

Cytomegalovirus Infection in Pediatric Renal Transplant Recipients: A Single Center Experience

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Purpose: To investigate the frequency, presentation, management, and outcome of cytomegalovirus (CMV) infection in pediatric patients who underwent renal transplantation.

Methods: We performed a retrospective chart review of 70 patients under the age of 18, who underwent renal transplantation between January 1990 and November 2014. A diagnosis of CMV infection was based on serology, molecular assays, antigenemia assays, and culture. CMV infection was defined as detection of virus and CMV disease was diagnosed when clinical signs and symptoms were present.

Results: The number of patients with CMV infection was 18 (25.7% of renal transplant recipients). Twelve were male (66.7%), and the mean±standard deviation (SD) age at infection was 13.3±3.9 years. Median time of infection after renal transplantation was 4 months (range 1.0-31.0 months). Pretransplantation CMV status in the infected group was as follows: donor (D)+/recipient (R)+, 11 (61.1%); D+/R-, 7 (38.9%); D-/R+, 0; and D-/R- 0. Nine patients had CMV disease with fever, leukopenia, thrombocytopenia, or organ involvement such as enteritis, hepatitis, and pneumonitis. The age of disease occurrence was 13.1±3.9 years and the median time to disease onset after renal transplantation was 8 months (range 1.0-31.0). Immunosuppressive agents were reduced or discontinued in 14 patients (77.8%), antiviral agents were used in 11 patients (61.1%), and all patients with CMV infection were controlled.

Conclusions: A quarter of the patients had CMV infection about 4 months after renal transplantation. CMV infection was successfully treated with reduction of immunosuppressants or with antiviral agents.

Key words: Cytomegalovirus, Kidney transplantation, Child

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Introduction

Renal transplantation became an optimal treatment for end-stage renal disease patients¹. Despite the recent advancements in immunosuppressive regimens and surgical techniques that have led to increased survival of renal recipients, there are considerable risks of developing infectious complications¹.

Cytomegalovirus (CMV) is one of the most common opportunistic viral pathogens in renal transplantation². CMV infection leads to viral syndrome and tissue-invasive disease, and furthermore acute and chronic allograft injury³. Because of its opportunistic behavior under immunosuppression,

active CMV infections generally have a large impact on the clinical courses of organ transplant recipients¹. In transplant patients, therefore, CMV infection can be associated with increased morbidity, mortality, and poor graft survival^{1,4}.

It has been well described that the pediatric renal transplant patients are at a particularly increased risk of CMV infection because the ratio of pre-transplant CMV-seronegative recipients is higher than that of adults, which results in a higher rate of transplantation from CMV-seropositive donors to CMV-seronegative recipients in children⁵. This makes the incidence of CMV infection reported in adult patients unable to be applied to the pediatric patients⁵. There are few published studies on pediatric renal transplant patients and most studies have limitations of small sample size.

The objective of this study was to investigate the frequency, manifestation, management and outcome of CMV infection or disease in pediatric renal transplantation recipients.

Materials and methods

We retrospectively reviewed 70 pediatric kidney transplant recipients who were under 18 years old in Asan Medical Center from January 1990 to November 2014. Patients with incomplete data of pre-transplant CMV status (recipients or donors) were excluded.

Data of all transplant recipients during the study period were reviewed and obtained from electronic medical records. Data collected included age, gender, type of donor, causative disease of recipient, pre-transplant CMV serostatus of recipient and donor, time of CMV infection after transplantation, clinical manifestations of CMV disease, ganciclovir prophylaxis, treatment and outcome of CMV infection and disease.

Post-transplantation surveillance tests for CMV infection were usually done every 3 months at the outpatient clinic, but the intervals were individualized according to patients' medical condition. CMV infection was defined as isolation of the CMV virus or detection of viral proteins or nucleic acid in any body fluid or tissue specimen⁴. CMV infection was diagnosed if one or more of the following positive find-

ings were noted: CMV seroconversion with IgM, antigenemia assays, polymerase chain reaction (PCR), and culture. CMV disease was diagnosed when there are evidences of CMV infection with clinical signs and symptoms, such as fever, leukopenia, thrombocytopenia, pneumonitis, hepatitis, retinitis, and gastrointestinal disease^{5,6}.

Patients' age and transplantation to CMV infection interval was expressed as mean±standard deviation, and we compared medians using the non-parametric Mann-Whitney U test. The associations between either of age, sex, donor type, pre-transplant CMV serostatus or CMV prophylaxis and post-transplant CMV infection were evaluated with chi-square test and Fisher's exact test. The level of statistical significance was set at *P* value less than 0.05.

Results

We analyzed a total of 70 pediatric patients (M:F=1.3:1) who received renal transplantation from January 1990 to November 2014 in Asan Medical Center. The number of patients with CMV infection after renal transplantation was 18 (25.7% of renal transplant recipient, M:F=2:1) and those with CMV disease was 9 (50% of CMV infection and 12.9% of renal transplant recipients, M:F=2:1) (Table 1).

The mean age at kidney transplantation of the total renal transplant recipients was 12.7±4.2 (median 13.0, range 2.0-19.0) years: those with CMV infection was 12.6±4.2 years (median 11.5, 5.0-19.0), and those without CMV infection was 12.7±4.4 years (median 13.5, 2.0-18.0). Among patients with CMV infection, the mean age of kidney transplantation showed no difference regardless of CMV disease (12.4±4.1 years, median 11.0, 5.0-18.0, with CMV disease and 12.7±4.0 years, median 12.0, 6.0-19.0, with asymptomatic CMV infection, *P*=0.237) (Table 1).

The causative renal diseases in renal transplant recipients were as follows: unknown (25, 35.7%), FSGS (12, 17.1%), VUR (10, 14.3%), HSP (7, 10.0%), IgA nephropathy (5, 7.1%), and others (13, 18.6%). The causative renal diseases of the patients with CMV infection were VUR (6, 33.3%), unknown (5, 27.8%), FSGS (2, 11.1%) and others (5, 27.8). (Table 2)

The sources of kidney donor of total patients were living-related (52, 74.3%), cadaver (7, 10.0%), living-unrelated (7,

10.0%), multiple (4, 5.7%) donors in the order of frequency. Those of patients with CMV infection were living-related (13, 72.2%), living-unrelated (3, 4.3%), and cadaver (2, 2.9%) donors. In single renal transplantation, 27.1% (16 of 59) of living donor kidney transplantation and 28.6% (2 of 7) of cadaveric donor kidney transplantation had CMV infection. The types of kidney donor and CMV infection showed no statistically significant difference (odds ratio (OR)=1.075, 95% CI: 0.189-6.109) (Table 3).

CMV detection was done by CMV IgM Ab, CMV antigenemia, CMV PCR, and CMV culture. Of eighteen patients who were diagnosed as CMV infection, CMV IgM Ab was detected in 9 patients and CMV antigenemia was positive in 11 patients. CMV blood PCR was positive in 7 patients, CMV biopsy tissue PCR positive in 2 patients, CMV bronchoalveolar lavage PCR was positive in one patient.

Pre-transplant CMV IgG status was checked in recipients and donors and we compared the two groups of patients with CMV infection and without CMV infection. In 52 patients without CMV infection, the subgroup number of IgG status was as follows; donor (D)+/recipient (R)+ 44 (84.6%), D+/R- 5 (9.6%), D-/R+ 0, and D-/R- 3 (5.8%). In patients with CMV infection, the number of each group was as follows: donor (D)+ recipient/(R)+ 11 (61.1%), D+/R- 7 (38.9%), D-/R+ 0 and D-/R- 0. The odds ratio of post-transplant CMV infection was 5.98 (95% CI: 1.60-22.44) in pre-transplant CMV IgG negative patients ($P=0.005$) (Table 4).

CMV infection took place at the age of 13.3 ± 3.9 (median 13.0, 6.0-19.0) years, with a mean period of 7.5 ± 8.9 months (median 4.0, 1.0-31.0) for developing CMV infection after transplantation. There were no significant differences in the onset age and period from kidney transplantation to

the development of CMV infections between CMV disease group (13.1 ± 3.9 years, 9.2 ± 8.8 months, respectively) and asymptomatic CMV infection group (9.2 ± 3.5 years, 6.3 ± 7.3 months, respectively) ($P=0.796, 0.161$, respectively) (Table 1).

The clinical manifestations in patients with CMV disease were leukopenia (7, 38.9%), fever (4, 22.2%), thrombocytopenia (2, 11.1%) or organ involvement such as enteritis (3, 16.7%), hepatitis (1, 5.9%) and pneumonitis (1, 5.9%) (Table 5). Two of three CMV enteritis patients were diagnosed

Table 2. The Causative Disease of Kidney Transplantation

Causative renal diseases	N (%)	
	Total	CMV infection
Unknown	25 (37.5%)	5 (27.8%)
FSGS	12 (17.1%)	2 (11.1%)
VUR	10 (14.3%)	6 (33.3%)
HSP	7 (10.0%)	1 (5.6%)
IgA nephropathy	5 (7.1%)	0 (0%)
Others*	13 (18.6%)*	4 (22.2%) [†]
Total	70	18

*Alport syndrome, congenital agenesis of kidney, cortical nephrocalcinosis, Denys-Drash syndrome, Juvenile nephrophthisis, Lupus nephritis, multicystic dysplastic kidney, neuroblastoma, non-immune complex mediate glomerulonephritis, urethra atresia, uric acid nephropathy, Membranoproliferative Glomerulonephritis

[†]Alport syndrome, cortical nephrocalcinosis, multicystic dysplastic kidney, neuroblastoma

Abbreviations: CMV, cytomegalovirus; FSGS, focal segmental glomerulosclerosis; VUR, vesicoureteral reflux; HSP, Henoch-Schönlein purpura.

Table 3. Donor of Renal Transplantation

Renal transplant donor	N (%)	
	Total	CMV infection
Related	52 (74.3%)	13 (72.2%)
Cadaver	7 (10.0%)	2 (2.9%)
Unrelated	7 (10.0%)	3 (4.3%)
Multiple	4 (5.7%)	0 (0%)
Total	70	18

Abbreviations: CMV, cytomegalovirus.

Table 1. The Mean Age of Recipients of Kidney Transplantation, CMV Infection and the Interval from Kidney Transplantation to CMV Infection

	Age (years)	Age (years)	Interval (months)	Sex
	kidney transplantation	CMV infection	Transplantation to CMV infection	M:F
Total N=70	12.7 ± 4.2 (med 13.0, 2.0-19.0)			1.3:1
No CMV infection N=52	12.7 ± 4.4 (med 13.5, 2.0-18.0)			1.1:1
CMV infection N=18	12.6 ± 4.2 (med 11.5, 5.0-19.0)	13.3 ± 3.9 (med 13.0, 6.0-19.0)	7.5 ± 8.9 (med 4.0, 1.0-31.0)	2:1
CMV infection without disease N=9	12.7 ± 4.0 (med 12.0, 6.0-19.0)	13.4 ± 3.7 (med 12.0, 8.0-19.0)	5.8 ± 8.0 (med 2.0, 1.0-27.0)	2:1
CMV infection with disease N=9	12.4 ± 4.1 (med 11.0, 5.0-18.0)	13.1 ± 3.9 (med 14.0, 6.0-18.0)	9.2 ± 8.8 (med 8.0, 1.0-31.0)	2:1

Abbreviations: CMV, cytomegalovirus; M, males; F, females; med, median.

with endoscopic biopsy tissue CMV PCR positive, whereas one patient was diagnosed with clinical symptoms, coinciding elevation of CMV blood PCR, and absence of other pathogens. One patient with CMV pneumonitis was diagnosed when CMV bronchoalveolar lavage PCR was positive.

Among twelve pre-transplant CMV IgG negative patients, three patients whose donor were CMV IgG negative did not received ganciclovir prophylaxis and other nine patients received ganciclovir prophylaxis. In 18 CMV infection patients, 7 patients were pre-transplant IgG negative, and received prophylaxis and 11 patients were pre-transplant IgG positive and did not received GCV prophylaxis. CMV prophylaxis with ganciclovir was significantly associated with low prevalence of post-transplant CMV infection ($P=0.001$). The duration of CMV prophylaxis in CMV infection group and without infection group were 3.8 ± 1.8 months, 7.3 ± 0.9 months each. Prophylaxis duration tended to be longer in CMV infection-free group, but the difference was not statistically significant ($P=0.500$).

For the treatment of CMV infection in total 18 patients of CMV infection, immunosuppressive agents were reduced or discontinued in 15 patients (83.3%). In all nine patients who had CMV disease, immunosuppressants were reduced or discontinued, whereby five of nine asymptomatic

CMV infected patients were treated with reduced immunosuppressants. In CMV disease patients, almost all patients received ganciclovir except one patient in whom only immunosuppressants were reduced. In asymptomatic CMV infection group, only 3 patients received ganciclovir (Table 6). CMV hyper-immune globulin was tried in one case with CMV disease.

CMV negative conversion was confirmed in all patients with CMV infection and in CMV disease group, clinical symptoms were resolved. Treatment duration was decided based on clearance of CMV viral load or antigenemia and mean \pm SD infection period was 3.5 ± 4.2 months.

Discussion

The proportion of population with evidence of prior CMV infection varies throughout the world, with seroprevalence rates ranging from 30% to 90% increasing with age^{7,8}. In a few studies carried out among pediatric patients in recent years, the number of recipients with negative results of CMV serology test at the moment of transplantation varies from approximately 55% to over 80%^{9,10}. However, in other reports from Korea, it was reported that the seronegative CMV rate is 16.1% which was much lower than the prevalence in other countries and similar to adult population^{11,12}. Similarly, 17.1% of patients were pre-transplant CMV IgG negative in our study population.

In our study, CMV infection and disease occurred in 25.7%, and 12.9% of renal transplantation recipients respectively. The incidence rates reported by other pediatric groups were similar: ranged from 16% to 35% in CMV infection, and from 4.5% to 12.9% as to CMV disease⁵. In previous studies, the median time interval ranged from 5.0 months

Table 4. CMV IgG Status before KT in Recipients

	Recipient +	Recipient -	Total
CMV (-) after KT			
Donor +	44 (84.6%)	5 (9.6%)	49
Donor -	0	3 (5.8%)	3
Total	44	8	52
CMV (+) after KT			
Donor +	11 (61.1%)	7 (38.9%)	18
Donor -	0	0	0
Total	11	7	18

Abbreviations: CMV, cytomegalovirus; KT, kidney transplantation.

Table 5. Clinical Manifestations of CMV Disease

CMV disease - Clinical manifestations	N (%)
Leukopenia	7 (38.9%)
Fever	4 (22.2%)
Enteritis	3 (16.7%)
Thrombocytopenia	2 (11.1%)
Hepatitis	1 (5.6%)
Pneumonitis	1 (5.6%)

Abbreviations: CMV, cytomegalovirus.

Table 6. Treatment of CMV Infection

	N (%)			
	Immunosuppressant Reduced or discontinued		GCV only	Untreated
	GCV (+)	GCV (-)		
Asymptomatic CMV infection (N=9)	1 (11.1%)	4 (44.4%)	2 (22.2%)	2 (22.2%)
CMV disease (N=9)	8 (88.9%)	1 (11.1%)	0 (0%)	0 (0%)
Total CMV infection (N=18)	9 (50%)	5 (27.8%)	2 (11.1%)	2 (11.1%)

Abbreviations: CMV, cytomegalovirus; GCV, ganciclovir.

to 9.4 months¹³⁻¹⁵). The median time interval between the transplantation and the CMV infection was 4.0 months in our study, which is shorter to previous studies. This can be explained by different immunosuppressant strategies and shorter ganciclovir prophylaxis period of our center.

Whether donor type of kidney transplantation is associated with CMV infection is still controversial. Sia and Patel reported that renal recipients of organ from living related donors showed less CMV morbidity¹⁶). In a study of Corona et al, donor type was not associated with risk of CMV infection¹⁷). In our study, CMV infection rate was not statistically different between patients who received kidney from cadaveric donor and those from living donor.

The risk of CMV infection and disease after transplantation is strongly dependent on recipient's serostatus: CMV-seronegative recipients of CMV-seropositive donors are at the highest risk of infection, whereas pre-transplant CMV-seronegative recipients of CMV-seronegative donors are considered to be at low risk⁷). In a retrospective study of E. Cordero et al, CMV infection incidence was more than two times higher in pre-transplant CMV sero-negative recipients (12.2%) than sero-positive recipients (5.2%)⁶). Similarly, A.L. Corona-Nakamura et al. reported that greater percentage of CMV infection was noted in CMV sero-negative recipients (44.74%) than in CMV sero-positive recipients (13.78%)¹⁷). In our study, pre-transplant CMV IgG negative patients showed higher odds ratio and this corresponded to previous studies.

There are two different strategies of preventing CMV infections: preemptive therapy and prophylaxis therapy. Preemptive therapy consists of regular monitoring using microbiological diagnostic procedures, like CMV antigenemia and CMV PCR and antiviral agent started after detection of CMV in regular laboratory test¹⁸⁻²⁰). In our study, we did ganciclovir prophylaxis to high-risk patients of pre-transplant CMV-seronegative recipients and applied preemptive therapy to pre-transplant CMV-seropositive recipients. Since it has been reported that pre-transplant CMV IgG positive recipients with CMV IgG positive donors also have moderate risk for CMV infection²⁰), the importance of prophylaxis to pre-transplant CMV IgG positive recipients is rising. Nevertheless, ganciclovir use in pre-transplant CMV IgG positive recipients is not covered with national health insurance in Korea, therefore acyclovir prophylaxis

has been applied to these recipients in recent years. The duration of CMV ganciclovir prophylaxis was not statistically different in patients with CMV infection and without CMV infection. However, recent studies support the idea that the duration of prophylaxis should be extended from 3 to 6 months as it significantly reduces CMV disease and viremia¹⁸⁻²⁰). Considering that our patients' median time from kidney transplantation to CMV infection was 4 months, extended prophylaxis longer than 4 months may be beneficial for reducing CMV infection.

Treatment of CMV infection was successfully obtained in almost all patients with reduced immunosuppressants and ganciclovir. Although patients in this study were in a single center, they were not treated with one single protocol as to CMV infection after kidney transplantation. From 1990 to 2014 there had been many changes in treatment strategies and patients were treated in different departments-internal medicine, general surgery, and pediatric nephrology. Most clinicians reduced immunosuppressants in CMV disease patients and in case of asymptomatic CMV infection with serologic diagnosis, they decided treatment based on CMV PCR titer.

Conclusion

A quarter of the patients had CMV infection about 4 months after renal transplant. Pre-transplant CMV IgG negative recipients showed high incidence of CMV infection. Ganciclovir prophylaxis is considered more important in pre-transplant CMV IgG negative recipients. CMV infection can be successfully treated with the reduction of immunosuppressant or with antiviral agents.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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