



The Association of Blood Cholinergic Esterases and Other Risk Factors on the Development of Postoperative Delirium

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Received date: November 29, 2017; Accepted date: December 04, 2017; Published date: December 07, 2017

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Abstract

Study Objective: Delirium is an important complication after surgical intervention. One of the potential risk factors for cognitive disorders is deterioration in cholinergic neurotransmission including anticholinergic medications. We hypothesize that changes in blood cholinesterases (CHE) are associated with postoperative delirium.

Design: Prospective cohort study.

Setting: Postoperative delirium was assessed at least once daily in all included patients (n=103) preoperatively and on the first and third postoperative day during their stay on the intensive care unit (ICU) or in hospital.

Patients: undergoing a surgery on the head were included.

Interventions and Measurements: Postoperative delirium was assessed using the Intensive Care Delirium Screening Checklist (ICDSC). Blood samples were taken parallel to delirium testing and analyzed for serum anticholinergic activity (SAA) using radioactive competitive assay; acetyl- and butyrylcholinesterase activities (ACHE, BuCHE) were measured spectrophotometrically. Furthermore, patients' characteristics and medication were recorded. Logistic regression analysis was used to evaluate potential predictors of postoperative delirium.

Main Results: Postoperative delirium was identified in 32% of patients and was associated with significant longer duration of surgery, prolonged artificial ventilation, and longer stays on the ICU and in hospital. In contrast to ACHE and SAA, a significantly reduced BuCHE (mean of n=3 time points \pm SD, U/l) was associated with delirious patients (2918.9 ± 645) compared to non-delirious (3484.0 ± 928.4). Reduction in BuCHE was associated with a higher number of administered drugs with greater anticholinergic potency (≥ 1 , classified according to the Anticholinergic Drug Scale).

Conclusion: Patients with reduced pre- or postoperative BuCHE activity are at higher risk for the development of postoperative delirium, this may be because of polypharmacy with anticholinergic drugs.

Highlights:

- Postoperative delirium was investigated in head and neck cancer patients.
- Delirium was associated with reduced pre- and postoperative BuCHE activity.
- Reduced BuCHE activity seems to be associated with polypharmacy of anticholinergic drugs.

Keywords Acetylcholinesterase; Butyrylcholinesterase; Cancer patients; Postoperative delirium; Risk Factors

Introduction

Postoperative delirium affects about 30-40% of the general surgical population, however, postoperative delirium rates vary widely, ranging from 9 to 87% depending on the age of patients and the type of surgery [1]. Delirium is a neuropsychiatric syndrome clinically characterized by sudden onset and fluctuating course as well as disturbances of

consciousness and different domains of cognition including orientation, attention, concentration, memory, language, perception [2]. Postoperative delirium has been associated with prolonged stay on intensive care unit (ICU) or in hospital, increased mortality and postoperative complications, functional decline, and increased cost [3-5]. Despite the high prevalence and negative sequelae of postoperative delirium, its detailed pathophysiology is unknown and seems to be multifactorial [6]. However, a failure in cholinergic neurotransmission [7] is considered to be one of the central mechanisms underlying the development of delirium.

It is very laborious to detect cholinergic changes in neurotransmission directly and this is also associated with significant limitations in patients. Thus, plasma acetylcholine (ACH) is extremely labile and difficult to use for clinical measurements [8]. Therefore, measuring serum anticholinergic activity (SAA) is employed as one alternative technique for evaluating cholinergic transmission [9,10]. Another possibility to demonstrate changes in cholinergic metabolism is to detect cholinergic esterase (CHE) activity, such as acetylcholinesterase (E.C. 3.1.1.7, ACHE) and butyrylcholinesterase (E.C. 3.1.1.8, BuCHE). Both enzymes are also expressed in the blood and are mainly responsible for hydrolyzing ACH and could be a peripheral marker for changes in cholinergic status.

One previous study examining elective hip-replacement surgery group with pronounced age suggested that there is a link between postoperative delirium and reduced CHE [11]. There was stated that further studies should evaluate whether these changes can be replicated in a more heterogeneous patients' sample in different clinical settings. Thus, the aim of the present study was to investigate whether ACHE and BuCHE are altered pre- and postoperatively and their relation to postoperative delirium to confirm or to decline the results of previous research [11] in a special cohort of patients undergoing a surgery on the head. Further, the CHE activities should be compared to changes of other likely risk factors relating to the cholinergic neurotransmission such as SAA and anticholinergic medication. To compare our findings with an already known risk factor for delirium not referring to the cholinergic system, the C-reactive protein (CRP) [12] was additionally investigated.

Material and Methods

Design

Study design: The present study was performed as a prospective cohort study on patients undergoing elective surgery on the head or neck and postoperative monitoring on an intensive or intermediate care unit (IMC) at University Hospital Heidelberg.

Study population: Patients were recruited between November 2013 and September 2014 at the University of Heidelberg (Germany), after giving their written informed consent. This clinical study was approved by the appropriate local Ethics Committee and Institutional Review board of the University of Heidelberg (S-452/2013) and was performed in accordance with the ethical standards of the actual revision of the Declaration of Helsinki. Study was registered under <http://www.clinicaltrials.gov>.

In addition to our previous studies, we hereby wanted to investigate a special subpopulation of our patients. Therefore, patients ≥ 18 years admitted for elective otorhinolaryngeal, oral-maxillo facial or neurosurgery and planned postoperative stay on the ICU or IMC were recruited for this study (n=120). Patients admitted with psychiatric problems were not included in this study. We also excluded patients whose planned surgical procedures were canceled (n=7), where postoperative intensive care observation was not necessary (n=8), who did not receive a postoperative blood withdrawal (n=1) as well as non-German- or non-English-speaking people (n=1). In all, 103 patients were included in this study.

Patients' characteristics

Patient characteristics such as age, gender, body weight, body mass index, main admission diagnosis, ASA-classification were documented

before surgery. Only patients with normal Mini Mental Status Examination performance (>26 points) were included in the present study. Four out of 103 patients experienced an earlier delirium in their medical history. From 103 patients, n=56 had chronic heart and / or vascular and n=27 pulmonary diseases. In a structured interview, patients were asked about their smoking habits and alcohol consumption. Furthermore, number and kind of medications taken for more than 24h with potential and known anticholinergic properties according to Carnahan et al. [13] were documented. Furthermore, duration of surgery, duration of intensive care unit stay, and length of hospital stay were determined.

Measurements

Anticholinergic drug scale and delirium assessment

Anticholinergic properties of medications can produce a range of adverse effects to people. The Anticholinergic Drug Scale (ADS) [13] is one of many scales in use to quantify anticholinergic burden from medications. Ratings on the ADS are defined as follows: level 0=no known anticholinergic properties; level 1=potentially anticholinergic as evidenced by receptor binding studies; level 2: anticholinergic adverse events sometimes noted, usually as excessive doses; and level 3: markedly anticholinergic. Drugs related level 1,2, or 3 are listed in the appendix of the paper of Carnahan et al. [13]. ADS total scores were determined by summation of the ratings of all drugs received by a subject.

Subjects' chronic and as-needed medications received on the day before blood draw or on the day of blood draw (blood was drawn at about 10 a.m.) were listed for each patient and categorized in accordance to ADS.

Delirium was assessed preoperatively, on the first postoperative day on the ICU and on the third postoperative day on the general or intensive care ward using the Intensive Care Delirium Screening Checklist (ICDSC). The ICDSC was assessed during this study by the same investigator (SS) after training with an expert (psychiatrist) using DSM-IV criteria. In 2001, Bergeron et al. [14] created the ICDSC. The ICDSC includes eight items based on the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and features of delirium including: altered level of consciousness; inattention; disorientation; hallucination-delusion psychosis; psychomotor agitation or retardation; inappropriate speech or mood; sleep/wake cycle disturbances; and symptom fluctuation according to a total score system from 0 to 8 points (a patient with more than 4 points is defined as delirium-positive). The patients were assessed with the ICDSC every morning between 8 and 10 a.m. According to ICDSC, a patient was defined as delirium-positive if their test score was higher than 4 points. The score data included information from the last 24 h (three previous shifts of 8 h) collected from the nurses' evaluation protocols.

Blood plasma analysis

For CHE analysis, a blood sample (1 ml blood, EDTA monovette®) was drawn to analyze acetylcholinesterase (ACHE) and butyrylcholinesterase (BuCHE) activity.

Blood was immediately stored at -20°C until analysis. In preliminary experiments we ensured the stability of enzyme activity using this experimental procedure.

ACHE and BuCHE were measured spectrophotometrically by applying the method of Ellman et al. [15] with some modifications. Here, 1µl of blood was mixed with 40 µl of 0.001% heparin and 0.1% H₂O₂ for hemolysis and subsequently mixed with 725 µl of 200 mM potassium phosphate buffer, pH 7.0, containing 50mM NaCl and 1mM EDTA. Then, 25 µl of 10mM DTNB (5,5'-Dithiobis (2-nitrobenzoic acid) were added. After 3 min of preincubation at room temperature 6.25 µl of substrate solution were added (86 mM acetylthiocholine chloride to measure ACHE activity or 10mM butyrylthiocholine chloride for BuCHE activity). Formation of free thiocholine and the resulting release of 5-thio-2-nitrobenzoate from DTNB was assayed at 405 nm for 4 min. Specific enzyme activity was expressed as U/g Hb for ACHE and U/l for BuCHE.

Protein was measured according to Lowry et al. [16]. Serum bovine albumin was used as standard.

C-reactive protein (CRP) value was determined as a marker of the acute phase response and was taken from the routine laboratory analysis.

For SAA analysis, the blood samples (1 ml) were taken in EDTA syringes and were centrifuged at 7,000 rpm for 10 min. Thereafter, the supernatant was taken and stored for at 80°C until final analysis.

An investigator blinded to all clinical data assessed the anticholinergic activities by a competitive radioreceptor binding assay as described by Tune and Coyle [9]. Briefly, homogenized cerebral cortex from untreated adult Wistar rats was used as the source of muscarinic receptors (mAChR). Anticholinergic agents in patients' serum competitively inhibit binding of tritiated L-quinuclidinyl(phenyl-4-3H)-benzilate (3H-QNB), which binds with high and specific affinity to all five mAChR subtypes obtained from a rat homogenate cortex. The displacement of 3H-QNB is used to quantify anticholinergic activity in plasma in comparison to a standard atropine curve. The results are reported in picomoles per milliliter (pmol/ml) of atropine equivalents as defined by Tune and Coyle [9].

Statistical analysis

Since, to our knowledge, only one study [11] is available in the literature concerning one of our primary objective, we could not build on previous research to calculate the exact required sample size for testing the association of ACHE / BuCHE and postoperative delirium with a given statistical power and type-1 error rate in this explorative study. So we orientated the number of cases in our investigation (n=100) to that clinical study.

All data were tested for normality before applying parametric statistics. Descriptive statistics were calculated to characterize the study population in terms of age, mean body weight, body mass index, gender, main diagnosis for planned surgery, ASA-classification, duration of surgery, duration of ICU stay, length of hospital stay and kind and number of medications.

T-tests (2-sided), Wilcoxon and chi-squared tests were used where appropriate to determine whether baseline features and blood data differed between patients with and without delirium. Associations between parameters were analyzed using correlation analysis according to Spearman or Pearson.

Logistic regression analysis was done for estimating the relationships between delirium and CHE activities, age, and duration of surgery. Above mentioned variables which showed a significant difference (p<0.1) between patients with and without delirium in

Wilcoxon, t-test or chi-squared tests were included in a mutually adjusted logistic regression model.

All statistical tests were two-sided and p values p<0.05 were considered to be statistically significant. However, since no adjustment for multiplicity was performed, all p values are to be interpreted only descriptively. The statistical analyses were generally performed using SPSS 19.0 (IBM SPSS Inc., USA). Risk factors were analyzed using SAS 9.1 (SAS Institute, Cary, NC, USA).

Results

Preoperatively delirium was detected in none of patients. Postoperative delirium was found in 33 of 103 patients (32%). Mean age of patients was 59.5 ± 15.1 (mean ± SD) years; 55 of patients were male and 48 females. Mean body weight was 73.9 ± 16.3 kg, body mass index 25.7 ± 5.2. In relation to ASA classification, n=7 patients had ASA 1 and n=1 patient ASA 4, n=38 and n=57 patients were characterized as ASA 3 or ASA 4, respectively. Mean duration of surgery was 7.4 ± 3.1 hours; mean duration of stay on the intensive and/or intermediate care unit was 5.2 ± 5.2 days, and mean duration in hospital was 21.2 ± 12.8 days. One patient died during its hospital stay.

Table 1 represents the primary diagnoses of included patients. Many patients (n=83 out of 103) had cancer in the head.

	Frequency	Percentage
squamous cell carcinoma	68	66
other malignant tumors	9	8.7
benign tumors	6	5.8
other mouth-jaw-facial diseases	15	14.6
other ear, nose and throat diseases	4	3.9
diseases of the spine	1	1
total	103	100

Table 1: Primary diagnoses of patients.

Table 2 represents the patients' specific characteristics relating to postoperative delirium.

Delirious patients were characterized by a significant prolonged duration of surgery (1.3-fold), resulting in prolonged postoperative artificial ventilation (2.5-fold), and prolonged stay on ICU (2.2-fold) and in hospital (1.6-fold). No significant differences between delirious and non-delirious patients were observed in patients' age, gender, body weight, body mass index and ASA classification. Furthermore, no significant differences between the groups were obtained relating alcohol and nicotine consumption (data not shown).

Table 3 shows blood analysis data relating to postoperative delirium. Significant differences between delirious and non-delirious patients were detected in CRP values and in pre- and postoperative BuCHE activities. Furthermore, Figure 1a-1c illustrates blood changes in cholinergic esterases and SAA between delirious and non-delirious patients. Whereas BuCHE levels were significantly lower in delirious patients, no significant changes were obtained in ACHE activities and in SAA levels.

	Delirious n= 33	Non-delirious n= 70	p-value
Age [years]	63.6 ± 10.1	57.7 ± 16.7	0.064
Gender (male : female)	17:16	38:32:00	0.793
Body weight [kg]	72.5 ± 14.8	74.6 ± 17.2	0.558
Body mass index	25.6 ± 4.2	25.7 ± 5.6	0.934
ASA 1-2	12 /33 (36%)	33 /70 (47%)	0.303
ASA 3-4	21 / 33 (64%)	37 / 70 (53%)	0.301
Stay on intensive care unit [days]	8.3 ± 6.7	3.7 ± 3.6	<0.001
Stay in hospital [days]	27.9 ± 12.3	17.9 ± 11.8	<0.001
Duration of surgery [hours]	9.0 ± 2.5	6.7 ± 3.1	<0.001
Time of postoperative artificial ventilation [hours]	37.6 ± 32.0	15.0 ± 14.5	<0.001

Values are expressed as mean ± standard deviation or as numbers with percentage (n=103). Significant differences were expressed at p<0.05 (t-test and Chi² test).

Table 2: Patients' specific characteristics relating to delirium

	Delirious n=33	Non-delirious n=70	p-value
ACHE preoperative [U/g Hb]	50.9 ± 12.4	48.6 ± 14.3	0.486
ACHE postoperative [U/g Hb]	51.5 ± 9.9	50.4 ± 10.7	0.549
BuCHE preoperative [U/l]	3314.1 ± 644.7	3888.7 ± 940.3*	0.01
BuCHE postoperative [U/l]	2523.9 ± 645.6	3079.4 ± 916.5*	0.007
SAA preoperative [pmol/ml]	6.1 ± 4.1	8.1 ± 5.2	0.228
SAA postoperative [pmol/ml]	5.2 ± 3.6	7.1 ± 3.3	0.129
CRP [mg/l]	117.5 ± 63.9	73.0 ± 62.6*	<0.001

Values are expressed as mean ± standard deviation. Significant differences were expressed as *: at p<0.05 (Wilcoxon test, two-sided). Because no significant differences between the postoperative values (days first and third) were obtained, the mean of the two-postoperative data was inserted in this table.

SAA: serum anticholinergic activity. ACHE: acetylcholinesterase, BuCHE: butyrylcholinesterase. CRP: C-reactive protein. Hb: hemoglobin. U: units are expressed as mmol substrate hydrolyzed per hour per milligram of protein at 25°C.

Table 3: Blood analysis.

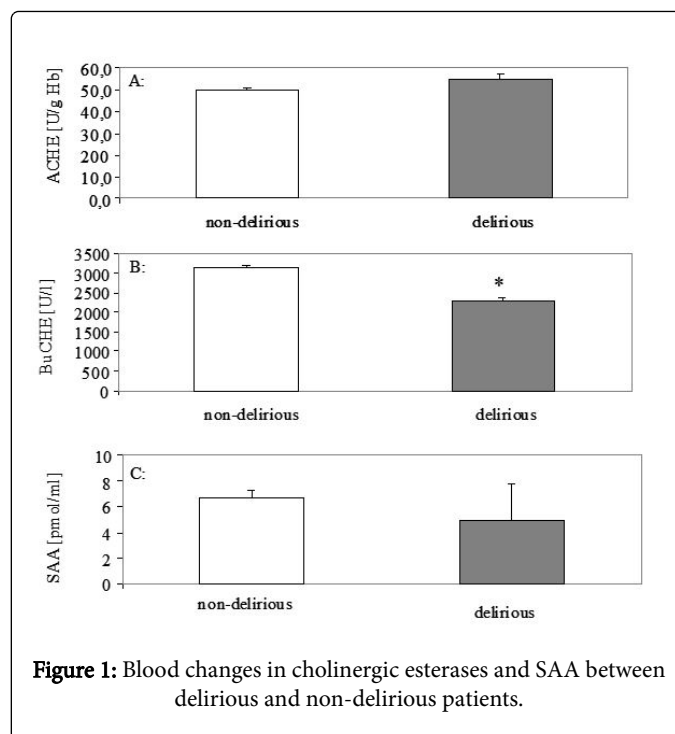


Figure 1: Blood changes in cholinergic esterases and SAA between delirious and non-delirious patients.

Figure 1 presents differences between delirious (n=33) and non-delirious patients (n=70) as mean ± SEM. A: ACHE: acetylcholinesterase. B: BuCHE: butyrylcholinesterase. C: SAA: serum anticholinergic activity.

Significant differences were expressed as *: at p<0.001 (t-test, two-sided).

Table 4 demonstrates the results of logistic regression analysis as to whether patient-specific characteristics or CHE may play a role as a risk factor for postoperative delirium. As you can see, reduced preoperative BuCHE activity is a significant risk factor for the development of postoperative delirium. Otherwise, the duration of surgery is a further important risk factor for postoperative delirium.

Parameter	Odds ratio	95% Wald	CI Limits	p
BuCHE preoperative	0.999	0.998	1	0.0084*
BuCHE postoperative	1	0.999	1.001	0.4309
Age	1.026	0.96	1.065	0.19
Duration of surgery	1.29	1.09	1.52	0.0029*

N=103. Significant differences were expressed as *: at p<0.05.

Table 4 presents the risk factor analysis using Wald statistics including p-values, the adjusted odds ratio with the 95% confidence interval (CI) for the major pre- and postoperative risk factors. The Wald test is a parametric statistical test. Whenever a relationship between or within data items can be expressed as a statistical model with parameters to be estimated from a sample, the Wald test can be used to test the true value of the parameter based on the sample estimate. A Wald test can be used in a great variety of different models including models for dichotomous variables and models for continuous variables.

Table 4: Analysis of risk factors.

Delirious patients took medication with a significant (Chi²=0.03) greater (≥ 1) anticholinergic potency compared to non-delirious. In

detail, the following medication with relatively low anticholinergic activity was administered in patients preoperatively: e.g. pantoprazole, bisoprolol, simvastatin, enalapril.

In postoperative state, however, medication with higher anticholinergic activity was administered, such as propofol and remifentanyl if the patients were artificial ventilated postoperatively, or piritramide, metamizole, and dimenhydrinate. No significant correlation ($p=0.394$) between number and kind (anticholinergic) of medication and SAA ($r=-0.112$) was detected, however, a small but significant ($p<0.001$) negative correlation was shown for BuCHE ($r=-0.240$), and for ACHE ($r=0.199$, $p=0.001$).

A stronger negative linear correlation was obtained between CRP and BuCHE ($r=-0.456$, $p<0.001$, Figure 2).

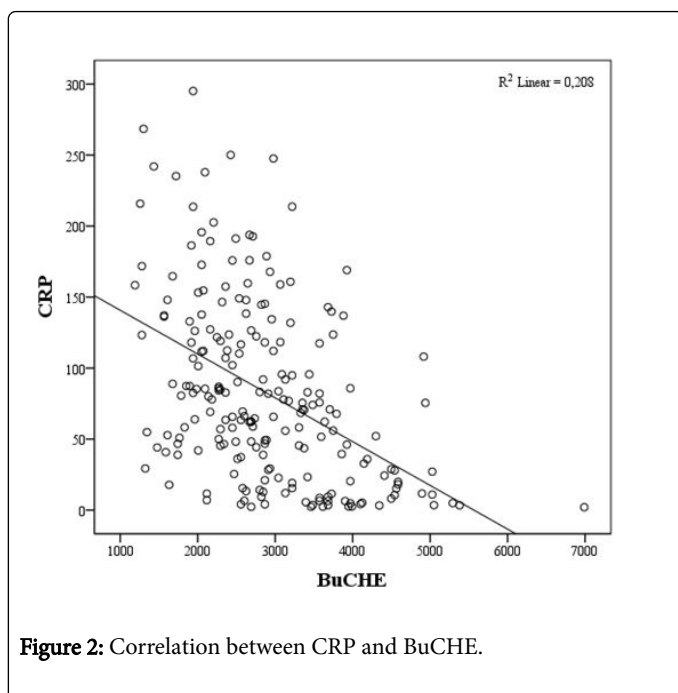


Figure 2: Correlation between CRP and BuCHE.

Discussion

Delirium incidence

In the present study, postoperative delirium was diagnosed in 32% of the patients included. The percentage of 32% agrees with our previous studies on postoperative delirium after cardiac surgery [17] or after visceral surgery [4] and with a current meta-analysis on critical ill patients [18]. In the present study, we mostly included patients with cancer in the head area because we know that delirium is also a complex but frequent neurocognitive complication in patients with cancer with a prevalence of 13 to 88% [19]. For delirium detection, we used the German version of the Intensive Care Delirium Screening Checklist (ICDSC) [14,20]. The ICDSC is a reliable instrument to detect postoperative delirium with a high sensitivity and specificity and can be used by both nursing staff and physicians. We detected delirium in about one third of the included patients. Differences in delirium prevalence compared to other studies might be explained by the facts that i) various delirium scales were used, and ii) patients differing in age, gender, and kind of surgery / cancer were investigated.

Risk factors

There are multiple risk factors for developing postoperative delirium [21-23]. Risk factors can be separated into patient-specific and operation-specific risk factors. In the literature [21,22], older patients had a greater risk for postoperative delirium, but this effect just failed statistical significance in our study ($p=0.06$). Relating to operation-specific factors, the duration of surgery was a predictor of postoperative delirium in our study. If duration of surgery alone is a risk factor for postoperative complications is controversial discussed [24,25] and seems to depend i) on the type of surgery, ii) on the kind and duration of anesthesia and other medication given during surgical procedure, and iii) on the general condition of the patients.

It has long been recognized that failure in cholinergic neurotransmission is involved in the pathophysiology of delirium along with patients'-specific endogenous factors [6], also in the light of evidence that cognitive impairment can be induced by anticholinergic agents [26,27]. Thus, several studies showed that an increased burden of serum anticholinergic activity (SAA) is associated with delirium [9,28]. In contrast, the present investigation and our own previous studies on SAA did not confirm the role of SAA as a biomarker for postoperative delirium [4] and long-term postoperative cognitive dysfunction [29]. This raised the question if there might be another blood marker characterizing cholinergic function. Therefore, the aim of this present study was to focus on the role of cholinergic esterases (CHE) such as acetylcholinesterase (ACHE) and butyrylcholinesterase (BuCHE) in comparison to other known blood markers of delirium (including SAA and CRP).

We showed in the present study that postoperative delirium was associated with increased CRP and reduced BuCHE.

As is well known, acetylcholine (ACH) is a crucial neurotransmitter in the central and peripheral nervous system [30], terminating its activity because of degradation by CHE [31]. The traditional view of ACHE acting solely as neurotransmitter has been revised based on recently published findings, including the role of ACH in the regulation of stress and inflammation (cholinergic anti-inflammatory pathway) [32]. If CHE are discussed as biomarkers for parasympathetic dysfunction and inflammation-related diseases [33] they could also be associated with cognitive dysfunction [34].

In contrast to Cerejeira et al. [11] we did not confirm in the present study the role of ACHE as a marker for postoperative delirium. One possible reason for this discrepancy might be a different methodological approach. In accordance to Ellman [15] we determine the activity of ACHE in blood, and not in plasma, because most of peripheral ACHE is found on red blood cells. Further, whether impairment of peripheral ACHE is reflecting cerebral changes and whether reduced ACHE activities are the reason or the response to changes in ACH is not clear in detail and should be analyzed in further studies.

Previous work investigating the activity of different plasma CHE in man has shown that activity is reduced in frail institutionalized older people compared to independently living older subjects [35], but activity is well maintained in healthy subjects [36]. Furthermore, reduced CHE activities have also been found in acutely ill older patients following hip fracture [37], and in older patients with pneumonia, where reduced CHE activities correlate with poor outcome [36]. In the present study on patients with a mean age of about 60 years, reduced BuCHE activity, however, was not associated with preoperatively determined ASA classification.

For many years, the main interest in BuChE (also known as pseudocholinesterase or nonspecific cholinesterase) was in the field of clinical anesthesia, following the introduction of the muscle relaxant succinylcholine for use during surgery [38-40]. It was discovered that BuChE was the principal enzyme that terminates the action of succinylcholine, and it was subsequently established that patients who experienced prolonged apnea had unusual genetic variants of BuChE [41,42] with reduced catalytic activity. In addition to succinylcholine, BuChE also metabolizes other anesthetic agents, e.g. mivacurium or other muscle relaxants. Furthermore, dietary factors might be also important in relation to the individual variation in the BuChE-mediated metabolism [43]. However, recent investigations suggest that BuChE could have more specific functions than previously recognized. For example, BuChE is expressed in distinct populations of neurons [44], is a co-regulator of cholinergic neurotransmission [45], and seems to be involved in some aspects of the development of the nervous system [46]. Structural similarities between AChE and BuChE have raised the possibility of a non-catalytic role for CHE [47]. Moreover, the biochemical properties of BuChE are altered in neurodegenerative diseases such as Alzheimer's disease (AD) [48]. Consequently, the possible role of peripheral BuChE in the involvement in delirium is now gaining recognition.

Thus, results of the present investigation showed reduced BuChE and increased CRP values in delirious patients. A study from Zhang et al. [49] and Dillon et al. [12] demonstrated increased CRP values as an independent predictor of delirium. Our results confirm these findings. While higher CRP values were associated with lower BuChE activities (Figure 2) we did not think that there is a mechanistic or pathophysiological link between these both characteristics.

Reduced BuChE activity was associated with an increased number of administered anticholinergic drugs. Thus, because changes in CRP could be associated more to endogenous patients'-like factors, we hypothesize that differences in BuChE could be related stronger to medication. The addition of more than three medications during acute hospitalization was found to be a predictor of occurrence of delirium in hospitalized elderly persons [49].

The findings of the present study are consistent with the hypothesis that reduced ability to metabolize drugs by reduced CHE activity is one of the risk factors that contributes to vulnerability to delirium [50,51]. Because BuChE activities were reduced pre- and postoperatively it was suggested that cholinergic homeostasis was equally affected by surgery independently of the pathophysiological changes underlying delirium [11]; therefore, preoperative rather than intra- or postoperative factors appear to play an important role in mediating the association between lower CHE and postoperative delirium. One important reason might be medication, the mechanism how medications can inhibit CHE, however, is unknown. One possible explanation might be the hypothesis that drugs are able to bind to the catalytic centre of the enzymes and therefore may inhibit enzymatic function and reduce activity. The pathophysiological mechanisms underlying such drug toxicity in delirium, however, are not well understood and should be investigated in further studies focusing the role of CHE.

Author Contribution

KP: designed study, analyzed data, wrote article, final approval

SS: collected data, revised article, final approval

JH: revised article, final approval

MW: revised article, final approval

TB: statistical analysis, final approval

CS: study design, revised article, final approval

JK: measured and analyzed data, revised article, final approval

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