

Epstein-Barr Virus, Cytomegalovirus, and Other Viral Infections in Children After Liver Transplantation

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We studied 51 consecutive pediatric patients for the frequency and morbidity of viral infections after liver transplantation. The incidence of primary (67%) and reactivation (48%) Epstein-Barr virus (EBV) infections and reactivation (88%) cytomegalovirus (CMV) infection was comparable to that seen in adult transplant recipients. However, fewer pediatric than adult transplant recipients experienced primary CMV infection ($P < .01$). Five (38%) of 13 CMV infections were symptomatic and included hepatitis, pneumonitis, enteritis, and mononucleosis. Two of 14 patients with primary EBV infection subsequently developed, at two months and two years after initial infection, an EBV-associated lymphoproliferative syndrome, and one of 10 patients with reactivated EBV infection developed a possible EBV-associated febrile encephalopathy. Other viruses causing infection in these children included herpes simplex virus, varicella-zoster virus, adenovirus, parainfluenza virus, respiratory syncytial virus, and rotavirus.

Both Epstein-Barr virus (EBV) and cytomegalovirus (CMV) are notable for their ubiquity, latency, and tendency to reactivate in the immunosuppressed host. Reports on the frequency and morbidity of EBV and CMV infections in adult transplant recipients from this center are available [1-3]. Comparable data in children have not been reported because, until recently, they had not undergone transplantations in large numbers. The behavior of EBV and CMV in pediatric transplant recipients is of interest not only because children may respond differently, but unlike adults, a large proportion of children have not been infected by these viruses before transplantation. Hence, a smaller number of children are at risk of developing reactivation infections; however, a greater number may be susceptible to primary infections and their consequent morbidity.

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This study reports EBV, CMV, and other viral infections in 51 children who received transplants at Children's Hospital in Pittsburgh within a 12-month period.

Patients and Methods

Patients. Fifty-one consecutive pediatric transplant patients were followed up to assess infection. Fifty patients received liver transplants and one patient, a liver- and heart-transplant. This was the first transplant for all patients except one, who received her second transplant.

Immunosuppression. Intravenous cyclosporine was given before surgery and was continued postoperatively. When the patient was able to take medications orally, oral cyclosporine was begun in addition to the intravenous dose. The intravenous cyclosporine was tapered and discontinued, and the oral dose was adjusted accordingly. Whole-blood levels of cyclosporine were monitored by high-performance liquid chromatography (HPLC) or by RIA to maintain levels of ~200-300 $\mu\text{g}/\text{ml}$ (HPLC) or 800-1,000 $\mu\text{g}/\text{ml}$ (RIA).

Steroids were given preoperatively, usually as a bolus of hydrocortisone or methylprednisolone. On the first postoperative day, a cycle of steroids (equivalent to a dose of 100 mg of prednisone) was given and decreased each day until a baseline dose of 20 mg/day was reached. This dose was usually main-

tained until discharge, when it was further reduced to 5-10 mg/day.

Surveillance. The objectives of surveillance were to prospectively identify and diagnose herpesvirus infections by isolating virus and by serology, even in the absence of clinical abnormalities. Specimens for isolation and serology were collected before transplantation (when possible), usually weekly for the first four postoperative weeks, biweekly thereafter, and when patients returned for six-month follow-up visits. When recipients did not return for follow-up visits, letters were sent, and serum specimens were obtained by their attending physicians. The mean duration of specimen collection in recipients who were evaluated for viral infection was 309 days, with a range of 91-553 days.

Throat swabs, urine samples, and blood buffy coats were obtained routinely for isolating CMV and herpes simplex virus (HSV). Specimens were inoculated into tube cultures of human foreskin fibroblasts, African green monkey kidney (AGMK) cells, and HEP-2 cells. Viruses were identified by their characteristic CPE and by host cell range. Throat swabs were also used for isolating EBV by transformation of umbilical cord blood lymphocytes [4]. Other viruses were isolated from specimens ordered when clinically indicated or were noted incidentally from throat or urine cultures. Specimens suspected of containing adenovirus or parainfluenza virus were inoculated into tube cultures of AGMK, HEP-2, Rhesus monkey kidney, and WI-38 cells. Viruses were identified presumptively by characteristic CPE or by hemadsorption and were sent to the Allegheny County Diagnostic Laboratories (Pittsburgh) for confirmation and typing. All cell cultures were obtained from commercial suppliers (M.A. Bio-products, Walkersville, Md; and Flow Laboratories, McLean, Va). Respiratory syncytial virus was identified by using the Ortho RSV antigen ELISA test (Ortho Diagnostics Systems, Raritan, NJ), and rotavirus was identified using the Rotazyme® II ELISA test (Abbott Diagnostic, North Chicago, Ill).

Serum or plasma specimens were tested for IgG antibody to EBV capsid antigen (VCA) and early antigen (EA) as previously described [5], for antibody to CMV by using the anticomplement immunofluorescence test [6] or the FIAX® test (International Diagnostic Technology, Santa Clara, Calif), and for antibody to HSV by using the neutralization test [7] or the FIAX test. Selected serum or plasma specimens were also tested for IgM antibody to VCA and

antibody to Epstein-Barr nuclear antigen (EBNA), as previously described [5]. Tumor tissue specimens were tested for their EBV genome content or EBNA by Dr. George Miller (Yale University), as previously described [5].

Infection. A primary infection was diagnosed by a conversion from seronegativity to seropositivity, and a reactivation infection was diagnosed by a fourfold or greater increase in titer. The isolation of virus from a seropositive recipient, in the absence of a fourfold or greater increase in antibody titer, was defined as asymptomatic shedding.

Serological data. To distinguish between primary and reactivation infections diagnosed during the period of follow-up after transplantation, we had to know the patient's serological state before infection, i.e., before transplantation. A pretransplant serum sample was therefore important for this study. This sample was available for 75% of the participants (38 of 51). When such sera were not available, a sample obtained during or immediately after transplantation was tested. Under these circumstances, however, passively transferred antibody from the large number of units of transfused blood products could obscure the true serological status of the recipient. This occurrence was particularly evident in the case of antibody to EBV. If, however, the titer of antibody to VCA became negative after it had been positive, a primary infection that occurred after transplantation could still be diagnosed. Fourteen patients whose posttransplantation titers of IgG to EBV were VCA positive later reverted to seronegativity. In the absence of such reversion, the distinction between primary and reactivation infection was difficult and required the use of ancillary clinical and laboratory data, e.g., antibody to EBNA, IgM to VCA, and cultures of virus.

Clinical follow-up. To obtain the clinical correlates of laboratory findings, one of us (B. Z.) reviewed the clinical courses of all patients. Symptomatic viral infections were suspected by the constant or intermittent presence of fever >38 C for at least one week if no other cause, such as other microbial infections or rejection, could be found. In addition to laboratory evidence of EBV or CMV infection, at least one of the following findings was required: (1) leukopenia (white blood cells, $<4,000$); (2) thrombocytopenia (platelets, $<100,000$); (3) atypical lymphocytes, $>3\%$; and (4) tissue evidence of local viral infection, such as isolation of virus from the liver or lung or histological evidence of such infection.

Patients with fever and one or more of the first three signs were considered to have the "mononucleosis" syndrome.

Statistics. Differences between means were compared by using Student's *t* test. Observed proportions were compared by using the χ^2 test.

Results

Patients. Our study population included 23 boys and 28 girls. Their ages at transplantation ranged from 9 to 179 months, with a mean age of 64 months. The majority of patients (32 of 51) had a pretransplantation diagnosis of biliary atresia/hypoplasia, and the remainder had a diverse group of diagnoses.

EBV infection. Forty-two patients had sufficient serological and/or virological data to be evaluated for EBV infection. Twenty-one (50%) had antibody to EBV before transplantation. Three (14%) of 21 swabs obtained from seropositive patients before surgery were positive for EBV. These patients were assumed to be asymptomatic shedders. A total of 223 throat swabs were obtained during follow-up, and 55 (25%) were positive for EBV. In no case was EBV cultured from a subject who remained seronegative.

Fourteen (67%) of the 21 seronegative recipients developed primary EBV infection (table 1). Eight experienced their infection in the hospital or shortly thereafter and hence, the mean day of onset was readily ascertainable (66 ± 10 days after transplantation). EBV was isolated from six of these eight patients. Two patients had symptoms attributable to EBV infection.

One patient was undergoing a primary EBV infection at the time of transplantation and, two months later, became symptomatic, with fever, tonsillitis, and lymphadenopathy. The tonsillar tissue showed monomorphous polyclonal lymphoproliferation and contained EBV DNA by hybridization. A right inguinal lymph node was positive for EBNA by immunofluorescent staining. This patient is well 2.5 years after the initial infection.

One month after transplantation, another patient experienced a primary EBV infection associated with exudative pharyngitis and atypical lymphocytes. Two years later, when he was admitted with a history of rectal bleeding and abdominal pain of three-weeks' duration, a perforated cecum secondary to a lymphoma and mesenteric mass was found. This finding was characterized by a monomorphous, malignant-appearing, diffuse lymphoproliferative

Table 1. EBV and CMV infections in pediatric transplant recipients.

Pretransplant serological status	No. of patients	No. with infection/total no. (%)	No. of symptomatic patients/total no. (%)
Negative for EBV	21	14/21 (67)	2/14 (14)
Positive for EBV	21	10/21 (48)	1/10 (10)
Negative for CMV	35	6/35 (17)	3/6 (50)
Positive for CMV	8	7/8 (88)	2/7 (29)

infiltration in all layers of the small bowel. Immunoperoxidase staining revealed monoclonal λ -light-chain-producing B cells. EBNA and EBV DNA were found in a specimen of the tumor. The tumor regressed after reduction of immunosuppression [8].

Twenty-one recipients had antibodies to EBV before transplantation. Ten (48%) developed serological evidence of reactivation infection (table 1). Five of the 10 were also found to shed EBV in the throat. The time of reactivation could be accurately dated in seven patients because reactivation occurred during hospitalization (61 ± 11 days after transplantation). Eleven of the 21 patients had no serological evidence of reactivation after transplantation; 8 patients shed EBV asymptotically. To date, only one of the initially seropositive patients has developed possible EBV-associated pathology. This patient had an asymptomatic, reactivated EBV infection that was diagnosed by elevated levels of antibody to VCA 52 days after transplantation. About two years later she was admitted with a febrile encephalopathy and titers of IgG antibody to VCA ($>1,280$) and EA (>80). These titers are unusually high for our patients and indicate possible active, chronic infection. No tissue was available for EBV studies. Thus, in this case, there is a presumptive, but not proven, association between the encephalopathy and EBV infection.

In summary, 24 (57%) of 42 patients developed EBV infection, and three (12%) were symptomatic.

CMV infection. Forty-three patients had sufficient serological and/or virological data to be evaluated for CMV infection, and eight (19%) had antibody to CMV before transplantation (table 1). Only one throat swab of 24 blood buffy coat, urine, and throat swab specimens obtained from seropositive patients before surgery was positive for CMV. The throat swab was from a patient who had serological evidence of CMV reactivation infection between seven and 21 days after transplantation. Asymptom-

atic shedding of CMV, unlike EBV, is rare before transplantation.

A total of 779 specimens, consisting of throat swabs, urine specimens, and blood buffy coats, was obtained during follow-up after transplantation; 74 (9.5%) were positive. CMV was recovered more frequently from urine cultures and throat swabs than from blood buffy coats. Thirty-four (13.7%) of 248 urine cultures were positive, and 32 (13.2%) of 242 throat swabs were positive; only 8 (2.8%) of 289 blood buffy coats were positive. In this pediatric population, as in the adult transplant population [1], isolation of CMV was diagnostic for infection; CMV was isolated from 12 patients during follow-up, and all patients had either primary infection or reactivation infection, as determined by serological criteria. Of these 12 patients, 3 were positive from one site only (all urine cultures), 6 were positive from two sites (all urine and throat), and 3 were positive from all three sites. One patient experienced her primary infection after discharge from the hospital, when samples for culture were not available, and diagnosis was made on the basis of serological changes only.

Six (17%) of the 35 seronegative recipients developed primary CMV infection (table 1). Five experienced a primary infection during their initial hospitalization (mean, 26 ± 6 days after transplantation). Three patients had symptoms associated with CMV infection.

The first patient had a primary CMV infection about the time of transplantation and had a post-operative course marked by fever and abdominal distension leading to laparotomy 16 days after transplantation. A perforation in the Roux-en-Y limb, along with mucosal ulcers, was found. CMV inclusions were found in the ulcer crater. He ultimately recovered from the CMV enteritis without an alteration of his immunosuppression regimen. In the second patient, CMV infection was associated with hepatitis, interstitial pneumonitis, and esophagitis, and the viral inclusions were found in these three respective anatomic sites. She was treated by temporarily stopping her cyclosporine; she eventually recovered. The third patient had the typical picture of CMV mononucleosis, including fever, leukopenia, and atypical lymphocytes. He recovered without a reduction in immunosuppression.

Eight recipients had antibody to CMV before transplantation, and seven (88%) had reactivation infection (table 1). The mean time of onset of reac-

tivation infection was 37 ± 10 days after transplantation. Two patients had disease attributable to reactivation infection. One patient received a second liver transplant because of initial-graft failure due to a thrombosed hepatic artery. Persistent fever and pulmonary infiltrates prompted a laparotomy, during which a mycotic aneurysm of the aortic graft ruptured, and the patient died. Necropsy demonstrated CMV inclusions in the second hepatic allograft. This represents a case of CMV hepatitis in the second allograft that was undiagnosed antemortem. The second patient had a mononucleosis syndrome associated with fever, a macular erythematous rash on his chest, and leukopenia. The rash became petechial despite a normal platelet count. He recovered spontaneously.

In summary, 13 (30%) of 43 patients had CMV infection, and five (38%) had CMV-associated disease.

Other herpesvirus infections. Seven recipients had herpetic lesions that were confirmed by isolating HSV. All of the recipients had reactivated infections because the patients had antibodies to HSV before transplantation. Two patients had lip lesions, and five had mouth and/or tongue lesions; the mean time of appearance was 22 days after transplantation. Two patients also experienced fever during the appearance of their lesions. All patients were treated intravenously with acyclovir, and all recovered uneventfully.

Three patients developed varicella, which was diagnosed clinically. One recipient had vesicular lesions on her trunk ~ 22 days after transplantation. A Tzanck preparation of the lesions showed multinucleated giant cells, but no virus was recovered from the vesicle fluid. She was treated with acyclovir for 10 days and recovered uneventfully. The second patient had an attack of varicella ~ 1.5 years after transplantation, was treated with acyclovir, and recovered uneventfully. The third patient was discharged 27 days after transplantation and had no subsequent laboratory or clinical follow-up until 137 days after transplantation, when an autopsy was performed after she died of disseminated varicella.

Other viral infections. Stool specimens to be tested for rotavirus were only obtained when clinically indicated. Twenty-one specimens were taken from 14 patients, and two patients (14%) were positive once. Both positive specimens were obtained 24 days after transplantation. Both patients had diarrhea, an increase in levels of serum aspartate ami-

nottransferase, and were treated for rejection. One patient developed progressive rejection and received a second transplant; the graft of the other patient survived. It is possible that diarrhea caused by rotavirus infection led to cyclosporine malabsorption, which may have been a factor contributing to rejection.

Adenovirus was isolated from four patients, and from one of these four, respiratory syncytial virus and parainfluenza virus were also isolated. Ascribing particular signs or symptoms to infection with these viruses was not easy because of other infectious complications that occurred after transplantation. Of three of the four patients from whom adenovirus was isolated, one was febrile, had nodular pulmonary infiltrates, and was experiencing a primary CMV infection when adenovirus (not typed) was isolated from his throat. Another patient was undergoing primary CMV infection when adenovirus 5 was isolated from buffy coats, urine specimens, and a liver biopsy specimen, which histologically showed granulomatous necrosis. The third patient was afebrile when adenovirus 2 was isolated from her throat. The fourth patient was febrile, had tachypnea and wheezing when parainfluenza was isolated from her throat, and had no respiratory symptoms when respiratory syncytial virus was isolated from her throat. She was febrile, had cholangitis, and pneumocystis pneumonia when adenovirus 2 was isolated from her throat and urine.

Discussion

The purpose of this study was to determine the importance of viral infections in pediatric liver transplant recipients. Viral infections, particularly herpesvirus infections, occur frequently after organ transplantation. The herpesvirus infections of special interest were those caused by EBV and CMV [1].

Twenty-four (57%) of 42 pediatric liver recipients had evidence of EBV infection. This incidence of EBV infection is significantly higher ($P = .03$) than that seen in adult transplant recipients, in whom 51 (36%) of 140 recipients had EBV infection [authors' unpublished observations; 5]. These rates for EBV infection in recipients immunosuppressed with cyclosporine are similar to the 34% reported by others in renal transplant recipients [9] and to our own previous work [10], in which 32% of renal transplant patients receiving azathioprine and prednisone developed EBV infection. Our experience with adult

transplant recipients receiving cyclosporine suggests that the frequency of EBV infection varies: heart and heart-lung recipients have the highest frequency, followed by liver recipients; kidney recipients have the lowest frequency.

The main difference between adult and pediatric recipients is the greater proportion of children who were seronegative for EBV before transplantation. Fifty percent of children were seronegative, whereas only 8% of adults were seronegative. The proportion of children who developed primary EBV infection after transplantation (67%), however, is similar to the proportion of adult recipients who developed primary infection (82%). There is also no significant difference between the proportions of pediatric (48%) and adult (33%) recipients who developed reactivation infection. The proportion of pediatric patients seropositive for EBV who excreted the virus in oral secretions after transplantation (13 [65%] of 20) is comparable to those (50%–80%) noted in previous studies [11–13] on renal transplant recipients.

Morbidity due to EBV infection after transplantation has not been as well defined as morbidity due to CMV infection. In reality, it is often difficult to specifically ascribe symptoms to either EBV or CMV, particularly when patients are experiencing EBV and CMV infections concomitantly or within a few weeks of each other, as was often the case in our pediatric population. Two patients who developed primary EBV infection, however, had symptoms specifically attributable to EBV. In both cases there was evidence of the presence of EBNA or EBV DNA in lymphoproliferative lesions.

Although small, this series of patients demonstrates a wide diversity of syndromes possibly related to EBV infection. In one case, a mononucleosis syndrome occurred two months after laboratory evidence of a primary infection; in the other, there was no evidence of a viral, mononucleosis-like syndrome at all, but two years after a primary infection, the patient developed an intestinal lymphoma with tissue evidence of EBV activity. A series of such lymphomas have been described in adults [5]. Most, but not all, such tumors were associated with a prior mononucleosis-like "viral syndrome." An important point in that study was that patients with primary infections were at higher risk for developing EBV-related lymphomas and lymphoproliferative syndromes. This finding is consistent with those in this study.

A different syndrome was observed in a patient who had an asymptomatic reactivation infection after transplantation, but who, two years later, still had serological evidence of an active, chronic EBV infection and who developed a febrile encephalopathy. Seizures and meningoencephalitis complicating EBV mononucleosis acquired during childhood have previously been described [14]. The encephalopathy in this case could not be unequivocally ascribed to EBV because we had no tissue evidence. It is apparent that in searching for morbidity due to EBV infections, one must also look for late and indirect effects.

Thirteen (30%) of 43 pediatric liver recipients had evidence of CMV infection, a frequency that is significantly lower than the frequency of CMV infection in adult recipients (70 [77%] of 91; $P = <.00001$) [2]. This difference is due to the high proportion of seronegative pediatric patients (35 [81%] of 43) and to the low incidence of primary CMV infection (six [17%] of 35). By comparison, only 21% (19 of 91) of adult recipients are seronegative, and the seroconversion rate is significantly higher (11 [58%] of 19; $P = .006$). The frequency of CMV reactivation infection, however, does not differ between pediatric (seven [88%] of eight) and adult (59 [82%] of 72) recipients [2]. As is the case in adult transplant recipients [1], more patients with primary CMV infection were symptomatic than were those with reactivation infections, although the numbers were small.

The risk of acquiring primary EBV or CMV infection, i.e., acquiring infection *de novo* after transplantation, was 67% (14 of 21) in the case of EBV and 17% (six of 35) in the case of CMV. Two important possible sources of CMV infection have previously been identified in organ transplantation in adults — transmission of the virus by the donated organ or by blood and blood products [1, 15]. Neither source has been documented for EBV infection. In view of the fact that there is evidence of EBV transmission by transfusion [16], however, it would not be unreasonable to assume that these two sources may also be important in the case of EBV.

There was no difference in the mean number of units of blood products received by those patients who acquired either primary EBV or primary CMV infection when compared with those who did not acquire infection. Nor have we seen any correlation of donor seropositivity to EBV with subsequent development of EBV infection in recipients. One complicating factor, vitiating the significance of this find-

ing, is that donors are transfused intraoperatively during harvest of the liver. We also asked whether passively transfused antibody might protect against infection. Passively transfused IgG antibody to EBV VCA was noted after transplantation in all 21 patients who were seronegative to EBV before transplantation. There was no difference, however, in either the duration or the titer of transfused antibody when comparing those who acquired EBV infection with those who did not.

There were 35 recipients who were seronegative for CMV. Only three seropositive donors were detected among the available donor sera. One donated to a subsequently infected recipient, and two donated to recipients who did not become infected with CMV. The relatively low rate of acquiring primary CMV infection (17%), compared with the experience in adult organ transplantation (58%), might be related to the high proportion of pediatric donors who were seronegative.

Adenovirus was isolated from four patients (9%); this incidence is not significantly different from that of 4.9% noted in bone marrow transplant recipients [17]. Three of the four patients had symptoms, including fever, when adenovirus was isolated. In two patients, however, the relation between symptoms due to other infections and to adenovirus was not clear. One patient did, however, have an invasive infection, as demonstrated by recovery of adenovirus from her liver at biopsy.

In this study, the prevalence of other viral infections, e.g., those caused by rotavirus and adenovirus, may be an underestimate of the true prevalence, because of the lack of routine periodic cultures. However, this study reemphasizes the fact that herpesvirus infections, particularly those caused by EBV and CMV and many of which are not clinically apparent, can be documented by routine periodic cultures and by serological studies.

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