



# Decreased platelet serotonin concentration in Alzheimer's disease with involuntary emotional expression disorder



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## HIGHLIGHTS

- AD patients with IEED have low platelet 5-HT concentrations.
- Aggressive behavior in AD is not related with platelet 5-HT deficiency.
- IEED in AD could be associated with the changes in serotonergic system.

## ARTICLE INFO

### Article history:

Received 6 February 2014

Received in revised form 18 May 2014

Accepted 13 June 2014

Available online 23 June 2014

### Keywords:

Alzheimer's disease

Affective symptoms

Aggression, Blood platelets

Emotional disturbances

Serotonin

## ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disorder manifested by progressive decline in cognitive functions. A variety of behavioral disturbances appear very often in AD which might be associated with altered function of serotonergic system. The aim of the study was to determine platelet serotonin (5-HT) concentrations in 49 patients with AD (NINCDS-ADRDA and DSM-IV-TR criteria) subdivided in three groups: (a) patients with aggressive behavior, (b) patients with involuntary emotional expression disorder (IEED) and (c) patients without aggression or IEED (controls). Platelet 5-HT concentrations were measured using ELISA. Platelet 5-HT concentrations were significantly lower in patients with AD and co-existing IEED compared to AD patients with aggressive behavior or control patients. No significant difference in platelet 5-HT concentrations was found between patients expressing aggressive behavior and controls. Our results suggest disruptions in serotonergic system in AD patients with comorbid IEED but not with aggressive behavior and support the presumption that platelet 5-HT concentration is a suitable and easy measured peripheral indicator of some behavioral and psychological symptoms of AD.

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## 1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder manifested by progressive decline in cognitive functions, and very often associated with different behavioral disturbances [1]. Behavioral and psychological symptoms of dementia (BPSD) include psychotic symptoms (delusion, hallucination), agitation

(repeat movement, aimless wandering), aggression (verbal, physical), apathy (loss of interest), mood abnormalities (depression, anxiety) and alterations in sleep and appetite [2]. It has been estimated that up to 90% of AD patients display BPSD [3], including aggression up to 65% [2]. The involuntary emotional expression disorder (IEED) appears in nearly 39% of patients with AD [4]. It is a syndrome characterized by sudden involuntary episodes of crying or laughing that are independent of any eliciting stimulus [5].

The neurobiology of AD, as well as aggression and IEED in AD is still unclear. Besides cholinergic [6], the alterations in other neurotransmitter systems, such as serotonergic [7,8] and glutamatergic systems [9] are also thought to be responsible for the development of cognitive and non-cognitive (behavioral, emotional) symptoms in patients with AD. The decrease in the brain serotonin (5-hydroxytryptamine, 5-HT) concentration [7], the loss of serotonergic 5-HT<sub>1A</sub> receptors in the hippocampus and nuclei raphe [10],

*Abbreviations:* AD, Alzheimer's disease; IEED, involuntary emotional expression disorder; BPSD, behavioral and psychological symptoms of dementia; 5-HT, serotonin.

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<http://dx.doi.org/10.1016/j.neulet.2014.06.034>

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and 5-HT<sub>2</sub> receptors in cerebral cortex [11] were found in patients with AD. The numerous neuroendocrine and pharmacological clinical studies are looking for the putative peripheral markers of the brain 5-HT dynamics [12]. Blood platelets have been proposed as an easy obtainable, peripheral model for some processes in the presynaptic and postsynaptic parts of the central serotonergic neurons [13]. The studies on platelet 5-HT concentration in AD yielded inconsistent results. The increased [14], decreased [15] or unaltered [16] platelet 5-HT concentrations were found in AD. In patients in the late phase of AD, the significantly lower platelet 5-HT concentration compared to patients in the early phase of AD was also revealed [17]. That was not related to the presence of psychotic features [18]. Recently we have described the decline in platelet 5-HT concentrations after treatment with uncompetitive NMDA receptor antagonist memantine in AD patients with deterioration of behavioral symptoms, especially aggression [19]. To our knowledge, there are no data on the association between platelet 5-HT levels and co-morbid IEED and aggression in patients with AD.

The hypothesis of the present study was that the changes in platelets 5-HT values are present in AD patients with co-existing aggressive behavior or IEED. The aim of our study was to determine platelet 5-HT concentration in AD patients with or without aggression or IEED.

## 2. Methods

### 2.1. Patients

The study included 49 (29 women, 20 men) patients with AD (mean age  $\pm$  SD, 76.9  $\pm$  9.9 years, range 53–96 years). All patients met the clinical diagnostic criteria of AD according to Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) [20] and criteria of National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) [21]. Global cognitive abilities were assessed with Slovenian version of Mini Mental State Examination (MMSE) [22].

The exclusion criteria were prior to current history of mood or anxiety disorders, psychosis, alcohol or drug abuse; coexisting neurological or systemic disease or abnormal hematological, hepatic and renal function tests that could influence the results of the present study. Patients were not treated with antidepressants and the treatment with acetylcholinesterase inhibitors or memantine must have been established at least one month before enrollment and were maintained at a constant dose throughout the study.

Patients were subdivided according to the coexisting aggressive behavior and IEED into 19 patients without changes in behavior (controls), 14 patients expressing aggressive behavior, and 16 patients with IEED. The severity of aggression was assessed with Overt Aggression Scale-Modified (OAS-M) [23]. OAS-M is a semi structured interviewer-rated instrument for recording the severity of aggression, divided into four subtypes of aggression: verbal aggression, aggression against property, physical aggression against others and auto-aggression (self-injurious behavior).

IEED was diagnosed according to the criteria described by Cummings et al. (2006) [5]. The severity of IEED was determined using the Pathological Laughter and Crying Scale (PLACS) [24] that has been validated in patients with AD [4]. The patients that scored 2 or 3 on item 2 (assessing the frequency of crying or laughing episodes), item 13 (assessing loss of voluntary control of emotions during episode) and item 18 (assessing distress and embarrassment associated with the episodes), and with a total score  $\geq$  13 on PLACS were diagnosed with IEED.

The study protocol and consent forms were approved by the institutional review boards and The National Medical Ethics

**Table 1**

Demographic data of AD patients with aggressive behavior, involuntary emotional expression disorder (IEED) and patients without aggressive behavior or IEED (controls). Results are expressed as means  $\pm$  SD. *N* is the number of subjects.

	Patients with AD ( <i>N</i> = 49)		
	Controls ( <i>N</i> = 19)	Aggressive behavior ( <i>N</i> = 14)	IEED ( <i>N</i> = 16)
Women/men	12/7	7/7	10/6
Age (years)	80.8 $\pm$ 7.1	81.4 $\pm$ 8.1	79.3 $\pm$ 4.5
Range	60–89	59–89	73–91
MMSE (scores)	10.4 $\pm$ 8.1	8.6 $\pm$ 6.4	10.6 $\pm$ 6.1
Range	1–23	0–18	2–21

Committee of the Republic of Slovenia and have been performed entirely in accordance with the ethical standards laid down in the Helsinki Declaration. Each patient and/or their caregiver signed a written consent for the participation in the study.

### 2.2. Biochemical analysis

Blood samples for measuring platelet 5-HT levels were taken during routine laboratory tests from a vein in the tubes containing EDTA, in the morning. The samples were transported to Institute of Clinical Chemistry and Biochemistry, University Medical Centre Ljubljana, where all biochemical determinations were performed by laboratory personnel who were blind to diagnosis. Platelet rich plasma was obtained after centrifugation of whole blood at 1000 g and the concentration of platelets in plasma samples was measured using Coulter Hmx hematology analyzer (Beckman Coulter Inc., Brea, CA, USA). Platelets were separated from plasma by further centrifugation and stored at  $-20^{\circ}\text{C}$  until analysis of 5-HT concentration. After thawing the material was dispensed in saline, sonicated and centrifuged. The concentration of 5-HT was measured in supernatant using ELISA (GenWay Biotech Inc., San Diego, CA, USA) and expressed as the amount (pmol) of 5-HT in  $10^9$  platelets.

### 2.3. Statistical analysis

The results were expressed as means  $\pm$  standard deviations (SD). The normality distribution of data was tested using Kolmogorov–Smirnov test. The platelet 5-HT concentrations and demographic data (age, MMSE) were analyzed by one-way analysis of variance (ANOVA) and Newman–Keuls test for post-hoc comparisons of means. The analysis of covariance (ANCOVA) was performed, controlling for age, gender, MMSE score and therapy with memantine. The correlation between demographic data (age, MMSE) OAS-M or PLACS scores, and platelet 5-HT concentration was determined by Pearson's product-moment correlation. The level of significance was set at  $p < 0.05$ .

## 3. Results

Demographic features of the patients are shown in Table 1. There was no significant difference between the three groups regarding age ( $F[2,46] = 0.390$ ;  $p > 0.05$ ) or MMSE scores ( $F[2,46] = 0.371$ ;  $p > 0.05$ ). The mean  $\pm$  SD OAS-M scores were 175  $\pm$  160 (range 12–577) in patients expressing aggressive behavior, while mean PLACS scores were 18  $\pm$  6 (range 13–30) in patients with IEED. The crying episodes were observed in 15 patients with IEED. One woman was expressing laughing episodes, while one man and one woman had both crying and some laughing episodes. All 14 patients with aggressive behavior were expressing verbal aggression and only two of them were not expressing other subtypes of aggressive behavior. Seven woman and 5 men were physical aggressive against others. Eight patients (3 woman and 5 men), were

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