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THE DYNAMICS OF HAEMOSTATIC PARAMETERS IN ACUTE PSYCHOTIC PATIENTS: A ONE-YEAR PROSPECTIVE STUDY

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SUMMARY

Background: *The primary goal of the present study was to replicate our previous finding of increased coagulation and thrombocytes activity in drug-naïve psychotic patients in comparison with healthy controls and ascertain whether the blood levels of thrombogenesis markers further increase over the course of a consecutive one-year antipsychotic treatment.*

Subjects and methods: *We investigated the plasma levels of markers indicating activation of coagulation (D-dimers and Factor VIII) and platelets (soluble P-selectin, sP-selectin) in an antipsychotic-naive group of nineteen men and seventeen women with acute psychosis (age 28.1±8.0 years, body mass index 22.6±4.2), and thirty-seven healthy volunteers matched for age, gender and body mass index. In the patient group, we repeated these assessments after three months and again after one year of antipsychotic treatment.*

Results: *D-dimers (median 0.38 versus 0.19 mg/l; p=0.00008), factor VIII (median 141.5% versus 110%; p=0.02) and sP-selectin (median 183.6 versus 112.4 ng/ml; p=0.00005) plasma levels were significantly increased in the group of patients with acute psychosis prior to treatment compared with healthy volunteers. The plasma levels of sP-selectin varied significantly (p=0.016) in the course of the one-year antipsychotic treatment, mainly between 3 and 6 months after start of therapy. The plasma levels of D-dimers and factor VIII did not change significantly, D-dimers remained elevated in contrast to the healthy controls.*

Conclusions: *Patients with acute psychosis had increased levels of markers of thrombogenesis in comparison to the healthy volunteers. The haemostatic parameters also remained elevated during the one-year antipsychotic treatment.*

Key words: *psychosis – thromboembolism - markers of thrombogenesis – coagulation - antipsychotic treatment*

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INTRODUCTION

Patients with schizophrenia have higher rates of somatic morbidity and mortality compared with the general population (Leucht et al. 2007). This is generally explained by an unhealthy lifestyle, poor dietary habits, and an exposure to antipsychotic medication (Joukamaa et al. 2006). A decreased possibility to obtain an adequate medical care for seriously mentally ill people (SMI) may also play a role. Rates of undiagnosed and untreated medical illnesses are higher in SMI individuals compared with the general population (De Hert et al. 2011). Additionally, physical morbidity and mortality in schizophrenia have recently been found to be increasing (Weinmann et al. 2009).

The risk for cardiovascular mortality among those with schizophrenia is increased twofold compared with patients without schizophrenia (Joukamaa et al. 2006). Obesity, smoking, hypertension and dyslipidemia are the most common modifiable risk factors (De Hert et al. 2011). Blood platelets play an important role in haemostasis, and their hyperaggregability may lead to thrombosis and cardiovascular diseases. Schizophrenia patients treated with antipsychotics show an increased risk of venous thromboembolism (VTE) (Hägg et al. 2009).

Venous thromboembolism, that clinically manifested as a deep vein thrombosis (DVT) or a pulmonary embolism (PE), is a multifactorial disease. The incidence of all types of thrombosis strongly depends on age. Risk factors for VTE include Virchow´s triad: reduced blood flow, changes in the vessel wall, and changes in blood composition (Virchow 1856).

Both schizophrenia and bipolar affective disorder are associated with VTE due to the increased prevalence of a sedentary lifestyle and the lack of movement in this population. Obesity, sedation, hyperprolactinemia (Hägg et al. 2008) and acute epinephrine secretion (Lazarus 2001) are factors that increase the likelihood of forming blood clots and are also important VTE risk factors observed in patients with acute psychosis. The risk of VTE is increased specifically in patients who are hospitalised or in physical restraints. Antipsychotic

medication is also associated with an increased risk for VTE (Zhang et al. 2011, Jönsson et al. 2012). This has particularly been shown in the low-potent first generation antipsychotics or clozapine (Zornberg & Jick 2000, Liperoti et al. 2005, Lacut et al. 2007, Jönsson et al. 2008, Jönsson et al. 2009). There has also been increasing evidence concerning the association between second generation antipsychotics (olanzapine, risperidone) and VTE (Kamijo et al. 2003, Hägg et al. 2008, Malý et al. 2009, Parker et al. 2010). The effects of antipsychotic drugs on blood platelet function are not yet fully explained.

In our pilot study, we formed that markers of thrombogenesis (D-dimers, blood factor VIII) and thrombocyte activation (sP-selectin) are more activated in unmedicated patients with acute psychosis compared with matched healthy volunteers (Masopust et al. 2011).

The primary goal of the present study was to replicate the aforementioned finding in a larger group of patients and to investigate whether the plasma levels of D-dimers, factor VIII and sP-selectin further increase during the consecutive one-year antipsychotic treatment.

SUBJECTS AND METHODS

The present study was a prospective, one-year assessment.

Subjects

The patients were recruited for the study at the Department of Psychiatry, University Hospital in Hradec Králové. The inclusion criteria were as follows: hospitalised patients with acute psychosis (schizophrenia F20, delusional disorder F22, acute schizophreniform psychosis F23.2 according to the ICD-10 classification) (WHO 2006), age of 18–55 years, unmedicated with antipsychotics, and without serious medical comorbidities or a history of VTE. We excluded patients with pre-existing cardiovascular, metabolic, pulmonary or neurological disease by reviewing the patients' medical records. We also conducted a comprehensive physical examination, attending to the primary symptoms of DVT (asymmetrical oedema of the limb) and PE (chest pain, breathlessness, haemoptysis, syncope or tachycardia). This was supplemented by obtainning the patients' family history. The patients did not use any medication at the baseline, so markers of thrombogenesis could not have been influenced by the medication. The laboratory and psychopathology assessment was performed at three successive visits: the first (V1 – visit 1) immediately before the start of antipsychotic treatment, the second (V2 - visit 2) three months later, and the last (V3 – visit 3) after one year of antipsychotic therapy. The choice of an antipsychotic drug for each patient was at the decision of the treating physician.

Healthy volunteers were recruited from the staff at the University Hospital in Hradec Králové. Healthy volunteers without any mental or serious somatic disorder were matched to patients by age, gender, weight, and body mass index (BMI). The possibility of mental illness among the volunteers was excluded by using a psychiatric examination. Each healthy control subject was evaluated only once in the course of the study.

All aspects of the present study were approved by the Ethical Committee of the University Hospital in Hradec Králové. Even if the patients signed the written informed consent in a state of acute psychosis, all of them also agreed to continue in the study in a remission state later on. All healthy volunteers signed the informed consent form.

Laboratory examinations

Venous blood from both the patients and healthy volunteers was taken between 7 and 9 AM after twelve hours of fasting. Laboratory examinations for markers of thrombogenesis and platelet activation are described in Table 1.

Table 1. Laboratory examinations

Marker	Method
D-dimers	STA LIA-test® D-DI (Diagnostica Stago) Normal values: <0.5 mg/l
Factor VIII	DG-F VIII (Grifols) APTT (C.K. PREST, Diagnostica Stago) Normal values: 50-150% of the factor activity
sP-selectin	ELISA method (R&D Systems) Normal values: 82±31 ng/ml

APTT – activated partial thromboplastin time; ELISA – enzyme-linked immunosorbent assay; LIA – isoturbidimetric method

Psychopathology assessment

In each patient, we assessed psychopathology according the PANSS (The Positive and Negative Syndrome Scale) (Kay et al. 1987), the severity of the mental disorder based on the CGI (Clinical Global Impression) (Guy 1976), and functional status using the GAF (Global Assessment of Functioning) (Endicott et al. 1976) at the beginning of the study, after three months, and after one year from the study onset. The antipsychotic medication was given immediately after the first assessment.

Statistical analysis

We compared values of descriptive statistics (age, weight, body mass index) between the patients and healthy controls using the Mann-Whitney U Test. For verification of gender frequency, we used Pearson Chi-Square. For laboratory assessments in patients versus healthy volunteers, we used the Mann-Whitney U Test. Friedman´s ANOVA and Wilcoxon Signed Rank Test was applied to determine differences among the medians of the values from V1, V2 and V3.

Development of body weight and BMI were measured by Repeated Measures ANOVA. For pathological values, frequency comparison was found with Fisher's Exact Probability Test.

RESULTS

Thirty-six (women n=17) patients with acute psychosis (schizophrenia n=21; acute schizophreniform psychosis n=14; delusional disorder n=1) were included in the study. The patients have been treated with antipsychotics based on the treating physician´s decision: olanzapine (18 patients), aripiprazole (6), risperidone (4), amisulpride (3), paliperidone (2) and combination of first generation depot antipsychotic with oral atypical antipsychotic (3). The control subjects were matched to patients by age, gender, weight, and body mass index. Twenty-five patients and twenty-five healthy volunteers from this sample have already been included into our previous study (Masopust et al. 2011). We did not find any significant demographic difference between the patients and healthy volunteers at the baseline (p=NS; Mann-Whitney U Test and Pearson Chi-Square) (Table 2).

Plasma levels of D-dimers, factor VIII and sP-selectin were significantly higher in the patients prior to treatment compared with the healthy volunteers (U=310.000, p=0.00008; U=451.5, p=0.002; and U=298.5; p=0.00005, respectively; Mann-Whitney U Test). The plasma level of D-dimer was pathologically increased (>0.5 mg/l) in eleven patients and in only three healthy controls. Frequency of pathological values is statistically significant different (p=0.015; Fisher's Exact Probability Test). sP-selectin values were frequently higher than laboratory normal range (>134 ng/ml) in twenty four patients and nine healthy controls; statistically significant difference (p=0.0003; Pearson Chi-Square). Factor VIII was pathologically increased in seventeen patients and eleven healthy controls with no difference of frequency between groups (p=NS; Pearson Chi-Square). Laboratory data on the patients prior to treatment and healthy volunteers are shown in Table 2.

In the course of one-year follow-up, the plasma levels of D-dimers and factor VIII remained stable (Table 3). The plasma levels of D-dimers in the patients with one-year follow-up treated with antipsychotics was always significantly higher at all visits compared with healthy controls (U=179.000, p=0.002; U=143.500, p=0.0003; and U=218.000, p=0.02; Mann-Whitney U Test) (Figure 1). The factor VIII levels showed only trend at V2 in comparison with healthy controls (U=247.000, p=0.07; Mann-Whitney U Test); other differences were non-significant because smaller number of patients with all visits compared to baseline (Figure 2).

Table 2. Demographic data and markers of thrombogenesis in patients prior to treatment and healthy volunteers

Variable	Patients (N=36; women N=17)			Healthy volunteers (N=37; women N=18)			p-value (Test)
	Average (SD)	Median	Range	Average (SD)	Median	Range	
Age (years)	28.1 (8.0)	27.5	18-52	28.1 (8.3)	28	18-53	NS (MW-U)
Weight (kg)	67.6 (13.8)	69	39-102	71.6 (11.9)	71	46-101	NS (MW-U)
BMI	22.6 (4.2)	21.9	16.2-39.8	23.1 (2.6)	23.5	17.5-29.6	NS (MW-U)
Duration of untreated psychosis (months)	10.5 (18.4)	2	0.25-80	-	-	-	-
D-dimers (mg/l)	0.94 (2.01)	0.38	0.12-11.81	0.28 (0.3)	0.19	0.04-1.6	0.00008 (MW-U)
Factor VIII (%)	156 (61.8)	141.5	73-364	127 (52.9)	110	69-290	0.02 (MW-U)
sP-selectin (ng/ml)	196.8 (108.8)	183.6	63.3-654.4	124.4 (36.7)	112.4	35.6-227.3	0.00005 (MW-U)

BMI – Body Mass Index, MW-U - Mann-Whitney U Test, NS – non-significant, SD – standard deviation

Table 3. Markers of thrombogenesis in the patients during the one-year study

		V1	V2	V3	P (Test)
D-dimers (mg/l) (n=19)	Average (SD)	1.15 (2.65)	0.49 (0.26)	0.36 (0.31)	NS (ANOVA)
	Median (range)	0.38 (0.12-11.81)	0.45 (0.12-0.95)	0.29 (0.17-1.59)	
Factor VIII (%) (n=19)	Average (SD)	150 (74.4)	148 (46.1)	133 (35.1)	NS (ANOVA)
	Median (range)	137 (73-364)	150 (61-229)	140 (67-183)	
sP-selectin (ng/ml) (n=22)	Average (SD)	223.8 (129.6)	217.3 (102.4)	251.3 (144.7)	0.016 (ANOVA) V1:V2 NS (W) V1:V3 0.088 (W) V2:V3 0.036 (W)
	Median (range)	208.7 (63.3-654.4)	193.1 (79.6-554.8)	211.5 (95.3-756.3)	

ANOVA – Friedman ANOVA, W – Wilcoxon Signed Rank Test, NS – non-significant, SD – standard deviation,
V1 – visit 1 (onset study), V2 – visit 2 (3 months), V3 – visit 3 (end of study)

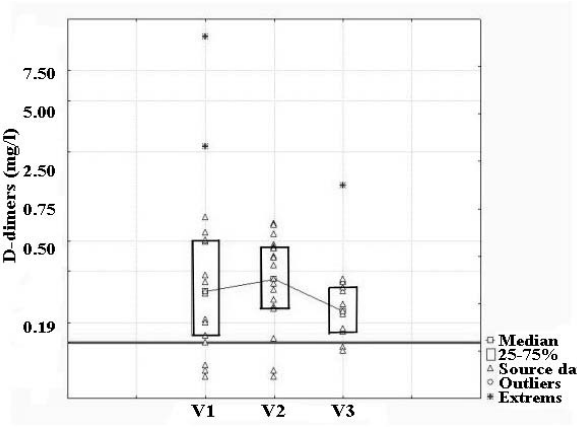

Figure 1. The plasma levels of D-dimers in the patients during the one-year study. D-dimers value in healthy volunteers is displayed with a red line

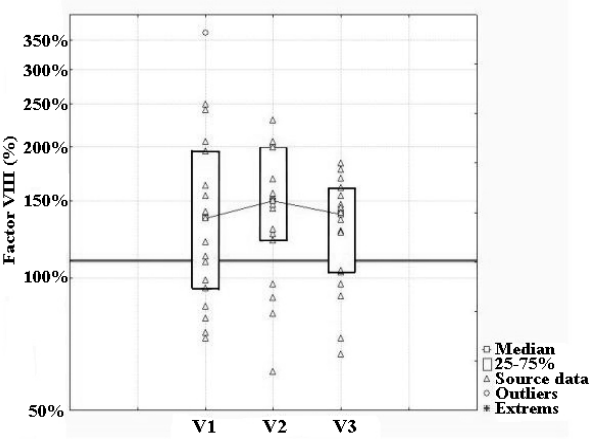

Figure 2. The plasma levels of factor VIII in the patients during the one-year study. Factor VIII value in healthy volunteers is displayed with a red line

The sP-selectin levels have varied significantly from the study onset to V3 (p=0.016; Friedman's ANOVA). Significant change were detected between V2 and V3, non-significant trend were found between V1 and V3 (p=0.036, p=0.088, respectively; Wilcoxon Signed Rank Test) (Table 3). Also the sP-selectin plasma levels were always significantly higher in the patients (V1, V2, V3) versus the healthy subjects (V1) (U=160.000, p=0.0001; U=129.000, p=0.00001; U=93.5000, p=0.000001; Mann-Whitney U Test) (Figure 3).

The body weight of the patients increased significantly from the study onset (mean 66.7±12.7 kg at the study onset versus 78.4±15.4 kg after one year, F(3, 42)=6.2515, p=0.01; BMI mean 22.1±3.1 at the study onset versus 26.1±3.7 after one year, F(3, 42)=5.8776, p=0.002, Repeated Measures ANOVA). Difference between V1 and other visits was found as important in post hoc analysis (Bonferonni test).

The PANSS total score decreased significantly during the study (median 98.5 at the beginning versus 47.0 after one year; p<0.001; Friedman's ANOVA). This was also reflected in the CGI (median 5.0 at the beginning versus 2.0 after one year; p<0.001; Friedman's ANOVA). Functioning competence of the patients in the study also improved according to the GAF (median 45.5 at the beginning versus 75.0 after one year; p<0.001; Friedman's ANOVA).

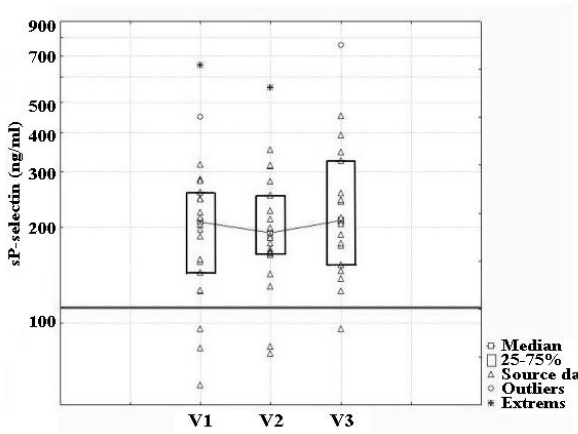

Figure 3. The plasma levels of sP-selectin in the patients during the one-year study. sP-selectin value in healthy volunteers is displayed with a red line.

DISCUSSION

This study found an increased risk of venous thromboembolism in patients with acute psychosis compared with the general population. The majority of markers of thrombogenesis also remained elevated at the follow-up visits after 3 and 12 months.

Data concerning markers of thrombogenesis in unmedicated schizophrenic patients are limited. Iwata et al. (2007) found increased levels of serum soluble L-selectin, but not sP-selectin, in 23 unmedicated patients with schizophrenia compared with patients with major depression or healthy subjects. The selectin family of adhesion molecules plays a prominent role in immune/ inflammatory responses. This finding provides support for the hypothesis of an immune dysfunction in the pathophysiology of schizophrenia as a neurodevelop-mental disorder.

In a study by Walsh et al. (2002), patients with schizophrenia (N=19) had increased platelet expression of surface receptors alpha(IIb) beta(IIIa) compared with healthy controls. It may contribute to an increased risk for cardiovascular illness.

We partially replicated the results of our previous pilot study in this way (Masopust et al. 2011). At the beginning of our study, the plasma levels of all assessed markers were significantly higher in the patients than in healthy controls. This also holds true for all other assessments during the study, except for factor VIII. In the case of sP-selectin, the plasma levels in the patients changed during the treatment.

Our findings suggest that acute psychosis may reflect a pro-coagulatory state. D-dimers are fragments of insoluble fibrin, detectable in plasma after fibrin

coagulum has been cleaved by plasmin. Increased plasma levels of D-dimer result from pathological activation of blood clotting and occurs following fibrinolysis. The specificity of D-dimers for the assessment of VTE is limited because increased plasma levels can also be found in various types of inflammation, necrosis, tumours or infections. Nevertheless, we did not find any clinical or laboratory markers of infection in our sample of patients. The increased plasma level of D-dimer in acute psychosis may be a marker of fibrinolysis in the course of pathological blood clotting, when elevated epinephrine secretion stimulates the activation of thrombocytes (Lazarus 2001, Hindersin et al. 1984).

The finding of elevated sP-selectin plasma levels as a marker of inflammation and increased thrombogenesis in our patients is consistent with the process described above. Thrombocytes are involved in atherogenesis if endothelial dysfunction is also present. The membrane pro-coagulatory protein sP-selectin is produced by activated thrombocytes (Mathur et al. 2001). sP-selectin induces migration and adhesion of leukocytes as well as stimulation of endothelial cells and thrombocytes. Additionally, sP-selectin plays an important role as a connecting element between inflammation and thrombosis (Ay et al. 2007). The persistent elevation of sP-selectin plasma levels and their continuous increase in the patient group documents a high risk for VTE in the subsequent course of treatment. Smoking was present in 11 patients (30.6%) and in no healthy volunteer. Smoking can theoretically influence the platelet activity (sP-selectin), but not D-dimers and factor VIII.

Increased blood levels of factors II, V, and VIII are associated with an increased risk of venous thromboembolism according to the current literature (Cushman 2007). Individuals with factor VIII coagulatory activity above 150 IU/dl have a threefold risk of developing VTE compared with subjects with activity <150 IU/dl, and they are six times more likely to develop this condition than people with activity <100 IU/dl. People with factor VIII coagulatory activity equal to 150 IU/dl are at a 2.7-fold increased risk of venous thromboembolism compared with the general population (Coster et al. 1995).

Patients in this study had factor VIII plasma levels significantly higher compared with healthy volunteers at the study onset and showed trend at V2.

The role of antipsychotic medications versus the presence of the mental disorder itself in the aetiology of VTE has not been fully clarified in patients with schizophrenia or other psychoses (Hägg et al. 2009). Antipsychotic agents may influence the blood clotting via their effect on serotonin function, which is involved into the primary haemostasis. The aggregation response of platelets induced by 5-HT (5-hydroxytryptamine) was greatly increased in psychiatric patients receiving chlorpromazine. When chlorpromazine therapy was stopped, 5-HT induced platelet aggregation responses became normal after three weeks (Boulin et al. 1978). A significant affinity of clozapine and risperidone to 5-HT2A receptors may cause a 5-HT2A-induced increased platelet aggregation (Kamijo et al. 2003). The influence of clozapine on an increased adhesion of thrombocytes was already confirmed (Axelsson et al. 2007). The impact of antipsychotics on blood platelets was reasserted in another study (Oruch et al. 2009). In another in vitro study, the direct effect of risperidone on thrombocytes activity or plasmatic coagulation was not confirmed (De Clerck et al. 2004). By contrast, other findings indicate that clozapine and olanzapine may decrease the ADP-induced aggregation of platelets in vitro (Dietrich-Muszalska et al. 2010, Schedel et al. 2010). A significantly increased stimulation of platelets was found in patients with hyperprolactinemia induced with antipsychotics in contrast with healthy volunteers. The prolactin plasma levels significantly correlated with the ADP-stimulated expression of P-selectin as a marker of platelet activation (Wallaschofski et al. 2003). We did not find a relation between prolactinaemia and plasma levels of sP-selectin or other markers of thrombogenesis in our group of patients.

Metabolic symptoms induced with antipsychotics, such as body weight increase, hyperleptinaemia, hyperglycaemia and dyslipidemia, belong to the TEN risk factors and influence coagulatory and fibrinolytic mechanisms (Dunn & Grant 2005, Liperoti 2010). Obesity (BMI ≥ 30) is associated with a twofold increase in the number of venous thromboembolic events. Obese individuals show increased plasma levels of factors VIII and IX (Abdollahi et al. 2003). Abdominal obesity is related to an activity of hormonally effective agents and leads to pro-coagulatory and pro-inflammatory states with a risk of thrombosis occurrence (Phillips & Prins 2008). Regardless of a marked body weight increase in our group of patients during one year, only two of them attained BMI ≥ 30.

We are aware of the limitations of our results. The study population is small, particularly at V3. The generalisability of the presented findings may also be limited due to the disease heterogeneity in psychoses. The patients have been treated with antipsychotics, based on the treating physician´s decision during the course of the study. Due to a large heterogeneity of antipsychotic pharmacotherapy in our sample, it was not possible to analyse the influence of individual medicaments on the markers of thrombogenesis.

CONCLUSION

In our initial sample of unmedicated patients with acute psychosis, we found an increased level of blood markers of the pathological activation of blood clotting and fibrinolysis, as well as the activation of thrombocytes compared with matched healthy volunteers. Plasma levels of these markers mostly remained increased at the follow-up assessment at 3 and 12 months of treatment. The high initial levels of

haemostatic parameters suggest that at least some venous thromboembolic events in patients with acute psychosis may be induced by pathogenic mechanisms related to psychosis, rather than by antipsychotic treatment.

Prospective studies are needed to elucidate the biological mechanisms involved in the relationship between venous thromboembolism and antipsychotic medication versus the mental disorder and its aetiopathogenesis itself. Finding an exact cause for venous thromboembolism in psychotic patients is necessary for effective treatment and prevention.

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Conflict of interest: None to declare.

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