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METABOLIC SYNDROME, TOTAL AND DIFFERENTIAL WHITE BLOOD CELL COUNTS IN PATIENTS WITH SCHIZOPHRENIA

Marko Pavlović[1,2], Dragan Babić[1,2], Pejana Rastović[2], Romana Babić[1] & Marina Vasilj[3]

[1]*Department of Psychiatry, University Hospital Center Mostar, Mostar, Bosnia and Herzegovina*
[2]*School of Medicine, University of Mostar, Mostar, Bosnia and Herzegovina*
[3]*Department of Laboratory Medicine, University Hospital Center Mostar, Mostar, Bosnia and Herzegovina*

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SUMMARY

Background: *Numerous studies suggest existence of association between total white blood cell (WBC) count and metabolic syndrome (MS) in general population. Aim of this study was to determine the value of total and differential WBC counts and their association with MS in patients suffering from schizophrenia.*

Subjects and methods: *This cross-sectional study included 100 subjects in the study group and 100 healthy subjects in control group. MS diagnosis was made according to ATP III criteria, which was the basis for dividing the study and control group into subgroups with regard to MS diagnosis. From blood samples of all subjects total and differential WBC counts were determined.*

Results: *Schizophrenic subjects with MS had significantly higher total WBC count, as well as neutrophil and monocyte count, when compared with both control subgroups. Total WBC and neutrophil count correlated positively with glucose concentration and MS prevalence and negatively with HDL concentration.*

Conclusion: *Total WBC and neutrophil count might have an important role in forecasting MS development in patients with schizophrenia.*

Key words: *metabolic syndrome - white blood cell count - differential leukocyte counts - schizophrenia*

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INTRODUCTION

The well-known fact about schizophrenic patients is that they have an increased prevalence of metabolic syndrome (MS) which leads to a higher risk of developing cardiovascular disease (Monteleone et al. 2009). Considering the fact that the MS is associated with cardiovascular disease, patients with MS have an increased mortality compared to general population (Babić et al. 2007, 2010, Jakovljević et al. 2008, Monteleone et al. 2009). Therefore, MS has become a "hot topic" and also the subject of numerous studies and scientific articles about schizophrenic patients in recent years (Jakovljević et al. 2007, Kozumplik et al. 2010, Maslov et al. 2008).

Lately it has become even more evident that inflammatory processes also have a certain role in developing metabolic abnormalities in schizophrenic patients, in addition to a lack of physical activities, poor nutrition, smoking and effect of antipsychotics (Leonard et al. 2012, Devaraj et al. 2009).

Total white blood cell (WBC) or leukocyte count, on the other hand, represents an objective biological marker of systemic inflammatory processes. Total WBC count increase is also often connected with smoking cigarettes, obesity and low physical activity (Abel et al. 2005, Sakuta & Suzuki 2006, Nakanishi et al. 2003). Leukocyte count increase is, on top of that, related to increased cardiovascular risk, and according to some studies, it is considered to be a predictor of cardiovascular mortality (Desai et al. 2006, Tamakoshi et al. 2007, Saito et al. 2000). Several previous studies have suggested an association between total WBC count increase and MS in general population (Nagasawa et al. 2004, Blé et al. 2001). It is also known that total WBC count increase, as well as increase in several leukocyte subtypes counts can be associated with an increase of number of MS components (Shim et al. 2006). According to some other studies, total WBC count is useful for forecasting of future MS development in healthy persons, but can potentially be a useful marker in forecast of increased risk of MS development in patients with schizophrenia (Odagiri et al. 2011, Fan et al. 2010). The mechanism underlying this relation is not clear enough yet, even though some authors consider that MS leads to an increase in total WBC count through insulin resistance (Kim et al. 2006). In addition, inflammatory processes can be important in etiopathogenesis of schizophrenia which is why inflammation could be a common pathophysiological process associated with the development of schizophrenia as well as metabolic disorders in schizophrenic patients (Fan et al. 2007).

The aim of this study was to determine the value of total and differential WBC counts and their association with MS and its components in patients suffering from schizophrenia.

SUBJECTS AND METHODS

Participants

We included 200 participants in this study. The study group consisted of schizophrenic subjects from the University Clinical Hospital Mostar (n=100), while the control group consisted of healthy subjects (n=100). The groups were comparable by gender and age. Excluding criteria for both groups were as follows: subjects younger than 18 and older than 70 years; persons with autoimmune, degenerative, rheumatic, acute and chronic infectious diseases; the presence of malignancy, pregnancy, alcoholism and drug addiction. The study was a cross-sectional. All subjects signed an informed consent prior to participating in the research. The research was conducted in accordance with the Declaration of Helsinki and principles of high quality clinical practice, with approval of a Medical Ethic Committee.

Diagnostic instruments

The diagnosis of schizophrenia was set in accordance with diagnostic criteria of the International Classification of Diseases and Related Health Problems, 10^{th} Revision (WHO 1992) by an experienced psychiatrist. The MS diagnosis was made according to criteria of National Cholesterol Education Program-Adult Treatment Panel III (ATP III) (Expert panel JAMA 2001), which was the basis for dividing the study and control group into two subgroups with regard to MS diagnosis, one with and one without MS.

Clinical and Anthropometric Measurements

Arterial blood pressure was measured by mercury sphygmomanometer. Waist circumference was measured by tailor tape at navel level on the skin at expiration.

Biochemical and Hematological Analysis

Blood samples were taken from cubital vein into vacuum tubes with and without anticoagulant at 8:30 in the morning after overnight fast. Biochemical parameters measured in blood serum were concentration of glucose, triglyceride and HDL cholesterol. The values obtained were determined by enzyme method immediately after taking blood samples by means of commercially available reagent (Olympus Diagnostic, GmbH, Hamburg, Germany) on an Olympus AU 600 automatic analyzer.

Total WBC count was determined from full blood samples taken with K3-EDTA anticoagulant, in automatic hematology analyzer on the principle of volumetric impedance. Results were expressed in number/L. The range 3.4-9.7 x 10^9 was taken as reference value. Differential WBC count was also determined from full blood samples taken with K3-EDTA anticoagulant in automatic hematology analyzer. Results were expressed in number x 10^9. As a reference values were taken 2.06-6.49 for neutrophilic granulocytes; 0.00-0.43 for eosinophilic granulocytes; 0.00-0.06 for basophilic granulocytes; 1.19-3.35 for lymphocytes; 0.12-0.84 for monocytes.

Statistical Analysis

Differences in the frequency of elevated leukocyte values expressed as categorical variables were tested by χ^2 test. For testing the differences in total and differential WBC counts as continuous variables between the group of schizophrenic subjects and control group Student t-test was used for normally distributed and Mann-Whitney test for the asymmetrically distributed results. Two-way variance analysis with independent samples on both factors was used for simultaneous testing the differences in total and differential leukocyte counts in schizophrenic subjects with MS in comparison to schizophrenic subjects without MS and control subgroups. After variance analysis was conducted, for additional determining of differences between the four separate subgroups a Scheffe's post-hoc test was used. For testing the correlation between total and differential leukocyte counts with MS and its components in the group of schizophrenic subjects Pearson's correlation test was used. Probability level of $p<0.05$ was taken as statistically significant. SPSS statistics software, version 17 (SSPS Inc., Chicago, IL), and Statistic version 7.0 (StatSoft Inc., Tulsa, OK, USA) were used for all statistical analyses.

RESULTS

The most common type of leukocytes with values above reference values in total sample were basophils (n=31; 15.5%), followed by total leukocytes and monocytes (n=18; 9%), neutrophils (n=13; 6.5%), lymphocytes (n=9; 4.5%), and eosinophils (n=7; 3.5%).

Table 1 shows frequency of elevated values of total and differential WBC counts in the study and control group. Control group had statistically significantly more frequently elevated basophil count ($\chi^2=16.835$; $p<0.001$) compared to the group of schizophrenic subjects, while no statistically significant differences in frequency of elevated values of total leukocyte, neutrophil, eosinophil, lymphocyte and monocyte counts between the study and control group were found (Table 1).

Table 2 shows differences in average values of total and differential WBC counts between the group of schizophrenic subjects and control group. Schizophrenic subjects had statistically significantly higher total leukocyte (Student t-test=3.285; $p<0.001$), neutrophil (Student t-test=3.503; $p<0.001$) and monocyte count (Student t-test=3.323; $p<0.001$) and neutrophil lymphocyte ratio (NLR) (Student t-test=4.175; $p=0.042$) compared to the control group. There were no statistically significant differences in eosinophil (Student t-test=1.877; $p=0.062$), basophil (Mann-Whitney U test=0.889; $p=0.374$) and lymphocyte count (Student t-test=0.508; $p=0.612$) between the study and control group.

Table 1. Frequency of elevated values of total and differential leukocyte counts in the study and control group

Variable N (%)	Group		χ^2	p
	Schizophrenia	Control group		
Leukocytes	10 (10)	8 (8)	0.244	0.621*
Neutrophils	8 (8)	5 (5)	0.740	0.390*
Eosinophils	5 (5)	2 (2)	1.332	0.248†
Basophils	5 (5)	26 (26)	16.835	0.000*
Lymphocytes	2 (2)	7 (7)	2.909	0.088†
Monocytes	11 (11)	7 (7)	0.977	0.323*

*χ^2 test; †Fisher's exact test

Table 2. Differences in total and differential white blood cell counts between the study and control group

Variable (X±SD)	Group		t^a/z^b	p
	Schizophrenia	Control group		
Leukocytes	7.17±2.03	6.25±1.88	3.285	<0.001[a]
Neutrophils	4.38±1.75	3.62±1.24	3.503	<0.001[a]
Eosinophils	0.15±0.13	0.12±0.11	1.877	0.062[a]
Basophils	0.02±0.02	0.04±0.06	0.889	0.374[b]
Lymphocytes	2.07±0.56	2.02±0.89	0.508	0.612[a]
Monocytes	0.62±0.54	0.42±0.26	3.323	<0.001[a]
NLR	2.25±1.05	1.98±0.80	4.175	0.042[a]

[a]Student t-test; [b]Mann-Whitney U test

Table 3. Differences in total and differential white blood cell counts with regard to the MS diagnosis

Variable (X±SD)	Metabolic syndrome		t^a/z^b	p
	YES	NO		
Leukocytes	7.09±2.19	6.48±1.85	2.097	0.037[a]
Neutrophils	4.35±1.73	3.79±1.42	2.466	0.014[a]
Eosinophils	0.12±0.12	0.14±0.12	0.832	0.407[a]
Basophils	0.03±0.04	0.03±0.05	0.647	0.518[b]
Lymphocytes	2.10±0.67	2.01±0.79	0.826	0.409[a]
Monocytes	0.54±0.63	0.50±0.25	0.651	0.515[a]

[a]Student t-test; [b]Mann-Whitney U test

Table 3 shows differences in average values of total and differential WBC counts in the whole sample, with regard to the MS diagnosis. Subjects with MS had statistically significantly higher total WBC (Student t-test=2.097; p=0.037) and neutrophil count (Student t-test=2.466; p=0.014) compared to subjects without MS. There were no statistically significant differences in eosinophil (Student t-test=0.832; p=0.407), basophil (Mann-Whitney U test=0.647; p=0.518), lymphocyte (Student t-test=0.826; p=0.409) or monocyte count (Student t-test=0.651; p=0.515) between subjects with MS and subjects without MS.

In further data processing we divided the study and control group into two subgroups, one with MS diagnosis and the other without it. This way we created four subgroups of subjects: schizophrenic subjects with and without MS diagnosis and control subgroups with and without MS diagnosis. Afterwards we compared values of total and differential WBC counts between all the above mentioned subgroups.

Table 4 presents differences in total and differential WBC counts between subgroups of schizophrenic and control subjects with and without MS. Total WBC count was significantly different between subgroups of schizophrenic and control subjects (p=0.001). After applying additional analysis with Scheffe's post hoc test it was found that schizophrenic subjects with MS had statistically significantly higher total WBC count compared to both control subgroups, with MS (p=0.025) and without MS (p=0.004). Total WBC count did not differ statistically significantly between schizophrenic subjects without MS and control subgroups with MS (p=0.689) and without MS (p=0.590). There were no statistically significant differences in total WBC count between subgroups considering a MS diagnosis (p=0.153), nor between subgroups of schizophrenic subjects (p=0.164), nor between control subgroups (p=0.999).

By comparison of neutrophil count between subgroups of schizophrenic subjects and control subgroups statistically significant differences were also detected (p=0.001). Schizophrenic subjects with MS had statistically significantly higher neutrophil count compared to control subgroup with MS (p=0.007), as well as compared to control subgroup without MS (p=0.001).

Table 4. Differences in total and differential white blood cell counts between subgroups of schizophrenic and control subjects with and without MS

WBC type	Group	MS diagnosis		F	p
		YES	NO		
		M±sd			
Leukocytes	Schizophrenia	7.6±2.26	6.7±1.73	10.930	0.001[a]
	Control group	6.2±1.80	6.3±1.93	2.049	0.153[b]
Neutrophils	Schizophrenia	4.7±1.88	3.9±1.55	12.93	0.001[a]
	Control group	3.6±1.23	3.6±1.29	3.043	0.083[b]
Eosinophils	Schizophrenia	0.15±0.14	0.15±0.12	5.545	0.019[a]
	Control group	0.08±0.07	0.13±0.12	1.724	0.191[b]
Basophils	Schizophrenia	0.017±0.016	0.022±0.023	7.607	0.006[a]
	Control group	0.039±0.059	0.036±0.059	0.014	0.905[b]
Lymphocytes	Schizophrenia	2.07±0.53	2.08±0.59	0.015	0.903[a]
	Control group	1.99±0.61	1.81±0.64	0.681	0.410[b]
Monocytes	Schizophrenia	0.68±0.77	0.56±0.20	13.628	<0.001[a]
	Control group	0.32±0.17	0.46±0.28	0.011	0.918[b]

[a]differences between the subgroups of schizophrenic subjects and control subgroups
[b]differences between the subgroups with and without MS

Table 5. Correlations of total and differential white blood cell counts with MS components in the group of schizophrenic subjects

	Leukocytes		Neutrophils		Eosinophils		Basophils		Lymphocytes		Monocytes	
	r	p	r	p	r	p	r	p	r	p	r	p
Waist circumference	0.10	0.310	0.10	0.316	0.18	0.066	-0.18	0.068	0.09	0.385	0.06	0.542
Systolic pressure	-0.02	0.859	0.05	0.593	-0.05	0.648	0.01	0.924	-0.20	0.047	-0.08	0.434
Diastolic pressure	0.10	0.342	0.15	0.142	-0.12	0.225	-0.07	0.468	-0.09	0.390	0.03	0.773
Serum glucose	0.22	0.031	0.26	0.009	-0.07	0.507	-0.13	0.189	-0.03	0.799	-0.00	0.968
HDL	-0.28	0.004	-0.27	0.007	0.00	0.998	0.10	0.321	-0.13	0.200	-0.14	0.162
Triglycerides	0.06	0.529	0.03	0.787	-0.03	0.768	-0.13	0.200	0.17	0.088	0.05	0.594
Metabolic syndrome (MS)	-0.22	0.029	-0.24	0.015	-0.00	0.963	0.11	0.296	0.00	0.963	-0.11	0.270
Number of MS components	0.16	0.116	0.19	0.054	0.00	0.966	-0.18	0.069	-0.01	0.919	0.04	0.699

Schizophrenic subjects without MS did not differ statistically in neutrophil count when compared to both control subgroups, with MS (p=0.837) and without MS (p=0.858). There were no statistically significant differences in neutrophil count after comparing subgroups regarding MS diagnosis (p=0.083).

Statistically significant differences were also determined after comparing eosinophil count between subgroups of schizophrenic subjects and control subgroups (p=0.019). Schizophrenic subjects with MS had statistically significantly higher eosinophil count compared to control subgroup with MS (p=0.020). In addition, schizophrenic subjects without MS also had statistically significantly higher eosinophil count compared to control subgroup with MS (p=0.018). As opposed to that, there were no differences in eosinophil count between schizophrenic subjects with MS and control subgroup without MS (p=0.413) or between schizophrenic subjects without MS and control subgroup without MS (p=0.422). No statistically significant differences were found in eosinophil count between subgroups with regard to the MS diagnosis (p=0.191). Schizophrenic subjects with MS had significantly lower basophil count compared to control subgroup with MS (p=0.039) as well as compared to control subgroup without MS (p=0.025). On the other hand, schizophrenic subjects without MS did not differ statistically in basophil count compared to both control subgroups, with MS (p=0.090) and without MS (p=0.068). There were no statistically significant differences in basophil count between subgroups with regard to the MS diagnosis (p=0.905). Lymphocyte count did not differ statistically significantly between subgroups of schizophrenic subjects and control subgroups (p=0.903) or between subgroups with regard to the MS diagnosis (p=0.410).

Significant differences were also determined by comparing monocyte count between subgroups of schizophrenic subjects and control subgroups (p<0.001). Schizophrenic subjects with MS had statistically significantly higher monocyte count compared to control subgroup with MS (p=0.006), as well as compared to control subgroup without MS (p=0.049). There were no

significant differences in monocyte count between schizophrenic subjects without MS and control subgroups with MS (p=0.114) and without MS (p=0.593), or between subgroups with regard to the MS diagnosis (p=0.918).

In the group of schizophrenic subjects total WBC and neutrophil count correlated positively with glucose concentration and MS prevalence and negatively with HDL concentration. Eosinophil, basophil and monocyte counts did not show statistically significant correlation with any of MS components, while lymphocyte count, on the border of statistical significance, correlated negatively with systolic pressure. None of WBC types showed statistically significant correlation with the number of MS components (Table 5).

DISCUSSION

There is growing evidence of inherent association between proinflammatory state and the so-called low-grade chronic inflammation with MS in general population but also in schizophrenic patients (Leonard et al. 2012, Devaraj et al. 2009, Sutherland et al. 2004, Del Prato et al. 2006). It is assumed that the proinflammatory state in MS probably occurs as a result of overeating and consequent obesity in genetically predisposed individuals. Obesity is characterized by chronic low-grade systemic inflammation and increased concentrations of several inflammatory biomarkers including the total WBC count (Lee & Pratley 2005). It is already known that the total WBC count is one of the widely available inflammatory markers of acute and chronic inflammatory processes, that is used in everyday practice. It consists of six leukocyte types: neutrophils, eosinophils, basophils, monocytes, lymphocytes and plasma cells. While the initial characteristic of acute inflammation is increase in neutrophil count, chronic inflammation is associated with the presence of of mononuclear cells, such as macrophages and lymphocytes. In accordance with previously outlined data about the association between MS, inflammatory processes and schizophrenia we assumed that schizophrenic patients with and without MS would have increased total and differential white blood cell counts compared to the healthy population.

According to the results of this study, schizophrenic subjects had, in comparison to the control group, significantly higher average values of total WBC, neutrophil and monocyte count, while subjects from control group had significantly more frequently elevated basophil count compared to schizophrenic subjects. On the other hand, there were no differences in average values of basophil count between the study and control group. Higher frequency of elevated basophil count in healthy subjects in comparison to schizophrenic subjects presents a very interesting finding which requires a more detailed study, particularly considering that one of the key basophil functions is creating heparin and histamine which participate actively in the processes of hemostasis and inflammation reaction.

In recent years, NLR has also been recognized as easily available marker of systemic inflammation that is associated with cardiovascular disease (Demir et al. 2014). Semiz et al. conducted a study in which they showed that NLR levels are increased in physically healthy, non-obese, patients with schizophrenia when compared with physically and mentally healthy individuals (Semiz et al. 2014). In our present study schizophrenic subjects also had significantly higher NLR compared to controls, although these two studies can not be fully comparable since the study conducted by Semiz et al. involved only physically healthy subjects while a significant number of our patients had a diagnosis of MS that was not excluding factor. NLR namely, has a significant correlation with MS, which is found in some recent studies (Buyukkaya et al. 2014).

In total sample of his study, subjects with MS had significantly higher total WBC count compared to subjects without MS. Such results are in accordance with data from some previous studies which suggested existence of significant correlation of total WBC count with MS in general population (Odagiri et al. 2011, Ford 2003). Moreover, between certain leukocyte subtypes, only neutrophils were found in higher count in subjects with MS in comparison with subjects without MS, while subjects with and without MS did not differ significantly in eosinophil, basophil, lymphocyte and monocyte counts. As opposed to our results, Shim et al. found in a similar study, conducted on subjects with diabetes type 2, that total WBC count and differential leukocyte count except basophil count were associated with MS (Shim et al. 2006).

Schizophrenic subjects with MS diagnosis had statistically significantly higher total WBC count compared to both control subgroups, with and without MS. There were no statistically significant differences in total WBC count between schizophrenic subjects with MS and schizophrenic subjects without MS, or between other subgroups. Such results speak in favor of a combined influence of schizophrenia and MS on the elevation of total WBC count in patients suffering from schizophrenia, while such influences are lost when schizophrenia and MS are investigated separately. With these results we did not confirm findings of Miller et al., who among other findings, showed that patients with schizophrenia and non-affective psychoses and MS had significantly higher total WBC count compared to patients without MS (Miller et al. 2013).

Some of the studies conducted on general population and subjects with diabetes type 2 showed existence of association between neutrophil count and MS (Shim et al. 2006, Kim et al. 2006). In the above mentioned study conducted by Miller at al., existence of specific association between neutrophil count and MS was not

found in schizophrenic subjects (Miller et al. 2013). Our results have shown that schizophrenic subjects with MS had significantly higher neutrophil count compared to schizophrenic subjects without MS and both control subgroups, with and without MS. Significant differences in neutrophil count between other subgroups were not detected. Such results can be explained by existence of mutual influences, those of MS and of schizophrenia, on elevation of neutrophil count in patients suffering from schizophrenia.

By comparing results in eosinophil, lymphocyte, and basophil count between the groups of schizophrenic subjects and control subgroups, we have not found influences of schizophrenia or MS on elevation of these leukocyte subtypes count.

Schizophrenic subjects with MS had significantly higher monocyte count compared to both control subgroups, but these differences were not present when schizophrenic subjects with and without MS were mutually compared. Such results were also not in accordance with the study conducted by Miller et al., in which patients with schizophrenia and non-affective psychoses with MS also had significantly higher monocyte count than patients without MS (Miller et al. 2013).

The differences obtained in monocyte count between four studied subgroups were the same as differences in total WBC count, i.e. the results regarding both spoke in favor of a combined influence of schizophrenia and MS on elevation of these leukocytes count. As addition to that, results of this study showed existence of mutual influence of schizophrenia and MS on elevation of neutrophil count. Similarity in results in the context of these three cell inflammatory indicators might be explained by means of pathophysiological changes that appear in visceral fat tissue of obese persons, which some authors consider as playing crucial role in development of MS and its clinical consequences (Nishimura et al. 2009). Fat tissue, namely, as place of chronic inflammation, is infiltrated with a large number of macrophages developed from monocytes, which besides other cells, participate in development of insulin resistance and in creation and secretion of various proinflammatory cytokines, such as IL-1, IL-6 and TNF-α. These proinflammatory cytokines then affect the elevation of count of circulating neutrophils, inflammatory cells which have the highest share in total WBC count (Nishimura et al. 2009, Tilg & Moschen 2008).

In the group of schizophrenic subjects, according to results of Pearson's correlation test, total WBC and neutrophil count correlated positively with MS prevalence and glucose concentration and negatively with HDL-cholesterol concentration. As opposed to the study by Na et al., which was conducted on population of schizophrenic subjects, total WBC count in our study did not show positive correlation with waist circumference (Na et al. 2012). Our results were not in accordance with results of one large study conducted on general population which emphasized waist circumference as an MS component with the most significant positive correlations with the studied inflammatory indicators, including the total WBC count (Rogowski et al. 2010).

CONCLUSION

Total WBC and neutrophil count in subjects with schizophrenia showed positive correlations with MS prevalence and glucose concentration and negative with HDL concentration. These inflammatory indicators might have an important role in forecasting MS development in patients with schizophrenia.

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Contribution of individual authors:

Marko Pavlović: design of the study, subjects recruitment, literature searches, analysis and interpretation of data, writing the manuscript.
Dragan Babić: design of the study, interpretation of data, writing the manuscript.
Pejana Rastović: subjects recruitment, statistical analysis and interpretation of data.
Romana Babić: subjects recruitment, literature searches and interpretation of data.
Marina Vasilj: laboratory analysis and interpretation of data.
All authors participated in the final revision of the manuscript and approved it.

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Correspondence:

Marko Pavlović, MD
Department of Psychiatry, University Clinical Hospital Mostar
Kneza Mihaila Viševića Humskog bb, 88 000 Mostar, Bosnia and Herzegovina
E-mail: makijato29@gmail.com