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Platelet Serotonin and Monoamine Oxidase in Alzheimer's Disease with Psychotic Features

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A B S T R A C T

Post mortem brain studies indicate that alterations in serotonergic and catecholaminergic systems might be associated with Alzheimer's disease (AD). The aim of the study was to determine serotonin (5-HT) levels and monoamine oxidase type B (MAO-B) activity in platelets of psychotic and non-psychotic patients with AD, established according to the NINCDS-ADRDA and DSM-IV-TR criteria. Cognitive impairment and psychotic features were evaluated using Mini Mental Status Examination and Neuropsychiatric Inventory. Platelet 5-HT concentration and MAO-B activity were determined spectrofluorimetrically in 116 (51 male, 65 female) healthy subjects and 70 psychotic (10 male, 60 female) and 151 non-psychotic (32 male, 119 female) patients. Psychotic and non-psychotic female and psychotic male patients had significantly lower platelet 5-HT concentration than corresponding sex matched control subjects. Platelet MAO-B activity was significantly increased in both male and female non-psychotic patients compared to the sex matched controls. Non-psychotic female patients had significantly higher platelet MAO-B activity than psychotic female patients. Our data suggest that platelet MAO-B activity, but not platelet 5-HT concentration, could differentiate between psychotic and non-psychotic subtypes of AD.

Key words: *platelets, serotonin, monoamine oxidase, Alzheimer's disease, psychotic features*

Introduction

Alzheimer's disease (AD) is a complex neurodegenerative disorder with different cognitive and behavioural abnormalities[1]. Various studies have found that majority of AD patients suffer from psychotic symptoms, like auditory and/or visual hallucinations and delusions[2]. Psychotic features upset the patients, complicate the treatment response, and are frequently associated with the rapid progress of the disease[2].

The aetiology of AD is still not clear. Post mortem brain studies in patients with AD[3] showed neuropathological and neurochemical alterations in catecholaminergic[4] and serotonergic[5] systems. The decrease in brain dopamine[6], serotonin (5-hydroxytryptamine, 5-HT)[6], and its main metabolite 5-hydroxyindoleacetic acid (5-HIAA) concentrations, and the loss of 5-HT2 receptors[7], was found in patients with AD. Blood platelets have been proposed as an easy obtainable peripheral model for some processes in the central serotonergic neurons[8–10] and for the expression of the brain amyloid precursor protein[11]. The studies on platelet 5-HT uptake[12,13], and platelet monoamine oxidase type B (MAO-B) in AD yielded inconsistent results[14]. MAO is a flavin-containing oxygen oxidoreductase. Two isoenzymes (MAO-A and MAO-B) differ in localization, substrates and inhibitors[15]. MAO-B exists in platelets, astrocytes and 5-HT neurons. Its substrates are β-phenylethylamine, benzylamine, dopamine, tyramine, and tryptamine, and its inhibitor is deprenyl[15]. It is assumed that altered levels of platelet MAO-B are associated with different psychopathologies and vulnerability to psychiatric disorders[15,16]. An increase in platelet

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MAO-B activity was observed in AD[17]. Recently we have found[18] that platelet MAO-B activity might be used as a peripheral biomarker for the early and late onset AD.

We have previously found that platelet 5-HT might differentiate between psychotic and non-psychotic depression[19], posttraumatic stress disorder (PTSD)[20], bipolar affective disorder in a manic phase[21]. In addition, a higher platelet MAO-B activity was found in psychotic compared to non-psychotic subtype of PTSD[22]. The hypothesis of the present study was that platelet biochemical markers would differ in AD patients with or without psychotic features. The aim of the present study was to determine peripheral biochemical markers (platelet 5-HT concentration and platelet MAO-B activity) in male and female patients with AD, subdivided according to the presence of psychotic features, and in sex matched healthy controls.

Subjects and Methods

The study included 221 (42 male, 179 female) medication-free patients (mean age 60.6±9.9 years) with AD, hospitalized in Psychiatric Hospital Vrapče, Zagreb. The diagnosis of the probable AD (NINCDS-ADRDA criteria[23]) was established by two psychiatrists according to the DSM-IV-TR criteria[24]. Cognitive impairment was evaluated using Mini Mental Status Examination (MMSE)[25]. Mean MMSE scores in AD patients was 18.9±3.2. According to the Neuropsychiatric Inventory[26], patients were subdivided into two groups: 70 patients (10 male and 60 female) with psychotic features and 151 patients (32 male, 119 female) without psychotic features. Control group consisted of sex and age-matched, medication-free healthy subjects (65 female, 51 male) (mean age 60.3± 11.2 years), with no history of psychiatric illness. All subjects were nonsmokers. The study was approved by the Ethic committee and all participants gave informed consent.

Blood samples (8 mL) were obtained from a jugular vein, after an overnight fasting, in a plastic syringe with 2 ml of acid citrate dextrose anticoagulant. Platelet rich plasma (PRP) was obtained after centrifugation of whole blood, and platelets were sedimented by further centrifugation of PRP. Platelet 5-HT concentration was determined by the spectrofluorimetric method, as previously described[27], using Varian Cary Eclipse spectrofluorimeter Platelet MAO-B activity was determined spectrofluorimetrically using kynuramine as a substrate[27,28]. Platelet protein levels were measured by the method of Lowry et al.[29].

The results were expressed as mean±SD. The differences between groups were analyzed using Kruskal–Wallis one-way analysis of variance (ANOVA) by ranks followed by Mann-Whitney rank sum test for pairwise comparisons. The statistical package used was Statistica 6 and SPSS 10.0 analysis.

Results

Platelet 5-HT concentration was significantly (H= 36.5, df=5, p<0.001; Kruskal Wallis ANOVA) different among healthy controls and patients with AD, subdivided according to the presence of psychotic features (Figure 1). A significant decrease in platelet 5-HT concentration was observed in psychotic (p=0.002, Mann Whitney test) and non-psychotic (p<0.001) female patients and non-psychotic (p=0.002) male patients compared to platelet 5-HT concentration in corresponding sex-matched healthy controls. There was no significant difference in platelet 5-HT concentration between male (p=0.712, Mann Whitney test) or female (p=0.422, Mann Whitney test) psychotic or non-psychotic AD patients.

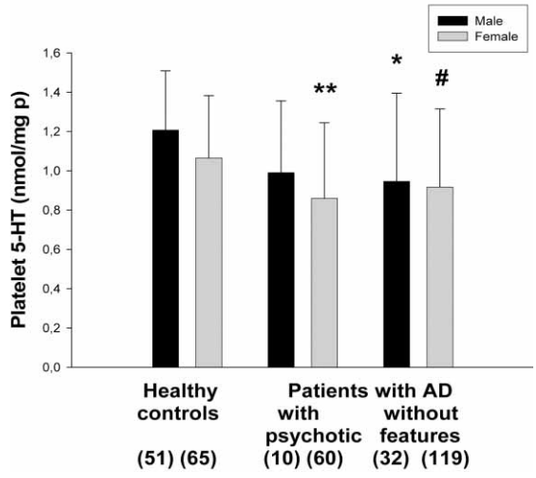

*Fig. 1. Platelet serotonin (5-HT) in male and female healthy controls and patients with Alzheimer's disease (AD) with or without psychotic features. *p=0.002 vs. healthy male; **p=0.002 vs. healthy female; #p<0.001 vs. healthy female (Kruskal Wallis ANOVA on ranks followed by Mann Whitney test)*

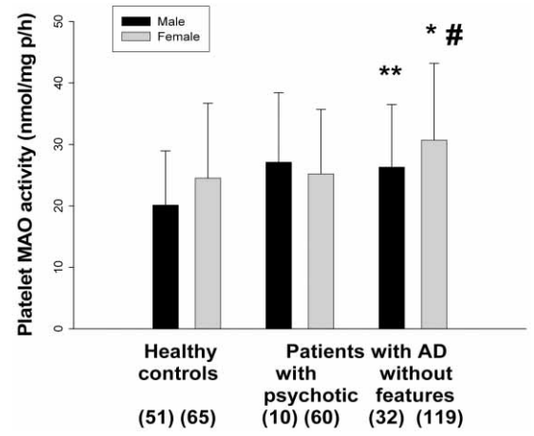

*Fig. 2. Platelet monoamine oxidase (MAO) in healthy controls and patients Alzheimer's disease (AD) with or without psychotic features. *p=0.017 vs. female psychotic patients; **p<0.006 vs. healthy male; #p<0.001 vs healthy female (Kruskal Wallis ANOVA on ranks followed by Mann Whitney test)*

Platelet MAO-B activity differed significantly ($H=28.8$, $df=5$, $p<0.001$, Kruskal Wallis ANOVA) in patients with AD, subdivided into groups with or without psychotic features, and in healthy control subjects (Figure 2). Platelet MAO-B activity was significantly higher in both male ($p<0.006$) and female ($p<0.001$) non-psychotic patients with AD than in sex matched healthy controls. Non-psychotic female AD patients had significantly ($p<0.017$) higher platelet MAO-B activity than psychotic female AD patients. There was no significant difference ($p=0.73$, Mann Whitney test) in platelet MAO activity between psychotic and non-psychotic male AD patients.

Discussion

The results of the present study show that patients with AD have different platelet 5-HT concentration and platelet MAO-B activity when compared to sex- and age-matched control subjects. To our knowledge this is the first report showing a decreased platelet 5-HT concentration in patients with AD. Although platelets represent a limited peripheral model for the central serotonergic neurons, it is noteworthy that similar reductions in 5-HT and 5-HIAA concentrations have also been found in the areas of the frontal and temporal cortices of AD patients[5]. In addition, our results showed that the alterations in platelet 5-HT values in AD patients were not related to the presence of psychotic features. This result is in contrast with the increased platelet 5-HT concentrations in psychotic unipolar depressed patients[19], bipolar patients in manic phase[21], war veterans PTSD with psychotic symptoms[20], or schizophrenic patients with predominantly positive symptoms[30], when compared to corresponding control subjects.

The discrepancies in platelet 5-HT concentration in patients with AD might be explained by the various factors, including a decrease in 5-HT synthesis, an increase in 5-HT metabolism and a change in 5-HT transporter. It has been suggested[31] that aging may be associated with lower activity of the tryptophan hydroxylase, a rate limiting enzyme in 5-HT synthesis. Since our study included age matched patients and control subjects, the difference in platelet 5-HT values between groups is presumably not related to the difference in age of the subjects. Platelet 5-HT transporter is the most important membrane protein, responsible for the active transport of 5-HT from plasma into platelets, and consequently for platelet 5-HT concentrations. However, recent molecular study[32] did not find an association between a deletion/insertion polymorphism within promoter region of the 5-HT transporter gene and AD.

Although blood platelets contain only MAO type B, which is not entirely specific for the metabolism of the 5-HT, we can not exclude the possibility that the decrease in platelet 5-HT concentrations in patients with AD is in part a consequence of the higher platelet MAO -B activity.

In the present study we have found an increase in platelet MAO-B activity in both male and female patients with AD compared to control subjects. This is in line with our previous finding of the high platelet MAO-B activity in patients with early onset AD, and with other studies showing increased MAO activity in brain[14,33] and platelets[14,17,18,34] of patients with AD. In addition, we have found that the increase in platelet MAO-B activity was restricted only to patients without psychotic features. Several factors such as sex, smoking, age, race, some neurodegenerative disorders, pernicious anaemia, and psychotropic drugs[15] affect platelet MAO-B activity. To control for these variables, we subdivided patients according to the sex, they were matched for race, age, and medication, and none of the patients were smokers. Higher platelet MAO-B activity reported in our non-psychotic AD patients might be connected with some hidden psychopatologies[15], personality traits[35,36], such as neuroticism[37] or high anxiety[36]. The increased platelet MAO-B activity in non-psychotic AD patients does not agree with the recent finding of an elevated activity of platelet MAO-B in war veterans PTSD with psychotic symptoms[22] when compared to corresponding control subjects. This discrepancy might be due to the differences in diagnoses (AD vs. PTSD), age[15] or smoking[20]. In addition, altered platelet MAO-B activity may be related to difference in yet unknown transcriptional factor(s)[38], rather than genotypic variation[22], that act on transcriptional regulation[38] of the amount of enzyme and/or in the kinetic regulation of the molecular activity of MAO-B in platelets[39].

Our results of the increased MAO-B activity in AD patients support the presumption that neurotoxic and reactive metabolites of catecholamine neurotransmitters could be involved in the aetiology and progress of AD. Recently, neurotoxicity of MAO-B metabolites of noradrenalin, adrenaline or dopamine has been shown in vitro and in vivo[40]. The serious consequence of the altered MAO activity is the increase in catecholamine metabolites like 3, 4-dihydroxyphenylglycholaldehyde (DOPEGAL) and 3,4-dihydroxyphenylacetaldehyde (DOPAL), which are highly reactive and toxic to neuronal cells in vitro and in vivo[40].

In conclusion, we have found altered biochemical parameters in platelets of patients with AD. Our results of decreased platelet 5-HT concentrations and increased platelet MAO-B activity suggest that both serotonergic and catecholaminergic system could be involved in the pathophysiology and progress of AD. In addition, platelet MAO-B activity, but not 5-HT concentration, might be used as a peripheral biological marker that can distinguish between psychotic and non-psychotic subtypes of AD.

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TROMBOCITNI SEROTONIN I MONOAMINOOKSIDAZA B U BOLESNIKA S AZHEIMEROVOM BOLESTI SA PSIHOTIČKIM SIMPTOMIMA

SAŽETAK

Post mortem istraživanja su pokazala promjene serotoninskog i kateholaminskog sustava u mozgu oboljelih od Alzheimerove bolesti (AB). Cilj istraživanja bio je odrediti koncentraciju trombocitnog serotonina (5-HT) i aktivnost trombocitne monoaminooksidaze tipa B (MAO-B) u bolesnika s AB sa ili bez psihotičnih simptoma i u skupini zdravih osoba. Dijagnoza vjerojatne AB (NINCDS-ADRDA kriterij) postavljena je u skladu s DSM-IV kriterijima. Za procjenu kognitivnog oštećenja korištena je Mini Mental Status Examination, a za određivanje psihotičnih simptoma Neuropsychiatric Inventory. U trombocitima 116 zdravih osoba (51muškaraca, 65 žena), 70 bolesnika (10 muškaraca, 60 žena) sa psihotičkim simptomima i 151 bolesnika (32 muškarca, 119 žena) bez psihotičkih simptoma određena je koncentracija 5-HT i aktivnost MAO-B pomoću spektrofluorimetrijskih metoda. Koncentracija trombocitnog 5-HT bila je značajno snižena u bolesnica sa psihotičkim i nepsihotičkim simptomima te u nepsihotičkih bolesnika u odnosu na koncentraciju trombocitnog 5-HT u odgovarajućoj skupini zdravih žena i muškaraca. Aktivnost trombocitne MAO-B bila je povećana u muških i ženskih nepsihotičkih bolesnika s AB u usporedbi s aktivnošću u zdravoj kontroli odgovarajućeg spola. U trombocitima nepsihotičkih ženskih bolesnica pronađena je značajno povećana aktivnost MAO-B u odnosu na aktivnost enzima u trombocitima bolesnica sa psihotičkim simptomima. Rezultati istraživanja upućuju da bi aktivnost trombocitne MAO-B mogla biti biokemijski pokazatelj za razlikovanje psihotičkog i nepsihotičkog oblika AB.