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Platelet serotonin concentration and depressive symptoms in patients with schizophrenia

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ABSTRACT

Depressive symptoms seem to be frequent in schizophrenia, but so far they have received less attention than other symptom domains. Impaired serotonergic neurotransmission has been implicated in the pathogenesis of depression and schizophrenia. The objectives of this study were to investigate platelet serotonin concentrations in schizophrenic patients with and without depressive symptoms, and to investigate the association between platelet serotonin concentrations and symptoms of schizophrenia, mostly depressive symptoms. A total of 364 patients were included in the study, 237 of which had significant depressive symptoms. Significant depressive symptoms were defined by the cut-off score of 7 or more on Calgary Depression Rating Scale (CDSS). Platelet serotonin concentrations were assessed by the enzyme-linked immunosorbent assay (ELISA). Prevalence of depression in patients with schizophrenia was 65.1%. Schizophrenic patients with depressive symptoms showed lower platelet serotonin concentrations (mean ± SD; 490.6 ± 401.2) compared to schizophrenic patients without depressive symptoms (mean ± SD; 660.9 ± 471.5). An inverse correlation was established between platelet serotonin concentration and depressive symptoms, with more severe symptoms being associated with lower platelet serotonin concentrations. Depressive symptoms in schizophrenic patients may be associated with reduced concentrations of platelet serotonin.

1. Introduction

Depressive symptoms are considered to be one of psychopathological symptom domains of schizophrenia, along with positive, negative, behavioral and cognitive domains. However, they have been studied far less than negative, positive and cognitive symptom domains (Cuesta and Peralta, 2001). They have been reported in all phases of schizophrenia, from prodromal (Tandon et al., 2009), acute (Lançon et al., 2001; Tapp et al., 2001; Majadas et al., 2012; Müller et al., 2006), stable (Cardoso et al., 2007), to chronic (Baynes et al., 2000; Perenyi et al., 1998; Kaneda, 2003). The presence of depressive symptoms in patients with schizophrenia has been associated with overall worse outcomes, greater comorbidity, poorer quality of life, work impairment, deterioration of psychosocial functioning, greater risk of relapse and increased risk of suicide (Majadas et al., 2012; Cotton et al., 2012; Schennach-Wolff et al., 2011).

In schizophrenia, depressive symptoms have been found to correlate with positive symptoms (Tandon et al., 2009; Tapp et al., 2001; Baynes et al., 2000; Cotton et al., 2012; Karadayi et al., 2011), negative symptoms (Kontaxakis et al., 2000; Rocca et al., 2005; Martin-Reyes et al., 2011) and general psychopathology (Lançon et al., 2001; Sung-Wan et al., 2010; Karadayi et al., 2011; Martin-Reyes et al., 2011). Of major concern is their frequent overlap with negative symptoms (Kontaxakis et al., 2000; Rocca et al., 2005; Martin-Reyes et al., 2011; Addington et al., 1994; Siris, 2000), as well as extrapyramidal symptoms which can both mask the presence of depressive symptoms (Siris, 2000; Krakowski et al., 1997). While using nonspecific tools to evaluate depression in schizophrenia, prevalence rates of depression ranged from 6% to over 80%, with a modal rate of 25% (Tapp et al., 2001; Baynes et al., 2000; Cotton et al., 2012; Serretti et al., 2004). Everything stated serves to illustrate the heterogeneity of data obtained while evaluating depressive and other symptom clusters in schizophrenic patients (Tapp et al., 2001; Majadas et al., 2012; Baynes et al., 2000; Perenyi et al., 1998; Cotton et al., 2012; Bottlender et al., 2000). Evidently, there was an unmet need to develop new tools that would allow specific assessment of depressive symptoms in schizophrenia, which was accomplished by construction

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and validation of Calgary Depression Rating Scale (CDSS) (Addington et al., 1994). This scale usually detects significant presence of depression in schizophrenia, with rates ranging from 30% to 70% (Lançon et al., 2001, Majadas et al., 2012; Müller et al., 2006; Schennach-Wolff et al., 2011; Sonmez et al., 2013; Reine et al., 2003).

Serotonergic system has long been implicated in the pathogenesis of depression, and also schizophrenia (Maes and Meltzer, 1995; Abi-Dargham et al., 1997). As central serotonergic neurons are rather inaccessible, blood platelets have been extensively used as a peripheral model of neuronal serotonin dynamics. That is especially the case as in both the process of serotonin release and reuptake seems to be practically the same (Stahl, 1985; Muck-Seler et al., 2004). However, some of the more recent findings argue against such modeling (Balija et al., 2011). There is little available data regarding platelet serotonin concentrations in depression and schizophrenia, but that which is available describes lower platelet serotonin concentrations in depressive patients compared to healthy individuals (Muck-Seler et al., 2004), while the situation is quite opposite in schizophrenia research, with platelet serotonin concentrations being higher in schizophrenic patients, especially in those untreated (Muck-Seler et al., 2004, 1999; Kaneda et al., 2001; Ertugrul et al., 2007). In the one available comparison of depressive and schizophrenic patients, platelet serotonin concentrations were reported to be higher in those suffering from schizophrenia (Muck-Seler et al., 2004).

The objective of this research was to investigate possible differences in platelet serotonin concentrations in healthy individuals and schizophrenic patients, with or without depressive symptoms. The second objective was to investigate possible associations between platelet serotonin concentrations and depressive symptoms, measured by CDSS, as well as other symptom clusters, measured by PANSS. Finally, the last objective was to investigate possible associations between depressive symptoms in schizophrenia, measured by CDSS, and specific symptom clusters, measured by PANSS and its subscales.

2. Methods

2.1. Subjects

The schizophrenia study group consisted of 364 patients, 127 without depression and 237 with depression. Control group consisted of 276 healthy participants who volunteered to participate in the research. The schizophrenia group with significant depressive symptoms included 175 males and 62 females. The schizophrenia group without significant depressive symptoms included 101 males and 26 females. Group of healthy individuals included 157 males and 119 females. Sociodemographic and clinical parameters of all included subjects are presented in Table 1. All subjects with schizophrenia were inpatients. The inclusion criteria for this study were the diagnosis of schizophrenia, using the DSM-IV-TR criteria and the absence of any other psychiatric disorder. Inclusion criteria for the group of healthy volunteers were no personal history of any kind of mental illness and negative hereditary loading for mental illness. Participants with any use of psychoactive compounds including alcohol in their medical history were excluded from the study. Exclusion criteria also included any kind of physical disorders. None of the patients included in this study had taken any psychotropic medication 30 or more days prior to the study, as it has previously been shown that antipsychotic treatment is able to alter platelet serotonin concentrations (Kaneda et al., 2001; Ertugrul et al., 2007; Van der Heijden et al., 2004). Furthermore, we were able to recruit such a relatively large sample of medication free patients due to the fact they did not adhere to antipsychotic treatment. This issue is of major concern, as patients with schizophrenia indeed tend to poorly adhere to their treatment, especially to antipsychotic medication, which usually results in increased symptom severity and more frequent hospital admissions (Sacchetti and Vita, 2014). Although they did not adhere to their treatment, prior to hospital admission majority of patients have been prescribed with an atypical antipsychotic (27% aripiprazole, 23% risperidone, 19% quetiapine, 13% olanzapine) and a minority with a typical antipsychotic medication (11% haloperidol and 7% fluphenazine). Informed consent was obtained from all included patients after a complete and extensive description of the study profile. The study was approved by Ethics Committee of the University Hospital Centre.

2.2. Medical examination and study design

The study included all patients that had been admitted for inpatient treatment with the diagnosis of schizophrenia in the period from November 2009 to May 2014. All patients with schizophrenia presenting the above described exclusion criteria were excluded from the study. Upon meeting the inclusion criteria, patients with schizophrenia were divided into groups with and without significant depressive symptoms, according to a predefined cut off score of 7 or more points on Calgary depression scale for schizophrenia (CDSS) (Addington et al., 1994). Structured clinical interview was performed by a psychiatrist, who made the diagnosis based on the Diagnostic and Statistic Manual of Mental Disorders, fourth edition text revision (DSM-IV-TR) criteria for schizophrenia (First et al., 2002). The severity of schizophrenia was assessed by the Positive and negative syndrome scale (PANSS) (Kay et al., 1987). As already mentioned, severity of depressive symptoms in patients suffering of schizophrenia was assessed by CDSS. Variables of disease features (number of episodes, duration of schizophrenia in years) were obtained from the structured clinical interview based on the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) and were performed by a trained psychiatrist.

2.3. Biochemical measurements

Blood samples were taken from patients for the analysis to determine platelet serotonin levels. Blood samples were taken from the cubital vein in one vacuumed eprouvette with EDTA anticoagulant for the determination of platelet serotonin in the morning, after 12 h of fasting and after a 30 min pause. The platelet serotonin was determined with the enzyme-linked immunosorbent assay (ELISA) procedure using commercial reagents (DRG Diagnostics, Germany). In our laboratory, the value of the inter-assay CV was 6% for platelet serotonin.

2.4. Preparation of platelet-rich plasma (PRP) for platelet serotonin determination

The number of platelets was determined in the full blood sample on a Beckman Coulter 750 hematological analyzer, with prior verification of a blank sample. The PRP was prepared a maximum of 2 h after taking the blood sample. The PRP was obtained by centrifuging the sample at $200 \times g$ for 10 min at room temperature. The supernatant was separated and the number of platelets within was also determined. Platelets were then lysed by separating 200 μl PRP in 800 μl 0.9% sodium chloride solution and centrifuging the suspended cells at $4500 \times g$ for 10 min at 4 °C. After separation of the supernatant, 200 μl of redistilled water was added to the sediment containing platelets and the mixture was mechanically mixed on a vortex mixer to fully lyse the platelets. This prepared platelet lysate was stored at −20 °C (for a maximum