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The role of acetylcholinesterase and butyrylcholinesterase activity in the development of delirium in acute stroke

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ABSTRACT

Aim: Our study aimed to test whether plasma acetylcholinesterase and butyrylcholinesterase enzyme activity were related to the presence and intensity of delirium in acute stroke patients.
Methods: We carried out a matched (age and gender) case-control study, in a sample of consecutive patients with an acute infarct or intracerebral haemorrhage (≤7 days). We assessed delirium using the DSM-5 criteria and the Delirium Rating Scale, and we measured plasma acetylcholinesterase and butyrylcholinesterase enzyme activity after the patient's admission in the stroke unit and before hospital discharge. Mantel-Haenszel's chi-square was used to test bivariate associations between cases (delirious patients) and controls (non-delirious patients).
Results: At admission in the stroke unit, cases and controls did not present significant differences in plasma acetylcholinesterase or butyrylcholinesterase activity. At hospital discharge (18 cases and 21 controls) patients who have had delirium at admission had higher levels of butyrylcholinesterase activity. Butyrylcholinesterase activity may secondarily increase due to the inflammatory process associated with neuronal dysfunction in delirium patients.

1. Introduction

Delirium may be detected in 10% to 48% of acute stroke patients, occurring mostly during the first two days after stroke onset [1–4]. Delirium is frequent in patients with ischaemic stroke but also patients with intracerebral haemorrhage [3–5]. Strategic stroke lesions in areas related to attention, memory, and emotional behaviour may be particularly associated with a higher risk. These include medial, anterior, or dorsomedial nucleus of the thalamus, head of the caudate nucleus (bilateral sided lesions), genu of the internal capsule, bilateral medial temporo-occipital lobes below the calcarine sulcus, right middle cerebral artery infarcts, infarct involving the left posterior cerebral artery, anterior cerebral artery territory infarcts (bilateral or right-sided lesions) [2]. Moreover, delirium is associated with a higher risk of an unfavourable outcome [5].

Elevated plasma acetylcholinesterase (AChE) enzyme activity has been consistently associated with cognitive impairment and delirium in several research settings [6]. In normal adults, erythrocyte AChE activity increases linearly with cell age (maximum value for adults =850 ± 110 nmol/min per 10^9 red cells) [7].

Many prescribed drugs such as those with anticholinergic activity can cause acute cognitive dysfunction, particularly delirium, due to their potential to lead to central cholinergic deficiency [8–11]. AChE enzyme activity is also a standard biomarker of anticholinergic burden [12,13].

Butyrylcholinesterase (BChE) is also widely distributed in the Central Nervous System (CNS) [14,15], mainly in glial cells, in the deep cortical and subcortical white matter, and endothelial cells. BChE has high expression in the hippocampus, thalamus, and amygdala [14,16] but also in, specific projections from the thalamus to the cortex. BChE neurons are implicated in working memory, attention, executive

Abbreviations: ACh, acetylcholine; AChE, acetylcholinesterase; BChE, butyrylcholinesterase; GCS, Glasgow Coma Scale; NIHSS, Neurological Institute Health Stroke Scale; IGSAA, Global Subjective Appreciation of Atrophy; INFARMED, Instituto Nacional da Fármacia e do Medicamento.

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functions, and behaviour [16].

The decrease of the enzyme AChE and the increase of the enzyme BChE, in neurons, has been associated with dementia and with memory, attention, and executive function impairments, as well as, behavioural disturbances, which could also be observed in delirious patients [14]. In Alzheimer's disease, AChE activity is reduced by 90%, probably due to the loss of presynaptic terminals, while BChE activity in the prefrontal cortex increases exponentially by 30–60% due to an increase in the number of BChE-glia [17,18]. The inhibition of BChE in Alzheimer's disease is correlated with cognitive improvement [19,20].

In series of surgical patients and of elderly patients, delirious patients were found to have higher levels of serum AChE and serum BChE activity and to have received more medications with anticholinergic activity before the development of delirium than their non-delirious counterparts [9,21,22].

In acute stroke, delirious patients presented a higher frequency of intake of anticholinergic drugs or drugs with subtle anticholinergic activity, before hospitalization or during hospitalization. This indicated that those drugs play a role in the pathogeneses of delirium [23].

The aims of our study were:

1) To analyse the association between plasma AChE and plasma BChE activity with the presence and severity of delirium in acute stroke patients, at admission in the stroke unit.
2) To compare plasma AChE and plasma BChE activity, at hospital discharge, between stroke patients with and without delirium.
3) To compare plasma AChE and plasma BChE activity in delirious patients at admission and after the delirium.

2. Methodology

2.1. Patients

The sample was selected from acute stroke patients admitted to the Stroke Unit located at the Neurology department of a University Hospital. We included consecutive patients with 1) an acute ($\leq$7 days of stroke onset) ischaemic stroke or with an intracerebral/ intraventricular haemorrhage; 2) a Glasgow Coma Scale (GCS) [24] score$\geq$5 on the day of the delirium examination. To avoid the confounding effect of aphasia, only the "eye-opening" (range 1 to 4) and the "best motor response" (range 1 to 6) items were added to obtain the GCS score.

The sample size was established by the Altman normogram [25] for a standardized difference of 0.9, a significance level of 5%, and a power of 80%. The standardized difference was calculated using the smallest difference of serum AChE activity between delirious and non-delirious hospitalized patients, as found in two previous studies [21,26]. We calculated the sample size as a minimum of 40 subjects: 20 delirious patients (cases) and 20 non-delirious patients (controls).

Cases were stroke patients presenting delirium in the 1st assessment. Controls were stroke patients not presenting delirium in the 1st assessment, and never ever had delirium until discharge. Cases and controls were matched by age (intervals of $\pm$5 years) and gender.

2.2. Evaluation of delirium in stroke patients

One trained psychologist (LC) assessed delirium daily, in the morning period. In the 1st assessment at admission, the presence and the severity of the symptoms of delirium were rated with the Delirium Rating Scale [27]. Patients were diagnosed as having delirium if they scored $\geq$ 10 [28] on Delirium Rating Scale and fulfil the DSM-5 criteria for delirium [29]. Scoring items 2, 3, and 4 may require verbal responses and a patient who is awake. Patients with moderate or severe communication disturbance, defined as a score $\geq$2 on the Neurological Institute Health Stroke Scale [30] (NIHSS) items "Best Language" or "Dysarthria", and not fully alert patients, defined as a GCS score between 5 and 9, scored zero on these items, unless perceptual disturbance, hallucinations or delusions are detected by clinical history or observation.

After the first assessment of delirium with DRS, either in cases and in controls we continued to screened delirium daily with the Confusion Assessment Method [31,32] a screening scale to assess if in cases delirium had cleared, and in controls to check if they did have delirium after being included in the control group. If controls become with delirium, they were excluded from the control group. In cases and controls, we considered the 2nd assessment of delirium as the one performed at hospital discharge. In cases, we considered the 3rd assessment of delirium, after delirium had cleared.

The neurological evaluation (TPM, PC) included the assessment of aphasia/dysarthria, hemiparesis, and neglect and was performed using the NIHSS, in the stroke unit by a stroke neurologist. The following pre-stroke predisposing conditions for delirium [28] were considered by a psychiatrist (FN): 1) dementia/cognitive decline, defined as a previous medical diagnosis of dementia or of mild cognitive impairment or a history of memory and another cognitive impairment with functional impairment in daily living activities, confirmed by a proxy, as previously reported to classify as having pre-existing cognitive decline [28]; 2) alcohol abuse, defined as 5 or more drinks daily; and 3) recurrence of stroke.

A physician/technician blinded to clinical data and results of delirium assessment measured the plasma AChE and BChE activity. Anticoagulated (heparin 10 IU/ml) blood samples were drawn after patient admission to the hospital and after breakfast time. Plasma AChE and BChE enzymes activities were evaluated using Kaplan`s and Kutty`s methods respectively both modified methods derived from Elman`s method for tissue sulfhydryl groups quantification [33–35–37]. The acethylthiocholine iodide is the specific substrate and BuChE was totally inhibited by ethopropazine present in the incubation medium. The butyrylthicholine iodide are the specific substrate of BChE, and using BW284C51 the AChE is completely inhibited. Quinidine sulphate is add to the phosphate buffer reaction medium to stop the enzymatic reaction of both esterase enzyme activity. The units of BChE are defined as the number of micromoles of thiocholine formed in 100µ formed per hour. Reference values in our centre are 160–257 for erythrocyte AChE and 500–1600 for the BChE We measured plasma AChE and BChE enzymes activity from blood sample: 1) at hospital admission (1st assessment) either for cases and controls, 2) at hospital discharge for cases and controls (2nd assessment), and 3) after delirium recovery for cases (3rd assessment)..

We assessed functional outcomes at hospital discharge with the Modified Rankin Scale [38,39]. An unfavourable outcome was defined as a modified Rankin grade $\geq$3 (death or dependency).

A neurologist (JMF), blinded to delirium assessment, defined stroke type (intracerebral haemorrhage/intraventricular haemorrhage and cerebral infarct) and location [40] based on clinical data and acute CT/MR or a repeated CT/MR, if the acute CT/MR had not shown a lesion. The lesion was grouped as 1) brainstem/cerebellum, hemispherical or both, and 2) left or right hemispherical or both, 3) hemispherical cortical or subcortical, 4) hemispherical cortical anterior or posterior.

The same neurologist (JMF) also scored the presence of a) cerebral atrophy [41], considering the Index of Global Subjective Appreciation of Atrophy (IGSAA) [42]; The IGSAA was measured through a global score of 0 (no atrophy), 1 (moderate atrophy), 2 (mean atrophy) or 3 (severe atrophy); b) leukoaraiosis [43]; and c) hydrocephalus. To quantify hydrocephalus, we measured the ventricular size using the Bicaudate Index [41,44]. We defined hydrocephalus when the ventricular size was too wide for age, exceeding the 95th percentile for age [42,44,45] as previously described [3].

The psychologist retrieved two sets of data about medications which were categorized as 1) before hospital admission/stroke, as reported in the admission note and case history, and 2) from hospital admission to the day of the assessment of delirium (within 7 days post-stroke maximum). The neurologist (JMF) defined if the medication was an

anticholinergic or not-anticholinergic based on a list of all medications with anticholinergic activity available in Portugal as previously reported [23]. This information was used to calculate measures of exposure to anticholinergic drugs that included: 1. Intake of any anticholinergic medication before admission; 2. The number of anticholinergic drugs taken during hospitalization; 3. The number of non-anticholinergic drugs taken during hospitalization.

The Ethics Committee of the Faculty of Medicine, University of Lisbon, approved the study.

2.3. Statistical analysis

Data were analysed using IBM Statistical Package for Social Sciences, version 24. Chi-square ($\chi 2$), odds ratios (OR), and 95% confidence interval (95%CI), obtained through Mantel-Haenszel estimate analysis, and the Mann-Whitney test (U) were used to test bivariate associations between cases (delirious patients) and controls (non-delirious patients). Chi-square with continuity correction was performed in analysis presenting zero subjects in one cell using the Mantel-Haenszel estimate analysis. Pearson (Pr) or Spearman (Sr) correlations were used in case of continuous variables when compared with other continuous variables or with other dichotomized variables.

The following variables were compared between cases and controls: age (<65 or ≥65 years), gender, educational level (≤9 or >9 years of school), predisposing and precipitating conditions for delirium (previous dementia/cognitive decline, alcohol abuse, and stroke), stroke type (CI, ICH), stroke location (brainstem/cerebellum or hemispherical/both; left or right hemispherical or both; hemispherical cortical or subcortical; hemispherical cortical anterior or posterior), cortical atrophy, leukoaraiosis, hydrocephalus, intake of anticholinergic medication previous to stroke, intake of anticholinergic medication and non-anticholinergic medication during hospitalization, plasma AChE, and BChE enzymes activity (higher or above the reference values), and the modified Rankin grade at hospital discharge (0–2 or ≥3).

We consider a p-value of 0.05 as statistically significant.

3. Results

3.1. Description of patients accordingly to the delirium rating scale (DRS)

We included 48 patients: 24 delirious (Cases) and 24 non-delirious (controls) patients, aged between 26 and 86 years old and with a range of 0–16 years of school (Table 1). DRS score was not correlated with age or with educational level (Table 2).

Nine cases had a GCS score <10 ($\chi 2$ continuity correction = 8.75, $p < .01$) compared with none of the controls. Twelve cases and 5 controls had a NIHSS scoring 2–3 ($\chi 2$ continuity correction = 3.73, $p < .05$). Comparing the 24 cases and controls the former were more frequently haemorrhagic stroke patients than the latter (Table 1).

Stroke type and IGSAA were measured in about 38 patients. In the remaining 10 patients it was not possible measure IGSAA due to mass effect and/or hydrocephalus in the remaining 10 patients. Therefore, we assessed the following: 1) IGSAA ($n = 36$; mean = 1.360; SD = 0.639, range: 0–3); 2) Leukoaraiosis ($n = 38$; Frontal: mean = 1.16, SD = 1.128; Temporal: mean = 0.13, SD = 0.529; Parieto-occipital: mean = 0.92, SD = 1.05; Brainstem/Cerebellum: mean = 0.08, SD = 0.487; Basal ganglia lesions: mean = 0.16, SD = 0.437). IGSAA was correlated with age ($r = 0.48$, $p \leq .01$) but not with DRS scores. Only frontal white matter changes were correlated with DRS scores ($r = 0.33$, $p \leq .05$).

Concerning the anticholinergic medication (Table 1), cases took more often anticholinergic medication, during hospitalization (Mantel-Haenszel = 8.29, $p < .01$), than controls. Regarding non-anticholinergic medication, and specifically rt-PA, there were no statistical differences between cases and controls. Intake of anticholinergic or non-anticholinergic medication before the stroke was not associated with delirium.

Table 1
Characterization of the patients, clinical profile, and values of AChE and BChE enzyme activity: 48 patients included in the study.

	Cases ($n = 24$)	Controls ($n = 24$)	Mantel-Haenszel statistic
Gender (male/female)	14/10	14/10	n.s.
Age (<65/≥65)	12/12 (mean±SD: 63.3 ± 13.1)	13/11 (mean±SD: 63.5 ± 15.3)	n.s.(n.s.*)
Years of school (≤9/>9)	16/2 (mean±SD: 5.1 ± 4.4)	18/4 (mean±SD: 5.6 ± 4.5)	n.s.(n.s.*)
TAC (with/without)	21/3	24/0	n.s.
MR (with/without)	6/18	5/19	n.s.
Infarct/Haemorrhage	9 (2[ℵ])/**15**	**15**/9	***p*≤.05**[∂]
Hemispheric/Brainstem-Cerebellum	22/2	22/2	n.s.
Left/Right	7/15	12/9	n.s.
Subcortical/Cortical/Cortico-Subcortical	12/9/1	11/8/2	n.s.[∂]
Cortical anterior/posterior	2/7	3/7	n.s.
ACH Medication previous Hospitalization (No/Yes)	12/12	10/14	n.s.
ACH Medication during Hospitalization (No/Yes)	8/**16**	19/5	***p*<.01; OR = 7.6, 95%CI = 2.07–27.9**
Non-ACH Medication during Hospitalization (No/Yes)	1/23	4/20	n.s.
rtPA (No/Yes)	22/2	21/3	n.s.
Previous Dementia (No/Yes)	17/1	21/2	n.s.
Previous Alcohol Abuse (No/Yes)	16/6	22/2	n.s.
Recurrence of stroke (No/Yes)	14/9	20/4	n.s.
Hemiparesis (No/Yes)	5/19	5/19	n.s.
Neglect (No/Yes)	18/6	21/3	n.s.
1st Plasma AChE (mean±SD)	488.3 ± 68.3	487.5 ± 30.4	n.s.*
1st Erythrocyte AChE (160–257/>257)	2/22(mean ± SD: 297.8 ± 32.1)	1/23(mean ± SD: 298.3 ± 26.7)	n.s.(n.s.*)
1st Plasma BChE (500–1600/>1600)	4/20 (mean±SD: 1919.5 ± 316.9)	1/23 (mean±SD: 1963.9 ± 236)	n.s.(n.s.*)

The comparison of frequencies was performed by Mantel-Haenszel estimate analysis; ***:** Mann-Whitney test for the group ($N = 48$ patients; mean±SD); **∂:** $\chi 2$ continuity correction; **n.s.:** p-value without significance; **ℵ:** Number of infarcts with haemorrhagic transformation.

3.2. The relation between plasma AChE and BChE activity with delirium in the 48 acute stroke patients (Table 1)

Comparing the 24 cases with the 24 controls, there were no differences concerning the 1st measure of AChE and BChE (Table 1).

Delirium Rating Scale scores were not correlated with the values obtained at the 1st measure of AChE and BChE (Table 2).

Considering the AChE and BChE levels, there were no mean differences (*U test:* $p > .05$) between patients who took ACH medication previous to hospitalization comparing with those who did not take ACH medication previously. This means that previous intake of ACH medication did not have an impact on the AChE and BChE levels in the blood samples of the patients.

Table 2
Correlations amongst Delirium Rating Scale (DRS), Confusion Assessment Method (CAM) and AChE and BChE measures, in the 1st and 2nd assessments in up to 48 patients.

	Age	Educational Level	DRS (1st assessment)	CAM (2nd assessment)
Educational Level (n)	*r*=−0.22; 0.14 (48)			
MMSE (n)	*r*=−0.18; 0.39 (24)	*r* = 0.23; 0.29 (24)		
DRS (1st assessment) (n)	*r* = 0.06; 0.68 (48)	*r*=−0.17; 0.24 (48)		
CAM (2nd assessment) (n)	*r* = 0.04; 0.84 (36)	*r*=−0.02; 0.93 (36)	***r* = 0.35; 0.04** (36)	
1st Plasma AChE (n)			*r*=−0.17; 0.26 (48)	
1st Erythrocyte AChE (n)			*r* = 0.03; 0.83 (48)	
1st Plasma BChE (n)			*r* = 0.01; 0.91 (48)	
2nd Plasma AChE (n)				*r*=−0.20; 0.23 (36)
2nd Erythrocyte AChE (n)				*r* = 0.01; 0.95 (36)
2nd Plasma BChE (n)				*r* = 0.20; 0.23 (36)

Results are presented as "r; p-value (number of patients included in the analysis)".
r: Pearson correlation.

3.3. Differences in the plasma AChE and BChE activity at hospital discharge (2nd assessment) between cases and controls

After delirium, we were able to obtain blood samples from 18 cases: 2 cases died before hospital discharge and in 4 cases blood samples coagulated. We also obtained blood samples from 21 controls: in 3 controls blood samples coagulated. Of these 39 stroke patients from whom it was possible to obtain the 2nd blood sample, plasma AChE and erythrocyte AChE levels were not higher in cases comparing with controls (e-Table 1). However, plasma BChE levels were higher in cases comparing with controls (e-Table 1).

Amongst cases and controls, there was no statistical relation between ACH or non-ACH medication on the 2nd AChE and BChE measures (*U test:* $p > .05$), meaning that there were no secondary effects of ACH or non-ACH medication on the 2nd AChE and BChE values.

4. Discussion

We included 24 delirious (cases) and 24 non-delirious (controls) acute stroke patients to test whether plasma AChE or BChE activity was related to the presence and intensity of delirium in acute stroke. The most significant result was that plasma BChE levels at hospital discharge were higher in cases when compared with controls.

An increase in BChE levels is associated with neurons malfunctioning and low BChE activity may be a non-specific risk factor for mortality in the elderly people residing in the community [46]. At hospital discharge, patients who presented delirium at hospital admission had higher levels of BChE. This could mean that, even after symptoms disappeared, the biological markers of malfunctioning related to the inflammatory activity are still present. Furthermore, these higher levels may represent a future risk of cognitive dysfunction and vascular disease, which could be the object of further studies.

The relationship between anticholinergic drugs and delirium is established in previous literature and in this study we identified a relationship between BChE and delirium. Thus, the intake of anticholinergic medication may mediate the association between increased BChE levels and delirium. Plaschke et al. [47] reported that AChE and enzyme activity tended to increase in blood after the cessation of anticholinergic medication but less is known about BChE enzyme activity.

In a review performed by Carnahan et al. [6], they found that severe delirious patients or inpatients had elevated plasma AChE activity levels, reflecting central AChE activity. In a study of Wester et al. [48], 21 patients with acute brain infarction, 8 with TIA, and 20 controls were assessed 1–5 days after the beginning of symptoms. Increased activity of AChE and BChE in lumbar cerebrospinal fluid was found in patients with acute brain infarction when compared to controls. Nevertheless, in intensive care unit inpatients, serum AChE activity may not be associated with delirium [47]. Our patients were accessed, for the first time, in a Stroke Unit, and neither plasma AChE activity nor plasma BChE activity was associated with delirium, corroborating previous results.

Some limitations or possible bias (modifiers/confounders) of this study must be taken into account: 1) timing of the collection of blood samples and fluctuations in plasma drug levels which can contribute to plasma AChE and BChE activity variability [21]; 2) In normal adults, erythrocyte AChE activity is a marker of erythrocyte membrane integrity [37,49], the type of stroke (haemorrhagic or ischaemic) may induce different disturbances on the erythrocyte membrane leading to different levels of erythrocyte AChE in blood samples. 3) the presence of anticholinergic substances, before the stroke, that may have increased the levels of plasma AChE activity in acute illness [50]; 4) Memory bias, i.e., possibly unreliable recall of the patients and proxies concerning the intake of anticholinergic or non-anticholinergic medications previously to stroke, is a common limitation of the studies relating intake of medications and delirium [23]. 5) Another important limitation is the fact that delirium assessments were made in the mornings when patients with delirium are generally more orientated and, therefore, lower rates of delirium may be found at this time of the day. In consequence some delirium cases could be missed. 6) Finally, higher levels of BChE are an inflammatory biomarker of any vascular dysfunction or even of cognitive impairment, previous to stroke [51,52].

5. Conclusions

At hospital discharge after acute stroke, patients with a diagnosis of delirium had higher plasma BChE levels when compared with controls which may be a reflection of the continuation of a malfunction of the neurons resulting from inflammatory processes. Our results showed that plasma BChE is an important measure to consider when evaluating patients with delirium. Future studies should focus on unveiling the role of BChE in delirium.

Declaration of Competing Interest

Authors declare no conflicts of interest.

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Supplementary materials

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.cccb.2021.100017.

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