Available online at www.sciencedirect.com

SCIENCE DIRECT

Clinical Immunology 116 (2005) 11 – 17

Clinical IMMUNOLOGY

www.elsevier.com/locate/yclim

Rapid Communication

Complement activation in diabetic ketoacidosis and its treatment

Rita S. Jerath[a], C. Lynne Burek[b], William H. Hoffman[c,*], Gregory G. Passmore[d]

[a]Section of Rheumatology, Department of Pediatrics, Medical College of Georgia, Augusta, GA 30912, USA
[b]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA
[c]Section of Endocrinology, BG-1012, Department of Pediatrics, Medical College of Georgia, Augusta, GA 30912, USA
[d]Biomedical and Radiological Technologies, Medical College of Georgia, Augusta, GA 30912, USA

Received 7 October 2004; accepted with revision 7 March 2005
Available online 20 April 2005

Abstract

Recent studies support the presence of an inflammatory response during the treatment of diabetic ketoacidosis (DKA). The objectives of this study were to monitor the complement activation products C3a, C4a, Bb, and C5b-9 prior to, during, and after correction of DKA. All patients had increased levels of C3a at 6–8 h and 24 h ($P < 0.05$). C4a was increased in only one patient. Bb showed an upward trend at 6–8 h, and was significantly elevated at 24 h ($P < 0.05$); sC5b-9 was elevated in all patients prior to treatment or in the first 6–8 h of treatment. Results indicate that the alternative pathway may be the primary pathway of activation. These results extend the observation that both DKA and its treatment produce varying degrees of immunologic stress during the time when acute complications are most likely to occur.
© 2005 Elsevier Inc. All rights reserved.

Keywords: C3a; Bb; C5b-9; Complement; Diabetic ketoacidosis; Immunologic stress; Systemic inflammatory response

Introduction

Diabetic ketoacidosis (DKA) is a metabolic crisis that can precipitate other life-threatening complications [1–4]. In children and adolescents, the most notable complication is clinical brain edema [5]. The pathophysiology of this life-threatening event is uncertain. However, there is increasing evidence of cellular and metabolic activation during DKA and its treatment. In vitro studies involving both animal [6] and human [7] brain microvascular endothelial cells have demonstrated a differential perturbation with expression of VEGF, ET-1, and ICAM-1 following increasing concentrations of ketone bodies. Furthermore, increased lymphocyte activation [8,9], and an increase of 3-deoxyglucose, a highly reactive dicarbonyl compound [10], have been reported during the treatment of DKA. Recently, we have reported an increase in plasma inflammatory cytokines [11] and C-reactive protein [12] shortly after the initiation of treatment of DKA, indicating the presence of a systemic inflammatory response (SIRS). Since activated complement peptides are also involved in SIRS [13], are synthesized in the brain as the result of head injury [14], are involved in blood–brain barrier (BBB) dysfunction [15], and contribute to experimental brain edema [16,17], we hypothesized that complement activation occurs in children and adolescents during DKA and/or its treatment. This question has importance since it has been suggested that the complement cascade can be a potential target in therapeutic intervention [18,19].

Few studies have reported complement activation following the diagnosis of type 1 diabetes mellitus (T1DM). Sundsmo et al. [20] studied patients 2 weeks after the diagnosis of T1DM and found increased plasma levels of C3a in nine of 16 patients, and increased C4a and C5a in seven of the nine patients. After 4–6 months, five of the patients were again studied and the bioactive fragments were normal in all five patients. Bergamaschini et al. [21] studied C3a, C4a, and sC5b-9 at least 2 years after the diagnosis and found no increased levels in 27 young patients. These reports suggest that elevated complement activation products are not normally present in controlled T1DM. In none of these studies was there a comment about

* Corresponding author. Fax: +1 706 721 1484.
E-mail address: whoffman@mail.mcg.edu (W.H. Hoffman).

1521-6616/$ - see front matter © 2005 Elsevier Inc. All rights reserved.
doi:10.1016/j.clim.2005.03.004

if or when the patients had DKA prior to the samples being obtained.

We studied four plasma complement activation products prior to, during, and following the treatment of severe DKA: (1) C3a, a potent anaphylatoxin and an acute-phase reactant which is released during both classical (CP) and alternative (AP) complement pathway activation; (2) C4a, a bioactive fragment released early in CP; (3) Bb, a product of factor B in the AP; and (4) C5b-9, the cytolytically active terminal membrane attack complex (MAC) of both the CP and AP. These components were studied to address the following questions: (1) whether complement is activated during DKA; (2) which pathway is involved if activated; (3) what is the time of activation in relation to the activation of other proinflammatory mediators [11,12]; and (4) what is the time of activation based on the occurrence of subclinical [22,23] and clinical brain edema [24] and interstitial pulmonary edema [25].

Our data clearly demonstrate for the first time a systemic increase in the activated peptides C3a, Bb, and C5b-9 prior to and during the treatment of DKA in adolescents with T1DM.

Materials and methods

Patients

Five children (3 females and 2 males) between the ages of 13 and 17 years, presenting in the Emergency Department (ED) with severe diabetic ketoacidosis (pH <7.2), were enrolled following an explanation of the study and obtaining informed consent. Exclusion criteria included a history or physical examination suggestive of chronic infection, an acute infection or abdominal findings suggestive of acute pancreatitis or an episode of DKA in the previous 12 months. The patients were examined by staff physicians on separate occasions: the ED physician and endocrinologist on admission, and then serial examinations by the Intensivist in the Pediatric Intensive Care Unit (PICU). All of the patients had previously been diagnosed to have T1 DM. The duration of diabetes ranged from 2 to 8 years. At the time of initial hydration, a blood sample was obtained with subsequent samples being obtained at 6–8 h, at 24 h, and at 120 h. Treatment of DKA was performed according to a previously published protocol [23].

Complement assays

All samples were drawn in chilled EDTA tubes and then immediately centrifuged at 4°C and 2500 rpm for 20 min. The plasma was separated and stored at −80°C until assayed. Complement components C3a and C4a (Phar Mingen, San Diego, CA) and Bb and C5b-9 (Quidel, San Diego, CA) were measured on commercial ELISA in the Complement Laboratory at the National Jewish Medical and Research Center, Denver, Colorado. All assays were performed in duplicate according to the instructions supplied by the manufacturer and met the quality assurance and quality control established for test validity.

Statistics

Descriptive statistics were calculated for all complement factors at each time period (pretreatment, 6–8 h, 24 h, and 120 h). Comparisons with respect to time were made using Wilcoxon's matched pairs signed rank test, and the correlations between the admission chemistries and complement factors were performed by Spearman rho.

Results

Admission chemistry

Admission chemistries are given in Table 1. The profiles for all patients indicated a severe degree of DKA. There was no correlation between the admission chemistries and any of the activated complement components. Ketoacidosis was corrected within 24 h and all patients had uneventful hospital courses.

Complement components

The response of the complement activation products C3a, C4a, Bb, and sC5b-9 for each of the patients prior to, during, and after treatment is shown in Figs. 1A–D. The 120-h time point (96 h after correction of acidosis) was considered as baseline. All patients had elevations of one or more of the activated complement peptides during the time studied.

Table 1
Admission chemistries

Patient (normal range)	Glucose (65–100) mg/dL	pH (7.35–7.45)	Na (134–146) mmol/L	K (3.5–5.3) mmol/L	Cl (95–108) mmol/L	HCO_3 (23–31) meq/L	BUN (6–21) mg/dL	Osm (285–295) mmol/kg
1	520	7.02	133	5.7	95	6	26	295
2	586	7.05	134	5.7	107	7	18	300
3	605	6.81	134	5.0	96	13	30	302
4	417	7.13	128	4.7	107	6	15	273
5	815	7.04	128	6.4	86	5	21	301

Download English Version:

https://daneshyari.com/en/article/9236681

Download Persian Version:

https://daneshyari.com/article/9236681

Daneshyari.com