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Prevention of Recurrent FSGS with Cyclosporine and Plasmapheresis Prior to Renal Transplantation

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= Abstract =

We report on two children with a high risk of recurrent focal segmental glomerulosclerosis (FSGS) after renal transplantation that could be effectively prevented by prophylactic administration of cyclosporine combined with preemptive plasmapheresis prior to renal transplantation. (J Korean Soc Pediatr Nephrol 2010;14:100-104)

Key Words : Focal segmental glomerulosclerosis, Renal transplantation, Plasmapheresis, Cyclosporine

Introduction

Primary focal segmental glomerulosclerosis (FSGS) may recur following renal transplantation [1]. Although plasmapheresis early after the onset of recurrence can markedly reduce protein excretion or even induce complete remission [1-3], it has been reported that preemptive plasmapheresis may also decrease the incidence of recurrent FSGS [4, 5].

Cyclosporine is another method of treatment of recurrent FSGS following transplantation and there are some limited evidences that recurrent nephrotic syndrome such as FSGS may be successfully treated with cyclosporine [6, 7].

Here, we report on two cases of successful prevention of recurrent FSGS with prophylactic administration of cyclosporine combined with preemptive plasmapheresis prior to renal transplantation in children.

Case report

Two children, a 2-year-old girl (patient 1) and a 3-year-old boy (patient 2), were admitted to our hospital for evaluation of steroid-resistant nephrotic syndrome. They were diagnosed with primary FSGS on renal biopsy (Fig. 1A and 1B) and they had no secondary etiologies of FSGS such as vasculitis, reflux nephropathy. They had no family history related to renal disease and no pathogenic mutation in the genetic study for podocin. Despite intensive immunosuppressive treatment, they showed rapid progression to end-stage renal

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disease (ESRD). Duration of progression to ESRD from onset was 13 and 15 months, respectively. After a period of peritoneal dialysis (42 and 12 months), a living-related (donor: mother) renal transplantation was performed on them. Before transplantation, preemptive plasmapheresis was performed to prevent recurrent FSGS. Based on the protocol of Cochat et al. [3], one and a half plasma volumes were replaced with 4% albumin per session and intravenous immunoglobulins (100-150 mg/kg) were substituted following each session in case of necessity. Although our target frequency of session was 5 times for ten days early before transplantation (a 2-day interval), only 4 sessions were conducted on the girl (patient 1) due to respiratory discomfort that developed during the middle of the fifth session. Concurrently, the prophylactic administration of cyclosporine was started ten days early before transplantation. The dose of cyclosporine was 10 mg/kg/day and whole blood trough level just before transplantation was 274.7 and 216.3 ng/mL, respectively. After transplantation, cyclosporine was discontinued. Immunosuppression for induction in both patients consisted of tacrolimus (0.3 mg/kg/day), mycophenolate mofetil (600 mg/m^2/day) and corticosteroid (2 mg/kg/ day). Trough levels of tacrolimus were maintained between 10 and 15 ng/mL during 2 months just after transplantation and tapered to about 5 ng/mL after six months of post-transplantation. Prophylactic plasmapheresis following transplantation was not performed. During follow-up periods, 15 and 23 months, respectively, there was no recurrence of FSGS or signs of rejection (Table 1).

Discussion

FSGS is one of the most important causes of ESRD in children and may recur following renal transplantation in 30-40% [1]. These patients who develop recurrent FSGS not only have recurrent proteinuria and an increased risk of graft loss, but a higher risk of recurrent FSGS in subsequent kidney transplants [2]. The rate of recurrence is >75% in subsequent grafts when the first graft was lost due to recurrence [8]. Moreover, patients

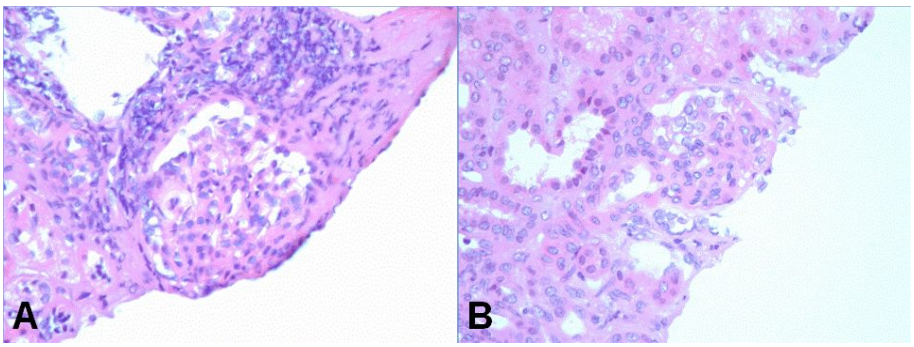

Fig. 1. Renal pathological findings at onset of FSGS. Two glomeruli show segmental glomerulosclerosis combined with mesangial proliferation (**A**: patient 1, **B**: patient 2) (H&E, ×400). Abbreviation : FSGS, focal segment glomerulosclerosis.

Table 1. Clinical Characteristics of Patients

	Patient 1 (female)	Patient 2 (male)
Age at diagnosis of FSGS	2 year 10 month	3 year 2 month
Duration of progression to ESRD (months)	13	15
Duration of dialysis (months)	42	12
Number of sessions of plasmapheresis	4	5
Dose of cyclosporine (mg/kg/day)	10	10
Whole blood trough level of cyclosporine just before KT (ng/mL)	274.7	216.3
Donor of transplant	living-related (mother)	living-related (mother)
Immunosuppressants for induction	T+M+C	T+M+C
Duration of follow-up (months)	15	23
Recurrence of FSGS	(-)	(-)
Final serum creatinine(mg/dL)	0.4	0.7

Abbreviations: FSGS, focal segmental glomerulosclerosis; ESRD, end-stage renal disease; KT, kidney transplantation; T, tacrolimus; M, mycophenolate mofetil; C, corticosteroid

with recurrent disease appear more susceptible to acute rejection and acute renal failure and have been associated with early loss in up to 40% to 50% of cases [9]. At present, one of the most representative, effective therapies for recurrence of FSGS after transplantation is plasmapheresis [2, 3]. Greenstein et al. reported that 5 of 6 pediatric patients treated with plasmapheresis went into remission and concluded that plasmapheresis is an effective form of treatment for recurring proteinuria following renal transplantation, especially if instituted early [2].

The effect of plasmapheresis may be related to the existence of the permeability factor. This putative factor, identified by Savin and colleagues, is a small glycoprotein, which is present in plasma at very low concentration and has been regarded as a main etiology of the development of primary FSGS and the recurrence of FSGS after transplantation [10]. Especially, because it has been reported the success of plasmapheresis in inducing remission in the majority of patients treated within 2 weeks of relapse [11, 12], some authors have suggested that prophylactic plasmapheresis of high-risk patients of recurrent FSGS (the patients with the histories of progression to ESRD within 3 years of diagnosis of FSGS, are younger than 15 years, with mesangial proliferation on biopsy, or prior allograft loss due to recurrent FSGS) in pre-transplant or peri-operative period may alter or even prevent disease recurrence [4]. Ohta et al. reported that pre-operative plasmapheresis was performed in 15 patients and recurrence developed in 5 patients, whereas 4/6 patients without pre-operative plasmapheresis developed recurrence and concluded that pre-operative plasmapheresis is effective in preventing the recurrence of FSGS and should be performed in all recipients with FSGS until the risk factors are definitely identified and reliable tests are available to predict the likelihood

of recurrence [5]. In addition, Rianthavorn et al. suggested that >5 pre-operative plasmapheresis sessions prevented the recurrence of FSGS [13].

Sharma et al. reported that cyclosporine inhibits the permeability factor and may help prevent recurrent FSGS in laboratory animals [14]. Although cyclosporine is beneficial for the primary FSGS rather than recurrent FSGS, there are some limited evidences that recurrent nephrotic syndrome such as FSGS may be successfully treated with cyclosporine [6, 7]. In an uncontrolled French study, recurrent proteinuria disappeared in 14 of 17 children after the administration of intravenous cyclosporine for a mean period of 21 days [6] and Raafat et al. suggested that high-dose cyclosporine therapy required ranging from 6 to 25 mg/kg/day was effective on recurrent FSGS in children [7]. So, a combination of cyclosporine and plasma exchange is the current mode of treatment for posttransplant FSGS [15].

In general, despite preemptive plasmapheresis, the recurrence of FSGS after transplantation may not be prevented completely. We postulated that this limitation would be related to the reproduction of the permeability factor during the interval of each session of plasmapheresis, especially between the last session of plasmapheresis and transplantation. Therefore, compatible with Hariharan's hypothesis [15], we believed that the prophylactic administration of immunosuppressant combined with preemptive plasmapheresis would be necessary to overcome this limitation, so, a regimen of preemptive plasmapheresis (5 sessions) and administration of cyclosporine (10 mg/kg/day for 10 days during plasmapheresis) prior to renal transplantation was performed in our two patients with high risk of recurrence of FSGS due to young age, rapid progression to ESRD from the onset of FSGS and the existence of mesangial proliferation on renal biopsy.

However, because our treatment protocol has some important limitations that this study is not a controlled trial, the number of study population is too small and the duration of follow-up is short, we could not confirm that this regimen has significant effects on prevention of recurrent FSGS after renal transplantation. This study is the first, preliminary trial for the effect of preemptive plasmapheresis and prophylactic administration of cyclosporine prior to renal transplantation on prevention of recurrent FSGS and an additional controlled trial is needed to confirm the clinical effectiveness of our regimen.

요 약

신이식 전 예방적 혈장교환술과 사이클로스포린을 이용한 재발성 국소 분절성 사구체 경화증의 효과적인 예방 2례

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국소 분절성 사구체 경화증은 소아 말기 신부전의 중요한 원인이며, 신이식 후에도 재발되는 특징을 보이는데, 이러한 재발에 대한 치료로는 혈장교환술과 사이클로스포린과 같은 면역억제제의 투여 등이 있다. 이에 저자들은 신이식 전 혈장교환술과 예방적 사이클로스포린을 투여하여 국소 분절성 사구체 경

화증의 재발을 효과적으로 예방한 경험 2례를 보고하는 바이다.

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