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Adhesion molecules in pediatric intensive care patients with organ dysfunction syndrome

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Abstract Objective: To determine serum concentrations of the soluble forms of vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), and E-selectin in ventilated neonatal and pediatric intensive care patients with varying severity of multiorgan dysfunction syndrome (MODS) with or without infection-triggered organ failure. **Design and setting:** Prospective pilot study, a level III neonatal and pediatric intensive care unit at a University children's Hospital. **Patients:** We studied 22 ventilated pediatric ($n = 15$) and neonatal ($n = 7$) intensive care patients (aged 3 days–16 years). Inclusion criteria were mechanical ventilation and signs of at least one additional organ dysfunction (cardiovascular, respiratory, neurological, hematological, or renal). **Measurements and results:** Serum concentrations of the adhesion molecules were analyzed on the day of maximum organ dysfunction score and were quantitated by a sandwich

ELISA technique. The overall mortality rate was 36% (8/22). Dysfunction of three or more organ systems was defined as MODS and was associated with a significant increase in VCAM-1 serum levels relative to dysfunction of three or fewer organ systems [median 1239 ng/ml (IQR 928–1615) vs. 766 ng/ml (644–915)]. A significant difference in E-selectin serum levels was found between organ failure of infectious (median 131 ng/ml, IQR 112–146) and noninfectious origin (68 ng/ml 49–105). **Conclusions:** Determination of adhesion molecules in pediatric intensive care patients raises the possibility of more specific pathophysiological understanding. E-selectin showed significantly different serum levels between infectious and noninfectious causes of organ failure.

Keywords Multiorgan dysfunction syndrome · Sepsis · Adhesion molecules · E-selectin · Vascular cell adhesion molecule 1 · Intercellular adhesion molecule 1

Introduction

Organ failure is an ongoing challenge to the intensive care specialist. This is particularly true in the field of pediatrics. Development of organ dysfunction involves the activation of the microvascular endothelial system by overexpression of adhesion molecules [1, 2, 3]. Adhesion molecules such as vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), and E-selectin are expressed on the surface of endothelial cells and mediate

the migration of leukocytes to inflamed tissue. E-selectin is expressed only on endothelial cells and is responsible for the first contact with leukocytes [4]. VCAM-1 and ICAM-1 are expressed on leukocytes and a wide variety of cell types as well as the endothelium. The soluble forms of these adhesion molecules which are detectable in the serum are correlated with their cellular expression [5]. Agonists such as lipopolysaccharides and proinflammatory cytokines can induce the expression of all three adhesion molecules, whereas other agents specifically activate

only one. Upon in vitro stimulation with endotoxin or cytokines E-selectin expression reaches a maximum at 6 h and returns to baseline at 24 h; levels of cell adhesion molecules as ICAM-1 and VCAM-1 peak between 12 and 24 h and remain elevated for at least 48 h [6]. Elevated serum levels of VCAM-1, ICAM-1, or E-selectin have been found in intensive care patients with various causes of organ dysfunction. A significant increase in these adhesion molecules has been demonstrated in children and adults with sepsis-induced multiorgan dysfunction syndrome (MODS) [2, 7, 8, 9]. In patients with multiorgan dysfunction serum levels of VCAM-1, ICAM-1, and E-selectin are stable over the course of days [8, 10].

The present study was designed to investigate levels of VCAM-1, ICAM-1, and E-selectin in pediatric intensive care patients in relation to the severity of MODS and to disease cause (infectious or noninfectious).

Materials and methods

Within the scope of a pilot study we examined 22 ventilated patients (7 neonatal and 15 pediatric) aged 3 days–16 years (median 10 months; 6 boys, 16 girls). Inclusion criteria were mechanical ventilation and dysfunction of at least one organ system. All patients were sedated according to our standard protocol. Trauma-induced organ failure was excluded. Relevant medical data as described for the assessment of the specific organ function were recorded continuously after admission to the pediatric intensive care unit in the following categories:

- Cardiovascular
 - cardiac arrest
 - pH < 7.2 with normal PaCO₂ value
 - continuous infusion of inotropic agents to maintain blood pressure and/or cardiac output (the use of dopamine ≤ 5 µg/kg/min was excluded)
- age < 12 month*
 - mean blood pressure < 40 mmHg
 - heart rate < 50 beats/min or > 200 beats/min
- age ≥ 12 month*
 - mean blood pressure < 50 mmHg
 - heart rate < 40 beats/min or > 200 beats/min
- Respiratory
 - PaCO₂ > 65 torr (8.6 kPa)
 - PaO₂ < 40 torr (5.3 kPa) in the absence of cyanotic heart disease
 - mechanical ventilation (for > 24 h in a postoperative patient)
 - PaO₂/FIO₂ < 200 (in the absence of cyanotic heart disease)

age < 12 month

- respiratory rate > 90 breaths/min

age ≥ 12 month

- respiratory rate > 70 breaths/min

- Neurological

- Glasgow Coma Scale score < 5
- fixed, dilated pupils

- Hematological

- hemoglobin concentration < 5 g/dl
- white blood cell count < 3 G/l
- platelet count < 20 G/l

- Renal

- serum urea nitrogen value ≥ 100 mg/dl (in the absence of preexisting renal disease)
- serum creatinine ≥ 2 mg/dl (in the absence of preexisting renal disease)
- dialysis

Eleven of 22 patients were treated for infection-associated organ failure, six of whom had primary pulmonary manifestations and six bacterial infections: five had viral infections (three with primary pulmonary manifestation: two respiratory syncytial virus, one cytomegalovirus; two systemic viral manifestations: herpes simplex virus and Epstein-Barr virus). Noninfectious organ failure was triggered by circulatory failure in four patients, during the course of oncological treatment in four, and as a postoperative complication in three.

The organ dysfunction score was derived from the assessment of five organ systems, in accordance with the classification of Wilkinson et al. [11]. One score point was given for each affected organ system. Any item within each category was considered as diagnostic for that organ system. The definition of Wilkinson et al. [11] was modified such that MODS was defined as the occurrence of three or more simultaneous organ system dysfunctions. A subgroup analysis included only patients with or without adult respiratory distress syndrome (ARDS) by the definition of the American-European Consensus Conference [12].

In each patient several serum samples were collected consecutively and stored at –20°C. Serum concentrations of VCAM-1, ICAM-1, and E-selectin were analyzed by a sandwich enzyme-linked immunosorbent assay technique (R+D Systems, Germany) on the day of maximum organ dysfunction score (median 2 days after admission to the pediatric intensive care unit, range 0–14). Data were analyzed with respect to the cause of organ failure and the occurrence of MODS. We report median values (interquartile range, IQR). For comparisons between two

groups the Wilcoxon/Mann-Whitney test was applied. Spearman's procedure was used for the correlation analysis. Statistical analysis used SSPS 11.0 (SPSS, Chicago, Ill., USA). The local ethics committee approved the study, which was performed in accordance with the standards of the Declaration of Helsinki.

Results

Nine patients had a MODS score of 3 or higher (median MODS 3 vs. non-MODS 1 score point or failure of organ systems (Table 1)). MODS occurred in 3 of 7 neonates (43%) and in 6 of 15 pediatric patients (40%), with no significant differences between these two groups in the levels of VCAM-1, ICAM-1, or E-selectin. All cases of MODS included a respiratory and circulatory component. There was no significant difference in levels of C-reactive protein serum levels or leukocyte count between MODS and non-MODS patients. The overall mortality rate was 36% (8/22, 2 neonatal and 6 pediatric deaths). Serum levels of VCAM-1, ICAM-1, and E-selectin were not associated with the mortality. Levels of VCAM-1, ICAM-1, and E-selectin were uncorrelated, aside from a slight positive correlation ($r = 0.573$, $p < 0.01$) between E-selectin and ICAM-1.

MODS was associated with significantly higher serum levels of VCAM-1 than in patients without MODS [median 1239 ng/ml (IQR 928–1615) vs. 766 ng/ml (644–915), $p < 0.01$]. There was no significant difference in levels of ICAM-1 or E-selectin in groups with and without MODS. No significant difference in the occurrence of MODS was seen between infectious (viral and bacterial) or noninfectious origin of organ dysfunction (54% vs. 36%). Significantly higher E-selectin serum levels were found in infectious triggered organ failure vs. organ failure of noninfectious origin [median 131 ng/ml (IQR 112–146) vs. 68 ng/ml (49–105), $p = 0.041$] while there were no differences in ICAM-1 and VCAM-1 levels. Only

Table 1 Patients and subgroups

	<i>n</i>	Age, median (months; range)	Deaths (%)
All patients	22	10 (0–192)	36
Neonatal	7	0.2 (0.1–1)	29
Pediatric	15	42 (2–192)	40
Infection triggered			
Yes	11	7 (0–192)	36
No	11	42 (0–174)	36
MODS score			
< 3	13	7 (0–174)	15
≥ 3	9	63 (0–192)	67
Lung failure paO_2/FIO_2			
< 200	15	7 (0–174)	40
≥ 200	7	113 (0–192)	29

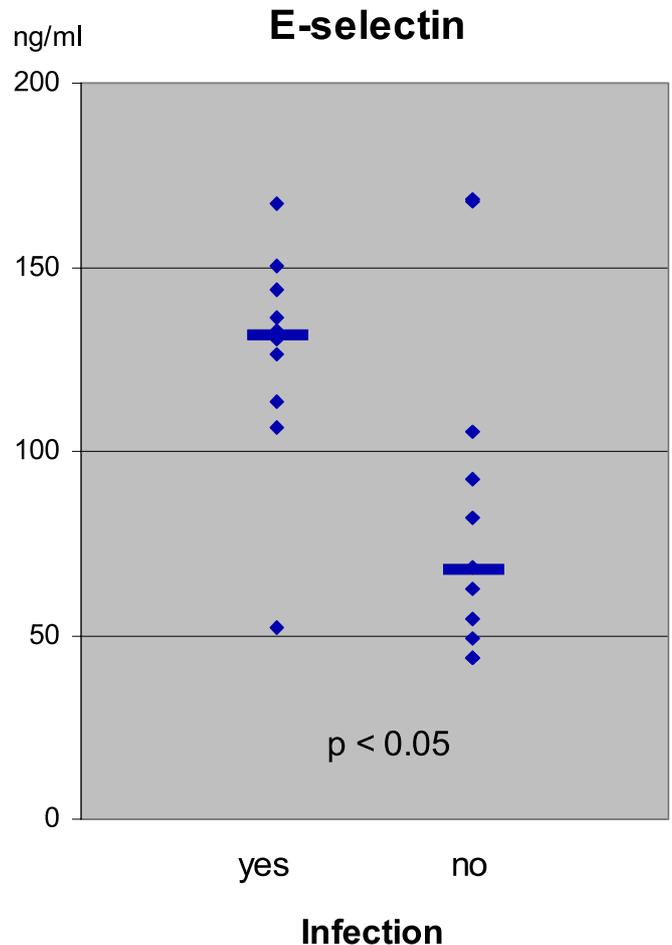


Fig. 1 E-selectin serum levels according to infectious or noninfectious origin of organ failure. Bars Median

one patient in the noninfection group had an E-selectin level of 110 ng/ml (Fig. 1) and only one in the infection group below 110 ng/ml.

Analysis of the subgroup of patients with ARDS ($n = 15$; median PaO_2/FIO_2 110 vs. 266 mmHg) was not associated with significant differences in VCAM-1, ICAM-1, or E-selectin serum levels.

Discussion

Our data support findings in adults in which E-selectin serum levels were associated with sepsis but not specific to MODS [13, 14]. In a population of neonates and pediatric intensive care patients with sepsis-induced MODS Whalen et al. [10] demonstrated a significant increase in VCAM-1, ICAM-1, and E-selectin relative to levels in a control group of healthy children. Our study compared patients with varying severity of organ dysfunction and found significantly higher serum levels of VCAM-1 but not

E-selectin or ICAM-1 in the more severely affected patients than in healthier patients. With respect to E-selectin, unlike in the Whalen et al. [10] study, our data support studies in adults establishing a critical role of E-selectin in infectiousy triggered organ failure [2, 15, 16]. The slightly positive correlation between only two of the measured adhesion molecules can be explained by their different functions in the inflammatory cascade, which is supported by the results for MODS and the cause of organ failure in our study.

The definition of MODS is of special interest when comparing the results of different studies. We used the criteria of Wilkinson et al. [10] which include five organ systems and define MODS as the occurrence of two or more organ dysfunctions. We defined MODS as failure of three or more organ systems. This was in accordance with the only comparable pediatric study concerning this issue of Whalen et al. [10]. However, in the study by Whalen et al. [10] organ failure included the assessment of six organ systems (additionally: hepatic system) according to the criteria of Doughty et al. [17]. The criteria that we used for the definition of an organ dysfunction were at least more stringent than the criteria of Doughty et al. [18] or of more recently published criteria. The patients in our MODS group

were therefore more severely affected than those in other studies. We found significantly higher E-selectin serum levels in infectiousy triggered organ failure. However, the interpretation of our results is limited by the number of patients and the heterogeneity of the study population with regard to age and cause of illness.

In contrast to other studies in pediatric patients and adults [10, 19], there was no association with mortality rate on the basis of a high level of one of the analyzed adhesion molecules or a combination of the adhesion molecules. There was also no difference in levels of the three adhesion molecules (VCAM-1, ICAM-1, E-selectin) in relation to the severity of pulmonary failure, although pulmonary endothelial damage is pivotal to severe pulmonary failure, and an increase in these adhesion molecules has been shown in adults with ARDS [20]. These differences may be related to the above discussed limitation of our study.

In conclusion, determination of adhesion molecules in intensive care patients raises the possibility of more specific pathophysiological understanding, especially with regard to the role of endothelium in the origin of organ failure. E-selectin showed significantly different serum levels between infectious and noninfectious causes of organ failure.

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