

Prevalence of human pseudocholinesterase (butyrylcholinesterase) deficiency in central Anatolian people: A cross-sectional study

Orta Anadolu toplumunda human psödokolinesteraz (butirilkolinesteraz) eksikliğinin yaygınlığı

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Abstract

Aim: Human pseudocholinesterase (PChE) is an enzyme responsible for hydrolysis of the muscle relaxant drugs like succinylcholine and mivacurium. PChE deficiency, which may lead to prolonged apnea, may occur due to hereditary or acquired causes. In our study, we aimed to investigate the prevalence of human pseudocholinesterase (PChE) enzyme deficiency around the central Anatolia region and present our results in light of the literature.

Methods: This cross-sectional study included 936 patients (age 18-70 years) who underwent any elective surgery under general anesthesia between August 2015 and September 2019. Human PChE level, plasma PChE activity, the human PChE activity/albumin, serum liver and kidney function tests were analyzed from blood samples. Human PChE enzyme deficiency and possible association of the PChE deficiency with other values was also investigated. The normal value of PChE was considered to range from 4650 U/L to 10,440 U/L.

Results: PChE activity was decreased in 19 (1.9%) of the 936 patients (442 males and 494 females). There was no statistically significant difference between the PChE levels in terms of gender ($P=0.236$). The mean human PChE activity of all patients was 7.490 (0.980). The PChE activity of 22 (2.35%) and 58 patients (6.4%) were below 5.000 U/ml and 6.000 U/, respectively. A statistically significant difference was found between serum urea, creatinine and human PChE levels ($P=0.034$, $P=0.236$, respectively). However, PChE deficiency had no correlation with liver function tests such as AST and ALT ($P=0.432$, $P=0.022$, respectively).

Conclusion: PChE deficiency can be observed in preoperatively evaluated patients and may cause serious life-threatening conditions, including respiratory failure and prolonged apnea.

Keywords: Human butyrylcholinesterase, Central Anatolian people, Pseudocholinesterase deficiency, Succinylcholine

Öz

Amaç: Human psödokolinesteraz (PChE), süksinilkolin ve mivakuryum gibi kas gevşeticilerin yıkımından sorumlu bir enzimdir. PChE eksikliği genetik kökenle veya edinilmiş sebeplerle ortaya çıkabilir ve bu durum uzamış apneye yol açabilir. Biz çalışmamızda, orta Anadolu bölgesinde Human psödokolinesteraz (PChE) enzim eksikliğinin sıklığını araştırmayı ve literatür ışığında sunmayı amaçladık.

Yöntemler: Bu enine-kesitsel çalışmada, Ağustos 2015 ve Eylül 2019 arasında genel anestezi altında herhangi bir elektif cerrahi geçiren 18-70 yaş arasındaki toplam 936 hasta çalışmaya dahil edildi. Hastaların kan örneğinde human PChE düzeyi, plazma PChE aktivitesi, human PChE aktivitesi / serum albümin düzeyi, serum karaciğer ve böbrek fonksiyon testleri analiz edildi. Human PChE enzim eksikliği ve serumda ölçülen diğer değerler ile muhtemel ilişkisi de ayrıca araştırıldı. PChE normal değeri 4650 U/L-10440 U/L olarak kabul edildi.

Bulgular: PChE enzim aktivitesi, toplam 936 hastanın (442 erkek, 494 bayan) 19'unda (%1,9) normalin altındaydı. Cinsiyet açısından PChE düzeyleri arasında anlamlı fark yoktu ($P=0,236$). Hastaların 22'sinde (%2,35) PChE aktivitesi 5,000 U/ml' in altındaydı. 58 (%6,4) hastada ise PChE aktivitesi 6,000 U/L' in altında ölçüldü. Human PChE seviyesi ile serum üre ve kreatinin arasında istatistiksel olarak önemli fark saptandı (sırasıyla, $P=0,034$, $P=0,236$). Ancak PChE enzim eksikliğinin AST ve ALT gibi karaciğer fonksiyon testleri ile ilişkisi saptanmadı (sırasıyla, $P=0,432$, $P=0,022$).

Sonuç: Psödokolinesteraz enzim eksikliği preoperatif hastalarda gözlenebilir ve uzamış apne ve solunum desteği dahil yaşamı tehdit eden ciddi sonuçlara sebep olabilir.

Anahtar kelimeler: Human butirilkolinesteraz, Orta Anadolu toplumu, Psödokolinesteraz eksikliği, Süksinilkolin

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Introduction

Human pseudocholinesterase (PChE), also known as butyrylcholinesterase (BChE) or plasma cholinesterase is a drug metabolizing enzyme responsible for hydrolysis of the muscle relaxant drugs like succinylcholine and mivacurium [1,2]. PChE deficiency is rare condition which may occur due to hereditary or acquired causes and is typically diagnosed only after exposure to succinylcholine or mivacurium. Although many physiopathological conditions may affect BChE synthesis or activity, the main cause of BChE deficiency is hereditary. Succinylcholine is short-time anesthetic agent used for rapid intubation, which normally provides motor block lasting for 10-12 minutes when used in standard doses (1 mg/kg, IV). PChE deficiency leads to prolonged motor block associated with succinylcholine and mivacurium. The major presenting symptom is prolonged skeletal muscle paralysis including the diaphragm and intercostal muscles, which are required for spontaneous breathing [3]. Deficiency due to any cause can lead to prolonged apnea and paralysis following administration of succinylcholine and mivacurium [4]. Patients with PChE deficiency will often be admitted to the intensive care unit and need continuous ventilator support postoperatively until muscle strength is restored [5]. Human PChE is a glycoprotein enzyme that is synthesized by the liver and immediately released into the plasma [6]. The plasma half-life has been estimated as approximately 12 minutes. Initial dose of succinylcholine is rapidly hydrolyzed by PChE within 10 to 13 minutes during which 90 % of the muscle strength is restored. Deficient PChE activity is usually considered to be caused by several allelic mutations in butyrylcholinesterase (BChE) gene, which provides instructions on how to make the enzyme pseudocholinesterase [7]. This study was designed to evaluate the PChE deficiency in middle Anatolian people for the first time. In addition, changing PChE levels were investigated with regards to liver and kidney function tests. In this study, we aimed to make anesthesiologists, specially trained nursing staff, and physicians of the intensive care unit aware of PChE deficiency and the significance of anesthetic management.

Materials and methods

This cross-sectional study was conducted between August 12, 2015, and September 20, 2019, and approved by the Ethics committee of the Bozok University Medical Faculty (date: 08/06/2015, number: 27/09). Preoperatively assessed 936 patients (442 men and 494 women) with a mean age of 44.85 years (18-70 years) were enrolled in the study group. The study was performed in the Central Anatolia Region of Turkey.

The participants were fully informed about the aim and scope of the study and the tests to be performed. Informed consent forms were obtained from all participants. Patients aged 18-70 years scheduled for any elective surgery under general anesthesia were included. Patients who use acetylcholinesterase inhibitors, anticholinesterases, cytotoxic agents, metoclopramide, steroids, ester-type local anesthetics, hexafluronium, pancuronium, oral contraceptives, or antidepressants, those with liver or renal diseases, malnutrition, malignancy, extensive burn injuries, pregnant patients and those who underwent cardiopulmonary bypass were excluded. After physical

examination, venous blood samples were collected for total blood count and biochemical tests (AST, ALT, albumin, BUN, urea and creatinine clearance). Fasting blood samples were drawn from all subjects between 7:00 AM and 8:00 AM, and immediately sent to the hospital laboratory for evaluation. A specimen of clotted blood was centrifuged at 3.000 g for 10 minutes for serum assessment, which was stored at -70°C until analysis.

Laboratory analysis for PChE activity was conducted by obtaining the plasma sample and performing a qualitative test of PChE activity. Moreover, quantitative testing via colorimetry was performed to determine the actual amount of PChE present in the sample.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS Inc, Chicago, IL, USA). Data was reported as mean (standard deviation) or percentages (number of patients) as appropriate unless otherwise specified. The Kolmogorov-Smirnov goodness-of-fit test was used to evaluate normality of the data. Correlation coefficients were derived by using Pearson's correlation test.

In the power analysis based on the data of previous studies and the population of region, a sample size of 866 patients were needed with 90% power ($1-\beta$ err prob=0.90) and 5% error margin (α err prob=0.05). 936 patients were enrolled in the study after taking possible loss of data into consideration.

Results

Nine hundred thirty-six preoperative subjects (442 males and 494 females) were recruited, with a mean age of 44.85 years (18-70 years). Demographic characteristics of the patients are presented in Table 1.

Among all patients, the PChE values of 19 individuals (1.9 %) were below normal (range: 4650 U/L to 10,440 U/L). No significant difference was found between PChE levels in terms of gender ($P=0.236$) (Table 2).

Table 1: Demographic data of the patients

	Gender				Total (n=936)	
	Male (n=442)		Female (n=494)			
Age (years)	n	%	n	%	n	%
≤15	64	14.4	56	11.3	120	12.8
16-40	213	48.3	246	49.8	459	49.1
41-64	119	26.9	154	31.2	273	29.2
≥65	46	10.4	38	7.7	84	8.9

Table 2: Comparison of Pseudocholinesterase (PChE) values in terms of gender

	PChE (ng/ml)				P-value
	Normal		Low		
Sex	n	%	n	%	
Male (n=442)	431	97.5	11	2.5	0.236
Female (n=494)	486	98.4	8	1.6	

The mean human PChE activity of all patients was 7.490 (0.980). The PChE activity of 22 (2.35%) and 58 patients (6.4%) were below 5.000 U/ml and 6.000 U/, respectively. PChE activity measurements are presented in Table 3.

Table 3: Pseudocholinesterase activity measurements

Value (U/ml)	PChE activity (U/ml)					
	<4.8	4.8-6	6-7	7-8	8-9	>9
Number	18	62	176	352	294	34
%	1.9	6.6	18.8	37.6	31.4	3.63

PChE: Pseudocholinesterase

The mean value for human PChE activity/albumin ratio of all patients was 1.657. The PChE activity/albumin ratio was measured under 1.200 in 12 (1,28%) patients and under 1,300 in 28 (2,99%) patients (Table 4).

Human PChE activity was found to significantly and positively correlate with plasma PChE levels, albumin, PChE activity/albumin ratio, urea and creatinine levels. Similarly, the human plasma PChE levels correlated with PChE activity, albumin, and creatinine. A statistically significant difference was found between serum urea, creatinine and human PChE levels ($P=0.034$, $P=0.236$, respectively). Serum creatinine, albumin, PChE activity, urea, alanine aminotransferase (ALT), aspartate transaminase (AST), and PChE measurements are presented in Table 5.

Table 4: The human PseudoCholinesterase (PChE) activity / albumin values

Range	PChE activity / albumin					
	<120	120-130	130-140	140-180	180-200	>200
Number	12	28	58	622	160	56
%	1.28	2.99	6.19	66.45	17.09	5.98

PChE: PseudoCholinesterase

Table 5: Evaluation of blood creatinine, albumin, PChE activity, urea, ALT, AST, PChE

	Minimum	Maximum	Mean (SD)	P-value
Creatinine (mg/dl)				
Male (n=442)	0.43	5.23	0.79 (0.33)	0.236
Female (n=494)	0.38	4.92	0.72 (0.38)	
Albumin (g/dl)				
Male (n=442)	3.01	6.39	4.55 (0.55)	0.654
Female (n=494)	3.34	7.12	5.15 (0.68)	
PChE activity (U/L)				
Male (n=442)	4.42	9.59	7.49 (0.98)	0.124
Female (n=494)	4.16	8.64	6.86 (0.77)	
Urea (mg/dl)				
Male (n=426)	5	92	14.12 (7.29)	0.034
Female (n=452)	6	98	17.42 (8.42)	
ALT				
Male (n=430)	6	331	21.93 (21.6)	0.022
Female (n=474)	8	298	17.83 (18.5)	
AST				
Male (n=432)	7	395	23.71 (22.97)	0.432
Female (n=488)	8	356	22.63 (20.81)	
PChE (ng/ml)				
Male (n=442)	9.51	75.57	25.68 (10.13)	0.452
Female (n=494)	8.63	72.43	24.57 (9.18)	

PChE: PseudoCholinesterase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase

Discussion

The normal value of plasma PChE value ranged from 4650 U/L to 10,440 U/L [8]. The main result of our study was that, of all 936 patients, 19 patients (1.9%) had decreased PChE values. In our country, a study on PChE deficiency was conducted by Yildirim et al. [9] in 2009, in which the incidence enzyme deficiency was reported as 3.77% in Sivas province.

We performed a qualitative test to determine PChE activity in the patients' plasma samples and used quantitative testing by colorimetry to detect the actual amount of PChE. The dibucaine inhibition test is one of the most used tests, and measures PChE inhibition by dibucaine. Dibucaine, an aminoamide local anesthetic, may be used to determine the activity of the atypical variants of the PChE. Although dibucaine will inhibit of the normal variant of the PChE by 80%, it will reduce the activity of the atypical variants of the PChE to much smaller degrees (heterozygotes by 60%, homozygotes by 30%) [10].

PChE deficiency is usually genetic in origin, and arises from inherited, acquired, and iatrogenic causes [6]. In inherited PChE deficiency, succinylcholine and mivacurium cannot be hydrolyzed by atypical PChE. The majority of people (96%) are homozygous for the normal PChE genotype and the remaining individuals (4%) carry 1 or much more of the atypical gene alleles [11]. A small minority of the people (0.2%, 1 per 480) carry both enzymes (heterozygous), and these patients hydrolyze succinylcholine in a longer time. The ratio of carrying homozygous and heterozygous alleles for abnormal PChE is 1

per 3200 and 1 per 500, respectively, and these patients cannot break down the succinylcholine and mivacurium [12]. Homozygotes may present with neuromuscular blockade for clinically significant longer durations, such as 3 hours after standard succinylcholine dosing [13]. Patients with atypical homozygous genotype do not only have reduced serum cholinesterase activities but also their elimination rate for some pharmacologically potent drugs decrease drastically [14].

A recent study revealed that there is a close relationship between number of multiple mutations in the collagen Q (COLQ) gene. A large number of multiple mutations in the COLQ gene may cause an abnormal release of cholinesterase, resulting in decreased serum PChE content associated with PChE deficiency [15].

Butyrylcholinesterase gene (BChE) is located at chromosome 3 (3q26.1-26.2) and has newly discovered significant variants such as the atypical (A-variant), the Kalow (K-variant), the fluoride (F-variant) and the silent (S-variants) variants. Atypical (A-variant) and Kalow (K-variant) are the most common BChE gene variants in the white population. Especially the atypical variant is most frequently related to prolonged apnea. Recent studies have revealed that new variants of the BChE gene may cause PChE deficiency and lead to the prolonged effect of succinylcholine or mivacurium eventually [2]. Atypical BChE gene is two times more common in males than in females (1/2 ratio) [16]. The patient's ethnic origin plays a significant role in PChE deficiency. Ethnic populations with the highest prevalence for PChE deficiency are Caucasian males of European descent, native Alaskan ethnicities, and Persian Jewish community [17].

Drugs that inhibit the enzyme's activity include acetylcholinesterase inhibitors (neostigmine, pyridostigmine, physostigmine, and edrophonium), anticholinesterases (especially echothiophate), cytotoxic agents such as cyclophosphamide, steroids, ester-type local anesthetics, pancuronium, oral contraceptives and antidepressants (fluoxetine, sertraline) [18]. Acquired causes, including chronic infections, liver disease, renal disease, malnutrition, pregnancy, malignancy, hemodialysis, extensive burn injuries, and myocardial infarction or cardiopulmonary bypass, can reduce PChE levels [19,5]. In patients with PChE deficiency, the use of cocaine can lead to sudden cardiac death. In these patients, the non-depolarizing muscular blocker mivacurium should not be used during anesthesia induction, but other non-depolarizing muscular blockers such as rocuronium, vecuronium and atracurium may be used safely in this period [18]. When prolonged neuromuscular paralysis associated with the use of succinylcholine or mivacurium occurs, complete recovery is generally achieved following the spontaneous return of muscle function in patients with careful monitoring and mechanical respiratory ventilation support [20]. Patients should be sedated during mechanical ventilator support. Fresh frozen plasma may also be administered to these patients to facilitate the recovery of muscle function [21]. In BChE deficiency, the use of Recombinant BChE injection is an interesting approach, but it is not performed in daily practice due to production difficulties and non-cost-effectiveness [22].

A peripheral nerve stimulator can be used for repeated evaluation of motor function [13]. Since PChE deficiency is associated with inheriting an abnormal variant of the BChE gene, family members of patients with PChE deficiency should be recommended to undergo laboratory testing. Moreover, the Association of Anesthesiology of Great Britain and Ireland require the usage of neuromuscular blockade monitoring devices throughout all anesthetic procedures, including regional and sedative anesthesia [23].

One of the main results in our study is the significant positive correlation of PChE activity with plasma PChE, albumin, BChE activity/albumin, and creatinine. PChE activity is not significantly correlated with liver function tests, which can be derived from the advanced liver failure patients who were excluded from this study. A recent study conducted by Abdullayev et al. [24], investigating the likely relationship between pseudocholinesterase deficiency and other laboratory tests, revealed a significant relationship between AST, urea levels and PChE. However, they could not detect any relationship between PChE and ALT, INR, aPTT and creatinine levels. They concluded that enzyme deficiency incidence was 4.5 times higher in patients with high AST levels, and 9-fold higher among patients with high urea levels. Yildirim et al. [9] revealed that a decrease in PChE levels is related to older age, male gender, AST, ALT, urea, creatinine, PT and aPTT elevation. The incidence of PChE deficiency was observed to be three times higher in high AST levels, and 5 times higher in case of urea and creatinine elevation in blood sample.

PChE deficiency can be confused with different diagnoses such as residual neuromuscular blockade, the effect of residual fentanyl, myasthenia gravis, hypokalemia and hypermagnesemia [25]. Since PChE deficiency can be fatal if not recognized and treated properly, the pre-operative assessment should include family history of a genetic origin [5].

Limitations

No further genotype examination via genetic tests was performed in patients with PChE deficiency detected by laboratory testing. In patients with PChE deficiency, whether the failure is caused by hereditary or acquired etiology has not been investigated. Moreover, due to limited conditions, we did not have possibility to determine the plasma cholinesterase levels of family members of patients with PChE deficiency.

Conclusions

Anesthesia providers should familiarize themselves with the significance of a PChE deficiency, because PChE deficiency may become a life-threatening condition if the patient must undergo general anesthesia for surgery. For this reason, the anesthesiologist, specially trained nursing staff, and physicians of the intensive care unit should always consider using less neuromuscular blocking agents such as succinylcholine and mivacurium. Necessary measures should be taken for ventilator support due to the possibility of prolonged apnea. The patient with PChE deficiency and family members should be also educated about future anesthetic practices. Patients should be registered in a database for PChE deficiency.

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