .05 \), a result that is expected. On the same note, we reported an expected significant association between posttransplant plasmapheresis and recurrence, explained by the fact that the former is the major treatment modality for the latter. However, recurrence and pretransplant plasmapheresis do not show any association.

We could not draw definite conclusions about association of PRA levels in our subjects with recurrence, as PRA testing has changed from traditional to Luminex-based during the study observation period. The limitations of this study include a study population that is skewed towards African Americans, a group that has traditionally been described as low risk for recurrence and the limitations of a single center experience. Another limitation of our study is that we relied for study entry criteria (primary FSGS) on the histopathology report from multiple clinical pathologists (patients were referred to/from outside institutions). Recurrent FSGS was defined based on pathology report, rather than review of individual slides/EM microphotographs, by the study pathologist. The biopsy reports were not utilizing Columbia FSGS classification, as it was published in 2004. However, we excluded patients with no glomeruli on the biopsy report, with no diagnosis of recurrent FSGS, or with missing biopsy reports.

Although our study did not confirm original hypothesis, we could state, with a power of 83%, that HLA mismatching is not a good surrogate marker for predicting FSGS recurrence. HLA mismatching also did not prove to be associated with an increased risk of acute rejection, and this observation is explained by the availability of more effective modalities of immunosuppression to treat acute rejection, despite fewer matches. A larger, multicenter study will be better able to distinguish between the incidence of pediatric and adult FSGS and the recurrence patterns for each and study them separately.

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