Pediatric Focal Segmental Glomerulosclerosis: Favorable Transplantation Outcome With Plasma Exchange

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Research Article

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Abstract

Background: Although kidney transplantation (KT) is the treatment of choice for pediatric kidney failure (KF); concerns for recurrence in cases of focal segmental glomerulosclerosis (FSGS) are still present. This study aimed to investigate the outcome of KT in children with KF secondary to FSGS, with implementation of preemptive perioperative plasma exchange (PE) for non-genetically proven patients.

Methods: Forty FSGS pediatric kidney transplant recipients were studied. Of them: 12 patients (30%) had genetically proven NPHS2 mutations/familial and 28 (70%) were sporadic FSGS patients. Sporadic patients electively received 6 preoperative PE sessions. Recurrence of proteinuria was managed with PE and Rituximab (RTX). Kaplan-Meier curves were used to analyze graft and recurrence free survival data.

Results: The mean follow-up duration after KT was 3.8 ± 2.86 years. Recurrence of proteinuria was encountered early postoperative in 11 patients (27.5%) and late (1.6 and 2.9 years after KT) in 2 patients (5%). Proteinuria was less in patients underwent native nephrectomy than others immediately postoperative and at assessment (p= 0.002 & 0.0031 respectively). One-year graft and patient survival was 93.8% with a mean 1-year serum creatinine of 0.67 ± 0.25 mg/dl. Three graft losses (7.5%) were due to chronic rejection 3.3, 3.75 and 4.17 years after KT and 2 patients' mortality (5%) occurred early postoperative (first 2 weeks) due to infection.

Conclusion: FSGS transplanted children have favorable outcomes with perioperative PE for non-genetically proven cases. Early recurrence after KT can be successfully managed with PE and RTX.

Background:

Focal segmental glomerulosclerosis (FSGS) is the third leading cause of chronic kidney disease (CKD) in children and accounts for 11.7% of kidney failure (KF) patients who undergo kidney transplantation (KT) [1].

The incidence of recurrent FSGS after KT has been a subject of immense research and intense discussion. The rate of recurrent FSGS varies from 20–50% after the first KT and can reach up to 100% after subsequent transplants [2]. The risk of recurrence is inversely related to age and increases significantly in patients who progress rapidly to KF [3]. Additionally, recurrence is more frequent in patients with primary idiopathic FSGS than in those with the familial/genetic type [4].

Although idiopathic FSGS is strongly believed to be due to a circulating permeability factor (CPF), there is no accurate biomarker to predict recurrence [5]. Since recurrence of FSGS was historically considered a significant risk factor for graft loss in up to 50% of cases, it was considered a relative contraindication of KT. Graft outcomes, however, in patients with recurrent FSGS continue to improve significantly [6].

The role of pre-emptive plasma exchange (PE) or immunoadsorption (IA) as a prophylactic strategy was established a long time ago with a variable success rate in patients with a high risk of FSGS recurrence.
However, there are no controlled trials to evaluate the efficacy of PE in children at risk for recurrent FSGS [8, 9]. To date, there have been no widely agreed upon guidelines for the treatment of recurrent FSGS after KT, but treatment is based mainly on PE and rituximab (RTX) [10].

In this study we aimed to investigate the outcome of KT in children with KF secondary to primary FSGS, with implementation of elective perioperative PE for non-genetically proven patients.

**Patients & Methods:**

**Patients:**

Forty pediatric kidney transplant recipients (KTRs) with KF due to primary FSGS received their first renal graft were included into the study. All included patients received living donor renal transplant and/ or followed up for at least 1 year at Pediatric Kidney Transplantation Unit, Cairo University Children Hospital (CUCH) between 2010 and 2020. Pre-transplantation results of genetic analysis for NPHS2 gene mutation were available in 12 patients only. Of them ten patients (25%) were proved to have NPHS2 gene mutation, and two patients (5%) with familial FSGS without NPHS2 gene mutation (Both were products of consanguineous parents; one with sibling mortality on dialysis due to FSGS & the other with KF sibling secondary to FSGS). Twenty eight (70%) patients had sporadic (non-genetically proven/ familial) FSGS (Fig. 1). Transplanted children with KF due to secondary FSGS or those with missing data were excluded from the study.

**Method:**

This is a retrospective observational cohort study. The study was approved by the ethical committee of Pediatric Nephrology Unit, Pediatric Department, Cairo University. All procedures followed were in accordance with the Helsinki Declaration of 1964. Data were collected by reviewing of patients` records and by direct clinical/ laboratory evaluation of patients peri-operatively and during follow up visits.

Bilateral native nephrectomy was indicated in 13 (32.5%) patients & unilateral intraoperative native nephrectomy in 9 (22.5%) patients. Eighteen patients (45%) were anureic at time of KT and did not undergo native nephrectomy.

Non-genetically proven /non familial idiopathic FSGS patients (Sporadic FSGS; n = 28; 70%) preemptively received six sessions of PE (three sessions preoperative starting day − 5 and three sessions during the first postoperative week) regardless their proteinuria state perioperative. Each PE session was performed using 1.5 plasma volume exchange with salt free albumin using Prismaflux Machine and were scheduled to be day after the other.

All patients (n = 40) were monitored for proteinuria according to KDIGO guidelines of proteinuria screening for post-transplant idiopathic FSGS as following: daily testing for one week, weekly testing for four weeks, and every three months thereafter [11]. Protocol graft biopsy was performed 1 month postoperative for 25 patients (62.5%) only as protocol biopsies started to be implemented at our center.
since 2015 [12]. Indication biopsy was performed for patients upon their medical indication during their follow up visits. Pathological findings were reported according to Banff criteria current at the time of biopsy interpretation.

Patients with recurrence of proteinuria (n = 13 including 3 patients with genetic/familial and 10 patients with sporadic FSGS) were managed with further 6 sessions of PE in sporadic & 8 sessions in genetic FSGS and 2–4 doses of weekly RTX (365mg/m²/dose). Remission after treatment was defined as proteinuria < 0.5 g/day (complete remission) or proteinuria between 0.5 – 3.5 g/day (partial remission) [8]. Graft survival was defined as the no need for re-establishment of regular dialysis while recurrence free survival was defined as the no recurrence of proteinuria after KT.

**Statistical analysis:**

Nominal data were expressed as frequencies and percentage, parametric data as means and standard deviations and non-parametric data as median and interquartile range (IQR). Two group comparisons were done using Chi-square test for qualitative data. Two independent group comparisons with quantitative data and parametric distribution were done by using independent t-test. Receiver operator characteristic (ROC) analysis was used to determine the optimum cut-off value for proteinuria level in predicting recurrence of natively non-nephrectomized recipients. P value < 0.05 was considered significant. Kaplan-Meier curves were used to present graft and recurrence free survival.

**Results:**

The study included 40 patients (20 males & 20 females), with mean age of 10.5 ± 4.03 years. Their mean KT age was 9.21 ± 3.88 years with mean post-transplant follow-up duration of 45.6 ± 34.35 months. Thirteen patients (32.5%) are products of consanguineous marriage with 10 patients (25%) have sibling affection with FSGS (familial FSGS). Demographic, clinical & transplantation related data of the studied patients are displayed in table 1.

Twenty patients (50%) received their renal grafts from their mothers, eleven (28%) from their father & others (9 patients; 22%) received renal grafts from non-genetically related donor. The mean donor age at transplantation was 39.16 ± 10.587 years.

All patients received induction immunosuppression in the form of T-cell-depleting antibody (antithymocyte globulin: ATG) except for 5 patients received basiliximabe due to ATG medical contraindications. In addition; immunosuppressive protocols consisted of standard triple therapy (cyclosporine (CsA) ‘n = 16’ or tacrolimus ‘n = 24’, steroids and mycophenolate) in all patients. The mean steroid dose at assessment was 5.8 ± 3.2 mg/day (ranging between 1.25 & 10 mg/day). Early graft function was excellent in 34 patients (85%), delayed (DFG) in 4 patients (10%) & transient oliguria due to acute tubular necrosis was encountered in 2 patients (5%).
By comparing transplant recipients with genetic/familial FSGS & those with non-genetic (sporadic; subjected to pre-emptive PE) FSGS (table 2), we found that; immediate (day 1) post-transplantation proteinuria was significantly more in sporadic than genetic FSGS patients (2514.65 ± 915 versus 546.25 ± 100.1 mcg/day; p = 0.00001). After 1 week post-operative (after at least 3 sessions of PE for sporadic FSGS patients), proteinuria significantly decreased in sporadic FSGS recipients (2514.65 ± 915 versus 954 ± 321 mcg/day; p ≤ 0.001). Graft function (serum creatinine) at assessment was not significantly different between patients with sporadic FSGS and those with genetic/familial FSGS (0.754 ± 0.3 versus 0.605 ± 0.3 mg/dl; p = 0.1437).

Recurrence of proteinuria was encountered in 13 patients (32.5%) out of the whole studied FSGS cohort. Of them; 2 patients were genetically proven NPHS1 mutation and 1 patient with NPHS2 mutation negative familial FSGS. All patients with recurrence developed early proteinuria (first 15 days postoperative) except for 2 sporadic FSGS patients; in whom proteinuria appeared 21 and 35 months after KT and was associated with chronic active antibody mediated rejection (ABMR). All patients with early recurrence of proteinuria (n = 11) achieved complete remission after therapeutic PE and RTX. Patients with delayed proteinuria (n = 2) were not responsive to therapy and developed progressive proteinuria, graft failure (re-establishment of regular dialysis) 3.75 and 4.17 years after KT. Three patient’s mortalities (7.5%) were reported; 2 genetic FSGS patients with early postoperative mortality and one sporadic FSGS patients with graft failure due to chronic ABMR and mortality on regular dialysis (Fig. 1).

Early (first 3 months) and delayed acute rejection was encountered in 5 (12.5%) and 8 (20%) patients respectively (total 14%/ patient-year). To evaluate impact of native nephrectomy on post-transplantation proteinuria; we compared patients underwent pre-transplant native nephrectomy (n = 22) & those who did not have medical indication for nephrectomy (n = 18) (table 3). Both immediate post-transplantation as well as current (after mean follow up duration of 3.8 years) proteinuria were significantly elevated in non-nephrectomized than nephrectomized patients (p = 0.002 & 0.0031 respectively). ROC curve displayed in Fig. 2a, illustrates that at a cutoff value of proteinuria ≥ 90 mcg/day (with sensitivity 75% & specificity 73%) non-nephrectomized differed from nephrectomized patients in their immediate post TX urinary protein level with good area under the curve (AUC) (0.85) and 95% confidence interval (CI) of 0.705 to 0.993. ROC curve displayed in Fig. 2b, illustrates that at a cutoff value of proteinuria ≥ 11 mcg/day (with sensitivity 62% & specificity 65%) non-nephrectomized differed from nephrectomized patients in their follow up urinary protein level with AUC (0.735) and 95% CI of 0.526 to 0.945.

One year graft and patient survival of the whole cohort was 93.8% with a mean (± SD) one year serum creatinine of 0.67 ± 0.25 mg/dl. Three graft losses (7.5%) were due to chronic active ABMR 3.3, 3.75 and 4.17 years after KT in addition to two postoperative mortalities were reported. Kaplan-Meier curves in Figs. 3 & 4 illustrate graft and recurrence free survivals respectively.

**Discussion:**
FSGS has been reported as having poorer transplant outcomes in children than most other causes of KF largely because of disease recurrence [13]. Proteinuria may herald recurrent FSGS even if an early biopsy does not show glomerular abnormalities [14]. Absence of a causative mutation represents the major risk factor for FSGS recurrence, while transplant can be curative in genetic forms of the disease [15]. Since recurrent FSGS was postulated to be caused by CPF affecting podocyte structure and function, interventions such as PE and RTX may result in improved outcomes in treatment rather than prevention of recurrence [16].

We already have reported our 10 year experience of KT in children as of 2018 as a specialized Center in Egypt [12]. In this study we displayed the role of pre-emptive PE in decreasing proteinuria and improving outcome of FSGS after a mean of 3.8 years follow up after KT.

This study represents a retrospective analysis of a cohort of 40 pediatric KTRs with KF caused by primary FSGS. Non-genetically proven/ familial recipients (28 patients; 70%) received perioperative pre-emptive six PE sessions. Eleven patients; 27.5% (including 3 genetic/familial FSGS) developed early recurrence were successfully treated by PE/RTX, while 2 patients (5%) with late proteinuria developed graft failure.

Our overall incidence of disease recurrence after KT among non-genetic patients (10/28; 35.7%) is less than what was reported by Morello & his co-workers [15] in their Italian experiences (53%). Additionally; previous data in the literature, stretching back almost three decades, reported higher incidence of recurrence than our report [13, 17, 18].

We reported significant reduction in early proteinuria of non-genetic FSGS transplant recipients with perioperative PE sessions [D1 to D7 (2514.65 ± 915 versus 954 ± 321mcg/day; p ≤ 0.001) and D7 to time of assessment after mean 3.8 years follow up duration (954 ± 32 versus 35.29 ± 60.94 mcg/day; p ≤ 0.001).

Bouts & his colleagues performed survey among European Society of Pediatric Nephrology (ESPN) members that gives insight into the variation in policies regarding the prevention and treatment of FSGS recurrence with response rate of 15% (59/391 active members), mostly all by pediatric nephrologists. In this survey, one-third of the respondents treated pre-emptively with PE and/or RTX or CsA [18].

To date, PE is of uncertain value in primary FSGS in the native kidney [19] unlike CsA which is the only evidence-based treatment for FSGS before KT [18, 20]. In the transplant kidney, pre-emptive PE implementation in FSGS patient with anticipated high recurrence risk makes sense: remove the injurious; podocyte toxic CPF from the blood before causing irreversible structural damage. However, a prospective, randomized trial of apheresis therapy versus placebo has never been conducted for either native kidney or post-transplant FSGS.

In the present study we reported 1 year graft and patient survival of the whole cohort of 93.8%, with a mean 1 year graft function (serum creatinine) of 0.67 ± 0.25 mg/dl. Moreover, we analyzed graft survival
and recurrence free survival data using Kaplan Mayer curves (Figs. 3 & 4 respectively) with very promising results.

The effect of PE on long-term graft survival is especially unknown [19]. However, reported response rates were 50–90% higher than expected with other approaches (30–40%) making it a reasonable approach until more data become available [8].

Genetic FSGS patients have defective components of the kidneys, rather than circulating factors and therefore their risk of recurrence is low [4, 21]. However apart from disease recurrence, which mostly occurs early after KT, graft outcome differences between genetic and non-genetic FGSG patients have not yet been discussed. Interestingly; we reported no difference in graft function in term of serum creatinine in sporadic than genetic FSGS transplant recipients (p = 0.1437) after a mean follow up duration of 3.8 years with implementation of pre-emptive PE to sporadic patients. This means that the postulated worse outcome of sporadic than genetic FSGS patients after KT that is associated with increased risk of recurrence can be partially overcomed by pre-emptive PE implementation

Native kidney nephrectomy prior to KT has been suggested by some as a preventive measure of recurrence [22], but it has not been effective and has even shown a higher risk of recurrence in other reports [23, 24].

Native nephrectomy was specifically analyzed among our cohort as one of the potentially modifiable risk factors of proteinuria recurrence after KT. We reported positive impact of native nephrectomy on the graft in term of less prost-transplant proteinuria (both early and current; p = 0.0296 & 0.0441 respectively). Our finding regard native nephrectomy does not go with what was recently published by Uffing & his co-workers [25]. They reported prior nephrectomy as a significant risk for recurrence, but their number of participants is too small to draw definitive conclusions. One of the hypotheses is that the native kidneys left in situ may act as a “sponge” to absorb the potential pathogenic CPF, leading to reduction of the free CPF that may injure the transplanted kidney [26]. Our explanation, however, of less proteinuria in patients with native nephrectomy is based on the absence of proteinuria derived from the native kidneys after KT. This contradictory findings could be simply explained by the fact that severe nephrosis from FSGS, which may also have conferred a higher risk for recurrence, might have been the indication for nephrectomy [19].

This study has a number of limitations. First; lack of genetic testing of the whole cohort and the limitation of genetic testing to only NPHS2 mutation for non-genetically proven familial patients. Second; lack of pathological analysis of most of patients with early proteinuria. Third; other confounders causing proteinuria as chronic rejection particularly in late proteinuria were not analyzed in details in this study. Further studies to overcome these limitations and to investigate the potentially modifiable predictors of outcome in this particular group of transplant recipients are highly recommended

Conclusion:
FSGS transplanted children have favorable outcomes with implementation of pre-emptive perioperative PE for non-genetically proven cases. Early recurrence can be successfully managed with PE and RTX. Native nephrectomy in FSGS is still questionable however; it omits post-transplant proteinuria originating from native kidney that may confuse the physician with recurrence after KT.

**Abbreviation:**

| Abbreviation | Description                                |
|--------------|--------------------------------------------|
| KT           | Kidney transplantation                     |
| KF           | Kidney failure                             |
| FSGS         | focal segmental glomerulosclerosis         |
| PE           | plasma exchange                            |
| RTX          | Rituximab                                  |
| CKD          | chronic kidney disease                     |
| CPF          | circulating permeability factor            |
| KTR          | kidney transplant recipients               |
| CUCH         | Cairo University Children Hospital         |
| IQR          | interquartile range                        |
| ATG          | antithymocyte globulin                     |
| CsA          | cyclosporine                               |
| ABMR         | active antibody mediated rejection         |
| AUC          | under the curve                            |
| CI           | confidence interval                        |
| ESPN         | European Society of Pediatric Nephrology   |
| CPF          | podocyte toxic                             |

**Declarations:**

**Ethics approval and consent to participate:** The study was approved by ethical committee of Pediatric Nephrology Unit, Pediatric Department, Faculty of Medicine, Cairo University. All procedures followed were in accordance with the Helsinki Declaration of 1964.

**Consent for participation:** Verbal informed consent was obtained from children care givers prior to inclusion in the study.
Consent for publication: Not applicable (no identifying information about participants is available in the article)

Availability of data and materials: The datasets used and/or analyzed during the current study are available with the corresponding author on reasonable request

Competing interests: The authors declare that they have no competing interests

Author contributions: Fatina I. Fadel was the principle contributor to the study conception and design. Material preparation, data collection and analysis were performed by Hafez M. Bazaraa, Doaa M, Salah and Mohamed A Abdel Mawla. The first draft of the manuscript was written by Doaa M. Salah & Mohamed A. Abdel Mawla. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Tables:
Table (1)
Demographic, clinical & transplantation data of the study group (n=40)

|                                | Mean   | SD    |
|--------------------------------|--------|-------|
| Follow up duration before TX (mo) | 33.54  | ± 27.81 |
| Dialysis duration (years)       | 3.41   | ± 1.958 |
| Pre-TX proteinuria (mcg/d)      | 3017   | ± 1425 |
| TX weight (kg)                  | 20.14  | ± 6.214 |
| Cold ischemia time (min)        | 66.32  | ± 16.93 |
| Post-operative hospital stay (days) | 16.64  | ± 12.72 |
| Immediate post-TX proteinuria (mcg/d) | 2895   | ± 954  |
| Current weight (kg)             | 35.44  | ± 18.91 |
| Current height (cm)             | 127.2  | ± 35.34 |
| Serum creatinine after 1 year (mg/dl) | 0.668  | ± 0.251 |
| Serum creatinine after 3 year (mg/dl) | 0.728  | ± 0.145 |
| Post-TX GFR                     | 94.92  | ± 22.4 |
| Current serum creatinine (mg/dl) | 0.728  | ± 0.145 |
| Current GFR                     | 65.88  | ± 35.16 |
| Current protein in urine (mcg/d) | 27.9   | ± 51.66 |
| TX (transplantation), GFR (glomerular filtration rate) | |

Table (2)
Comparison between genetic & sporadic FSGS patients

|                                | Sporadic FSGS (n = 28) | Genetic/Familial (n = 12) | P-value |
|--------------------------------|------------------------|---------------------------|---------|
| Pre-TX proteinuria (mcg/d)     | 3003 ± 1505            | 2101 ± 608                | 0.0388  |
| D1 Post-TX proteinuria (mcg/d) | 2514.654 ± 915         | 546.254 ± 100.1           | 0.00001 |
| D7 Post-TX proteinuria (mcg/d) | 954 ± 321              | 189 ± 56                  | 0.00001 |
| Current Proteinuria (mcg/d)    | 35.29 ± 60.94          | 10.62 ± 7.53              | 0.3027  |
| Current serum creatinine (mg/dl)| 0.754 ± 0.3           | 0.605 ± 0.3               | 0.1437  |
| TX (transplantation)           |                        |                           |         |
Table (3)
Comparison between patients with & without native nephrectomy(s)

|                               | Nephrectomized patients (n = 22) | Non nephrectomized patients (n = 8) | P-value |
|-------------------------------|----------------------------------|------------------------------------|---------|
| Current Creatinine            | 0.854 ± 0.334                    | 0.798 ± 0.356                     | 0.6115  |
| Post-TX proteinuria (mcg/d)   | 2050 ± 805                       | 3101 ± 1102.56                    | 0.002   |
| Current proteinuria (mcg/d)   | 27 ± 10.5                        | 39 ± 14                           | 0.0031  |

Figures
Figure 1

Flowchart describing FSGS type, patient management and their outcome
Figure 2

2a: ROC curve of immediate post-operative protein in urine in patients with and without native nephrectomy

2b: ROC curve of current protein in urine in patients with and without native nephrectomy

| Figure 2 a: Immediate postoperative proteinuria | Figure 2 b: Current postoperative proteinuria |
|-----------------------------------------------|-----------------------------------------------|
| Area under the ROC curve                      | Area under the ROC curve                      |
| Area                                          | Area                                          |
| 0.8487                                        | 0.7353                                        |
| Std. Error                                    | Std. Error                                    |
| 0.07334                                       | 0.1069                                        |
| 95% CI                                        | 95% CI                                        |
| 0.7049 to 0.9025                              | 0.5257 to 0.9449                              |
| P value                                       | P value                                       |
| 0.004908                                      | 0.06236                                      |

2a: ROC curve of immediate post-operative protein in urine in patients with and without native nephrectomy

2b: ROC curve of current protein in urine in patients with and without native nephrectomy
Figure 3

Kaplan-Meier curve of overall graft survival
Figure 4

Kaplan-Meier curve of FSGS recurrence free survival