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Beneficial role of endogenous immunoglobulin subclasses and isotypes in septic shock

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Abstract

Purpose: There is increasing evidence on the relationship between endogenously produced immunoglobulins and the clinical outcome in septic shock (SS).

Materials and methods: Levels of immunoglobulin G (IgG) subclasses, immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin E were measured in plasma from 42 patients with SS and in 36 patients with systemic inflammatory response syndrome at diagnosis. Association of immunoglobulins levels with disease severity and outcome was evaluated.

Results: Eighteen patients with SS finally died. Both patients with systemic inflammatory response syndrome and SS showed subnormal levels of total IgG, IgG2, and IgM. Patients with SS who died showed the lowest levels of total IgG and IgG1. Total IgG, IgG1, IgG2, IgG3, IgG4, and IgA correlated inversely with Acute Physiology and Chronic Health Evaluation II score in SS. Univariate Cox regression analysis showed that levels of IgG1, IgG2, IgG3, IgM, IgA, and total IgG were inversely associated to the probability of death at 28 days. Multivariate analysis showed that IgG1, total IgG, IgM, and IgA behaved as independent protective factors against mortality (hazard ratio, *P*): 0.23, 0.026; 0.16, 0.028; 0.11, 0.042; 0.05, 0.010, respectively, whereas IgG3 showed a protective trend also.

Conclusions: Our study evidenced that, in addition to IgG1, other major endogenous immunoglobulins isotypes and subclasses seem to play a beneficial role in SS.

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1. Introduction

There is increasing evidence on the relationship between endogenously produced immunoglobulins and prognosis in septic shock (SS). Recently, Venet et al [1] reported low plasma levels of immunoglobulin G (IgG) and immunoglobulin M (IgM) in patients with SS in the first 4 days of the disease course, with no association with mortality, morbidity, or severity. In turn, we have recently reported decreased levels of IgG in plasma from patients with SS with fatal outcome [2]. Taccone et al [3] demonstrated in a pilot study the existence of persistent low concentration of γ-globulins, especially IgG, in patients with community-acquired SS, associated to greater vasopressor requirements, acute respiratory distress syndrome, and higher mortality.

In spite of the available evidence on the relationship between immunoglobulin levels in the early stages of SS and disease outcome, results on the potential beneficial role of replacement therapies with intravenous immunoglobulin (IVIG) in sepsis are actually controversial. The meta-analysis performed by Laupland et al [4] demonstrated an overall reduction in mortality with the use of IVIG for the adjunctive treatment of severe sepsis and SS in adults. On the contrary, the SBIT study found that IVIG did not reduce mortality in a cohort of septic patients whose severity was defined by clinical scores [5]. Polyclonal immunoglobulins preparation enriched with immunoglobulin A (IgA) and IgM seem to provide better results in reducing mortality compared with preparations containing only IgG [6]. Lack of information on endogenous immunoglobulin isotypes levels before treatment is the general rule in these studies. In addition, there is a great absence of information on the individual role of IgG subclasses in SS. Here, we evaluated in a cohort of 42 patients, the association between levels in plasma of IgG subclasses, IgA, and IgM with severity of SS at diagnosis and clinical outcome.

2. Materials and methods

2.1. Patients

Patients with SS or systemic inflammatory response syndrome (SIRS) were prospectively recruited from the Reanimation Unit of the Hospital Clínico Universitario de Valladolid in Spain from January to December 2011. Recommendations of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference were followed to define SS and SIRS [7]. Approval for the study protocol for both the scientific and the ethical aspects was obtained from the Scientific Committee for Clinical Research of our hospital. Informed consent was obtained directly from each patient before enrollment.

2.2. Sample collection and immunoglobuling quantification

A 5-mL EDTA tube was collected in the 24 first hours following diagnosis of SIRS or SS. The tubes were appropriately centrifuged, and plasma was obtained and stored at −80°C until immunoglobulin quantification. Levels of IgG1, IgG2, IgG3, IgG4, IgA, IgM, and immunoglobulin E (IgE) in plasma were measured by using a multiplex Immunoglobulin Isotyping kit purchased to Biorad TM (Hercules, CA, USA) on a Luminex platform.

2.3. Microbiology

Standard cultures in biological samples guided by the presumptive source of the septic insult were performed to assess the presence of bacterial and fungal infection [8]. Potentially contaminant microorganisms were not considered.

2.4. Statistical analysis

For the demographic and clinical characteristics of the patients, differences between groups were assessed using the χ^2 test for categorical variables and the Mann-Whitney U test for continuous variables when appropriate. We determined the hazard ratio (HR) and 95% confidence interval by Cox regression analysis, which was used to assess the impact of immunoglobulin levels on mortality over time. In addition to immunoglobulin levels, the following independent variables were introduced in the regression analysis as covariables: age, sex, cardiac/abdominal surgery, Acute Physiology and Chronic Health Evaluation (APACHE) II score, number of hemoderivative units received, and number of failing organs. The number of failing organs was calculated based on the variables included in the Sequential Organ Failure Assessment score (respiratory, coagulation, liver, cardiovascular, central nervous system, renal) [9]. A Sequential Organ Failure Assessment score of 3 or 4 in a given variable was considered as organ failure. Logarithmic concentrations of the immunoglobulins evaluated and logarithmic values of APACHE-II score were used in the regression analysis to satisfy the linearity assumption. We determined the occurrence of death by using Kaplan-Meier curves. Groups were compared by the log-rank test (Mantel-Haenzel). The accuracy and the predictive values of the immunoglobulins analyzed for survival were studied by calculating areas under the receiver operating characteristic curve. Correlation studies between immunoglobulin levels and APACHE II score were performed using the Spearman-Karber test. All statistical tests were 2 sided, and $P < .05$ was considered significant. Data analysis was performed using SPSS for Windows version 15.0 software (SPSS, Chicago, Ill).