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Role of sICAM-1 and sVCAM-1 as biomarkers in early and late stages of schizophrenia

Maja Pantović Stefanović [a, *], Nataša Petronijević [b, c], Bojana Dunjić-Kostić [a], Milica Velimirović [b, c], Tatjana Nikolić [b, c], Vladimir Jurišić [d], Maja Lačković [a, b], Aleksandar Damjanović [a, b], Sanja Totić-Poznanović [a, b], Aleksandar A. Jovanović [a, b], Maja Ivković [a, b]

[a] Clinic of Psychiatry, Clinical Centre of Serbia, Pasterova 2, 11000, Belgrade, Serbia
[b] School of Medicine, University of Belgrade, Dr Subotica 8, 11000, Belgrade, Serbia
[c] Institute of Clinical and Medical Biochemistry, Pasterova 2, 11000, Belgrade, Serbia
[d] School of Medicine, University of Kragujevac, Svetozara Markovic 69, 11000, Kragujevac, Serbia

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ABSTRACT

Schizophrenia (SZ) is a neuroprogressive disorder presenting with biochemical, functional, and structural changes, which differ from early to late stages of the illness. We explored the differences in serum levels of soluble intercellular cell adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) between early and late stages of SZ, in regard to clinical characteristics and treatment application.

Serum levels of sICAM-1 and sVCAM-1 were measured in 80 patients with SZ (40 early stage; 40 late stage), and compared with 80 healthy controls, matched by age, gender, body mass index, and smoking habits with each SZ group. Serum levels of sICAM-1 and sVCAM-1 were measured using ELISA. The severity of psychopathology was assessed using the Clinical Global Impression Scale and five-factor Positive and Negative Symptoms in Schizophrenia Scale.

After adjustment for confounders, we noticed normal levels of sICAM-1 in the early stage, and elevated levels of sICAM-1 in the late stage of SZ. sVCAM-1 levels were decreased in both stages of SZ. Higher sICAM-1 levels have been related to more pronounced cognitive deficit and excitement symptoms in the early stage of SZ and to favorable characteristics of treatment application in both stages.

SZ is associated with changes in the levels of adhesion molecules that vary from early to late stages of the illness. This implies that the concept of biochemical staging is applicable in SZ, at least for markers of cellular adhesion.

1. Introduction

Schizophrenia (SZ) is a neuroprogressive disorder that presents with biochemical, functional, and structural changes, which differ from the early to late stages of the illness (Agius et al., 2010; Davis et al., 2014; Meyer, 2013; Schennach et al., 2012). Differentiating the evolution of SZ into stages aims to distinguish the earlier and milder clinical symptoms from those that mark illness progression. Such a staging model of SZ is based on the longitudinal development of the disorder, ranging from the asymptomatic at-risk stage to the emergence of prodromal symptoms, first episode of illness, and recurrence and eventually to a chronic and treatment-resistant forms (Agius et al., 2010). In addition, well-defined clinical presentations are associated with each individual stage. Prospective studies and retrospective research indicate that behavioral deviations can be dated to early infancy, progressing to subtle changes in cognition and effect as well as sub-threshold psychotic symptoms and finally to full-blown psychosis in late adolescence. On the other hand, chronic forms are most often characterized by the progressive deterioration of function and more prominent changes in the neurobiological basis of the disorder (Agius et al., 2010; Davis et al., 2014; Meyer, 2013; Parnas, 1999).

According to the recent literature, inflammatory processes are strongly involved in the impairment of several physiological

* Corresponding author.
E-mail address: majapantovic@yahoo.it (M.P. Stefanović).

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systems in SZ (Drexhage et al., 2011; Pedrini et al., 2012; Reddy and Yao, 1996), and cellular adhesion is an important part of this cross-talk between the central nervous system and immune system (Dimopoulos et al., 2006; Miguel-Hidalgo et al., 2011; Thomas et al., 2002; Witkowska and Borawska, 2004). Moreover, adhesion molecules such as intercellular cell adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) as well as their respective receptors are considered to be critically involved in both the normal organization of CNS and various neuroinflammatory disorders (Dimopoulos et al., 2006; Kavzoglu and Hariri, 2013; Meyer et al., 2009; Miguel-Hidalgo et al., 2011; Schwarz et al., 2000; Thomas et al., 2002, 2004; Witkowska and Borawska, 2004).

ICAM-1 and VCAM-1 are transmembrane proteins reported to be expressed on cerebral vascular endothelial cells, astrocytes, microglial cells, and neurons and are widely distributed in the mature brain (Thomas et al., 2002, 2004; Schwarz et al., 2000). Studies also suggest that ICAM-1 and VCAM-1 act as signal transducers within CNS (Gimenez et al., 2004; Lee et al., 2000). Likewise, their soluble forms (sICAM-1 and sVCAM-1) play key roles in blood brain barrier permeability, which allows peripheral cytokines to enter CNS and induce changes in the psychopathology by further increasing the proinflammatory immune response and modulating central neurotransmitters (Dimopoulos et al., 2006; Schwarz et al., 2000).

Altered levels of sICAM-1 and sVCAM-1 have been found in psychotic and affective disorders (Dimopoulos et al., 2006; Graham et al., 2008; Kavzoglu and Hariri, 2013; Meyer et al., 2009; Miguel-Hidalgo et al., 2011; Schwarz et al., 2000; Thomas et al., 2002, 2004). Furthermore, there is evidence supporting the association between sICAM-1 and sVCAM-1 and aging-dependent neurodegeneration and memory impairment (Anderson et al., 2014; Dimopoulos et al., 2006; Miguel-Hidalgo et al., 2011; Thomas et al., 2002, 2004; Witkowska and Borawska, 2004) in affective disorders, whereas the data on psychotic disorders are still limited. This implies that sICAM-1 and sVCAM-1 may be important for clinical staging models in psychiatry and targeting new immune biomarkers, which could help understand the disease expression, course of illness, and treatment response. It has also been proposed that the adhesion molecules are involved in immune modulations in SZ mediated by antipsychotic treatment (Jones et al., 2005; Schwarz et al., 2000); however, the nature of the mechanism is still unclear. Although adhesion molecules are strongly implicated in ethiopathogenesis and the progression of SZ, there is no data on the levels of serum adhesion molecules as biomarkers of staging in this population.

Bearing in mind the previous findings, we have carefully selected sICAM-1 and sVCAM-1 because it would be important to determine if their variations reflect the biochemical staging model in SZ. Therefore, our main aim was to explore the differences in the alterations of the investigated soluble adhesion molecules with regard to early and late stages of SZ, compared with healthy control groups. Our secondary aim was to further explore the relationship between the type and severity of presented psychopathology, progression of the disorder (duration of untreated disorder, duration of the illness), and immune alterations in the early and late stages of SZ. Our final aim was to explore the possible treatment response and effect associated with the alteration of longitudinal immune markers in SZ.

2. Material and methods

2.1. Patients and design

The required sample size to obtain the power of $1-\beta = 0.80$ at $\alpha = 0.05$ was calculated on the basis of the data from the previous studies (Schwarz et al., 2000). Twenty-two subjects per group were found to be sufficient for determining the inter-group differences. Ninety-six patients hospitalized at the Clinic for Psychiatry, Clinical Centre of Serbia, Belgrade for the treatment of acute episode of SZ provided written informed consent to participate in the study. Subsequent screening for inclusion/exclusion criteria derived a final sample of eighty SZ patients (40 in the early and 40 in the late stage of SZ). The study was approved by the Ethics Committee of Clinical Centre of Serbia and conducted in accordance with the Helsinki Declaration of 1989. In the patient group, psychiatric diagnosis was confirmed on the basis of the DSM-IV criteria for SZ (American Psychiatric Association, 2000) and the Structured Clinical Interview for DSM-IV-Axis I Disorders (SCID-I). Monitoring of global psychopathology and therapy response was assessed by Clinical Global Impression (CGI) Scale (Guy, 1976). The severity of symptoms (negative, disorganized/cognitive, excitement, positive, and depression/anxiety) within the SZ group was assessed by five-factor model of Positive and Negative Syndrome Scale (PANSS) in SZ (Emsley et al., 2003; Kay et al., 1987). All psychometric measurements were performed in the acute phase of the illness as well as in remission. Patients with SZ were enrolled in the study if they met the following criteria: (a) their baseline PANSS score was $\geq$95 points in the acute episode and (b) their CGI episode severity score was $\geq$4 (Leucht et al., 2005). Clinical remission was defined according to the Remission in Schizophrenia Working Group criteria (Andreasen et al., 2005; Leucht et al., 2005; Pinna et al., 2014) as experiencing 50% decrease from baseline to endpoint in the overall PANSS score as well as PANSS item scores of $\leq$3, using the 1–7 range for each item and was assessed 8 weeks after enrolment in the study. Diagnosis and psychometric evaluations were made by 2 experienced psychiatrists through complete semi-structured interviews in combination with all other available data from medical records. All clinical data concerning the course of illness and previous treatment with antipsychotics were obtained by a blinded research assistant who reviewed charts and complete medical records of each patient enrolled in the study. The duration of untreated psychosis was calculated as the time from the onset of first psychotic symptoms to initiation of adequate treatment (Marshall et al., 2005). To explore the different behavior patterns of immune mediators in regard to the progression of the disorder, the patients were divided into early (within 3 years after first psychotic episode) and late stage (minimum 10 years after the diagnosis of SZ) of SZ, according to the criteria proposed by Pedrini et al. (2012) and Parellada et al. (2005). To control the effects of previously applied treatments, only those patients who were not being treated with major psychotropic drugs for at least 4 weeks prior to hospitalization were included in the study (Schwarz et al., 2000). Daily chlorpromazine-equivalent doses of prescribed antipsychotic treatment, which were applied at the initiation of the current psychotic episode and maintained till the remission phase, were calculated for each individual using conversion tables (Gardner et al., 2010). Because treatment resistance has been associated with increased immune mediators in both treatment-responsive SZ and healthy individuals, it may be considered as a particular inflammatory phenotype within schizophrenia (Noto et al., 2015; Kirkpatrick and Miller, 2013; Miller et al., 2011). In addition, patients with treatment-resistant SZ fail to respond to treatment even with clozapine within 8 weeks and consequently achieve remission (Schulte, 2003). To avoid the false elevation of immune mediators that may be potentially attributed to this inflammatory phenotype of SZ and to ensure that the patients are assessed in both acute phase and remission, our study only included patients with a history of good response to previous antipsychotic treatment. Patients with a history of any other psychiatric illness such as other psychosis, substance or alcohol abuse, obsessive–compulsive disorder,