Clinical Investigations

LEVELS OF CERTAIN ENDOTHELIAL BIOMARKERS DURING THE ACUTE PHASE AND CONVALESCENCE IN PATIENTS WITH DIFFERENT SEVERITY OF MEDITERRANEAN SPOTTED FEVER

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ABSTRACT

INTRODUCTION: Mediterranean spotted fever (MSF) is a tick-borne disease caused by Rickettsia conorii subsp. conorii. It is transmitted by the bite of the tick Rhipicephalus sanguineus. Modified by the rickettsial invasion, the micro-vascular endothelium acquires an activated inflammatory phenotype and initiates secretion of cytokines and expression of cell adhesion molecules (CAMs) and chemoattractants.

AIM: This study aims at investigating the alterations in the soluble cellular adhesion molecules (sCAMs) and chemokine MCP-1 levels in patients with MSF of varying severity in the acute and convalescence stage in order to assess their diagnostic and prognostic value.

MATERIALS AND METHODS: The soluble forms of cellular adhesion molecules (sCAMs) – sE-selectin and sP-selectin, the intercellular (sICAM-1) and vascular (sVCAM-1) adhesion molecules as well as the monocyte chemoattractant protein-1 (MCP-1) were studied in the sera of 80 patients with MSF. The presence of MSF was confirmed serologically by indirect fluorescence assay (IFA). In order to study disease dynamics, serum samples from 80 patients were drawn on day 1 following the onset of rash; in 60 patients (part of the surveyed 80) a second sample was taken in the convalescence period – 14 days post hospital discharge. The investigation was focused on mild, moderate and severe forms of MSF. Enzyme linked immune-sorbent assay was used for sCAMs determination (Quantikine IVD colorimetric ELISA).

RESULTS: Overall, in the acute stage, patients presented with increased levels of sE-selectin, sICAM-1, sVCAM-1 and MCP-1, whereas sP-selectin level was decreased. The levels of sE-selectin, sICAM-1 and sVCAM-1 were significantly elevated in mild, moderate and severe forms of the disease with sE-selectin level exhibiting a plateau tendency and sICAM and sVCAM levels demonstrating an upward trend from mild towards severe MSF forms. MCP-1 level was elevated only in severe MSF. In all forms of MSF, in the convalescence period, sICAM-1, sVCAM-1 and MCP-1 concentration returned to reference levels whereas sE-selectin level persisted elevated. In the convalescence stage, sP-selectin concentration also showed an upward tendency, which in severe forms of MSF slightly exceeded the level in controls. sP-selectin levels correlated directly with platelet count, whereas sICAM-1 and sVCAM-1 levels showed a reverse correlation. sE-selectin, sICAM-1 and MCP-1 levels directly correlated with aminotransferase activity (ALT and/or AST).

CONCLUSION: The soluble forms of CAMs reflect the endothelial inflammatory potential. There is evidence that endothelium activation is more potent in severe forms of MSF. Assessment of the endothelial response in the course of the disease is an important predictor of the outcome, the choice of therapeutic approach and disease prognosis.

Key words: Mediterranean spotted fever, adhesion molecules, chemoattractant MCP-1

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INTRODUCTION

Mediterranean spotted fever (MSF) is a vector-borne disease, belonging to the Spotted Fever Group (SFG). The disease is caused by Rickettsia conorii subsp. conorii and is transmitted to humans by the bite of the brown dog tick Rhipicephalus sanguineus. Over the last two decades, it has been the most widespread rickettsiosis in the endemic regions of Bulgaria. However, due to the rapid development of tourism imported cases are also likely to occur in non-endemic areas and countries. Rickettsiae invade the microvascular endothelium and commence to multiply there, causing disseminated vasculitis. As a result of the invasion, the vascular endothelium acquires activated inflammatory phenotype with secretion of cytokines, expression of cell adhesion molecules (CAMs) and chemotactant ligands. CAMs are shed into the plasma via proteolytic cleavage of their membrane bound forms by activated leucocytes and endothelial cells (EC) or via the typical maculopapular rash; four-fold rise of \( R. conorii \) antibody titer in repeated serum samples (on hospital admission and 14 to 21 days post admission) were considered indicative of MSF. sCAMs and MCP-1 were studied in the blood serum of 80 patients (4-81 years of age, mean age 52.38 ± 2.09) in the acute stage of the disease (on day 1 following the onset of the rash and before initiation of antibiotic treatment). In 60 patients (part of the surveyed 80), another serum sample was taken in the convalescence period (14 days following hospital discharge). Clinical recovery is defined as subsidence of all symptoms, followed by a three-day afebrile period.

Patients were enrolled in the study based on the following criteria:

**Inclusion criteria:** presence of pathognomonic eschar “tache noire” and febrile illness with flu-like symptoms for 3-4 days prior to the onset of the typical maculopapular rash; four-fold rise of \( R. conorii \) antibody titer in repeated serum samples; lack of antibiotic treatment prior to hospitalization.

**Exclusion criteria:** patients with concomitant acute or chronic diseases.

The control group comprised 20 healthy individuals (5-79 years of age, mean age 51.98 ± 2.99). The study and control group were homogenized according to severity de...
criteria, developed and reported in our previous study. The criteria are briefly as follows:

**Mild forms** – good general condition; low-grade fever; scarce maculopapular rash; no significant deviations in the laboratory parameters; no data for organ involvement.

**Moderate forms** - fever up to 39 °C, muscle and joint pain, malaise; moderately manifested rash; deviations from the reference range in some laboratory parameters; no organ involvement.

**Severe, including “malignant” forms** – hyperpyrexia, chills, headache, vomiting, “typhoid” mental state; abundant rash with partially or entirely haemorrhagic characteristics; clinical manifestations indicative of single or multiple organ involvement (multiple organ involvement, including CNS, is typical for “malignant” forms – the most severe MSF forms); low platelet count; considerable deviations in the electrolytes and other important laboratory parameters.

Commercially available Enzyme-linked immunosorbent assay (Quantikine IVD colorimetric ELISA) of R&D Systems, MN (USA) was used to test sCAMs: sE-Selectin (CD62E), sP-Selectin (CD62P), sVCAM-1 (CD106), sICAM-1 (CD54) and the chemokine MCP-1 (CCL2). Absorption, which is proportional to the biological concentration, was measured colorimetrically by TECAN ELISA reader, set at wave lengths of 450 and 630 nm. SPSS.11 statistical software packet was used to construct a standard curve, measuring the biological concentration of the molecules. The reference ranges were determined, based on serum samples from healthy individuals.

**STATISTICAL ANALYSIS**
In the absence of normal Gauss-Laplace distribution, nonparametric Mann-Whitney U rank-sum test (two tailed p values) was used at a level of statistical significance p < 0.05. Spearman Rank Correlation Coefficient (two tailed) at a level of statistical significance 0.05 and 0.01 was applied to verify the significance of the correlations (Table 1).

**RESULTS**

**SERUM LEVELS OF sE-SELECTIN AND sP-SELECTIN IN MSF PATIENTS**
In general, the levels of sE-selectin were significantly higher compared to those in the controls in acute stage as well as in the convalescence stage. On the contrary, the levels of sP-selectin were significantly lower than those in the controls (Table 1). There was no significant difference in the sE-selectin levels in patients with the mild, moderate and severe forms of MSF. In all three severity forms, sE-selectin levels remained elevated during the studied periods – in the acute and in the recovery stage of MSF (Fig. 1a). The levels of sP-selectin showed no statistically significant difference in mild, moderate and severe MSF in the acute stage. In mild forms of the disease, the sP-selectin level was significantly lower compared to the control group. In the convalescence stage, sP-selectin levels showed a tendency to increase with direction from mild towards severe disease forms. In severe MSF, the sP-selectin levels exceeded that in controls, the difference being statistically not quite significant (p = 0.05) (Fig. 1b).

**Table 1.** sCAMs and MCP-1 levels in patients with Mediterranean spotted fever during acute and convalescent stages of the disease

<table>
<thead>
<tr>
<th></th>
<th>Acute stage¹</th>
<th>Convalescence²</th>
<th>Controls³</th>
</tr>
</thead>
<tbody>
<tr>
<td>nº</td>
<td>n = 80</td>
<td>n = 60</td>
<td>n = 20</td>
</tr>
<tr>
<td><strong>Mean ± SEM</strong></td>
<td><strong>Mean ± SEM</strong></td>
<td><strong>Mean ± SEM</strong></td>
<td><strong>Mean ± SEM</strong></td>
</tr>
<tr>
<td>sE-selectin ng/ml</td>
<td>53.3 ± 2.6</td>
<td>56.8 ± 4.9</td>
<td>11.9 ± 1.9</td>
</tr>
<tr>
<td>sP-selectin ng/ml</td>
<td>115 ± 9.2</td>
<td>110.8 ± 16.4</td>
<td>144.6 ± 14.6</td>
</tr>
<tr>
<td>sICAM-1 ng/ml</td>
<td>667.6 ± 29.2</td>
<td>289.4 ± 17.6</td>
<td>362.6 ± 2.91</td>
</tr>
<tr>
<td>sVCAM-1 ng/ml</td>
<td>1535.6 ± 123.4</td>
<td>657.6 ± 26.4</td>
<td>683.6 ± 61.6</td>
</tr>
<tr>
<td>MCP-1 pg/ml</td>
<td>438.68 ± 67.12</td>
<td>385.74 ± 25.45</td>
<td>424.99 ± 31.47</td>
</tr>
</tbody>
</table>

Mann-Whitney U rank-sum test, two tailed p values.
Figure 1. Soluble cellular adhesion molecules (sCAMs) and MCP-1 serum levels of patients with different severity forms of Mediterranean Spotted Fever in the acute and convalescence stages of the disease, compared to healthy controls.

sCAMs and MCP-1 levels in the acute stage ( ) in patients with Mediterranean Spotted Fever with mild (n = 22), moderate (n = 32) and severe (n = 26) disease forms;

sCAMs and MCP-1 levels in the convalescence stage ( ) of patients, recovering from mild (n = 19), moderate (n = 25) and severe MSF (n = 16), compared to the control group ( ) (n = 20);

Only statistically significant differences between patients and controls are presented:*p < 0.001; ^p < 0.01; +p < 0.05; \p = 0.05 n.q.s. (not quite significant); (Mann-Whitney U rank-sum test, two tailed p values, Mean ± SEM);

Bridging lines indicate the statistical difference between the different severity forms of MSF.

Figure 1. Soluble cellular adhesion molecules (sCAMs) and MCP-1 serum levels of patients with different severity forms of Mediterranean Spotted Fever in the acute and convalescence stages of the disease, compared to healthy controls.
Levels of Certain Endothelial Biomarkers during the Acute Phase and Convalescence in Patients with Different Severity of Mediterranean Spotted Fever

Serum Levels of Intercellular (sICAM-1) and Vascular (sVCAM-1) Adhesion Molecules in MSF Patients

The levels of sICAM-1 and sVCAM-1 increased significantly in the acute stage of MSF when compared to the controls (Table 1). The increase of sICAM-1 levels paralleled the severity of MSF, and the trend was directed from mild towards severe forms (Fig. 1c). Similarly, the levels of sVCAM-1 in mild, moderate and severe MSF were significantly higher compared to the controls. The increase of sVCAM-1 concentrations showed a distinct upward trend from mild towards severe forms of the disease (Fig. 1d). In the convalescence period sICAM-1 as well as sVCAM-1 levels in the three severity forms showed no significant difference compared to the controls.

Serum Concentrations of MCP-1 in MSF Patients

Generally, in the acute stage of MSF, the serum levels of MCP-1 were significantly higher in patients with MSF compared to controls (Table 1). In mild forms of MSF, however, the levels of MCP-1 were lower in patients compared to controls. The concentrations of MCP-1 increased in parallel with the severity of MSF and were highest in severe forms of the disease. In the recovery period, the level of MCP-1 in all three severity forms showed no statistically significant increase compared to controls (Fig. 1e).

Correlation Between Serum Levels of SCAMs and MCP-1 and Some Laboratory Parameters in MSF Patients

We studied the correlations between SCAMs and/or MCP-1 levels and blood platelet count and serum aminotransferase (ALT and AST) activity in the acute stage in patients with MSF. Decreased platelet count is one of the indicators of the disease severity.10 Median platelet count in our patients was decreased compared with controls, mostly in severe MSF (172.08 ± 10.0, p < 0.01). Parallel correlation with the platelet count was found for sP-selectin, and inverse correlation - for sVCAM-1 and MCP-1. The findings that lower platelet level was associated with higher sVCAM and MCP-1 concentration further illustrates the correlation between the levels of these molecules and the severity of MSF. Based on our investigation, AST and ALT activity was slightly or moderately elevated in mild and moderate MSF. This activity was significantly increased in severe forms with organ involvement.10 The median

Table 2. Correlations between SCAMs, MCP-1, platelet counts and ALT/AST activity in patients with Mediterranean spotted fever during the acute stage of the disease

<table>
<thead>
<tr>
<th>SCAMs</th>
<th>sE-selectin ng/ml</th>
<th>sP-selectin ng/ml</th>
<th>sICAM-1 ng/ml</th>
<th>sVCAM-1 ng/ml</th>
<th>MCP-1 pg/ml</th>
</tr>
</thead>
</table>
| sE-selectin | r = 0.347**  
p = 0.002 | NS | NS | NS | NS |
| sP-selectin | NS | r = 0.387**  
p = 0.000 | NS | NS | NS |
| sICAM-1 | r = 0.347**  
p = 0.002 | NS | - | - | r = 0.285*  
p = 0.010 |
| sVCAM-1 | NS | r = 0.387**  
p = 0.000 | NS | - | r = 0.305**  
p = 0.010 |
| MCP-1 | NS | NS | r = 0.285*  
p = 0.000 | r = 0.305**  
p = 0.006 | - |
| PLT x10⁹/l | NS | r = 0.230*  
p = 0.041 | NS | r = - 0.352**  
p = 0.001 | r = - 0.290*  
p = 0.010 |
| ALT IU/l | r = 0.261*  
p = 0.026 | NS | r = 0.579**  
p = 0.000 | NS | NS |
| AST IU/l | r = 0.297*  
p = 0.011 | NS | r = 0.570**  
p = 0.000 | r = 0.291*  
p = 0.013 | NS |

Spearman Rank Correlation Coefficient; Sig. - significance; NS - non significant;  
* Correlation is significant at the 0.05 level (2-tailed);  
** Correlation is significant at the 0.01 level (2-tailed).
ALT level in our patients was 88.91 ± 13.31 IU/L, and that of AST - 76.68 ± 6.41 IU/L; both were higher than those in controls (p < 0.05). sE-selectin, sICAM-1 and sVCAM-1 levels correlated directly with ALT and/or AST serum activity. MCP-1 showed a similar correlation with sICAM-1 and sVCAM-1 levels, but not with the selectin concentration. sE-selectin level correlated with sICAM-1 level and sP-selectin level correlated with sVCAM-1 level. All correlations were statistically significant, regardless of the fact that the correlation coefficients showed various (weak, or moderate, or strong) correlation dependencies (Table 2).

DISCUSSION

Adhesion molecules have been known for some time already and their role in certain medical conditions have been extensively studied. However, in the available literature, there is paucity of data on sCAM levels in patients with MSF.12-14 For Bulgaria this is the first investigation in this field. The novel in our approach is the study of the different severity forms of MSF and the standardized methodology, allowing investigation of patients at a set point in the course of the disease – day 1 after the onset of rash and prior to initiation of antibiotic therapy. The development of the rash marks the collision between the disseminating in the skin micro-vascular spaces pathogen and the body immune resistance. Investigations in the convalescence period are also performed at a set point of time – two weeks following clinical recovery – therefore patients with different clinical forms of MSF are tested at an equal interval from the point of clinical disease subsiding, regardless of preceding duration of symptoms. The convalescence period in MSF is so far the least studied and we did not find similar studies in the available literature. In our opinion, investigation on whether MSF severity is influenced by the inflammatory potential of EC requires patients being tested under standard conditions – at times identical for each patient and severity form. This would contribute to better clarification of the diagnostic and prognostic values of sCAM in MSF.

E-selectin is a specific endothelial biomarker, which function is to slow down the movement of white blood cells in the circulatory bed and thus to facilitate their migration to the site of inflammation, which indicates the presence of the pathogen. P-selectin is an adhesion molecule with similar function. It is expressed on the surface of activated EC and activated platelets. In our study, elevated levels of E-selectin were found. They remained almost unchanged to the end of the two-week convalescence period in all three severity forms of MSF. It is quite possible that the persistence of high sE-selectin levels is associated with the attraction of T\textsubscript{H1} lymphocytes to the inflammatory foci, reflecting the long-term immune response to the EC lesions caused by R. conorii.16 Although selectins share common ligands on the leukocyte surface and are crucial for the leukocyte attraction, the roles of E-selectin and P-selectin posses some differences and their serum levels do not correspond.4 Similarly to our results, sP-selectin has been detected in the serum of patients with various medical conditions but in lower concentrations compared to sE-selectin.4,5,15,17 A possible explanation of this finding is that sP-selectin participates in the cell migration processes at a very early stage. Its expression on the endothelial surface is short lived, therefore it may serve as an indicator of the earliest endothelial-leukocyte interactions.4 In our study, the sP-selectin levels showed an upward tendency during the convalescence period from mild to severe MSF but they exceeded the level in controls only in the severe forms of the disease. Most likely their lower levels in the acute stage and their surge in the recovery period are related to the platelet origin of sP-selectin. This fact provides evidence for the direct correlation between sP-selectin and platelet count i.e. at the disease climax decreased platelet counts correspond to lower selectin levels and vice versa - levels increase in the convalescence in parallel with platelet count. This is more pronounced in severe clinical forms as in these forms thrombocytopenia is more expressed in the acute stage and resolves in the recovery period. VCAM-1 are produced by various cell types in vitro but their serum levels are derived from the endothelium as these molecules are not expressed by the circulating blood cells. In our study, the levels of sICAM-1 and sVCAM-1 were significantly elevated compared to controls only in the acute stage of MSF. They reached normal level 14 days after patients’ discharge. The steady increase in the concentration of these molecules proportionally to the MSF severity makes them a determinant not only of the activity of the process but of disease severity as well. Rickettsial diseases are unique for their target cells’ type as well as for the expression of the endothelial ligands ICAM-1 and VCAM-1. The latter, simultaneously with antigen presentation by the endothelial MHC molecules may provide the signals necessary for the activation of T-cell effector mechanisms.18-20 Therefore it seems that...
CAMs act as a key pathogenetic mechanism in rickettsioses. Another hypothesis is that sCAMs could mediate the anti-inflammatory activity through modifying the leukocyte adhesion and reducing the neutrophil, lymphocyte and monocyte infiltration.13

In our study, an elevated serum level of MCP-1 during the acute stage of MSF was established, especially in severe forms of the disease. A recent report on a fatal case of MSF in Greece documented extremely high serum levels of MCP-1, which is in agreement with our data.21 CCL2 remains one of the most studied chemokines in a number of diseases, but its role in rickettsioses needs further investigations.22

It has been established that ICAM-1, VCAM-1 and P-selectin mediate the thrombogenic effect of antiphospholipid antibodies (aPL) on the endothelium and facilitate the aPL role in the formation of microvascular thromboses.23,26 The increased expression of these adhesion molecules induces monocyte adherence to the endothelium with increased production of tissue factor, resulting in development of EC hyper-coagulation state.25 It seems that the correlations between sICAM-1, sVCAM-1, sP-selectin and MCP-1, as well as their relationship with platelet count and the degree of disease severity reflect the pro-thrombogenic potential of the activated EC in MSF as well.

The correlation with aminotransferases (ALT and/or AST) activity was studied as increased activity of these enzymes is a common finding in MSF. However, the degree of this activity varies depending on the extent of organ involvement in the disease course.10 A direct correlation was established between ALT and AST levels and sE-selectin and sICAM-1 levels, and between AST activity and sVCAM-1 level. A likely explanation for this correlations is that these relationships reflect the degree of organ involvement on the background of persisting endothelial inflammation in the processes of leukocyte migration.

CONCLUSIONS

Regardless of the fact, that a number of mechanisms for leukocyte trans-endothelial migration are known, a lot remains to be investigated in order to understand clearly the role of EC in the pathogenesis of rickettsial diseases, as unique endothelium targeting bacterial infections.20 The investigation of cell migration processes as a key pathophysiological mechanism in R. conorii induced vascular lesions improve our knowledge of the rickettsial endothelial pathology. The soluble forms of CAM reflect endothelial activation and the degree of endothelial inflammatory potential. It seems that endothelial activation is higher in severe forms of MSF. This finding adds diagnostic value to sCAMs for early discrimination of severe forms of the disease. Reversion of sCAMs’ levels within the normal ranges seems a good predictor, but the persistence of high levels of sE-selectin in the convalescent period could be an indicator of unresolved immunological processes. In this respect we would like to stress the prognostic role of sCAMs in the monitoring of disease evolution. Furthermore, the benefit of preventive therapy administration should be noted in view of the ongoing attempts at effective cell migration inhibitors synthesis.27

REFERENCES

ИЗУЧЕНИЕ СЫВОРОТОЧНЫХ УРОВНЕЙ НЕКОТОРЫХ ЭНДОТЕЛІАЛЬНЫХ БИОМАРКЕРОВ ВО ВРЕМЯ ОСТРОГО И РЕКОВАЛЕСЦЕНТНОГО ПЕРИОДОВ У БОЛЬНЫХ С РАЗЛИЧНЫМИ ПО ТЯЖЕСТИ ФОРМАМИ СРЕДИЗЕМНОМОРСКОЙ ПЯТНИСТОЙ ЛИХОРАДКИ

И. Балтаджиев, М. Мурджева

РЕЗЮМЕ

ВВЕДЕНИЕ: Средиземноморская пятнистая лихорадка – СПЛ – представляет собой клещеперенесенную болезнь, вызываемую Rickettsia conorii subsp. conorii и вектором Rhipicephalus sanguineus. Под влиянием инвазии риккетсий микроваскулярный эндотелий приобретает активированный инфламматорный фенотип с выделением цитокинов, а также наблюдается экспрессия адгезионных молекул и гемоатрактантов.

ЦЕЛЬ: Работа ставит себе цель установить наступают ли изменения в стоимостьх растворимых клеточных адгезионных молекулах (sCAMs) и в гемоатрактантах при разных по тяжести формах СПЛ во время остrego и рековалесценциального периодов болезни и оценить диагностическую и прогностическую стоимость этих изменений.

МАТЕРИАЛЫ И МЕТОДЫ: В сыворотке крови 80 больных СПЛ, доказанной иммунофлюоресцентным методом, исследованы во время остrego периода - первый день от появления сыпи - и у 60 из тех же больных, во время рековалесценциального периода – 14 дней после выписки - стоимость следующих sCAMs: sE-selectin и sP-selectin, интерцелюлярных (sICAM-1) и васкулярных (sVCAM-1) адгезионных молекул, и Monocyte chemoattractant protein-1 (MCP-1). Исследование проведено при легких, средне-тяжелых и тяжелых формах СПЛ. Исследованные молекулы определены с помощью Quantikine IVD colorimetric ELISA.

РЕЗУЛЬТАТЫ: Во время остrego периода у пациентов в целом наблюдаются повышенные стоимости sE-selectin, sICAM-1, sVCAM-1, MCP-1, но нет у sP-selectin. Уровни sE-selectin, sICAM-1 и sVCAM-1 сенситивно повышенны и при трех формах, при чем стоимости sE-selectin очерчивают плато, а стоимости sICAM-1 и sVCAM-1 показывают тенденцию при повышениях от легких к тяжелым формам болезни. MCP-1 превышает контрольные стоимости только при тяжелых формах СПЛ. В конце рековалесценциального периода уровни sICAM-1, sVCAM-1 и MCP-1 восстанавливаются в референтных границах; стоимости sE-selectin сохраняются повышенными и при трех формах; стоимости sP-selectin показывают нарастание и при тяжелых формах налицо легкое превышение по отношению к контрольным. Что касается числа тромбоцитов, пряма зависимость показывает sP-selectin, а обратную - sVCAM-1 и MCP-1. С аминотрансферазной активностью прямо коррелируют sP-selectin, - sICAM-1 и sVCAM-1.

ЗАКЛЮЧЕНИЕ: Расторовыми формами CAMs отражают эндотеллярный инфламматорный потенциал. Установлено, что эндотеллярная активация более сильная при тяжелых формах СПЛ и ее измерение может служить ориентиром для потенциального исхода болезни, для выбора терапевтического подхода и прогноза заболевания.