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Herpes simplex virus in bronchoalveolar lavage fluid of medical intensive care unit patients: Association with lung injury and outcome☆,☆☆

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ABSTRACT

Purpose: In intensive care unit (ICU) patients in whom bronchoalveolar lavage fluid (BALF) was analyzed for suspected infectious pulmonary disease, we investigated the association of herpes simplex virus (HSV) in the BALF with lung injury and patient outcome.
Materials and methods: In this retrospective cohort study, we included 201 patients treated in a medical ICU of a German university hospital in whom BALF samples were analyzed for the presence of HSV using quantitative polymerase chain reaction analysis.
Results: Eighty-seven patients (43%) were HSV-negative, and 114 patients (57%) were HSV-positive. At the day of BALF sampling (day 0), there was no clinically relevant (or statistically significant) difference in the Modified Clinical Pulmonary Infection Score, Lung Injury Score, and single indicator transpulmonary thermodilution–derived extravascular lung water index and pulmonary vascular permeability index between HSV-negative patients and HSV-positive patients or HSV-positive patients with greater than 10^5 HSV copies/mL. The ICU and hospital length of stay was statistically significantly longer in HSV-positive patients compared with HSV-negative patients. Intensive care unit and hospital mortality was not statistically significantly different between the groups.
Conclusions: We did not find a clinically relevant or statistically significant association of HSV in the BALF of medical ICU patients with lung injury or with ICU and hospital mortality.

1. Introduction

Primary infection with human herpes simplex virus (HSV) is very common and is followed by lifetime virus latency in sensory neurons resulting in high HSV prevalence among adults [1].

Among numerous other infection sites, HSV-associated pulmonary infections can occur after virus reactivation, especially in immunosuppressed patients [1-3].

In the bronchoalveolar lavage fluid (BALF) of intensive care unit (ICU) patients, HSV can be frequently detected [4-6]. However, the clinical relevance of HSV in the lower respiratory tract of critically ill patients is unclear because there are inconsistent data on its relation to morbidity and mortality [6]. It still remains unclear if the detection of HSV in the lower respiratory tract of critically ill patients is causally linked to bronchopneumonitis and poor outcome or if it is an epiphenomenon reflecting severity of disease and immunoparalysis [7].

Single indicator transpulmonary thermodilution allows the determination of extravascular lung water index (EVLWI) [8] and pulmonary vascular permeability index (PVPI) [9] to estimate the degree and origin of lung injury [10-15]. In patients with established acute respiratory distress syndrome, EVLWI (using predicted body weight for indexation) is associated with mortality [11,14,16]. To the best of our knowledge, there are no previous data on EVLWI and PVPI measurements in patients with lung injury in the presence of HSV.

We conducted a cohort study in medical ICU patients in whom BALF was analyzed for suspected infectious pulmonary disease. We aimed to

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explore clinical characteristics of patients without HSV detection in the BALF, patients with HSV, and the subgroup of patients with greater than 10^5 HSV copies/mL and to investigate the association of HSV in the BALF with lung injury and clinical outcome measures.

2. Materials and methods

2.1. Study design, setting, and patients

We conducted this retrospective cohort study in critically ill patients treated in a medical ICU of a German university hospital (Klinikum rechts der Isar der Technischen Universität München, Munich, Germany).

The ethics committee of our university hospital (Ethikkommission der Fakultät für Medizin der Technischen Universität München) reviewed and approved the study and waived the need for informed consent due to the retrospective nature of the study.

We included all adult patients in whom BALF was collected and tested for HSV between 2008 and 2011. The indication to perform bronchoscopy and collect BALF for HSV testing was made unrelated to the study as part of a standard panel of virological and bacteriological examinations if the treating ICU physicians suspected infectious pulmonary disease. During the study period, in 201 patients, BALF was analyzed for the presence of HSV. We extracted demographic and clinical data from the patients' medical charts.

2.2. Definitions

We classified patients as being "HSV-positive" if HSV was detected in at least 1 BALF sample during the ICU stay. In the HSV-positive group, we defined "day 0" as the day when the first HSV-positive BALF had been collected. Accordingly, we classified patients to the "HSV-negative" group if HSV was not detectable in any BALF sample sent for virological testing. In this group, we defined the day of the first BALF sampling as day 0.

As previously described [4], we used a cutoff value of 10^5 HSV copies/mL to define a "clinically relevant HSV viral load" and separately evaluated HSV-positive patients and the subgroup of HSV-positive patients with greater than 10^5 HSV copies/mL.

2.3. Collection of BALF

Intensive care unit physicians collected BALF samples by repeatedly installing and recovering sterile 0.9% normal saline after wedging a fiberoptic bronchoscope into a subsegmental bronchus on both sides of the lungs. Bronchoalveolar lavage fluid samples were subsequently sent to the Institute of Virology of our hospital for quantitative polymerase chain reaction (PCR) analysis.

2.4. Virological testing

We measured HSV load with in-house real-time PCR. The primers T-HSV-F 5′CCTGGAGGTGCGGTTGATAA3′ and T-HSV-R 5′AGAAAAAG TACATCGGCGTCATCT3′ amplified a 101-nt-long part of the DNA polymerase (UL30) gene. For quantitation, we used the probe HSV 5′FAM-CCAGATCCACGCCCTTGATGAGCAT-TAMRA 3′. Low viral loads below the linear range of our PCR (<500 copies/mL) were evaluated as 500 copies/mL.

2.5. Transpulmonary thermodilution

For the assessment of EVLWI and PVPI, we used single indicator transpulmonary thermodilution (PiCCO system; Pulsion Medical Systems SE, Feldkirchen, Germany) as described previously [17,18]. For the measurement of EVLWI and PVPI using single indicator transpulmonary thermodilution, we injected 15 mL of iced 0.9% saline in the central venous circulation via a central venous catheter. Extravascular lung water index and PVPI were calculated after analysis of the thermodilution curve recorded using a thermistor-tipped catheter (Pulsiocath PV2015L20; Pulsion Medical Systems SE) placed in the abdominal aorta through the femoral artery. Each EVLWI and PVPI value represents the mean of 3 consecutive single indicator transpulmonary thermodilution measurements. For indexation of EVLWI, we used predicted body weight [19].

Extravascular lung water index and PVPI values were only available in patients in whom advanced hemodynamic monitoring using transpulmonary thermodilution was performed independently from the present analysis. In the HSV-positive and HSV-negative groups, EVLWI values at day 0 were available in 70 (61%) of 114 patients and 53 (61%) of 87 patients, respectively (46/67 [69%] patients and 21/33 [64%] patients at day −4, 66/92 [72%] patients and 44/57 [77%] patients at day +6, and 48/65 [74%] patients and 25/38 [66%] patients at day +12). Pulmonary vascular permeability index values at day 0 were available in 70 (61%) of 114 patients and 48 (55%) of 87 patients, respectively (45/67 [67%] patients and 19/33 [58%] patients at day −4, 64/92 [70%] patients and 40/57 [70%] patients at day +6, and 48/65 [74%] patients and 25/38 [66%] patients at day +12).

2.6. Calculation of scores

To characterize the patients with regard to the degree of critical illness and lung injury, we used several scoring systems. We calculated the Acute Physiology and Chronic Health Evaluation II score (APACHE II score) as proposed by Knaus et al [20]. At days −4, 0, +6, and +12, we calculated the Multiple Organ Dysfunction Score (MODS) [21], the Sequential Organ Failure Assessment score (SOFA score) [22,23], and the Lung Injury Score (LIS) [24]. In addition, we calculated the Modified Clinical Pulmonary Infection Score (MCPIS) [25] at day 0. To account for the fact that bronchoscopy and bronchoalveolar lavage can deteriorate gas exchange, we used the arterial partial pressure of oxygen to fraction of inspired oxygen ratio before bronchoscopy and BALF sampling for the calculation of the LIS and the MCPIS on day 0.

2.7. Statistical analysis

We conducted all statistical tests in an exploratory manner on a 2-sided 5% significance level. For statistical analyses, we used IBM SPSS Statistics for Windows, Version 22 (IBM Corp, Armonk, NY).

We describe categorical data by absolute and relative frequencies. The distribution of continuous data is presented by median and interquartile range (ie, 25th to 75th percentile range). Group comparisons of continuous variables and categorical variables were performed by nonparametric Mann-Whitney *U* test and the χ^2 test (or Fisher exact test when appropriate), respectively. We performed multivariate binary logistic regression analyses with stepwise forward variable selection to identify independent factors associated with the presence of HSV in the BALF. We performed multivariate linear regression analyses with stepwise forward variable selection to identify independent factors associated with the total duration of mechanical ventilation. In these multivariate regression analyses, we included factors showing a *P* value less than .10 in the univariate analyses and factors that we a priori considered to be relevant. In addition, we performed multivariate binary logistic regression analyses adjusting for baseline factors (age, APACHE II score, MODS day 0, SOFA score day 0) to evaluate whether HSV is independently associated with ICU and hospital mortality.

3. Results

3.1. Patients

We included 201 patients in whom BALF samples were collected and analyzed for the presence of HSV using quantitative PCR analysis. In 114