

Research Paper:

Post-Kidney Transplantation Epstein-Barr Virus Infection in Children: Case Series Study



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ABSTRACT

Background: One of the main problems following organ transplantation is the spread of various microbial infections, especially opportunistic infections, including Epstein-Barr Virus (EBV).

Objectives: We aimed to determine the prevalence rate of EBV infection in children undergoing kidney transplantation by recognizing the virus titers before and after transplantation.

Methods: In this case series study, 16 children who underwent kidney transplantation and hospitalization were retrospectively assessed. The EBV serology was assessed by virus Deoxyribonucleic Acid (DNA) quantitative assessment using the Polymerase Chain Reaction (PCR) technique. A brief review was also performed on post-kidney transplantation EBV infection in the explored children.

Results: All studied patients were seronegative for EBV before transplantation; while two (12.5%) male children had positive serology after transplantation with the loads of 278 copies/mL and 14655 copies/mL, and none resulted in the rejection of kidney transplantation. The duration after transplantation was significantly longer in those children with positive serology after transplantation ($P=0.025$). No significant association was detected between the serological positivity for EBV and patients' gender, causes for kidney insufficiency before transplantation, baseline underlying disorders, initial medications, the type of donor, and the mean age.

Conclusions: Among the investigated children undergoing renal transplantation, none were seropositive to EBV before transplantation; while 12.5% have been converted to EBV seropositivity after transplantation. The odds of EBV seropositivity was only linked to the time interval from the transplantation.

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1. Introduction

One of the main problems following organ transplantation is the spread of various microbial infections, especially opportunistic ones. One of these infections is caused by the Epstein-Barr Virus (EBV) (1-3). The virus exacerbates the immune system and treatment with immunosuppressive medications could aggravate this infection (4, 5). Some researchers believe that the virus could disrupt and stimulate the immune system and is prone to reject kidney transplantation (6). Individuals who are transplanted will be infected through various manners, including a virus-infected donor or blood transfusion. Only in the United States, approximately 50% of children aged <5 years are infected with EBV (7). The infection is transmitted through contact with oral secretions and remains in the body for life after infection (8). The prevalence of this disease is directly related to a younger age at the time of transplantation, as well as living status in high-income, underdeveloped, and populous countries (9, 10). The active infection with this virus could be manifested as mononucleosis, fever, leukopenia, and lymphocytosis. Post-transplant Lymphoproliferative Disease (PTLD) (11) could also occur after being infected with this virus (12). After the spread of the virus in the entire body, some serious complications appear, such as spleen rupture, aplastic anemia, hemolytic anemia, thrombocytopenia, neutropenia, as well as neurological, respiratory, cardiac, renal, and hepatic conditions (13, 14). This virus is a significant cause of lymphoma, especially Burkitt type (15). Overall, EBV virus plays a putative pathophysiological role in the development of Post-Transplant Lymphoproliferative Disease (PTLD). In children undergoing kidney transplantation, EBV-related conditions, such as PTLD are among the main problems associated with several immunosuppressive medications, like tacrolimus (16). Studies have revealed that 80%-90% of patients, in the first year after transplantation are infected with the secondary infection of EBV (17). According to the guidelines, in children undergoing kidney transplantation, the virus load should be monitored and controlled, especially in those with a negative serum level who received tissue from a positive donor (18).

All the explored presentations and studies have supported the effect of EBV infection on the rejection of the transplant or PTLD, requiring a more precise assessment of the patients. Studies on the rate of EBV infection in Iranian children after transplantation are scarce; thus,

we aimed to determine the prevalence of EBV infection in children undergoing kidney transplantation by exploring the virus titers before and after the transplantation. We also conducted a brief review concerning post-kidney transplantation EBV infection in children.

2. Methods

In this study, all children who underwent kidney transplantation at Ali-e-Asghar Hospital from 23 September 2015 to 22 September 2016 were included. They were 16 children with advanced renal disease who were candidates for renal transplantation and were assessed, retrospectively. A checklist was used to collect the required data by reviewing the hospital records. The pointed information included age, gender, the cause of renal insufficiency, pre-transplantation viral serology in patients, transplantation time, childhood underlying illnesses, patient's medications, and post-transplant serology results in donors and recipients. The EBV serology was assessed by virus Deoxyribonucleic Acid (DNA) quantitative assessment using the Polymerase Chain Reaction (PCR) technique. For this purpose, the Artus EBV RG PCR Kit and the real-time PCR kit were used with the sensitivity of 200 copies/UL and the specificity of 95%.

The obtained data were analyzed by SPSS. Moreover, quantitative results were expressed by Mean±SD, and the normality of variables was established by the Kolmogorov-Smirnov test. For comparing the categorical variables, Chi-squared test or Fisher's Exact test were employed. For comparing the quantitative variables, Independent Samples t-test or Mann-Whitney U test were implemented. P<0.05 was considered as statistically significant. The relevant ethics code was also obtained for this study (Code: IR.IUMS.FMD.REC.1396).

3. Results

In total, 16 children (Mean±SD age: 11.26±3.4 years at the time of transplantation, 75% male) were assessed in the present study. The main causes of kidney insufficiency included cystinosis in 4 (25.0%) children, Focal Necrotizing Glomerulonephritis (FNGN) in 3 (18.8%) children, polycystic kidney in one (6.3%) child, hypoplastic kidney in one (6.3%) child, neurogenic bladder in one (6.3%) child, bilateral reflux in one (6.3%) child, Posterior Urethral Valve (PUV) in one (6.3%) child, and unknown causes for 4 (25%) cases (Table 1).

Regarding underlying disorders, 10 (62.4%) children had no history of diagnosed disorders; one (6.3%) child had Attention-Deficit/Hyperactivity Disorder (ADHD),

Table 1. Characteristics of studied cases

Case	Gender	Cause of Renal Insufficiency	Pre-Transplantation EBV Serology	Post-Transplantation EBV Serology	Virus DNA Copies	Childhood Underlying Illnesses	Rejection of Kidney Transplantation
1	Male	neurogenic bladder	negative	positive	278 copies/mL	no disease	No
2	Male	unknown	negative	positive	14655 copies/mL	no disease	No
3	Male	cystinosis	negative	negative	-	no disease	No
4	Male	cystinosis	negative	negative	-	hyperactivity disorder	No
5	Male	bilateral reflux	negative	negative	-	no disease	No
6	Female	polycystic kidney	negative	negative	-	no disease	No
7	Male	focal necrotizing glomerulonephritis	negative	negative	-	hypertension	No
8	Male	cystinosis	negative	negative	-	no disease	No
9	Female	cystinosis	negative	negative	-	hypothyroidism	No
10	Male	focal necrotizing glomerulonephritis	negative	negative	-	no disease	No
11	Male	posterior urethral valve	negative	negative	-	no disease	No
12	Male	hypoplastic kidney	negative	negative	-	hypertension	No
13	Female	unknown	negative	negative	-	no disease	No
14	Male	unknown	negative	negative	-	hypertension	No
15	Female	focal necrotizing glomerulonephritis	negative	negative	-	hypertension	No
16	Male	unknown	negative	negative	-	no disease	No

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one (6.3%) child had hypothyroidism, and 4 (25.0%) children had hypertension. Overall, 7 (43.7%) children received the kidney from survived ones, and 4 (25.0%) from deceased donors, while the donors remained unknown in other children (31.3%). The Mean±SD of time since transplantation was 34.92±31.93 months ranging from 5 to 103 months (Table 2).

All explored patients were seronegative for EBV infection before transplantation. The immunosuppression regime after transplantation was the same in all children, including Cellcept, tacrolimus, and prednisolone. Of the studied children, only two (12.5%) males

had positive serology after transplantation (with the loads of 278 copies/mL & 14655 copies/mL); however, none resulted in the rejection of kidney transplantation. We detected no significant association between the odds of serological positivity for EBV and patients' gender (P=0.38), causes for kidney insufficiency before transplantation (P=0.18), baseline underlying disorders (P=0.71), initial medications (P=0.91), the type of donor (P=0.42), and the mean age (P=0.19). However, the duration after transplantation was significantly longer in the children with positive serology after transplantation (P=0.025) (Table 3).

Table 2. Duration of follow-up

Group	Mean±SD
	Time Since Transplantation (mon)
Seropositive for EBV after transplantation	57.5±64.34
Seronegative for EBV after transplantation	31.17±26.87
P	0.025

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Table 3. Comparing baseline factors between groups with seropositive and seronegative characteristics for EBV

Baseline Factors	No. (%)		P
	Seropositive for EBV after Transplantation (n=2)	Seronegative for EBV after Transplantation (n=14)	
Male ratio	2 (100)	10 (71.4)	0.38
Reason for grafting:			0.18
Cytosis	0 (0.0)	4 (28.6)	
Focal necrotizing glomerulonephritis	0 (0.0)	3 (21.4)	
Polycystic kidney	0 (0.0)	(7.1)	
Hypoplastic kidney	0 (0.0)	1 (7.1)	
Neurologic cystitis or febrile	1 (50.0)	1 (7.1)	
Posterior urethral valve	0 (0.0)	1 (7.1)	
Unknown	1 (50.0)	3 (21.4)	
Underlying disorders	0 (0.0)	6 (42.8)	0.71
Survived donor	1 (50.0)	6 (42.8)	0.42

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4. Discussion

The present study determined the prevalence of EBV infection and transplant rejection among 16 children in terms of age, gender, cause of failure, the pre-transplantation serology of virus, childhood underlying diseases, patient's medications, donor, and post-transplant viral serology. We observed that all of the investigated children had negative serology for EBV before transplantation. Eventually, only two children had positive post-transplantation serology; none of which presented complications and symptoms of the virus infection. Besides, none of these children experienced organ rejection. In other words, low seropositivity for EBV after transplantation could explain the lack of evidence for serious complications of post-transplantation, like PTLD in our study subjects. In a similar study by Comak et al., prior to transplantation, EBV was positive in 86.7% of the cases. The follow-up period was 36 months; half of the explored children with negative EBV developed primary EBV infection, and two patients with primary infection developed PTLD (18). Suzuki et al. studied 32 children, of whom, 6 (18.7%) were EBV-seronegative before the transplantation that the conversion to seropositivity occurred in 5 of them after grafting (19). In an study by Armstrong et al. rises to EBV antibody titers occurred in 32% of children after transplantation (20).

Every year, some children develop advanced renal disease. Advances in surgical procedures, such as kidney transplantation and immunosuppression therapy have dramatically reduced the mortality rate induced by

kidney failure. A problem developed after organ transplantation is introducing various microbial infections, especially opportunistic infections, like EBV. The virus exacerbates the immune system and treatment with immunosuppressive drugs aggravates this infection. Some researchers believe that the virus could disrupt and stimulate the immune system and is prone to reject kidney transplantation. EBV significantly affects the progression of patients to PTLD after transplantation and is the strongest predictor of this condition. The higher the EBV virus load is in the body, the greater the risk of PTLD generation.

The literature indicates a wide range of seropositivity for EBV within post-transplantation period from 3% to 96% regardless of the seropositivity for this virus before transplantation. Moreover, the prevalence rate of PTLD development after transplantation also varied; however, the strong association between this complication and seropositivity to EBV was clearly presented. As per some studies, several factors could influence the rate of EBV-seropositivity as well as the occurrence of its related PTLD after transplantation. Such conditions include the employed immunosuppressive regimen, patients' age, the industrialization level of country, and the time past since renal transplantation (1, 21-25). Different studies reported an association between age and the rate of EBV seropositivity. In line with our study, a relationship was suggested between the time after transplantation and the risk for viral seropositivity; however, unlike our study, a high rate of

EBV infection, approaching 100% within three months after transplantation was reported (21).

5. Conclusion

Of the investigated children undergoing renal transplantation, none were seropositive to EBV before transplantation; while 12.5% were convert to EBV seropositivity after transplantation. None of the studied children experienced severe post-transplantation complications, such as PTLD and rejection. The odds of EBV seropositivity was only linked to the time interval since the transplantation. These results represent an appropriate use of medication and suitable patient training in this center. This study can be extended to the whole population of Iran because the research patients were selected from all cities of Iran; they referred to Ali-e-Asghar Hospital in Tehran to receive treatment. The limitation of this study was the small sample size; thus, conducting further studies with a high sample size is recommended.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles were considered in this article. The participants were informed about the purpose of the research and its implementation stages; they were also assured about the confidentiality of their information. Moreover, they were allowed to leave the study whenever they wish, and if desired, the results of the research would be available to them.

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Authors' contributions

All authors contributed in designing, running, and writing all parts of the research.

Conflicts of interest

The authors declared no conflicts of interest.

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