Rev Argent Microbiol. 2016;48(2):110–118

asociación argentina de microbiología aam

REVISTA ARGENTINA DE
MICROBIOLOGÍA

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ORIGINAL ARTICLE

Epstein–Barr virus load in transplant patients: Early detection of post-transplant lymphoproliferative disorders

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Received 21 August 2015; accepted 21 February 2016
Available online 4 May 2016

KEYWORDS
Epstein–Barr virus;
Early PTLD detection;
Lymphoma;
Real-time PCR;
Transplant patients;
Viral load

Abstract High levels of circulating EBV load are used as a marker of post-transplant lymphoproliferative disorders (PTLD). There is no consensus regarding the threshold level indicative of an increase in peripheral EBV DNA. The aim of the study was to clinically validate a developed EBV quantification assay for early PTLD detection.

Transversal study: paired peripheral blood mononuclear cells (PBMC), plasma and oropharyngeal lymphoid tissue (OLT) from children undergoing a solid organ transplant with (n = 58) and without (n = 47) PTLD. Retrospective follow-up: 71 paired PBMC and plasma from recipients with (n = 6) and without (n = 6) PTLD history. EBV load was determined by real-time PCR. The diagnostic ability to detect all PTLD (categories 1–4), advanced PTLD (categories 2–4) or neoplastic PTLD (categories 3 and 4) was estimated by analyzing the test performance at different cut-off values or with a load variation greater than 0.5 log units.

The higher diagnostic performance for identifying all, advanced or neoplastic PTLD, was achieved with cut-off values of 1.08; 1.60 and 2.47 log EBV gEq/10^5 PBMC or 2.30; 2.60; 4.47 log gEq/10^5 OLT cells, respectively. EBV DNA detection in plasma showed high specificity but low (all categories) or high (advanced/neoplastic categories) sensitivity for PTLD identification. Diagnostic performance was greater when: (1) a load variation in PBMC or plasma was identified; (2) combining the measure of EBV load in PBMC and plasma.

The best diagnostic ability to identify early PTLD stages was achieved by monitoring EBV load in PBMC and plasma simultaneously; an algorithm was proposed.
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http://dx.doi.org/10.1016/j.ram.2016.02.006
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PALABRAS CLAVE
Virus *Epstein-Barr*;
Detección temprana de PTLD;
Linfoma;
PCR en tiempo real;
Pacientes trasplantados;
Carga viral

Carga de virus *Epstein-Barr* en pacientes trasplantados: detección temprana de desórdenes linfoproliferativos postrasplante

Resumen La carga alta del virus *Epstein-Barr* se utiliza como un marcador de desórdenes linfoproliferativos postrasplante (*post-transplant lymphoproliferative disorders* [PTLD]). El objetivo de este estudio fue validar clínicamente un ensayo de cuantificación del virus *Epstein-Barr* para la detección temprana de PTLD.

Se efectuó un estudio transversal en el que se analizaron muestras pareadas de células mononucleares periféricas (CMP), de plasma y de tejido linfoide orofaríngeo de niños con trasplante de órgano sólido, con PTLD (n = 58) y sin PTLD (n = 47). En el seguimiento retrospectivo se incluyeron 71 muestras pareadas de CMP y de plasma de trasplantados, con PTLD (n = 6) y sin PTLD (n = 6). La carga viral se determinó por PCR en tiempo real. Se estimó la capacidad diagnóstica para detectar PTLD (categorías: todas *vs*. avanzadas *vs*. neoplásicas) analizando diferentes valores de corte o una variación de carga mayor de 0,5 logaritmos.

El mayor desempeño diagnóstico para identificar todos los PTLD, los avanzados y los neoplásicos, se obtuvo con valores de corte de 1,08; 1,60 y 2,47 log copias/10^5 en CMP y de 2,30; 2,60 y 4,48 log copias/10^5 en células de tejido linfoide orofaríngeo, respectivamente. La detección del ADN del virus *Epstein-Barr* en el plasma mostró una especificidad alta, pero una sensibilidad baja (todas las categorías) o alta (categorías avanzadas o neoplásicas) para identificar PTLD. Se observó el desempeño diagnóstico más alto en las siguientes condiciones: *1*) al identificar una variación de carga en CMP o en plasma; 2) combinando la medición de la carga viral en CMP y en plasma.

La mejor capacidad diagnóstica para identificar las etapas tempranas de los PTLD se logró mediante el seguimiento simultáneo de la carga viral en CMP y en plasma; se propone un algoritmo.
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Introduction

The *Epstein–Barr virus* (EBV) infection is associated with the development of post-transplant lymphoproliferative disorders (PTLD) in solid-organ and stem cell transplant recipients[17].

PTLD encompass a wide range of disorders including benign to malignant lymphoproliferations[22]. Briefly, category 1 includes early benign PTLD; category 2, benign and neoplastic PTLD and categories 3 and 4, neoplastic PTLD. It had been noted that a therapeutic intervention, particularly during the early PTLD phases, could reverse lymphoproliferation and prevent progression to the irreversible lymphoma stage[3].

The association of PTLD and elevated levels of circulating EBV were first described in the nineties[18]. Since then, different authors showed that PTLD, especially those occurring early after transplantation, are generally associated with an increase in EBV DNA in peripheral blood samples. This has led to using the EBV load as a risk marker for this disease[7,8,10].

Initially, many studies explored the clinical usefulness of these tests in a single sample in the presence of disease[19,20]. Then, the importance of surveillance through frequent repetitive monitoring was brought up[11]. At present, a high viral load is used for two purposes: an *early diagnosis* (indicating when to start the search for disease in a potential site), and as a *prevention strategy* (indicating when to therapeutically intervene)[6,10]. Furthermore, some authors have proposed to calculate an average load in a set time, rather than use a single cut-off value[6]. Thus, a reduction in PTLD morbidity and mortality was reported in centers that had implemented systematic EBV load monitoring, and the viral burden was maintained at levels defined as ''low'', by regulating the degree of immunosuppression[12].

In the literature, the definition of a threshold indicative of a ''high load'' is inconsistent because each laboratory has implemented its own cut-off values to distinguish PTLD from baseline levels[13]. The broad diversity of methods (type of quantitative PCR, amplified viral fragment), type and quantity of clinical sample analyzed (peripheral blood mononuclear cells, PBMC; whole blood; plasma), controls used to standardize assays, expression of results (number of viral genome equivalents per number of cells, DNA quantity, volume), sampling frequency, among others, have made it difficult to compare published data and extrapolate cut-off values from one laboratory to another. Therefore, the overall sensitivity, specificity, positive and negative predictive values obtained by different authors relied on the population studied (adult *vs*. pediatric), type of transplanted organ (solid organ *vs*. stem cells), pre-transplant infection status, among others.

An assay to quantify EBV by real-time PCR was developed in our laboratory to monitor transplant patients[5]. Thus, considering the lack of consensus on the EBV level that identifies PTLD, the optimal type of clinical sample, and using the logistics implemented to handle transplant patients' samples in our laboratory (already underway using a semi-quantitative PCR)[4], the EBV load in this report was

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