## Research Article

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# Evaluation of Children with Steroid-resistant Nephrotic Syndrome Showing Pathologic Findings of Focal Segmental Glomerulosclerosis (FSGS) after Renal Transplantation in Iranian Educational Medical Centers from 1998 to 2018

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**Introduction**: Steroid resistant nephrotic syndrome due to idiopathic focal segmental glomerulosclerosis (FSGS) or genetic mutations is one of the most common causes of end-stage renal disease (ESRD) that leads to renal transplantation. The relapse of the disease in the transplanted kidney, despite proper therapeutic management pre and post transplantation, may result in graft loss. Lack of accurate data about the status of transplanted patients due to FSGS encouraged us to obtain data from all pediatric nephrologists in Iran to achieve better pre and post transplantation therapeutic management.
**Materials and Methods:** The personal data of the pediatric nephrologist as well as the data of surgical and medical management prior to transplantation, relapse in the allograft kidney, and the therapeutic response rate after relapse were collected via a questionnaire.
**Results:** Of 82 cases of FSGS from 1998 to 2018, 23 had relapse, mostly within 1 year after transplantation. When relapse occurred, nearly all centers used plasmapheresis and rituximab and some used angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in addition to immunosuppressive medications and methyl prednisolone pulse therapy. Genetic studies were done in only two centers and there was no difference in immunosuppressive medications between these two centers and the idiopathic group. Pre-transplant plasmapheresis and rituximab were administered in four centers, while two centers used IVIG and one center only used plasmapheresis. Delayed graft function (DGF) was negative in 7 and positive in 9 centers. In most centers, immunosuppressive therapy consisted of a corticosteroid, mycophenolate mofetil, and tacrolimus. Relapse and recovery rates varied from less than 10% to more than 50% in all centers. Seven centers had no response to any medication. The lowest relapse rates were seen in two centers that had deceased donors and used rituximab and plasmapheresis prior to transplantation.
**Conclusions:** It can be concluded that with regard to the possibility of relapse after transplantation and variable therapeutic management modalities before and after transplantation, it is reasonable that genetic analysis of mutations, identification of idiopathic and high-risk cases, and use of appropriate therapeutic protocols should be considered to decrease the relapse rate.

**Keywords**: FSGS; Renal transplantation; Nephrotic syndrome; Child.

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**Running Title:** Evaluation of Children with FSGS after Renal Transplantation

## Introduction

Focal segmental nephrotic syndrome is a pathologic term that is characterized by patchy sclerotic lesions and distinct clinical manifestations that are usually resistant to steroid therapy and progress to chronic renal failure and finally renal transplantation [1].

Focal segmental nephrotic syndrome is classified as primary (idiopathic) and secondary based on mutation in NPHS1, ACTN4, INF2, NPHS2 and

TRPC6, obesity, sickle cell anemia, viral infections and drugs [1-4].

Some circulatory factors such as cardiotrophin-like cytokine-1 (CLC-1) and soluble urokinase plasminogen activator receptor (suPAR) play a role in pathogenesis. CLC-1 acts via inactivation of galactose [4]. In the transplanted kidney, the relapse rate varies from less than 10% up to 80% [1,5,6].

Using immunosuppressive medications at the time of transplantation and alteration in therapeutic protocol strategies in relapses with administration of plasmapheresis and rituximab before and after transplantation have a pivotal role in the prevention and treatment of relapse [5-7].

## Materials and Methods

In this cross-sectional study, a questionnaire was used to collect the pediatric nephrologists' personal data, number of their patients, transplantation date, presence of genetic mutations, pre- transplantation surgical and non-surgical managements, delayed graft function, donors' data, results of biopsy for documentation of the diagnosis and recurrence in post transplantation period, relapse medication and management, and relapse responsiveness. The data were collected via the Telegram application, in person during a transplantation congress, or via an email forwarded by the Iranian Society of Pediatric Nephrology. Some nephrologists did not work in transplantation centers and some did not complete the questionnaire that were all excluded from the study. This study was approved by the local Ethics Committee of department of pediatric nephrology and Iranian society of pediatric nephrology.

## Results

Of 82 cases of FSGS from 1998 to 2018, 23 had relapse in the post transplantation period (6 cases within one week, 7 cases during one week to one month, 7 cases during one month to one year, and 3 cases after one year). Of these, 70 cases had deceased donors while the donor status was unknown in 12 cases. When relapse occurred, three centers used rituximab, one center used plasmapheresis, and the remaining used both together. Six centers used angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in addition to immunosuppressive drugs and methyl prednisolone pulse therapy. Two centers used cyclosporine A instead of mycophenolate mofetil. Genetic studies were done in only two centers and there was no difference in immunosuppressive medications between these two centers and the idiopathic group. Unilateral nephrectomy was done in only two centers prior to transplantation. Pre-transplant plasmapheresis and rituximab were used in four centers, while two centers used IVIG and one center only used plasmapheresis. Delayed graft function (DGF) was negative in 7 and positive in 9 centers. In most centers, immunosuppressive therapy consisted of a corticosteroid, mycophenolate mofetil, and tacrolimus. Three centers used interleukin 2 receptor blocker (IL2RB), anti-thymoglobulin (2 centers), and cyclosporine (6 centers) with or without mycophenolate mofetil or tacrolimus. Relapse was diagnosed and confirmed by histologic findings. Relapse and recovery rates varied from less than 10% to more than 50% in all centers. Seven centers had no response to any medications. The lowest relapse rates were seen in 2 centers that had deceased donors and used rituximab and plasmapheresis prior to transplantation.

## Discussion

Many studies have evaluated renal transplantation in children with end-stage renal disease due to FSGS. All of these studies have demonstrated that the relapse rate is high, especially in idiopathic FSGS. Relapse rates vary from less than 10% to more than 80% [1,5-7], while it ranged from less than 10% to more than 50% in several centers in the present study.

The pattern of relapse is classified into two forms. Early relapse occurs within hours to days after transplantation and is characterized by heavy proteinuria, and late relapse occurs within months to years after transplantation with a gradual onset and better prognosis than early relapse [6].

In our study, relapse was reported in 23 patients out of 82 FSGS transplanted cases. Six relapses occurred during 7 days and 17 occurred after 7 days.

Rapid progression to uremia, younger age at onset, white race, second transplantation, and a positive history of relapse in the first transplantation are risk factors that increase the odds of relapse rate [6, 8].

In this study, 70 recipients had deceased donors while the donor status was unknown in 12 recipients. Nineteen patients in the deceased donor group and only 4 cases in the unknown group experienced relapse. Since the donor status in some cases was not clear, no conclusion can be drawn on the impact of the donor status on the relapse rate. There is no consensus on the

correlation of donor status with relapse rate in different studies. Some of these differences can be due to racial differences and the lower rate of FSGS in some races, or an undiagnosed genetic subtype [8, 9].

Generally, delayed graft function (DGF), graft loss, and ATN were more common in children with FSGS compared to other children [6, 8, 10]. In this study, DGF was reported in more than 50% of the centers.

Unilateral or bilateral nephrectomy has a partial role in controlling proteinuria and normalization of serum protein [11]. In our study, unilateral nephrectomy was done in two centers.

Plasmapheresis and rituximab are recommended in high-risk patients prior to transplantation and in patients who have high antibody titers. IVIG is recommended to decrease the level of anti-HLA antibodies [7, 12, 13].

In this study, pre-transplant plasmapheresis and rituximab were used in four centers, while two centers used IVIG and one center only used plasmapheresis. When relapse occurred, three centers used rituximab, one center used plasmapheresis, and the remaining centers used both together, as other centers around the world [4, 6, 12].

It is recommended to perform pre- transplantation plasmapheresis in idiopathic FSGS, especially to eliminate circulatory factors such as suPAR as a cause of relapse [13].

In some studies, serologic and urinary markers such as the urinary cell mRNA profile is recommended as a diagnostic tool for relapse instead of allograft biopsy due to potential risk of tissue injury during biopsy [14].

In some cases, tissue examination by light microscopy may be normal. In these cases, electron microscopy should be done, which often reveals foot process effacement accompanied by rapid progression of proteinuria and graft loss [12,14].

In this study, tacrolimus, mycophenolate mofetil, methyl prednisolone pulse therapy, angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) were used at the time of relapse. In two centers, cyclosporine was used instead of mycophenolate mofetil. Graft survival may be improved by changing the immunosuppressive regimen at time of relapse [4, 12, 15-16].

Absolute unresponsiveness to therapy was reported in seven centers, which was similar to other reports [10].

Galactose has a high affinity to permeability factors that have a main role in idiopathic relapse. In some studies, galactose administration is recommended, but no center used it in our study [3, 4, 14].

Recent studies place emphasis on agents that remove or neutralize pathogenic factors, such as plasmapheresis, immunoadsorption, galactose, immunomodulation with corticosteroids, immunosuppression with calcineurin inhibitors such as tacrolimus or cyclosporine, antibodies against B-cell (rituximab) and T-cell (abatacept), and attenuating graft tissue fibrosis with antibodies against cytokines such as TGF-β and TNF-α. Adding ACEI and ARB with antiproteinuric effects is also recommended [18].

## Conclusions

Studies show that drug-resistant FSGS is due to genetic causes in 30% of the cases. The relapse rate in these cases is lower than other causes of FSGS after transplantation. Therefore, proper evaluation to determine idiopathic cases, plasmapheresis, and administration of rituximab prior to transplantation and administration of cyclosporine and other immunosuppressant drugs as maintenance therapy can have proper effects on prevention of relapse after transplantation. Moreover, identification of high-risk patients with appropriate management can decrease the rate of DGF and improve the graft survival.

## Conflict of Interest

Authors declare that they have no conflicts of interest.

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