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The Role of Comorbid Pathology in the Progressive Course of ANCA-Associated Systemic Vasculitis

A. Chudinov1,2, Y. Ye3, H. Wu4, P. L. Krauß1,2, P. Löwe1,2, M. Pfeiffenberger1,2, A. Chudinov1, I. Belyaeva2, V. Mazurov2, O. Inamova1.

Germany Rheumatism Research Centre (DRFZ) Berlin, a Leibniz Institute, Berlin, Germany

Background: ANCA-associated systemic vasculitis (AAV) is characterized by a high incidence of complications and high damage index. Comorbid pathology at the onset can significantly worsen the prognosis AAV. The most significant comorbid conditions in patients with AAV are coronary artery disease, hypertension and dyslipidemia.

Objectives: The aim of this study was to determine the role of comorbid pathology in the progressive course in patients with AAV.

Methods: Patients with granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) were observed during the first 3 years of the disease and included in this study between 2010 and 2018. At the onset of AAV 75% of patients had significant comorbidities (coronary artery disease, hypertension, dyslipidemia, chronic obstructive pulmonary disease, peptic ulcer, diabetes mellitus, autoimmune thyroiditis and others).

Results: In total 209 (165 [79%] female and mean age 51.8 ± 13.2 years) AAV patients (94 GPA; 46 MPA; and 69 EGPA) were included in the analysis. Formulation of chronic kidney disease was significantly more frequent in the group of AAV patients with hypertension than in the patients without hypertension (respectively 37% and 23.6%, p=0.041). Development of thromboembolic complications was significantly more frequent in the group of AAV patients with coronary artery disease at the onset of AAV, than in patients without coronary artery disease (respectively 34% and 14.8%, p=0.034). Dyslipidemia also was risk factor for cardiovascular complications (OR – 3.81, 95% CI (2.43; 8.2) p=0.009).

Presence of diabetes mellitus in the AAV onset was risk factor for infectious complications (OR – 1.77, 95% CI (1.14; 3.45) p=0.038).

Conclusion: Our study has shown that comorbid pathology increase risk of serious complications and can significantly worsen the prognosis AAV. Prevention of development of comorbid conditions and control of lipid levels, hypertension levels are necessary to prevent the formation of irreversible organ damage.

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Hyperinflammation and Covid19

PO0313 PRELIMINARY CRITERIA FOR MACROPHAGE ACTIVATION SYNDROME ASSOCIATED WITH CORONAVIRUS DISEASE-19

S. Amikishiev1, M. G. Gunver2, M. Bektas3, S. Aghamuradov4, B. Ince1, N. Koca3, E. S. Torun1, A. Alyeva1, S. Sarı1, C. Cetin1, B. Ç. Yağcı-Dündar1, R. Deniz2, F. Kemik1, B. F. Agargun1, U. A. Gulseren1, B. Besisik1, Ö. Alkan1, C. Başınçlı2, Y. B. Tor1, Y. Catma1, G. Durak3, S. Mese1, A. Agilçanlı4, K. Kose1, M. Ereli1, A. A. Çatışlay1, S. S. Yavuz1, S. K. Besik1, F. Esen1, A. Güll1, *Istanbul Faculty of Medicine, Istanbul University, Division of Rheumatology, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Biostatistics, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Division of Rheumatology, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Internal Medicine, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Radiology, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Medical Microbiology, Division of Virology and Fundamental Immunology, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Chest Diseases, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Infectious Diseases and Clinical Microbiology, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Division of Hematology and Therapeutic Apheresis Unit, Istanbul, Turkey; 1Istanbul Faculty of Medicine, Istanbul University, Department of Anesthesiology, Istanbul, Turkey

Background: COVID-19 runs a severe disease associated with acute respiratory distress syndrome in a subset of patients, and a hyperinflammatory response developing in the second week contributes to the worse outcome. Inflammatory
features are mostly compatible with macrophage activation syndrome (MAS) observed in other viral infections despite resulting in milder changes. Early detection and treatment of MAS may be associated with a better outcome. However, clinical criteria for MAS associated with other causes have not been helpful.

Objectives: To identify distinct features of MAS associated with COVID-19 using a large database enabling to assess of dynamic changes.

Methods: PCR-confirmed hospitalized COVID-19 patients followed between March and September 2020 constituted the discovery set. Patients considered to have findings of MAS by experienced physicians and given anakinra or tocilizumab were classified as the MAS group, and the remaining patients as the non-MAS group. The MAS group was then re-grouped as the cases with exact-MAS and borderline-MAS cases by the study group. Clinical and laboratory data including the Ct values of the PCR test were obtained from the database, and dynamic changes were evaluated especially for the first 14 days of the hospitalization. The second set of 162 patients followed between September-December 2020 were used as the replication group to test the preliminary criteria. In the second set, hospitalization rules were changed, and all patients required oxygen support and received dexamethasone 6mg/day or equivalent glucocorticoids. Daily changes were calculated for the laboratory items in MAS, borderline, and non-MAS groups to see the days differentiating the groups, and ROC curves and lower and upper limits (10-90%) of the selected parameters were calculated to determine the cutoff values.

Results: A total of 769 PCR-confirmed hospitalized patients were analysed, and 77 of them were classified as MAS and 83 as borderline MAS patients. There was no statistically significant difference in the baseline viral loads of MAS patients compared to the non-MAS group according to the Ct values. Daily dynamic changes in the MAS group differed from the non-MAS group especially around the 6th day of hospitalization, and more than a twofold increase in ferritin and a 1.5-fold increase in D-dimer levels compared to the baseline values help to define the MAS group. Twelve items selected for the criteria are given in Table 1 below. The total score of 45 provided 79.6% sensitivity for the MAS (including borderline cases) and 81.3% specificity around days 5 and 6 in the discovery set, and a score of 60 increased the specificity to 94.9% despite a decrease in sensitivity to 40.8%. The same set provided a similar sensitivity (80.3%) in the replication, but a lower specificity (47.4-66%) on days 6 to 9 due to a group of control patients with findings of MAS possibly masked by glucocorticoids.

Table 1. Preliminary Criteria for Macrophage Activation Syndrome Associated with Coronavirus Disease-19

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥37.0°C)</td>
<td>1</td>
</tr>
<tr>
<td>Ferritin concentration &gt; 550ng/mL</td>
<td>2</td>
</tr>
<tr>
<td>More than 2 times increase of ferritin concentration within 7 days of disease onset</td>
<td>3</td>
</tr>
<tr>
<td>Neutrophil count &gt; 6000 cell/μL</td>
<td>4</td>
</tr>
<tr>
<td>Lymphopenia &lt; 1000 cell/μL</td>
<td>5</td>
</tr>
<tr>
<td>Neutrophil/lymphocyte ratio &gt; 6</td>
<td>6</td>
</tr>
<tr>
<td>Ferritin concentration &gt; 550ng/mL</td>
<td>7</td>
</tr>
<tr>
<td>LDH concentration &gt; 300U/L</td>
<td>8</td>
</tr>
<tr>
<td>D-dimer concentration &gt; 1000ng/mL</td>
<td>9</td>
</tr>
<tr>
<td>More than 50% increase of D-dimer concentration within 7 days of disease onset</td>
<td>10</td>
</tr>
<tr>
<td>CRP concentration &gt; 50mg/L</td>
<td>11</td>
</tr>
<tr>
<td>ALT or AST concentration &gt; 50U/L</td>
<td>12</td>
</tr>
<tr>
<td>Procalcitonin concentration &lt; 12</td>
<td></td>
</tr>
</tbody>
</table>

Point for each positive item assessed on Days 5-7: Total points / 12 = Possible MAS ≥45 and Definite MAS ≥60

Conclusion: This study defined a set of preliminary criteria using the most relevant items of MAS according to the dynamic changes in the parameters in a group of COVID-19 patients. A score of 45 would be helpful to define a possible MAS group with reasonable sensitivity and specificity to start necessary treatments as early as possible.

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Metabolic pathways during the regulation of inflammation and immunity


Methods: To date, 16 adult patients enrolled in a COVID-19 CSS clinical trial at UAB had whole genome sequencing. Four (25%) had rare heterozygous DOCK8 mutations (3 missense, 1 intronic). A COVID-19 CSS adult patient in Seattle also had a DOCK8 missense mutation. In addition, DOCK8 missense mutations were identified in five children (UAB & Northwell) hospitalized with MIS-C. DOCK8 mutations, or wild-type (WT) sequence controls, were introduced into human NK-92 cells by FOAMY virus transduction. WT and mutant DOCK8-expressing NK-92 cells were incubated with K562 target cells and compared for cytolytosis and degranulation (CD107a).

Results: One COVID-19 patient DOCK8 mutation (Gly523Arg) reduced NK cell degranulation by 30% and cytolytosis by 23% (n=3) (Figure 1). Similar studies of 3 MIS-C patients with DOCK8 missense mutations (Arg899Trp, Ala2Thr, Pro-687Leu) resulted up to 31% reduced NK cell degranulation and 48% reduction in cytolytosis by 3 distinct mutations (n=3). Two-way ANOVA analysis revealed statistically significant (p<0.05) differences in NK cell degranulation and lysis for four unique DOCK8 mutations.

Conclusion: Heterozygous DOCK8 missense mutations may contribute to severe COVID-19 and MIS-C CSS by partial dominant-negative effects yielding decreased NK cell cytolytosis.

REFERENCES:


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