Abstract

Objectives: Pediatric renal transplant recipients are at increased risk of Epstein-Barr virus infection which may be due to the high percentage of Epstein-Barr virus seronegative recipients at the time of transplant in the pediatric age group. We aimed to assess the Epstein-Barr virus serostatus of recipients and donors and the incidence of posttransplant lymphoproliferative disorder in pediatric renal transplant at the Labafinejad Hospital in Tehran, Iran.

Materials and Methods: We reviewed the clinical records of 183 children who had a renal transplant at the Labafinejad Hospital in Tehran, Iran, between 2003 and 2011.

Results: Of all the patients, 61.2% were Epstein-Barr virus seropositive at the time of transplant. Graft survival rate and the rate of acute rejection episodes were not statistically different between the seropositive and seronegative recipients. Three patients (0.005%) had posttransplant lymphoproliferative disorder after transplant.

Conclusions: We showed that the rate of seronegative recipients in our cohort is similar to other studies, but the rate of posttransplant lymphoproliferative disorder was low in our recipients.

Key words: Kidney transplant, Children, EBV, Outcome

Introduction

Epstein-Barr virus (EBV) is a ubiquitous herpesvirus that infects B lymphocytes. In immunosuppressed transplant recipients, primary EBV infection and/or relapse cause various signs ranging from mononucleosislike syndrome to lymphoma. Epstein-Barr virus plays a central role in posttransplant lymphoproliferative disorders (PTLDs). Occasionally, EBV infection may cause rapid and resistant allograft rejection in children.

Pediatric renal transplant recipients are at increased risk of EBV infection. The cause of this increased incidence may be due to high EBV seronegative pediatric patients who receive a graft from EBV-positive donors. Determining the pretransplant antibody status of donors and recipients is necessary for identifying high-risk patients with EBV infection and consequently PTLD after renal transplant. Posttransplant lymphoproliferative disorder is associated with primary EBV infections in most cases. Extra nodal and atypical forms of PTLD are seen more commonly in transplant recipients.

To our knowledge, this is the first study regarding the EBV serostatus of recipients and donors in Iranian pediatric renal transplant patients. This study sought to identify the prevalence of seronegative EBV pediatric recipients and PTLD at Labafinejad Hospital.

Materials and Methods

We reviewed the clinical records of 183 children with renal transplant at Labafinejad Hospital in Tehran, Iran, between 2003 and 2011. All transplanted kidneys were from living donors. Patient charts were evaluated, and pretransplant EBV serostatus of recipients and donors were recorded. In all patients, the following data were also analyzed: age, sex,
underlying renal disease, donor age, number of rejection episodes, and graft survival rates. Graft failure was defined as the need for dialysis or death of the patient owing to renal complications. During the induction phase, intravenous methylprednisolone and high-dose cyclosporine (10-12 mg/kg/d) were administered. Patients with delayed graft function were treated with thymoglobulin, 1 mg/kg/d for 7 to 10 days. During administration of the antibodies, mycophenolate mofetil was withheld, and the dosage of cyclosporine was reduced. We determined our immunosuppressive protocol after the transplant of previous studies.\textsuperscript{2,3}

We classified our patients based on pretransplant EBV status: recipient positive–donor negative, recipient positive–donor positive, recipient negative–donor negative, and recipient negative–donor positive. We analyzed graft survival for these 4 groups. We did not have any program to monitor seronegative recipients after transplant. This study included comparisons between these 4 groups regarding graft survival, graft function, and acute rejection episodes. We also determined the incidence of PTLD in our patients and their EBV status.

Statistical analyses
Values are expressed as mean (± SD). Survival was analyzed using the Kaplan-Meier formula, and the log-rank test was used to compare group survival rates. \(P\) values less than .05 were considered statistically significant growth. Additionally, comparisons between data were performed by the chi-square and \(t\) tests.

Results
At Labafinejad Hospital, 517 renal transplants in children were performed from 1985 until the time of this writing. The EBV serostatus of recipients and donors were assessed after the year of 2003 in Labafinejad Hospital. Thus, we reviewed medical records of 183 children (≤ 18 y) who received a renal transplant at the Labafinejad Hospital after the year 2003.

All recipients and donors who were assessed with pretransplant EBV serostatus were included in this study (183 recipients with their donors). In all, 112/183 recipients (61.2\%) were EBV seropositive at the time of transplant. The mean age of seropositive recipient was 12.9 years (± 3.58) and seronegative recipients was 12.46 years (± 3.89; \(P = .42\)).

Table 1 shows the comparison of some variables between seronegative and seropositive recipients. The graft survival rates were 97\%, 97\%, and 92.3\% at 1, 5, and 7 years after transplant in seronegative recipients. In comparison, graft survival rates were 99\%, 89\%, and 87\% at 1, 5, and 7 years after transplant in seropositive recipients (\(P = .48\)).

We classified our patients based on pretransplant the EBV status of recipients and donors: recipient positive–donor negative (24 patients), recipient positive–donor positive (88 patients), recipient negative–donor negative (33 patients), and recipient negative–donor positive (38 patients). The comparison of the graft survival rate of these 4 groups is shown in Figure 1. There was no difference between these groups regarding graft survival rate (\(P = .4\)).

In our 517 patients, 3 patients (0.005\%) with PTLD were seen as follows: Two patients with non-Hodgkin lymphoma and 1 patient with acute lymphoblastic leukemia. Posttransplant lymphoproliferative disorder occurred approximately 3 to 4 years posttransplant in these patients, and all were taking cyclosporine and mycophenolate mofetil as maintenance therapy. None of the PTLD patients received antithymocyte globulin/antilymphocyte

<table>
<thead>
<tr>
<th>Variable</th>
<th>Epstein-Barr Virus Seronegative Recipient</th>
<th>Epstein-Barr Virus Seropositive Recipient</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12.46 (± 3.89)</td>
<td>12.9 (± 3.58)</td>
<td>.4</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>0.62</td>
<td>0.58</td>
<td>.46</td>
</tr>
<tr>
<td>Cause of end-stage renal disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inherited diseases</td>
<td>25.7%</td>
<td>30.3%</td>
<td></td>
</tr>
<tr>
<td>Structural diseases</td>
<td>48.5%</td>
<td>43.5%</td>
<td>.79</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>20%</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>13%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean transplant (y)</td>
<td>2004</td>
<td>2005</td>
<td>&gt; .5</td>
</tr>
<tr>
<td>Acute rejection episode</td>
<td>24.1%</td>
<td>30%</td>
<td>.6</td>
</tr>
<tr>
<td>Graft failure</td>
<td>5.6%</td>
<td>10%</td>
<td>.6</td>
</tr>
<tr>
<td>Follow-up (mean)</td>
<td>59.19 mo</td>
<td>47.45 mo</td>
<td>&gt; .05</td>
</tr>
</tbody>
</table>
globulin as induction therapy. The EBV serostatus of patient with antilymphocyte leukemia was not available. In 2 patients with non-Hodgkin lymphoma, both were EBV seronegative, and their donors were EBV seropositive at the time of transplant.

**Discussion**

Epstein-Barr virus is a human gammaretrovirus with a marked tropism for B lymphocytes. Epstein-Barr virus is classified as a group 1 carcinogen. Epstein-Barr virus replicates in the epithelial cells of oropharynx and infects activated B lymphocytes.

After transplant, immunosuppression inhibits the T-cell’s ability to monitor and clear the virus; thus, putting the recipient at risk for EBV infection. Risk factors associated with posttransplant infection include use of T-cell depleting antibodies, especially OKT3, degree and type of posttransplant immunosuppression, cytomegalovirus-negative or EBV-negative recipients who have received organs from donors positive for these viruses. Fifty percent of children are likely to be EBV seronegative at the time of transplant, and thereafter, they are susceptible to primary infection after transplant. Epstein-Barr virus infection occurs in 75% of these patients. In a study in adult renal recipients in Iran, pretransplant EBV (IgG) seroprevalence was 100% among all recipients.4

Epstein-Barr virus infection after transplant may be primary or reactive. Primary infection can occur by contact with infectious individuals, by the transplanted organ, or by blood transfusion. Epstein-Barr virus infections occur mostly early after transplant. In children, most EBV infections are clinically silent. The clinical presentations of EBV-associated infection vary, and include unexplained fever, a mononucleosis-like syndrome (with fever and malaise, with or without pharyngitis), gastrointestinal complications, graft dysfunction, and central nervous system involvement. Posttransplant lymphoproliferative disorder as the most common malignancy after transplant is associated with EBV infection in 90% cases. Primary EBV infection increases the risk of EBV-related PTLD by 10-fold to 76-fold posttransplant.5

Epstein-Barr virus-related PTLDs affect 1% to 2% of renal transplant recipients, with the highest incidence during the first year after transplant owing to the intensive immunosuppressive therapy during this time.6 Recently, a marked increase in PTLD incidence in renal transplant recipients has been reported. This increase may be due to the introduction of more-potent immunosuppressive agents, like tacrolimus. In comparison with general population, extranodal and central nervous system involvement is more seen in transplant recipients with PTLD. In addition, poor response to conventional therapies and poor outcome are seen more often in PTLD.

In our study, 37.8% of children were EBV seronegative at the time of transplant. In a similar study in adult group patients in Iran, 100% of patients were seropositive at the time of transplant. The EBV serostatus of our recipients is similar to other studies. We also showed that there was no difference between EBV seronegative and seropositive recipients regarding acute rejection episodes and graft outcomes.

In our study, we showed that 3 patients had PTLD. The incidence of PTLD in children who underwent renal transplant in Labafi Nejad was low (0.005%), and this incidence is much lower than other reports in children.

**References**

