Pseudocholinesterase levels in patients under electroconvulsive therapy

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ABSTRACT

Objectives: In this study, we aimed to retrospectively assess the correlation of pseudocholinesterase (PChE) levels with age, gender, body weight and diagnosed psychiatric diseases in electroconvulsive therapy (ECT) cases.

Methods: This retrospective study was conducted at Bülent Ecevit University Hospital, Zonguldak, Turkey, between 2007 and 2011. In the study, 193 ECT case files were retrospectively scanned to evaluate PChE values before ECT and other file information.

Results: There was no difference between gender in terms of PChE levels. Correlation analysis determined a weakly positive correlation between age (p=0.013; correlation coefficient [cc]: 0.178) and body weight (p<0.001; cc: 0.273) and PChE levels. No correlation was found between age, gender, weight or psychiatric diagnosis, and PChE levels.

Conclusion: Neuromuscular blockage is a significant factor that increases patient safety, while increasing the efficacy of ECT. In choosing muscle relaxant agents, both patient factors and the pharmacological properties of the neuromuscular blocker should be considered. We think that in situations with delayed recovery of ECT cases without identified PChE levels, low PChE levels must be considered.

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Electroconvulsive therapy (ECT) is an effective, life-saving method applied for the treatment of severe psychiatric disorders that are nonresponsive to pharmacological approaches; the approach is based on electrical stimulation administered with anesthesia to create widespread convulsions. Schizophrenia, catatonia, Parkinson's disease, neuroleptic malignant syndrome, and epilepsy represent diseases in which ECT is applied.[1]

During ECT, anesthesia and neuromuscular blockage are required to prevent physiological and psychological trauma.[1] Succinylcholine is a depolarizing muscle relaxant commonly used during ECT due to its short duration of action; it is also rapidly hydrolysed by pseudocholinesterase (PChE). If the PChE enzyme is deficient (atypical) or present in insufficient amounts, the muscle relaxant effect of succinylcholine is prolonged. Pseudocholinesterase has a complicated molecular structure, and its physiological role is not understood. It is an enzyme with a tetrameric glycoprotein structure and a weight of 342 kDa; it is synthesized in the liver. It is also known as acetylcholine acylhydrolase, EC 3.1.1.8, butyrylcholinesterase, plasma or serum cholinesterase. Pseudocholinesterase is found in the intestinal mucosa, blood plasma and white matter.[2]

Deficiency of the plasma PChE enzyme may be genetic or acquired. Although it has 65 genetic variants, the most common variants, according to their clinical importance, are the atypical (dibucaine resistant), fluoride resistant, silent, and Kalow types.[2,3] Pseudocholinesterase levels may decrease due to some diseases (chronic infections, liver and kidney diseases, malignancy, malnutrition, myocardial infarctus, myxoedema), medications (neostigmine, oral contraceptives), physiological situations (age, pregnancy), toxic inhibition (organophosphate, carbamate, chemical weapons) or severe burns.[2,4,5]

Deficiency of the PChE enzyme may be measured by biochemical and molecular analysis of blood samples. Biochemical investigation of the amount of enzyme in plasma is carried out quantitatively, with variation in blood PChE enzyme levels linked to different laboratory standards; here, a level of 3200-7500 IU/L is accepted as a normal value.[3] Correlations have been reported between some psychiatric disorders, such as major depression, severe anxiety disorder, and obsessive-compulsive disorder (OCD) and increased PChE activity.[6-8] The aim of our study was to retrospectively assess the correlations between PChE levels and age, gender, body weight and diagnosed psychiatric diseases in ECT cases receiving anesthesia at the third-stage Educational Hospital in Zonguldak province in the northwest region of Turkey.

Methods. Our study was performed after receiving permission from the Faculty of Medicine Clinical Research Ethics Committee, Bülent Ecevit University (Meeting protocol no.: 2012-76-15/05, data 12/06/2012). The files of 193 cases administered ECT from 2007 to 2011 were reviewed. This study was performed retrospectively using demographic data, PChE levels and current psychiatric diagnoses were scanned from the records. Written informed consent

was not obtained from patients due to the retrospective nature of this study. Cases with organ failure (liver, kidney) or malignancy, prescribed medication causing enzyme induction (anticonvulsants, barbiturates, oral contraceptives) or inhibition (cimetidine, propranolol), pregnancy and ECT administered without examination of the PChE levels were excluded from the study. Plasma PChE levels were determined from blood samples taken during the screening tests before ECT.

Pseudocholinesterase serum levels were determined in our hospital laboratory with an Advia 2400 Chemistry System (Siemens Health Care Diagnostics Inc., Germany). The assay method is based on the catalytic activity of ChE to hydrolyse butyrylthiocholine to thiocholine, which then reacts with a dye compound. Our hospital laboratory accepts a 4900-11 900 U/L interval as the reference value.

Statistical analyses. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS) Version 15.0 for Windows (SPSS Inc., Chicago, IL, USA) program. Shapiro-Wilk tests were performed for numerical variables to understand whether the distributions were normal. Categorical variables were presented in frequencies and percentages; numerical variables were presented in means and standard deviations or medians and interquartile ranges (IQRs). The relationships between categorical variables were investigated using the Chi-square test; in addition, the correlations between numerical variables were analyzed with the Spearman correlation coefficient (cc). The Mann-Whitney U test or Kruskal-Wallis test was used to compare the independent medians. The independent means were compared by the Student t-test or analysis of variance (ANOVA). A multivariate logistic regression analysis was performed to explain the low levels of PChE. Statistical significance was accepted as $p<0.05$.

Results. The demographic characteristics, diagnosis distribution, and PChE levels of cases are shown in **Table 1**. When cases with low plasma PChE levels were compared with other cases, there was no difference in terms of gender, age, weight or diagnosis ($p>0.05$).

In the correlation analysis of all cases included in the study, there was a weakly positive correlation between age ($p=0.013$, cc: 0.178) and body weight ($p<0.001$, cc: 0.273) with PChE levels. When only female cases were assessed, there was no correlation between body weight and PChE activity ($p=0.050$; cc: 160). As the body weight of male cases increased, it was observed that the PChE levels increased ($p<0.001$; cc: 0.382). There was no correlation found between the age of only female cases ($p=0.485$; cc: 0.076) or male cases ($p=0.104$; cc: 0.158) and PChE activity. When the relationships between the demographic characteristics of all cases and diagnosis were assessed, as expected, we found a weak correlation between age and diagnosis, while there was generally no correlation observed for the other parameters. The PChE levels of cases varied in the range of 3138-11 867 U/L (normal values: 4900-11

Table 1 - Comparison of pseudocholinesterase (PChE) levels according to demographic characteristics and diagnosis (p>0.05).

Demographic characteristics	Normal PChE (n=184)	Low PChE (n=9)	Total (n=193)	*P*-value
Age (median, IQR)	35 (23)	25 (21)	35 (22.5)	0.164*
Gender (%)				
Female	103 (56)	4 (44.4)	107 (55.4)	0.515†
Male	81 (44)	5 (55.6)	86 (44.6)	
Weight (median, IQR)	72.5 (18.8)	68 (18)	72 (18)	0.310†
Diagnosis				
OCD	18 (9.8)	2 (22.2)	20 (10.4)	
Bipolar	38 (20.7)	3 (33.3)	41 (21.2)	
Depressive	53 (28.8)	1 (11.1)	54 (28.0)	>0.05*
Schizophrenia	52 (28.3)	1 (11.1)	53 (27.5)	
Anxiety disorder	16 (8.7)	0 (0)	16 (8.3)	
Other	7 (3.8)	2 (22.2)	9 (4.7)	

*Chi-square Test; †Mann Whitney U Test. IQR - interquartile range, OCD - obsessive-compulsive disorder

Table 2 - Analysis of independent factors related to low levels of pseudocholinesterase.

Variables	Odds ratio	95% Confidence interval	*P*-value
Age	0.975	0.91 - 1.04	0.424
Female	0.515	0.11 - 2.37	0.393
Weight	0.971	0.92 - 1.03	0.292
Diagnosis			0.291
OCD	0.593	0.06 - 5.90	0.656
Bipolar	0.319	0.04 - 2.44	0.271
Depressive	0.104	0.01 - 1.55	0.100
Schizophrenia	0.066	0.01 - 0.86	0.038

OCD - obsessive-compulsive disorder

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900 U/L), with a mean of 8227.10 ± 1998.96 U/L determined. A multivariate logistic regression analysis performed to explain the low PChE did not show significant correlations between age, gender, weight or diagnosis and PChE levels (**Table 2**).

Discussion. There was no difference in terms of gender and no correlation determined between the diagnoses of cases and enzyme levels. Correlation analysis showed weak positive correlations between age (p=0.013, cc: 0.178) and body weight (p<0.001, cc: 0.273), and PChE levels. There was no correlation determined between gender or diagnosis of cases and PChE levels.

It has been reported in the literature that PChE levels are generally lower in women.[4] In a study of healthy volunteers aged 18-85 years, Khaled et al[5] found that the enzyme activities of acetylcholine esterase, benzoylcholine esterase, butyrylcholine esterase and aspirin esterase did not change with age; however, as the number of female cases above 60 years of age was insufficient, they were prevented from researching differences based on gender. Generally, from previous studies, we see that the PChE activity in males does not change, while it is at lower levels in women of reproductive age.[9] In our study, cases were aged 14-81 years, and despite the weak positive correlation of age with PChE activity and low enzyme activity of females, there was no significant difference according to gender.

Modai et al[10] assessed the PChE activity of a total of 123 cases, including 16 agitated depressive, 12 retarded depressive, 7 acute schizophrenic, 14 residual schizophrenic and 16 healthy individuals, as well as 45 surgery patients and 13 first-degree relatives of 4 agitated depressive patients. The PChE activity among agitated depressive and acute schizophrenic patients was significantly higher than it was in other depression and schizophrenia types, while the levels of first-degree relatives of agitated depressive patients were high and comparable to those of the agitated depressive patients. The researchers stated that genetic components may play an important role in PChE activity. However, they also stated that the cause of the situation observed at the end of the study was still uncertain. Furthermore, Aizenberg et al[8] studied 20 OCD patients and 20 healthy volunteers and showed that the PChE activity in the OCD group was significantly higher. However, they found no correlation between enzyme activity and psychopathological degree, and they stated that the correlation between anxiety, depression and PChE was complicated; the cause of high PChE levels is still unknown.

In a study determining the acetylcholine esterase and PChE activity of manic depressive patients, their healthy first-degree relatives and non-related healthy volunteers, Thakar et al[11] found that PChE and acetylcholine esterase activities were significantly lower in the healthy first-degree relatives of bipolar, unipolar, affective disorder and manic depressive patients compared to healthy volunteers. Half the bipolar disorder patients were on lithium treatment, and their cholinesterase activities were comparable to those of the patients not receiving lithium treatment. According to this result, the authors stated that the cholinergic mechanism plays an important role in the aetiology of manic depressive disease.

It is thought that there may be an effect of pharmacotherapy on PChE activity. Some authors have reported that despite the claim that most psychopharmacological agents do not affect PChE levels, some medications cause hepatic and serum PChE activity.[10,12] In our study, there was no correlation determined between the cases' diagnoses and PChE enzyme levels.

Berry et al[13] stated that during routine ECT administration of succinylcholine to 1676 patients, they encountered lengthened apnea in 23 cases, and these cases had PChE deficiency. When the PChE variants of relatives of these patients were investigated, these individuals had abnormal PChE variants. Moreover, the authors showed that in these psychiatric patients sensitive to PChE, the incidence of the fluoride resistant variant was increased. Studies have reported that attaching importance to the high succinylcholine sensitivity rates among patients with depression may not be meaningful.

The reason for choosing short-effect neuromuscular blocker agents is to avoid encountering long apnea durations during ECT anesthesia. For patients with different comorbidities, other non-depolarizing neuromuscular blockers may be used instead of succinylcholine. Non-depolarizing neuromuscular blockers do not cause severe side effects like malignant hyperthermia or hyperkalaemia; however, their long-effect durations should be considered before use during ECT. Rocuronium is a steroid-structure and medium-term-effect agent that is currently used at increasing rates as an alternative to succinylcholine for ECT administration. When used at appropriate doses, it provides the closest rapid neuromuscular blockage to succinylcholine.[14,15]

Study limitations. First of all this is a retrospective study and it has typical limitations of such work. For

example, the drugs used by these patient population and the possible effects of that drugs on plasma PChE levels and activity are not analyzed. The drugs or drug combinations prescribed for the patient population in this study are highly variable, as well as regular patient consumption knowledge, thus it is difficult to interpret the affect of them. Second, the number of subjects with low plasma PChE level is found to be 9 (4.7%), a relatively small number, which may have effect the correlation analysis.

In conclusion, PChE enzyme levels are affected by some medications used for psychiatric diseases; some cases require intubation after succinylcholine use for ECT, and this is linked to low plasma PChE levels. As a result, to provide reliable anesthesia for ECT, we think it is appropriate to obtain a comprehensive anesthesia history and family history from all patients, especially those who have not undergone general anesthesia before ECT. Moreover, we recommend that patients scheduled to receive succinylcholine should be investigated for PChE enzyme deficiency. We consider that in cases with delayed recovery from ECT without identified PChE levels, low PChE levels must be considered.

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