Markers of inflammation as risk predictors of lethal outcome in patients diagnosed with delirium

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Abstract

Background/Aim. Delirium is an acute or subacute, and most frequently reversible syndrome of higher cortical functions disturbances that is manifested as generalized disorder. If not prevented, it is associated with various adverse outcomes. The aim of this study was to determine the connection between the markers of inflammation and lethal outcome in patients diagnosed with delirium, hospitalized in the psychiatric intensive care unit. Methods. This retrospective study included 120 patients hospitalized in the psychiatric intensive care unit in whom examination of differences in inflammation markers was done. The examinees have been divided into two groups: the case group of 40 patients who died during the hospitalization, and the control group of 80 examinees who were discharged with the diagnosis Post delirium status. The following variables were taken into account: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, C-reactive protein – CRP) and type of delirium (withdrawal or organic). Results. The average age of the patients was 50.3 ± 13.1 years. The patients who survived delirium, were on the average 10.5 years younger than the deceased (p < 0.001). More than half (57.5%) of the deceased had pneumonia. There was a statistically significant correlation between pneumonia and lethal outcome in the patients with delirium (p < 0.001). The examinees with lethal outcome had significantly higher median CRP levels than the group of examinees who survived (75.6% ± 54.0 vs 30.3 ± 42.5 ng/l, p < 0.001). Conclusion. Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostic algorithms in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore the total cost of treatment.

Key words: delirium; intensive care units; inflammation; biological markers; c-reactive protein; prognosis.
Introduction

Delirium is an acute or subacute, and usually reversible syndrome of higher cortical functions disturbances, manifested as generalized disorder. Its cardinal symptom is attention disorder (includes distractibility, reduced vigilance and tenacity) as well as disturbances of consciousness, predominantly of space orientation. Additional symptoms – disorders of thought, sleep-wake cycle, perception, affect and motor behavior, amend this complex neuropsychiatric syndrome of acute onset and fluctuating course. If not prevented, delirium is associated with multiple and rapid unfavorable outcomes, including the higher risk of institutionalization, as well as of functional deterioration, dementia and death. Contemporary scientific knowledge explains the pathogenesis of delirium by the neurotransmitter imbalance (dopamine, norepinephrine, acetylcholine, serotonin) at the central level, as well as by amino acids level changes, oxidative stress and inflammation.

Current studies show a connection between the increase of C-reactive protein (CRP) and interleukin 6 (IL-6) levels on the one hand, and the delirium incidence in postoperative course of surgical patients, on the other hand. These biomarkers could be general indicators of the complex inflammation process that causes delirium. CRP could stimulate series of reactions that lead to the increase of permeability of blood-brain barrier which results in neuronal dysfunction that can be manifested with delirium.

A number of meta-analysis find that the prolonged increase of CRP is associated with the increase of mortality rate. Patients in intensive care with high CRP levels have more serious organic dysfunction, longer hospitalization in intensive care unit, and higher mortality rate than patients in intensive care unit with normal CRP blood levels. However, association between CRP and delirium was not yet been proven. Only a few pilot studies have addressed this relation, so far.

The first study published in 2007, investigating the relation of CRP level and delirium, found high levels of CRP as a predictor of delirium. Similar results were published in the following years, concluding that control of the blood CRP level can be very effective in prevention and reduction of cost of delirium in the intensive care unit.

Considering the exceptional expansion of studies with delirium as a topic in the last ten years, it is expected that soon very complex and heterogeneous pathogenesis of this syndrome will be additionally clarified. The answer to intriguing question on relationship between infection and inflammation syndrome in a seriously ill patient with rapid onset of delirium, its complicated course and general neuronal dysfunction (which today is still described as delirium), could contribute a lot in the field of unfavorable outcome prevention.

The aim of this study was to examine the relation between the markers of inflammation and lethal outcome in patients diagnosed with delirium and hospitalized in the intensive psychiatric care unit.

Methods

In this clinical observational case-control study, the examined group comprised of all inpatients diagnosed with delirium in the period from January 1st 2010 to June 30th 2013 at the Clinic for Psychiatric Disorders “Dr Laza Lazarević”, Belgrade, treated in the psychiatric intensive care unit of the Department for Urgent Psychiatry. The examinees were recruited by the consecutive sampling method. The sample was divided into two groups: the case group of the deceased, and the control group of examinees, discharged with the diagnosis “post delirium status”.

Delirium was diagnosed according to the criteria of the currently valid International Classification of Diseases (ICD10) and included diagnostic categories F05, F10.4 and F19.4. The sample included adult patients previously examined or treated in other institutions, or previously treated in other departments, as well as the patients first examined in the Clinic for Psychiatric Disorders “Dr Laza Lazarević”. The day of admission in the intensive care unit was considered as the first hospital day, disregarding if the patient was previously hospitalized in another institution and diagnosed with other psychiatric disorder.

Patients diagnosed with cancer or other forms of malignity, and those in a postoperative course during the observed period, were excluded from the study.

The group of the deceased was compared with the group of the survived. The following variables were compared: age, gender, clinical diagnosis of infection (pneumonia and urinary tract infection), laboratory parameters (total of white blood cells, granulocytes, monocytes, CRP, erythrocyte sedimentation rate) and the type of delirium (withdrawal or organic delirium). Laboratory parameters taken into consideration were the result of laboratory analysis taken at time when the diagnosis of delirium was suspected.

The data were obtained from the electronic medical records (patients’ history, mental status, course of the disease, laboratory analyses). For statistical analysis of the data SPSS (Statistical package for the social sciences) version 22 was used. The data were presented by classical methods of descriptive statistics (arithmetic mean and standard deviation, median and interquartile range, absolute and relative frequencies), and were analyzed using parametric (Student t-
Results

The study included 120 patients, the average age of 50.3 ± 13.1 years. Men were predominant (80.8%). Those who survived delirium were 10.5 years younger on the average (confidence interval – CI 95% 5.8 to 15.2) than patients with lethal outcome. This difference was statistically significant (t = 4.462, df = 118, p < 0.001). Frequency of lethal outcomes did not differ significantly between the genders (χ² = 2.689, df = 1, p = 0.101) (Table 1).

In the group of the survived 16.3% developed pneumonia, in comparison to 57.5% in the group of patients with lethal outcome. There was a statistically significant relation between pneumonia and lethal outcome in the patients diagnosed with delirium (χ² = 21.607, df = 1, p < 0.001). The patients with urinary tract infection had similar mortality rate (35% patients who survived and 37.5% who died had urinary infection, χ² = 0.072, df = 1, p = 0.788).

In the group of patients with delirium as part of the withdrawal syndrome 20.2% died, whereas in the group with delirium caused by other reasons 63.9% of the examinees died. In the group of the survived 83.75% had withdrawal syndrome, in comparison to 42.5% in the group of those with lethal outcome. There was a statistically significant correlation between etiology of delirium and lethal outcome (χ² = 21.607, df = 1, p < 0.001).

The mean of total leukocyte count in the group of the survived was 9.7 × 10⁹/L ± 4.3 × 10⁹/L, while the leukocyte mean level in the group who did not survive was 11.9 × 10⁹/L ± 5.6 × 10⁹/L. The examinees with lethal outcome had a significantly higher number of white blood cells (ZU = -2.45, p = 0.014) and granulocytes (t = 4.976; p < 0.001), but significantly lower values of monocytes (t = 4.038; p < 0.001) and lymphocytes (t = 4.903; p < 0.001).

The mean CRP levels in those who survived were 30.3 ± 42.5 ng/L, whereas in the diseased they were 75.6 ± 54.0 ng/L. There was a statistically significant difference in the median CRP levels (ZU = 5.328; p < 0.001). Those with lethal outcome had significantly higher median CRP levels.

Table 2 shows regression coefficient of bivariate logistic regression analysis. Statistically significant predictors of lethal outcome in bivariate logistic regression models were age, pneumonia, number of white blood cells, portion of granulocytes in leukocyte formula, as well as CRP concentration. A portion of lymphocytes and a portion of monocytes were protective factors.

Table 3 presents regression coefficient of the final logistic multivariate regression model including predictors: age, pneumonia and CRP. Counts of white blood cells, granulocyte, lymphocyte and monocyte portions were not included in the final model, since after the introduction of CRP as predictor these variables did not contribute significantly to the predictive power of the model. From statistical point of view, this model had significantly higher predictive power comparing to the null model (χ² = 28.298, df = 3, p < 0.001, pseudo-R² Cox-Snell = 0.331) and could accurately classify 80% of cases (comparing to 66.7 in null model).

Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Patients (n = 120)</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>survived (n = 80)</td>
<td>deceased (n = 40)</td>
</tr>
<tr>
<td>Age (years), x ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>12 (15)</td>
<td>11 (27.5)</td>
</tr>
<tr>
<td>male</td>
<td>68 (85)</td>
<td>29 (72.5)</td>
</tr>
<tr>
<td>Pneumonia, n (%)</td>
<td>13 (16.3)</td>
<td>23 (57.5)</td>
</tr>
<tr>
<td>Urinary infection, n (%)</td>
<td>28 (35)</td>
<td>15 (37.5)</td>
</tr>
<tr>
<td>Total leukocytes, x ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*3.5–10 × 10⁹/L</td>
<td>9.7 ± 4.3</td>
<td>11.9 ± 5.6</td>
</tr>
<tr>
<td>CRP, x ± SD, *0–5 ng/L</td>
<td>30.3 ± 42.5</td>
<td>75.6 ± 54.0</td>
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<tr>
<td>Granulocytes, x ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*43.0–76.0%</td>
<td>75.7 ± 8.9</td>
<td>84.3 ± 8.9</td>
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<tr>
<td>Monocytes, x ± SD</td>
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<td></td>
</tr>
<tr>
<td>*4.3–10.0%</td>
<td>5.7 ± 2.1</td>
<td>4.0 ± 2.1</td>
</tr>
<tr>
<td>Lymphocytes, x ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*17.0–48.0%</td>
<td>18.7 ± 7.5</td>
<td>11.7 ± 7.0</td>
</tr>
<tr>
<td>Type of delirium, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>withdrawal</td>
<td>67 (83.7)</td>
<td>17 (42.5)</td>
</tr>
<tr>
<td>organic</td>
<td>13 (16.3)</td>
<td>23 (57.5)</td>
</tr>
</tbody>
</table>

*Interval of reference values of laboratory parameters; CRP – C-reactive protein; x – arithmetic mean; SD – standard deviation.
It is evident, in the patients diagnosed with delirium that every year of age increases lethal outcome rate for 8.3% when it is controlled for other factors in the model. Pneumonia increases the risk for lethal outcome 6.8 times when controlled for other factors. For any increase in CRP by 1 mg/L the risk for lethal outcome in delirium diagnosed patients increases for 1.3% when controlled for other factors.

**Discussion**

In the currently available literature, so far there has not been studies especially examining leading risk factors for mortality of patients with delirium. Previous studies mostly investigated mortality of patients with delirium within certain diagnostic categories.

This study took into consideration age, gender, the type of delirium and markers of inflammation as risk factors for mortality of patients diagnosed with delirium in an intensive psychiatric care unit.

In the year 2013 Zhang et al. published results of meta-analysis of delirium treatment outcomes in inpatients treated in the intensive care unit. Meta-analysis included 14 studies in which the data on mortality were found. Nine studies showed the significant relation between delirium and mortality. The increase of mortality in these studies was controlled by the increase of age and seriousness of illness, including infections. The first European report on mortality risk factors in the intensive care units was also published in the year 2013. This study confirmed the significant relation between delirium and mortality rate defining delirium as an independent risk factor for unfavorable outcome (institutionalization and death) during one month period of follow up.

Our study also showed that older and more seriously ill patients diagnosed with delirium die more frequently, but having in mind that patients in this study were, on the average, significantly younger than the patients in studies whose results we compared with ours. The reason is probably that studied patients were hospitalized in the psychiatric institution or already previously treated for some psychiatric disorder. Namely, the previous psychiatric disorder created base for development of delirium in the context of reduced cerebral reserve. Delirium itself is the result of interaction between precipitating factors and acute illnesses added to vulnerability. Higher age directly determines the degree of vulnerability of an individual. That is to say that the level of dependence and comorbidity increases with age. Patients with worse premorbid functional status who develop delirium die significantly more frequently, i.e., delirium directly or indirectly converts vulnerability to unfavorable outcome. The seriousness of illness makes a significant influence on mortality rate in patients with delirium. In contrast to most of authors who tried to measure the seriousness of illness with indexes, this was not possible in our study due to the study design (the data were obtained retrospectively).

In our study, the inflammation syndrome is considered as a potential risk factor for death. Clinical and laboratory markers of inflammation are individually analyzed.

Pneumonia is a frequent disease being a cause of more than one million hospitalizations per year in the USA. In this country it is the ninth leading cause of death. It is clinically characterized by a group of signs and symptoms that can vary intensively. Having this in mind, the diagnosis of pneumonia itself can be doubtful and difficult. Although it has very clear respiratory symptoms and marks, pneumonia may have totally atypical clinical course as well, without elevated body temperature, typical respiratory sounds or typical radiologic findings. This occurs most frequently in older people who also have high mortality rates of pneumonia, precisely

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for lacking of accurate diagnosis 24. For this group of patients it is very characteristic that pneumonia is manifested with clinical features of delirium only 25.

In our study, when the presence of pneumonia is taken in consideration, every year of age increases the risk of lethal outcome in patients with delirium for 8.3%. The presence of pneumonia in patients with delirium increases the risk for lethal outcome almost seven times after controlling for age and CRP blood level.

The results of the study by Calle et al. 24 carried out in geriatric intensive care unit, published in 2014, show that the mortality of people with pneumonia is significantly higher if they develop delirium. This rate increases significantly when the variable of consciences disorders is included in the model, and this is explained by the presence of hypoactive form of delirium that often remains unrecognized, and therefore consequently inadequately treated 26–28.

CRP levels as well as total of white blood cells and granulocytes were significantly higher in deceased patients compared to those who survived delirium. This confirms results of previous studies 4, 29, 30. In other words, elevated level of CRP and granulocytes are significantly correlated to infection, inflammation response and mortality rate in patients with delirium in the intensive care. However, in the logistic multivariate model of prediction the CRP level and granulocytes have no value as lethal outcome predictors. In this model they are overridden by pneumonia. After being controlled for age and other factors in the model, the elements of leukocyte formula do not significantly contribute to prediction in the multivariate regression model. When controlled for age, CRP is a statistically significant predictor of lethal outcome, but only in patients without pneumonia. Every increase in CRP level by 1 mg/L increases the risk for lethal outcome for 1.3%. In patients with pneumonia, after controlling for age, the CRP does not contribute significantly to predictive power of multivariate regression model. CRP is a significant predictor of lethal outcome only in patients with no pneumonia, and this points to possible role of CRP as a predictor of lethal outcome in other diseases. CRP is significantly correlated with elevated risk for myocardial infarction and sudden cardiac death in seriously ill patients 31 as well as with acute renal failure in patients before dialysis 32, and as such could be valid early marker of morbidity and mortality in patients having multiple organ damages. Some future studies should yet clarify the role of CRP in prediction of lethal outcome in infective syndromes, but with look upon other markers as well, such are procalcitonin and Il-6 (3.29 pg/mL).

Delirium is a syndrome that can be prevented in 30–40% of cases 33. High mortality rates are consequences of frequent overlooking of this diagnosis, especially in hypoactive form. In any case, the British guidance which states that every sudden change of behavior and mental status in both psychiatric patients and those who are not is considered delirium, until proven otherwise, seems useful 1. According to that concept, in patients with such changes, as well as in patients clearly diagnosed with delirium, it would be useful to conduct comprehensive diagnostic procedures in order to exclude pneumonia or some other infective syndrome, renal and cardiac failure. Etiologic treatment would help to avoid complications of delirium and would also help to prevent bad outcomes such as institutionalization, cognitive deterioration and high mortality of patients with delirium. In this way, the number of days spent in a hospital, patients’ personal characteristics, as well as overall costs of treatment that are in charge of health insurance would be significantly reduced. In our country these costs have never been estimated; The data from the USA could serve as an illustration, where costs go from 164 billion dollars per year 34, or over 182 billion dollars in eighteen European countries together 35, 36.

The limitation of our study is its retrospective design, which excluded the possibility to consider some significant variables (procalcitonin, Il–6…).

Another limitation could be heterogeneity of the sample (withdrawal deliriums were also included in the study).

**Conclusion**

Aiming to better and more precise diagnostics of this complicated and still unclear neuropsychiatric syndrome it would be useful to consider introduction of more precise diagnostics in every unit of intensive care. That would significantly reduce the number of delirium diagnosis overlook, especially of hypoactive forms, decrease complication of clinical features and would also reduce the unfavorable outcome rate, therefore consequently the total cost of treatment.

**REFERENCES**
