Original Article

Post transplant evaluation of children with steroid-resistant Focal Segmental Glomrulosclerosis (FSGS)

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ABSTRACT

Background: 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. Relapse of the disease in transplanted kidney despite all proper therapeutic managements prior and post transplantation may lead to graft loss. Lack of precise data about the status of transplanted patients due to FSGS, makes us to obtain data from all pediatric nephrologists in Iran to get better pre and post transplantation therapeutic managements. Material and methods: All data obtained via questionnaire that contains information about our colleagues' personal data, surgical and medical management prior to transplantation, relapse of disease in allograft kidney and therapeutic response rate after relapse. Results: Of 82 cases of FSGS since 1998 to 2018, 23 cases had relapse, most of them in less than 1 year after transplantation. When relapse occurred, nearly all centers used plasmaphresis and rituximab and some used Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) in addition to immunosuppressant medications and methyl prednisolone pulse therapy. Genetic studies were done only in two centers and there was no difference in immunosuppressant medications between these two centers and idiopathic group. Pre-transplant plasmaphresis and rituximab were done in four centers, while two centers used IVIG and one center only used plasmaphresis. Delayed graft function (DGF) was negative in 7 and positive in 9 centers. In most centers immunosuppressant medications consisted of corticosteroid, mycophenolate mofetile and tacrolimus. Relapse and recovery rates were variable from less than 10% to more than 50% in all centers. Seven centers had no response to any medications. Lowest relapse rates were in 2 centers that had deceased donors and used rituximab and plasmaphresis prior to transplantation. Conclusion: Therefore, it is concluded that with regard to possibility of relapse after transplantation and variable therapeutic management before and after transplantation, it is reasonable that genetic analysis of mutation and determination of idiopathic and high risk cases and using appropriate therapeutic protocols, should be done to decrease relapse rate.

Keywords: FSGS, Renal transplantation, Nephrotic syndrome.

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) or secondary due to mutation in NPHS1, ACTN4, INF2, NPHS2 and TRPC6, obesity, sickle cell anemia, viral infections and drugs [1-4].

Some circulatory factors such as cardiotropin-like Cytokine-1 (CLC-1) and Soluble Urokinase Plasminogen Activator Receptor (suPAR), play role in pathogenesis. CLC-1 acts via inactivation of galactose [4]. In transplanted kidney, relapse rate is variable from less than 10% up to 80% [1, 5, 6].

Using immunosuppressant 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 pivotal role for prevention and treatment of relapse [5-7].

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Material and Method

It is a cross-sectional study that uses questionnaire as the source of information. This questionnaire consists of 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, performing biopsy for documentation of the diagnosis and recurrence in post transplantation period, relapse time medication and management, relapse response or unresponsiveness. All data obtained via telegram social media or personally collected during transplantation congress or via an email that was distributed by Iranian Society of Pediatric Nephrology. Some nephrologists didn't work in transplantation centers and some had not respond or had incomplete responses to questionnaire that all were excluded from study.

Results

Of 82 cases of FSGS since 1998 to 2018, 23 cases had relapse (6 cases in less than one week, 7 cases during one week to one month, 7 cases during one month to one year and 3 cases after one year) in post transplantation period. Of these, 70 cases had deceased donors and 12 cases had living or deceased (unknown) donors. When relapse occurred, three centers used rituximab, one center used plasmaphresis and the remaining used both together. Six centers used Angiotensin Converting Enzyme Inhibitor (ACEI) or Angiotensin Receptor Blocker (ARB) in addition to immunosuppressant medications and methyl prednisolone pulse therapy. Two centers used cyclosporine A instead of mycophenolate mofetil. Genetic studies were done only in two centers and there was no difference in immunosuppressant medications between these two centers and idiopathic group. Unilateral nephrectomy was done only in two centers prior to transplantation. Pre-transplant plasmaphresis and rituximab were done in four centers, while two centers used IVIG and one center only used plasmaphresis. Delayed graft function (DGF) was negative in 7 and positive in 9 centers. In most centers immunosuppressant medications consisted of corticosteroid, mycophenolate mofetile and tacrolimus. Three centers used Interleukin2 Receptor Blocker (IL2RB), anti-thymoglobulin (2 centers) and cyclosporine (6 centers) with or without mycophenolate mofetile or tacrolimus. Relapse was diagnosed and confirmed by histologic findings. Relapse and recovery rates were variable from less than 10% to more than 50% in all centers. Seven centers had no response to any medications. Lowest relapse rates were in 2 centers that had deceased donors and used rituximab and plasmaphresis prior to transplantation.

Discussion

There are many studies about renal transplantation in children who got to end stage renal disease due to FSGS. All of these studies demonstrate that relapse rate is high especially in idiopathic FSGS. Relapse rates are variable from less than 10% to more than 80% [1, 5, 6, 8], while in present study it was less than 10% to more than 50% in several centers.

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

In our study, relapses were reported in 23 patients of 82 FSGS transplanted cases. Six occurred during 7 days and 17 cases after 7 days of post transplantation period.

Rapid progression to uremia, younger age at time of onset, white, second transplantation and positive history of relapse in first transplantation are risk factors that increase relapse rate [6, 9].

In this study 70 recipients had deceased donors and 12 had living or deceased (unknown) donors. Nineteen patients had relapse in deceased donor group while it occurred only in 4 cases in the unknown group. Since donor status in some cases was not clear, the impact of donor status on relapse rate can't be concluded. There was no general consensus about the correlation of deceased or living donor on relapse rate in studies. Some of these differences can be due to racial differences and lower rate of FSGS in some races, or undiagnosed genetic subtype [9, 10].

Generally, in children who got to FSGS, delayed graft function (DGF), graft loss and ATN are higher than other cases [6, 9, 11]. In this study DGF was reported in more than 50% of centers.

Unilateral or bilateral nephrectomy have relative role in the control of proteinuria and normalization of serum protein [12]. In our study, unilateral nephrectomy was done in 2 centers.

Plasmapheresis and rituximab are recommended in high risk patients prior to transplantation and in patients who have high titers of antibodies. IVIG is recommended to decrease level of anti-HLA antibodies [8, 13, 14].

In this study, Pre-transplant plasmaphresis and rituximab were done in four centers, while two centers used IVIG and one center only used plasmaphresis. When relapse occurred, three centers used rituximab, one center used plasmaphresis and the remaining used both together like other centers around the world [4, 6, 13].

It is recommended to perform pre- transplantation plasmaphresis in idiopathic FSGS, especially to eliminate circulatory factors such as suPAR as a cause of relapse [14].

In some studies, serologic and urinary markers such as 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 [15].

In some cases, tissue examination by light microscopy may be normal. In these cases, electron microscopic study should be done that reveals foot process effacement that is accompanied with rapid progression of proteinuria and graft loss [13, 15].

In this study, tacrolimus, mycophenolate mofetile, 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 mycofenolate mofetil. Changing

immunosuppressant regimen at relapse can increase graft survival [3, 4, 13, 15, 16].

In 7 centers absolute unresponsiveness to therapy was reported that was same as other reports [11].

Galactose has high affinity to permeability factors which have main role in idiopathic relapse. In some studies, administration of galactose is recommended, but in our study no center used it [3, 4, 15].

Recent studies emphasize on agents that remove or neutralize pathogenic factors such as plasmapheresis, immunoadsorption and galactose, immunomodulation by corticosteroids, immunosuppression by calcineurin inhibitors such as tacrolimus or cyclosporine, antibody against B-cell (rituximab) and T-cell(abatacept) and attenuating graft tissue fibrosis by antibody against cytokines such as TGF-β and TNF-α. Adding ACEI and ARB with anti-proteinuric effect also is recommended [17].

Summary

Studies demonstrate that drug resistant FSGS is due to genetic cause in 30% of cases. Rates of relapse in these cases are lower than other causes of FSGS after transplantation. Therefore, proper evaluation to determine idiopathic cases, performing plasmaphresis and administration of rituximab prior to transplantation and administration of cyclosporine and other immunosuppressant drugs as maintenance therapy, can have proper effect to prevent relapse after transplantation. Also determination of high risk patients with appropriate management, can decrease rate of DGF and improve graft survival [4, 13, 15, 18].

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