Original Article

Impact of Cytomegalovirus (CMV) Infection on Renal Transplantation and Graft Rejection.

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Abstract

Introduction: cytomegalovirus (CMV) infection is a common problem among kidney transplant patients. It can affect patient morbidity and graft survival. It is also associated with acute and chronic graft rejection.
Aim of the study: The aim of this work is to show the prevalence and natural course post-kidney transplantation of CMV infection and the effect of CMV on patient morbidity and mortality.
Methods: This cohort study was performed at Children Hospital, Cairo University during the period from May 2016 to January 2018, including thirty pediatric renal transplanted patients diagnosed as end-stage renal disease (ESRD) and had kidney transplantation. Patients were divided into two groups; patients' group with CMV infection and control group without CMV infection. CMV infection was diagnosed by quantitative polymerase chain reaction.
Results: Patients were divided according to PCR as CMV positive group [8 patients (26.7%)] and negative group [22 patients (73.3%)]. There was a statistically significant difference between 2 studied groups as regard chest infection (p= 0.019), height (p= 0.003) and hemodialysis duration (p= 0.022) in the CMV positive patients. Urinary tract infection was the major co-morbidity in the 2 groups (59.1% in the negative patients and 75% in the positive patients), followed by hypertension (18.2% in the negative patients and 37.5% in the positive group). No statistically significant difference in the rejection episodes in both groups.
Conclusion: CMV disease can increase the risk of infections like chest infection and UTI and a risk factor for cardiovascular diseases as hypertension

Keywords: CMV; renal transplantation; children.

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INTRODUCTION

Despite largely efficient antiviral medications, CMV remains a significant infection in transplant recipients [1].

Infection is most prevalent without prophylaxis 1–6 months after transplantation, depending on the organ, immunosuppressive treatment, and immune condition of the patient. With up to a 91.9% frequency of viremia and a 50-65% prevalence of symptomatic infection by 90 days posttransplant without prophylaxis, primary infection in immunologically native, seronegative recipients (R) of seropositive organs (D+) poses the highest risk to transplant recipients [2].

CMV infection can be either primary or recurring in transplant patients. Recurrent infection involves both reinfection (with the same CMV strain) and reactivation, while the former refers to CMV detection in a person who was previously seronegative (infection by different strain) [3].

Human immunodeficiency virus (HIV) infection, high- or low-dose corticosteroid therapy, immunosuppressive therapy following transplantation, history of blood transfusion, advancing age, chemotherapy, and anything that can lower an individual's immunity are risk factors that predispose people to cytomegalovirus (CMV) [4].

Human fibroblast culture, serologies, antigen tests, PCR, and cytopathology have all been used to find CMV. Patients with a recent CMV infection have raised IgM levels, or their IgG titers have increased by a factor of four. Patients with Ebestien bar virus (EBV) or human herpes virus-6 (HHV) infections, as well as those with elevated rheumatoid factor levels, may experience false-positive CMV IgM findings [5].

The aim of this work is to show the prevalence and natural course post-kidney transplantation of CMV infection. It aims also to show the effect of CMV on graft rejection and its effect on patient morbidity and mortality.

METHODS

Thirty pediatric renal transplant patients, 2 to 16 years old, of both sexes, who were diagnosed with end-stage renal disease (ESRD) and underwent kidney transplantation were included in this cohort study, which was conducted at Children Hospital, Cairo university, between 2016 and 2018. Patients receiving treatment for an active cancer and those with severe, unmanageable medical conditions (early recurrence after transplantation, urological and immediate rejection) were excluded from the trial.

The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained. The study protocol was approved by the local Ethics Committee

All patients were subjected to the following;

Full history taking including: age, gender, residence, weight, height, body mass index (BMI), presence of hypertension before and after transplantation, diabetes, use of immunosuppressive drugs, symptoms of system invasion due to CMV, cause of renal failure, renal replacement therapy (RRT) before transplantation,

age at transplantation and type and duration of dialysis (if present).

Clinical examination including: vital signs, anthropometric measures, abdominal examination (for organomegaly) & lymph node examination. Laboratory investigations were recorded from the patients' files including: Complete blood count (CBC), liver function tests (alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), prothrombin time PT), bilirubin (total and direct), total protein and serum albumin], kidney function tests [including serum creatinine, serum urea and blood urea nitrogen (BUN)].

Cytomegalovirus (CMV) (IgM and IgG) by enzyme linked immunosorbent assay (ELISA) technique for detection of primary infection or reactivation of latent one (pre-transplantation). Post-transplantation CMV-polymerase chain reaction (PCR) was done for high-risk cases which are donor positive and recipient negative or cases on treatment. Cytomegalovirus (CMV) IgM by ELISA: By enzyme-linked-immunosorbent assay (ELISA) technique **[6].** IVD kit for CMV IgM (Autobio co. Ltd, China) was used for the qualitative determination of IgM antibodies to cytomegalovirus in human serum or plasma specimens (EDTA, heparin or sodium citrate) by ELISA. Cytomegalovirus (CMV) IgG ELISA: By ELISA technique **[7].**The Calbiotech (Spring Voly-California) CMV IgG ELISA Kit was used for the detection of IgG antibody to Cytomegalovirus (CMV) in the patients sera.

Collection of the samples: Whole-blood (5 ml) was collected by acceptable medical techniques. The serum was separated, centrifuged and serum samples were stored in a deep freeze at -20°C until examined.

Statistical analysis

Data were coded and entered using Microsoft office excel 2010. Statistical analysis was done using IBM SPSS version 24. Frequencies (number) and relative frequencies (percent) were used to summarize qualitative variables, mean and standard deviations were used for quantitative variables.

The comparison between the qualitative variables was calculated using the chi square test. Comparison between groups were done using Fisher's Exact Test and Mann-Whitney Test. To compare two dependent groups of normally distributed variables, the paired t-test was employed Spearman's rho non- parametric correlation was used to test for possible correlations between quantitative variables. P value less than or equal to 0.05 was considered significant

RESULTS

Our study included 7 females and 23 males, with mean age 13.5±3.46 years (median 14.5, range 3-18). Body mass index (BMI) was 20.38 ± 3.31 (median 20.85, range 12.4-27.8).

Table 1 shows demographic data and laboratory parameters of the 2 studied groups. This table shows statistically significant differences

between the two studied groups as regard height (p=0.003) and HD duration (p=0.022). The patients were divided according to the results of PCR CMV which was done after transplantation into: positive group (8 patients) and negative group (22 patients).

Figure 1 shows prevalence of CMV infection among the studied population. Causes of ESRD of the positive group are neurogenic bladder in 2 patients, autosomal recessive polycystic kidney disease (ARPKD) in 2 patients, vesico-ureteric reflux (VUR) in 2 patients, focal segmental glomerulo-sclerosis (FSGS) in 1 patient and interstitial nephritis 1 patient. Causes of ESRD of the negative group are focal segmental glomerulo-sclerosis (FSGS) in 6 patients, bilateral atrophic kidneys in 3 patients, nephronophthisis in 3 patients, neurogenic bladder in 3 patients, ARPKD in 2 patients, vesico-ureteric reflux (VUR) in 1 patient, interstitial nephritis in 1 patient, oxalosis in 1 patient, sarcoidosis in 1 patient, glomeruloneohritis (GN) in 1 patient and anti-phospholipid syndrome in 1 patient.

Table 1: Demographic and laboratory data of the studied groups

Variable		Negative (n=22)	Positive (n=8)	p-value
Age (years) Mean ± SD		14 ± 2.83	12.13 ± 4.76	0.195
Sex	Males	17 (77.3%)	6 (75%)	0.896
	Females	5 (22.7%)	2 (25%)	
Weight (Kg) Mean ± SD		47 ± 9.05	41.38 ± 15.52	0.227
Height (cm) Mean ± SD		151.64 ± 9.21	37.88 ± 13.38	**0.003**
Age at TX (years) Mean ± SD		9.86 ± 3.17	9.06 ± 4.49	0.588
HD duration (months) Mean ± SD		7.05 ± 1.96	10.5 ± 5.98	0.022
Hemoglobin (g/dl)		11.31 ± 1.13	11.88 ± 1.69	0.288
MCV		76.09 ± 6.22	76.75 ± 7.13	0.807
MCH		30.86 ± 2.21	31.88 ± 2.36	0.285
MCHC		26.55 ± 3.25	26.63 ± 4.53	0.958
TLC (mm3)		8.72 ± 4.83	7.86 ± 2.99	0.644
PLT		293.95 ± 6.26	351.88 ± 86.95	0.147
Creatinine (mg/dl)		0.868 ± 0.343	0.850 ± 0.245	0.892
ALT (mg/dl)		28 ± 23.56	33.38 ± 18.60	0.566
AST (mg/dl)		33.09 ± 23.01	28.38 ± 10.9	0.585

All parameters were presented in mean±SD, p value < 0.05 is considered statistically significant
test done by Student "t" test .TX: Transplantation; HD: Hemodialysis; SD: Standard deviation;
MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin Concentration; TLC: Total leucocyte count; PLT: Platelets; ALT: Alanine transaminase; AST: Aspartate transaminase

Table 2 shows clinical data and co-morbidities of the 2 studied groups. It shows a statistically significant difference between the two studied groups as regard chest infection (p= 0.019). Number of episodes of rejection per year is 1.68±1.39 in the negative group and 1.63±1.19 in the positive group, which is statistically not significant (p= 0.057).

Table 3 shows recipient and donor CMV infection. Regarding donor CMV; there were 3 (10%) patients with positive IgM and 29 (96.7%) patients with positive IgG. **Table 4** shows classification according to serology. Considering recipient CMV; 2 (6.7%) patients with positive IgM and 30

(100%) patients with positive IgG are present.

Figure 2 shows medications received by the 2 studied groups. There was a significant difference between the two groups regarding Valcyte. Valcyte therapy is 100% effective. Outcome after transplantation, between 2 groups CMV positive and negative patient illustrated in **Table 5.** Almost all cases were in moderate risk as High risk of CMV: if donor is seropositive and recipient is seronegative, Low risk: if both donor and recipient are seronegative, intermediate risk: if recipient are positive and donor is seropositive or seronegative regarding IgG.

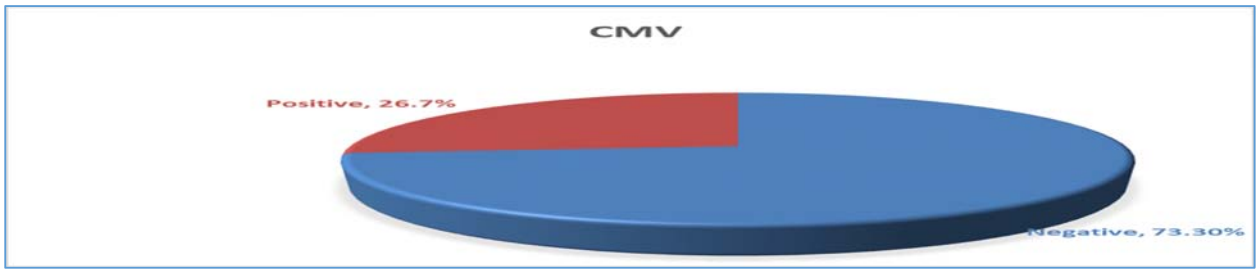

Figure 1: Prevalence of CMV infection among the studied population

Table 2: Clinical data and comorbidities between of two studied groups

	Negative (n=22)	Positive (n=8)	P-value
Hypertension	4 (18.2%)	3 (37.5%)	0.269
Hepatic focal lesion	1 (4.5%)	0 (0%)	0.540
Organomegaly	1 (4.5%)	0 (0%)	0.540
Hepatitis C	2 (9.1%)	1 (12.5%)	0.783
UTI	13 (59.1%)	6 (75%)	0.424
Gastroenteritis	4 (18.2%)	0 (0%)	0.195
Chest infection	1 (4.5%)	3 (37.5%)	**0.019**
Angular stomatitis	0 (0%)	1 (12.5%)	0.092

UTI: Urinary tract infection, Chi-squared test, P value less than 0.05 was considered significant

Table 3: Recipient and donor CMV infection

			Recipient CMV IgM		Recipient CMV IgG
			Negative	Positive	Positive
Donor CMV IgG	**Negative**	n	1	0	1
		%	100.0%	0.0%	100.0%
	Positive	N	27	2	29
		%	93.1%	6.9%	100.0%
Total		N	28	2	30
		%	93.3%	6.7%	100.0%
Donor CMV IgM	**Negative**	N	27	0	27
		%	100.0%	0.0%	100.0%
	Positive	N	1	2	3
		%	33.3%	66.7%	100.0%
Total		N	28	2	30
		%	93.3%	6.7%	100.0%

CMV: Cytomegalovirus

Table 4: Classification according to risk of CMV infection post transplantation according to serology:

Donor positive IgM	Recipient CMV IgM Positive	Recipient CMV IgG Positive	Donor positive IgG
3 (10%)	2(6.7%)	*30 (100%)	*29 (96.7%)

Table 5: Outcome of CMV positive and negative cases

	CMV positive (n=8)	CMV negative (n=22	P value
Rejection episodes	1.63±1.19	1.68±1.39	0.05
Mortality	1(12.5%)	0	0.12

Figure 2: Medications received by patients of the 2 groups.

DISCUSSION

A frequent pathogen that affects kidney transplant recipients is the cytomegalovirus (CMV). The use of lymphocyte-depleting drugs for induction or rejection therapy, donor-recipient mismatching, and co-morbid infections and illnesses are among the most frequent risk factors for CMV infection [8].

Between 2016 and 2018, the Pediatric Nephrology Department (PND) at Children Hospital, our university, performed kidney transplants on thirty paediatric patients with end-stage renal disease (ESRD), who ranged in age from 3 to 16 years.

Our patients had a prevalence of CMV of 73.3%, which is comparable to Gonçalves et al(2013) investigation of 78 transplanted patients at the Pediatric Nephrology Unit from September 1995 to August 2010 [9]. 74% of cases of infectious complications were viral (CMV in 39.7% of cases), 56.4%, and bacterial (53.8%). (mainly urinary tract infections). Erdbruegger et al. (2012) [10] observed that 153 out of 594 patients (26%) got a CMV infection within a year following transplantation, which is similar to our findings.

In contrast to the current study, Bhadauria et al. (2012) [11] conducted a retrospective analysis on renal transplant recipients' CMV illness. From 2003 through 2009, 512 recipients of live-related kidney transplants were the subject of the study. 74 allograft recipients (14.2%) with a median time of 7.18 months following transplantation acquired CMV illness. This variation in CMV prevalence may be the result of large number in this study, may be selection of low risk case of CMV infection.

Blood transfusions (therapy for clotting factors, etc.), contaminated transplants, hemodialysis, and the number of times you get dialysis in a week are all risk factors for primary CMV infection [12].

The duration of hemodialysis varied significantly between the 2 groups in the current study (p=0.022). More patients with CMV infection experienced it. This can be explained by the fact that hemodialysis patients have impaired immune systems and may be susceptible to primary infection or reactivation of latent CMV infection.

There were 29 (96.7%) patients with positive IgG and 3 (10%) individuals with positive IgM for donor CMV. Regarding recipient CMV, 2 (6.7%) patients and 30 (100%) patients exhibited positive IgM and IgG, respectively. Saadoon (2015) [13] examined the prevalence of CMV-IgG and IgM antibodies among hemodialysis patients and included 116 hemodialysis patients, which is similar to our study. CMV-IgG was discovered in 102 out of 116 individuals (87.9%), whereas CMV-IgM was discovered in 10 out of 116 patients (8.6%).

In this study, there was a statistically significant difference in height between the two groups (p = 0.003). The CMV positive group was shorter this can be explained as indirect effect , as patiet with positive CMV infection was on hemodialysis for a longer periods, expose more to uremic complication renal ostodystropdy and affection their height .

According to ***Nissel*** et al. (2004) [14], pubertal growth spurt start is delayed in kidney transplant recipients by 1.6 years, while the duration is decreased, resulting in a 20% reduction in overall pubertal height increase.

According to the results of the current study, there was no statistically significant difference between the two groups in terms of the number of rejection incidents each year. In contrast to the current investigation, Hasanzamani et al. (2016) [15] discovered that the incidence of graft rejection was 9.4% in a group of 64 control patients compared to 36.4% in a group of 66 CMV disease patients.This can be expiained by small sample size in our study. According to Giuliano etal. 2019 [16], CMV illness can lead to immune system dysfunction. The likelihood of transplant rejection may rise as a result of this immune system imbalance.

According to the current study, there was a significant difference regarding chest infection between the 2 analysed groups (p=0.019). The most common co-morbidity in both groups (59.1% of patients in the negative group and 75% of patients in the positive group) was urinary tract infection this can be attributed to alteration of immune system due to CMV viremia and suppresion of CD8 T cell activity. Also lung is one of the most frequently involved organs in a variety of complications in the immuno-compromised host, Post-transplantation pneumonia are very common specially in first 6 months reaching up to 60%, also CMV can cause pulomnary infiltrates can cause alveolar damage and/or interstitial inflammation **[17].**

The present study showed that there was a significant difference between the 2 studied groups as regard hypertension (37.5% in the positive patients and 18.2% in the negative patients). Recent research has indicated that patients with a CMV infection have an increased risk of essential hypertension **[18],** which is a major contributing factor to cardiovascular illnesses.

In accordance with our research, Erdbruegger et al. (2012) [10], found that patients with CMV infection between 6 weeks and 3 months received antibiotic therapy (30%) more frequently than people without CMV (17%). Our research revealed a significant valcyte-related difference between the two groups. After receiving 100% effective therapy with Valcyte, the prevalence of

CMV positivity significantly decreased in individuals who are still positive may have resistant infections or require a higher dose.

In the present study, there was no significant difference between the two studied groups as regard creatinine at 6 and 12 months. In contrast to the current investigation, Erdbruegger et al. (2012) [10] evaluated the creatinine clearance to determine the long-term allograft function. After 1 and 2 years, patients without CMV infection had significantly higher creatinine clearance than those with CMV infection this could be due to longer period of observation in the study(almost 3 years) and large number of patients (594).

The present study showed that age, sex, triple therapy, ATG, basiliximab, creatinine and rejection episodes were not found to be independent risk factor for CMV infection.

Contrary to the findings of the current study, Kairi et al. in 2022 [19] investigated the possibility that a number of clinical factors, such as pre-transplant information, donor factors, and recipient's co-morbidities, were linked to a higher incidence of CMV infection. Notably, no correlation between CMV infection and various immunosuppressive medication regimens was found.

In our study, only one case mortality occurred. He was CMV positive. He died due to CNS infection. Mara et al. (2017) [20] investigated mortality and graft loss of individuals with and without CMV infection, which is similar to the present study. In the 377 transplanted patient, significant percentage with graft loss (0.02)was in patients with CMV infection.

The present study showed that there was a statistically significant difference between two groups as regard ATG and basliximab groups. Five patients were positive in ATG group while no patients were detected in basliximab group. This can be explained by the fact that basliximab acts at a specific site on T-lymphocytes and thus prevents T cell proliferation.Thus, the additional risk of adverse events is minimal compared with lymphocytes-depleting agents [21]. Similar to the current study, Bhadauria et al. 2012 [11] discovered that 13 patients (30.24%) who received ATG and 7 patients (28%) who received basliximab had CMV illness.

Similar comparisons between the safety and effectiveness of utilising ATG and basliximab as induction therapy were made by Patel et al. 2016 [22]. In this study, 85 kidney transplant recipients received living donors. Due to ATG's larger immunosuppressive spectrum, adverse events were more common in that group, and 3 patients (out of 43) in the basliximab group got CMV infection.

Finally, it is critical to understand whether or not CMV is associated with a worse long-term prognosis. Our research couldn’t identify a link between CMV and rejection episodes. Boratynska et al. 2006 [23] observed the lowest renal function in patients with CMV infection and acute rejection (AR). But other studies like Nett et al. 2004 [24] highlighted relation between the harmful effects of AR and CMV illness may be amplified.

The small number of the study population is a limitation of our study.

CONCLUSION

We concluded that CMV disease can increase the risk of infections like chest infection and UTI and also a risk factor for cardiovascular diseases as hypertension. We recommend that future studies with large sample size are needed for better study the role of CMV as a risk factor for rejection.

ABBREVATIONS

ALT	Alanine amino transferase	**FSGS**	Focal segmental glomerulosclerosis
ALP	Alkaline phosphatase	**GGT**	Gamma glutayl transferases
AST	Aspartate aminotransferase	**GN**	Glomerulonephritits
ATG	Antithymocyte globulin	**HD**	Hemodialysis
BMI	Body mass index	**HIV**	Human immunodeficiency virus
BUN	Blood urea nitrogen	**PCR**	Polymerase chain reaction
CBC	Complete blood count	**PT**	Prothrombin time
CMV	Cytomegalovirus	**RRT**	Renal replacement therapy
ELISA	Enzyme_linked_immunosorbent assay	**VUR**	Vesico-ureteric reflux
ESRD	End stage renal disease		

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Authors' contributions

The submitted manuscript is the work of the author & co-author.
All authors have contributed to authorship, have read and approved the manuscript.
Conception and design of study: Fatina I Fadel
Acquisition of data: Aliaa R Ali
Analysis and/or interpretation of data: All authors
Drafting the manuscript: All authors
Revising the manuscript critically for important intellectual content: All authors
Approval of the version of the manuscript to be published: All authors

STATEMENTS

Ethics approval and consent to participate

This study protocol and the consents were approved and deemed sufficient by the Ethical Committee of Cairo University hospital and informed written consent was obtained in every case from their legal guardians.

Consent for publication: The attached manuscript its contents and materials have not been previously reported at any length or being considered for publishing elsewhere.

Availability of data and material: The authors have indicated that the data and material are factual and genuine.

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