Betaherpesviruses in Pediatric Organ Transplantation: A Longitudinal Evaluation

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Multiplex PCR performed by PrimeraDx, Mansfield, MA with the assistance of Ming-Chou Lee and Lilly Kong.

Abstract

Background: The impact and incidence of betaherpesvirus infections other than CMV has not been explored extensively in transplant recipients. We hypothesize that these viruses reactivate frequently and multiple viruses may reactivate concurrently after transplant.

Methods: We report on an IRB approved longitudinal prospective study of pediatric transplant recipients after informed consent/assent. Clinical data and whole blood were collected from patients pre-transplant, at fixed intervals for 2 years after transplantation (every 2 weeks for 6 months, every 1 month for 6 months, and every 3 months for the second year) and during episodes of acute illness. Multiplex PCR for CMV, EBV, HHV-6, HHV-7 and BK virus was performed with capillary electrophoresis using the PrimeraDx Semiautomated Thermocycler and Capillary Electrophoresis (ViraQuant, Primera Biosystems, Mansfield MA) which has undergone independent validation.

Results: Twenty-five subjects were enrolled and transplanted with heart (12), lungs (1), heart-lung (1), liver (6), and kidney (5) between 11/2005 and 5/2008. Sixteen subjects completed 1 year on study, and 12 completed 2 years. The median age at transplant was 11.9 years (8m to 19.3y, mean: 11y) The median number of blood draws is 9 (range: 2-22). To date 202 samples have been analyzed from 22 subjects. Betaherpesviruses have been detected in 5 subjects (1 each with CMV, HHV-6, 3 with HHV-7). In addition, six subjects had EBV detected while 2 had BK virus. Three episodes of co-infection occurred, all with EBV infection An 11-year old heart recipient was positive for EBV and HHV-6 (HHV-6 detected serially 6-62 days posttransplant, range 75K-3.7million copies/mL). An 8-month old heart recipient had HHV-7 with EBV while a 14-year old kidney recipient was positive for BKV and EBV. A 16 year-old lung recipient with persistent circulating HHV-7 from 8-89 days posttransplant (564-971 copies/mL).

Conclusions: Betaherpesvirues were recovered in only a fraction of the pediatric solid organ transplant recipients in the first two years after transplantation. Co-infection of a betaherpesvirus and EBV occurred in two subjects. Clinical correlation of viral reactivation and symptoms is under investigation and viral sample collection is on-going in sixteen subjects.

Hypotheses

We hypothesize that the betaherpseviruses reactivate frequently and multiple viruses may reactivate concurrently after transplant.

Materials & Methods

We report on a longitudinal prospective study of pediatric transplant recipients. Clinical data and whole blood were collected from patients pre-transplant, at fixed intervals for 2 years after transplantation (every 2 weeks for 6 months, every 1 month for 6 months, and every 3 months for the second year) and during episodes of acute illness.

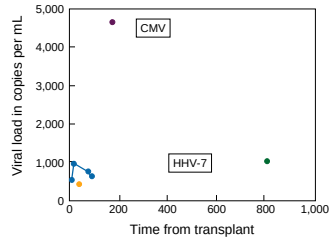
Multiplex PCR for CMV, EBV, HHV-6, HHV-7 and BK virus was performed with capillary electrophoresis using the PrimeraDx Semiautomated Thermocycler and Capillary Electrophoresis (ViraQuant, Primera Biosystems, Mansfield MA) which has undergone independent validation.

Demographics of Enrolled and Evaluated Subjects

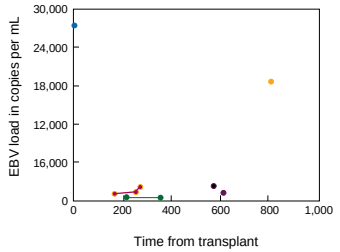
Transplant Type & Age (years)	CMV serostatus	EBV serostatus	Viruses Recovered Time to Recovery (days)	Viral load (copies/mL)
Heart/0.7	D+/R-	D-/R-	EBV/HHV-7 : 804	EBV: 18722 HHV-7: 1039
Heart/12.2	R-	R-		
Heart/7.1	D-/R-	D-/R+		
Heart-Lung/11.9	D+/R-	R+	EBV: 613 BKV: 0-74	EBV: 1260 BKV: 615-1522
Heart/6.3	D-/R-	Unknown		
Heart/17.9	D-/R+	D+/R+		
Heart/11.8	D+/R-	D+/R+	EBV/HHV-6: 6-62	EBV:27300 HHV-6: 79925-3732500
Heart/1.9	D+/R+	R-		
Heart/11.7	D-/R-	D+/R-		
Heart/19.2	D+/R+	D+/R-		
Heart/1.7	D+/R-	D+/R-		
Heart/17.5	D+/R+	D+/R+	EBV: 574	EBV: 2303
Heart/6.7	D+/R-	D+/R-		
Kidney (CAD)/14.9	D+/R-	D+/R+	CMV: 174	CMV: 4657
Kidney (LRD)/15.5	D+/R-	D+/R+		
Kidney (CAD)/18.6	D-/R-	D+/R+		
Kidney (LRD)/18.7	D-/R-	D+/R+	HHV-7: 38	HHV-7: 449
Kidney (LRD)/14.1	D-/R-	D+/R-	EBV: 217-355 BKV: 355	EBV: 530-566 BKV: 23559
Liver/4.2	D-/R-	R-		
Liver/5.6	D+/R-	R-		
Liver/5.6	D+/R-	R-		
Liver/19.3	R+	R+		
Liver/13.6	R+	R-		
Liver/6.8	D+/R-	D-/R-		
Liver/0.8	D+/R-	R-	EBV: 169-273	1131-2121
Lung/16.6	R+	D+/R-	HHV-7: 8-89	564-971

Time to Events

HHV-7 and CMV Viral Loads (copies/mL) from Time of Transplant by Patient



EBV Viral Loads (copies/mL) from Time of Transplant by Patient



Conclusions & Future Plans

Betaherpesvirues were recovered in only a fraction of the pediatric solid organ transplant recipients in the first two years after transplantation. Co-infection of a betaherpesvirus and EBV occurred in two subjects. Clinical correlation of viral reactivation and symptoms is under investigation and viral sample collection is on-going in sixteen subjects.

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