CLINICAL RESEARCH / KLİNİK ÇALIŞMA

THE INCIDENCE OF PSEUDOCHOLINESTERASE DEFICIENCY AND CONTRIBUTING FACTORS IN PEDIATRIC PATIENTS IN TURKEY

TÜRKİYE'DE PEDİYATRİK HASTALARDA PSÖDOKOLİNESTERAZ EKSİKLİĞİ VE KATKIDA BULUNAN FAKTÖRLERİN İNSİDANSI

[1]Sengül ÖZMERT, [1]Feyza SEVER, [2]Sevil TOKAT, [1]Sibel SAYDAM, [1]Mine AKIN, [1]Gülsen KESKİN, [1]Devrim TANIL KURT, [3]Murat KIZILGÜN, [4]Arif Osman TOKAT

[1]University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Department of Anesthesiology and Reanimation, Ankara, Turkey
[2]Yüksek İhtisas Training and Research Hospital, Anesthesiology and Reanimation Clinics, Ankara, Turkey
[3]University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital, Department of Biochemistry and Clinical Biochemistry, Ankara, Turkey
[4]Bozok University Faculty of Medicine, Department of Thoracic Surgery, Yozgat, Turkey

[1]Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Anabilim Dalı, Ankara, Türkiye
[2]Yüksek İhtisas Eğitim ve Araştırma Hastanesi, Anesteziyoloji ve Reanimasyon Kliniği, Ankara, Türkiye
[3]Sağlık Bilimleri Üniversitesi Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim ve Araştırma Hastanesi, Biyokimya ve Klinik Biyokimya Anabilim Dalı, Ankara, Türkiye
[4]Bozok Üniversitesi Tıp Fakültesi, Göğüs Cerrahisi Anabilim Dalı, Yozgat, Türkiye

ABSTRACT

Objective: *It is aimed to reveal the frequency of pseudocholinesterase (PCE) deficiency, which is highly important for the possible complications observed during the general anaesthesia applications.*

Method: *The records of patients (age, sex, serum PCE effect levels, liver and kidney functions) were computerized and studied on the data.*

Results: *PCE level in 5.5% of the patients (n=15.309) were under the normal values. The PCE deficiency percentage was high with high alanine amino transferase, aspartate amino transferase, ure and creatinin levels (p<0.001). The patients whose ALT, AST, ure and creatinin level were high as a whole, PCE deficiency percentage was 50% (p<0.001).*

Conclusion: *PCE deficiency is a widespread situation. It is probable to think about the occurrence of the PCE deficiency in case of the increased values especially in the liver and/or kidney functions during the preoperative run in the child patient group.*

KEYWORDS: *Pseudocholinesterase, Hepatic failure, Renal failure, Cholinesterase*

ÖZ

Amaç: *Genel anestezi uygulamalarında gözlenen olası komplikasyonlar açısından oldukça önemli olan psödokolinesteraz (PKE) eksikliği sıklığını ortaya koymak amaçlanmıştır.*

Yöntem: *Hastaların kayıtları (yaş, cinsiyet, serum PKE etki düzeyleri, karaciğer ve böbrek fonksiyonları) bilgisayar ortamında yapıldı ve veriler üzerinde çalışıldı.*

Bulgular: *Hastaların %5.5'inde (n = 15.309) PKE düzeyi normal değerlerin altındaydı. PKE eksikliği yüzdesi, yüksek alanin amino transferaz, aspartat amino transferaz, üre ve kreatinin düzeyleri olan hastalarda yüksek bulundu (p<0.001). ALT, AST, üre ve kreatinin düzeyi bir bütün olarak yüksek olan hastalar, PKE eksikliği yüzdesi % 50 idi (p<0.001).*

Sonuç: *PKE eksikliği yaygın bir durumdur. Çocuk hasta grubunda preoperatif dönemde, özellikle karaciğer ve/veya böbrek fonksiyonlarında artmış değerler varlığında PKE eksikliğinin görülme ihtimali göz önünde bulundurulmalıdır.*

ANAHTAR KELİMELER: *Psödokolinesteraz, Karaciğer yetmezliği, Böbrek yetmezliği, Kolinesteraz*

Çıkar çatışması/*Conflict of Interest*: Yazarlar herhangi bir çıkar çatışması bildirmemişlerdir./ *Authors do not report any conflict of interest.*
Geliş tarihi/*Received*: 09/02/2018 Kabul tarihi/*Accepted*: 14/05/2018

Yazışma Adresi (Correspondence):
Dr. Sengül ÖZMERT, Ankara Çocuk Sağlığı ve Hastalıkları Hematoloji Onkoloji Eğitim Araştırma Hastanesi, Dışkapı, Ankara, Türkiye
E-posta (E-mail): sengulozmert@yahoo.com.tr

INTRODUCTION

Pseudocholinesterase (PCE), known as cholinesterase or butyrylcholinesterase, is an enzyme responsible for the hydroxylation of pharmaceuticals including esters such as cocaine, aspirin, bambuterol, heroin, succinylcholine and mivacurium. PCE is primarily synthesized in the liver and found in many tissues except red blood cells (1). PCE deficiency can result in life-threatening complications by causing abnormal extension in the deterioration of exogenic cholinesterase and prolonged action of these which are used as neuromuscular blocking agents in general anesthesia (2). Liver and kidney failure are known to be acquired factors causing PCE deficiency (1).

Although there have been many studies on the deficiency, frequency, and genetic properties of PCE around the world, there are no data about the pediatric population in Turkey. In this study, which examined serum PCE levels of patients over a five-year period, the primary aim was to determine the frequency of PCE deficiency in childhood in Turkey. Secondary aims were to find out the correlation between PCE deficiency and age and gender, and its possible relationship with liver and kidney functions.

MATERIAL AND METHOD

Preoperative PCE analysis is a routine preoperational procedure among pediatric patients in our hospital, so a retrospective examination was made of the biochemistry laboratory reports for the PCE results of patients aged <18 years in the period, 2008-2013. The liver and kidney function tests results were also included in the research to demonstrate correlation between age, gender and possible abnormalities. In addition to the serum PCE levels, alanine aminotransferase (ALT), aspartate amino transferase (AST), urea, and creatine levels, which were tested on the same date, were also examined. Informed consent forms were taken from all the patients who admitted to the anesthesia clinic. In addition, research approval was taken from Ethics Comittee of Ankara Children's Hematology Oncology Training and Research Hospital (No: 2013-018).

Serum PCE levels <5320 UL^{-1} (Cobas; Cholinesterase Gen.2. Roche/Hitachi) according to the kits used in the biochemistry laboratory of the hospital, were considered as PCE deficiency. In the evaluation of liver functions, the highest level of the laboratory kits were 41 UL^{-1} and 33 UL^{-1} for alanine amino transferase (ALT), 40 UL^{-1} and 32 UL^{-1} for aspartate amino transferase (AST) for males and females, respectively. In the evaluation of kidney functions, urea level >41 mg dL^{-1} for patients younger than 1 year old and >39 $mgdL^{-1}$ for patients aged 1-18 years, and for creatine, the measurement method (Cobas, Creatinin Jaffe Method. Roche/Hitachi) that was used in the hospital according to different age groups were accepted as normal limits. Levels seen at more than the normal rates, as stated in Table I were regarded as pathological.

Table I. Normal levels of creatine according to age groups

0-2 months	0.24-0.85 $mgdL^{-1}$
2-12 months	0.17-0.42 $mgdL^{-1}$
1-3 y/o	0.24-0.41 $mgdL^{-1}$
3-5 y/o	0.31-0.47 $mgdL^{-1}$
5-7 y/o	0.32-0.59 $mgdL^{-1}$
7-9 y/o	0.40-0.60 $mgdL^{-1}$
9-11 y/o	0.39-0.73 $mgdL^{-1}$
11-13 y/o	0.53-0.79 $mgdL^{-1}$
13-15 y/o	0.57-0.87 $mgdL^{-1}$
15-18 y/o	0.70-1.20 $mgdL^{-1}$

y/o: years old

Statistical Analysis

Statistical analyses of the data obtained were made using SPSS 15.0 software. Numerical variables were stated as mean ± standard deviation as descriptive statistics and categorical variables were stated as number (n) and percentage (%). The Chi square test was used to evaluate the relationships between categorical variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

During the 5-year period of the research, the serum PCE levels of a total of 15.309 patients aged <18 years were examined. The patients comprised 8704 (61.2%) males and 5529 (38.8%) females with a mean age of 7.1±5.05 years.

Pseudocholinesterase deficiency was determined in 773 (5.5%) patients. The mean age of this group was determined as 6.5 ± 6.59 years, and in patients with normal PCE levels the mean age was 8.01 ± 7.28 years ($p<0.01$). The age difference was statistically significant but was not considered to be of clinical importance. Of the patients diagnosed with PCE deficiency, 482 (5.6%) were male and 291 (5.3%) were female, with no statistically significant relationship determined between PCE deficiency and gender.

When the liver and kidney function test results were examined, 992 (7%) of 14.099 patients with ALT levels available, 3298 (23.5%) of 14.018 patients with AST

levels available, 561 (5.2%) of 10.730 patients with urea levels available and 400 (3.7%) of 10.867 patients with creatine levels available were determined with levels higher than the normal range. When the frequency of PCE deficiency was examined among the patients with higher levels in the laboratory results, it was observed that the patients with liver or kidney function problems were determined with PCE deficiency at a statistically significantly higher rate (Table II).

There was a statistically significant relationship between PCE deficiency and patients with high ALT and AST levels in the liver function evaluations, and patients with high urea and creatine in the kidney function evaluations. A statistically significant relationship was determined between PCE deficiency and patients with high liver and kidney function test results (Table III).

DISCUSSION

Pseudocholinesterase deficiency is a rarely diagnosed disease, which may be inherited or acquired (3). The most important manifestation of the disease in clinical practice is that it causes prolonged metabolism of exogenic cholinesters, such as succinylcholine and mivacurium, and prolonged apnea (2).

Since 1950s, it has been known that PCE deficiency causes significant problems such as prolonged apnoea in the postoperative period, and that it is generally a genetically inherited disease (4). Nearly 95% of cholinester administered is hydrolyzed before reaching the neuromuscular junction, and only 5% causes muscle paralysis (5).

The common features of diseases with genetic mutations show regional variations (6,7). In 1967, it was reported that the PCE genetic mutation was observed more frequently in Turkey compared to European countries (8).

Pseudocholinesterase deficiency is known as one of the most common diseases in the Jewish population with a prevalence of 10%, compared to 1/100.000 in the general European population (2). High prevalence has also been reported in Eskimos and some regions of India based on probable geographical and cultural values (6,7). The reason for the widespread distribution of the disease based on genetic reasons is explained by the repetition of genetic features in societies living more conservatively in a specific geographic region, and the transfer of disease-carrying genes (5).

According to a hypothesis in the 1980s, while low-density lipoproteins increase the level of PCE, high-density lipoproteins cause a decrease, and therefore the nutritional preferences and cultural features of a society have an effect on the disease (9).

Table II. Relationships between liver and kidney function levels and PCE deficiency

Laboratory test		without PCE deficiency number (%)	with PCE deficiency number (%)	p value
ALT	**Normal**	12.482 (95.2%)	625 (4.8%)	p<0.001
	High	847 (85.4%)	145 (14.6%)	
AST	**Normal**	10.226 (95.4%)	494 (4.6%)	p<0.001
	High	3025 (91.7%)	273 (8.3%)	
Urea	**Normal**	9528 (93.7%)	641 (6.3%)	p<0.001
	High	495 (88.2%)	66 (11.8%)	
Creatine	**Normal**	9806 (93.7%)	661 (6.3%)	p<0.001
	High	343 (85.8%)	57 (14.3%)	

PCE: Pseudocholinesterase
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase

Table III. Relationship between higher liver and kidney function levels and PCE deficiency

Laboratory test	without PCE deficiency	with PCE deficiency	p value
High ALT and AST	736 (86%)	120 (14%)	p<0.001
High urea and creatine	113 (75.8%)	36 (24.2%)	p<0.001
High ALT, AST, urea and creatine	7 (50%)	7 (50%)	p<0.001

PCE: Pseudocholinesterase
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase

Although atypical genes causing PCE deficiency are very rarely seen in South Africa, Japan, Korea and South America, the incidence is known to be quite high in Egypt, North West India and Turkey (2). In a study of atypical genes in Turkey by Sayek et al in 1967, 725 patients randomly selected from a patient population, the atypical variant heterozygote rate was found to be 5.9% (8). In 2000, a study by Kaya G et al, 202 patients in Sivas, Turkey revealed 3.47% heterozygote enzyme variant and 2.9% PCE deficiency (10). In addition to these studies on genetics, in a recent study by Yıldırım S et al in 2012, serum PCE levels were examined again in Sivas (11). In a sample of 6413 patients from all age groups, PCE deficiency was determined at 3.77%.

The rates obtained in previous studies correlate with the rate of 5.5% in the present study, and support that there is a high rate of PCE deficiency in Turkey. However, with the exception of the study by Yıldırım S et all, there has been no previous research of PCE deficiency in patients aged <18 years (11). The result of the current study of 5% from a patient group with a maximum age of 18 years strongly contradicts the results of the 2012 study by Yıldırım S et al (11).

Liver and kidney failure, malnutrition, cancer and burns are known to be factors causing acquired PCE deficiency (2,3). Oropollo AT et al (12), determined deficiency at the rate of 5.35% in serum PCE in a study conducted on 2000 hospitalized surgery patients, and it was reported that PCE enzyme levels were decreased in half of the patients with cholecystitis in a general surgery ward.

Similar to the current study, Yıldırım S et all, found the PCE deficiency rate to be 3-fold higher in patients with high AST levels, and stated that high liver enzymes increased the PCE deficiency rate (11). These results showed that the probability of PCE enzyme deficiency was increased in patients with high ALT and AST levels, and therefore these patients require much more careful preoperative preparation. Due to an excessive number of patients, the rates of those with liver failure or liver disease has not been determined.

Pseudocholinesterase deficiency requires special attention in patients with kidney failure (2). Cholinester accumulation leading to reduced excretion of cholinester in addition to the low enzyme level in patients with abnormal kidney functions might cause neuromuscular blockage lasting for days (13). Similarly, PCE deficiency has been reported to be 5-fold higher in patients with high urea levels (11).

In the light of this knowledge in literature, the determination of 50% PCE deficiency in patients with high ALT, AST, urea and creatine levels, which are used routinely to examine liver and kidney functions, demonstrates the extent to which patients are at risk.

In clinical practice, succinylcholine is prefered for short interventions because of its rapid onset and short duration. Refractory laryngospasm should also be treated with low-dose succinylcholine and positive pressure ventilation with 100% oxygen (14). However, especially in patients with PCE deficiency, the application of cholinesteroid drugs such as succinylcholine and mivacurium can cause prolonged apnea and respiratory failure (15). The rapid onset of action of rocuronium, which is a steroidal neuromuscular agent, makes it an alternative to succinylcholine in all applications (16).

A new agent for the reversal of neuromuscular blockade, sugammadex, which is a modified gamma-cyclodextrin, selectively forms a complex with rocuronium and removes it from the circulation and terminates neuromuscular blockade (16). Many studies have debated the cost-effectiveness of the rocuronium-sugammadex combination and it has been rejected by many establishments and hospital administrations because of the high cost (17). Omur D et al (18), reported that Turkish anaesthesiologists are still widely using succinylcholine. It is mostly used in emergency cases and when difficult intubation/ ventilation is anticipated, although the potential side effects must be considered together with the benefits. When the high proportion of PCE deficiency determined in this study is taken into consideration, if prolonged apnea or respiratory failure is encountered with the use of succinylcholine, especially in short-term and urgent interventions in children, PCE deficiency must be kept in mind.

CONCLUSION

The frequency of PCE deficiency was found to be 5.5% in this Turkish pediatric population. However, the incidence of PCE deficiency can be considered to be higher in patients with increased levels of liver/kidney function enzymes, so preoperative preparations should be applied more carefully. It is not possible to generalise a mean rate for the whole country as the patient group only consisted of patients receiving treatment in one hospital. Moreover, different frequency rates determined in previous studies of the same geographical regions and nations have shown the necessity for further studies in different regions. Nevertheless, the results of this study showed some light on the frequency of PCE deficiency in the paediatric population and highlights the need for further research of this significant disease.

REFERENCES

1. Kalow W. Heritable factors recognized in man by the use of drugs. In: Kalow W (ed). Pharmacogenetics: Heredity and the Response to Drugs. Philadelphia: WB Saunders Co, 1962: 69-136.
2. Davis L, Britten JJ, Morgan N. Cholinesterase: its significance in anesthetic practice. Anesthesia 1997; 52: 244-260.
3. Ama T, Bounmythavong S, Blaze J, Weismann M, Marienau MS, Nicholson WT. Implications of pharmacogenomics for anesthesia providers. AANA J 2010; 78: 393-399.
4. Kaufman L, Lehmann H, Silk E. Suxamethonium apnea in an infant. Expression of familial pseudocholinesterase deficiency in three generations. Br Med J 1960; 16: 166-167.
5. Templeton AR. The theory of speciation via the founder principle. Genetics 1980; 94: 1011-1038.
6. Manoharan I, Wieseler S, Layer PG, Layer PG, Lockridge O, Boopathy R. Naturally occurring mutation Leu307Pro of human butyrylcholinesterase in the Vysya community of India. Pharmacogenet Genomics 2006; 16: 461-468.
7. Scott EM, Wright RC. A third type of serum cholinesterase deficiency in Eskimos. Am J Hum Genet 1976; 28: 253-256.
8. Sayek İ, Karahasanoğlu AM, Özand P. Pseudocholinesterase. 3. The presence of pseudocholinesterase variants in a Turkish population. Turk J Pediatr 1967; 9: 8-12.
9. Kutty KM, Payne RH. Serum pseudocholinesterase and very-low-density lipoprotein metabolism. J Clin Lab Anal 1994; 8: 247-250.
10. Kaya G, Akef A, Atalay A. [Pseudocholinesterase activity and genetic variants at 202 volunteers in Sivas]. Cumhuriyet Med J 2000; 22: 93-97.
11. Yıldırım S, Şahin AF, Döngel İ, Erşan İ, Özkan F. Sivas ilinde psödokolinesteraz eksikliği görülme sıklığı ve ilişkili klinik parametreler. Türkiye Klinikleri J Anest 2012; 10: 84-88.
12. Oropollo AT. Abnormal pseudocholinesterase levels in surgical population. Anesthesiology 1978; 48: 284-286.
13. Smith CL, Hunter JM, Jones RS. Prolonged paralysis following an infusion of alcuronium in a patient with renal dysfunction. Anaesthesia 1987; 42: 522-555.
14. Butterworth JF, Mackey DC, Wasnick JD. Morgan & Mikhail's Clinical Anesthesiology. Postanesthesia Care CH: 56. The McGraw-Hill Companies 2013: 1257-1276.
15. Ghazal E, Amin A, Wu A, Felema B, Applegate II RL. Impact of rocuronium vs succinylcholine neuromuscular blocking drug choice for laparoscopic pyloromyotomy: is there a difference in time to transport to recovery? Pediatric Anesthesia 2013; 23: 316-321.
16. Turkkal D. C, Gokmen N, Yıldiz A et al. A cross-over, post-electroconvulsive therapy comparison of clinical recovery from rocuronium versus succinylcholine. J Clin Anesth 2009; 20: 589-593.
17. Ledowski T, Hillyard S, Kozman A et al. Unrestricted access to sugammadex: impact on neuromuscular blocking agent choice, reversal practice and associated healthcare costs. Anaesth Intensive Care 2012; 40: 340-343.
18. Omur D, Kiraz HA, Sahin H et al. Use of succinylcholine by anaesthetists in Turkey: A National Survey. Turk J Anaesthesiol Reanim 2015; 43: 323-331.