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Case Report

Delayed Neuromuscular Recovery after General Anesthesia: A Case of Atypical Plasma Cholinesterase

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Abstract

Pseudocholinesterase Deficiency (PChED), also called atypical plasma cholinesterase, or butyrylcholinesterase deficiency, is a rare genetic disorder that affects the body's ability to metabolize ester bonds, affecting the duration of action of muscle relaxants such as succinylcholine and mivacurium. This condition may lead to prolonged paralysis after general anesthesia when muscle relaxants are used, requiring prolonged postoperative mechanical ventilation of the patient. We present a case of a 63-year-old male patient that presented for direct laryngoscopy and esophagoscopy under general anesthesia, and experienced prolonged paralysis after succinylcholine administration. PChED should be considered in cases of otherwise unexplained prolonged muscular weakness after anesthesia.

Keywords: Pseudocholinesterase deficiency; Atypical plasma cholinesterase; Butyrylcholinesterase deficiency; Case report; Succinylcholine; Prolonged neuromuscular blockade.

Abbreviations: SCh: Succinylcholine; PChED: Pseudocholinesterase Deficiency; PChE: Pseudocholinesterase; PSMN: Presynaptic Motor Neuron; ACh: Acetylcholine; AChE: Acetylcholinesterase; BChE: Butyrylcholinesterase; NMJ: Neuromuscular Junction; PACU: Post Anesthesia Care Unit; nACh: Nicotinic Acetylcholine

Introduction

Pseudocholinesterase (PChE), also known as plasma cholinesterase or Butyrylcholinesterase (BChE), is an enzyme produced in the liver and found in the plasma [1-4]. It is not found at the Neuromuscular Junction (NMJ) [4]. It is involved in the metabolism of choline-based esters in the blood, including muscle relaxants such as Succinylcholine (SCh) and mivacurium, and ester-based local anesthetics such as tetracaine, chloropropane, and cocaine [4]. The word "PChE" comes from the Greek word pseftis (ψεύτης), which means liar, and cholinesterase, so it stands for "false cholinesterase" [5]. The "True Cholinesterase," also called acetylcholinesterase (AChE), is an enzyme found in the synapse of the NMJ and is responsible for metabolizing Acetylcholine (ACh) [5]. Because AChE is found at the synapse, ACh released by the presynaptic motor neuron is rapidly metabolized and lasts only 5-15 milliseconds [6]. SCh is only metabolized in the blood by PChE, and it is not metabolized by AChE in the synapse, so it lasts much longer at the NMJ, 5-10 minutes. When SCh is injected into the blood, 85-95% of it is metabolized by PChE in the plasma, and only 5-15% leaves the bloodstream to reach the NMJ [6]. However, once SCh reaches the NMJ, it is in its safe place, since nothing there can break it down, as PChE is only found in the plasma (hence called Plasma Cholinesterase) and not at the NMJ, so it lasts much longer than ACh [6]. PChED (a misnomer, as the patient is not deficient in the enzyme but instead has a poorly functioning enzyme) may be inherited as an autosomal recessive trait [1,4,7]. PChED is caused by genetic variants and is a *qualitative* rather than a quantitative problem; these patients have the same amount of enzyme as everyone else, but their enzyme is a poorly functioning one [1,4,7]. Patients with PChED experience prolonged paralysis from SCh since a smaller percentage of it is metabolized in the plasma, and much more ends up reaching the NMJ [1,4,7]. Also, lower levels of plasma cholinesterase (a quantitative problem) may prolong SCh paralysis, but by much less com-

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pared to the prolongation caused by genetic variants [1,4,7]. PChED is suspected when patients experience prolonged paralysis following the administration of SCh or mivacurium [1,4,7]. This case study aims to raise awareness among healthcare providers about atypical plasma cholinesterase.

Case Description

A 63-year-old male, 120 kg, 5' 7'' with a history of head and neck and anal cancer, diabetes mellitus type 2, hypertension, hyperlipidemia, obstructive sleep apnea, and Bell's Palsy, presented for direct laryngoscopy and esophagoscopy. His past surgical history included laparoscopic left inguinal hernia repair, cardiac ablation for supraventricular tachycardia, and colonoscopy. All his previous anesthetics were uneventful. The patient denied any history of smoking or using illicit drugs and admitted social alcohol consumption. His vital signs and physical examination were unremarkable. The list of home medications included atenolol, metoprolol, atorvastatin, and metformin. The patient was allergic to Percocet and intravenous contrast dye. Preoperatively, the patient received a scopolamine patch to reduce the risk of postoperative nausea and vomiting. In the operating room, the patient was preoxygenated, and induction of general anesthesia was achieved with 250mg of propofol, 50 mcg of fentanyl, and 100mg of SCh (Succinylcholine) to facilitate intubation. General anesthesia was maintained with sevoflurane. Initial vital signs remained stable throughout the surgery. The surgical procedure (direct laryngoscopy and tissue biopsy) lasted 26 minutes. Sevoflurane was discontinued, and fresh gas flow was increased to facilitate anesthetic washout. The ventilator was switched to bag mode, expecting the patient to start breathing spontaneously; however, when the patient started breathing, the breath tidal volumes were minimal at 10-15 ml. Train of Four (TOF) showed 0/4 twitches. The patient could follow commands but was very weak. Sugammadex 200 mg was administered to rule out accidental rocuronium administration, but this resulted in no motor function improvement. Since the patient was awake and was following commands but had weakness, PChED was suspected. Midazolam 2 mg was administered for patient comfort, sedation, anxiolysis, and amnesia, and the patient was kept intubated and transferred to the Post-Anesthesia Care Unit (PACU). Upon arrival at the PACU, vital signs were stable. Gradually, the respiratory efforts became more effective, and the ventilation mode was changed to spontaneous ventilation with tidal volumes of 500-600ml. The patient met extubating criteria about three and a half hours after receiving SCh and was successfully extubated. A note was written in the patient's medical chart, and SCh was listed as an allergy, to avoid SCh administration in the future.

A dibucaine number test was ordered, instructing the spouse to wait 2 days before the blood draw; this was eventually done 7 months later, but the patient had not been re-exposed to SCh before the blood was drawn for the test. The dibucaine number came back at 637 initially, which was perplexing, considering the value denotes the percentage of PChE inhibited by dibucaine; and can only be from 0 to 90. After calling the lab, they admitted making a mistake, stating that 637 was the plasma cholinesterase level, which has a normal range of 903-2964 units per liter (U/L), and that the dibucaine number was 45. The patient and his spouse were informed of the results, and a medic alert bracelet was ordered for the patient, noting he has PChED.

Discussion

PChED is a rare genetic disorder inherited as an autosomal recessive trait. It affects the body's ability to metabolize ester bonds, prolonging the duration of action of muscle relaxants such as SCh and mivacurium. It is more common in certain populations, such as Persian Jewish people and Alaska Natives. The genetic basis of PChE deficiency involves mutations in the BChE gene, located on chromosome 3q26, leading to different alleles with varying enzyme activity [2,4,8-10]. About 20 genetic variants have been described, including usual (U, normal), atypical (A), fluoride-resistant, K variant, and silent [10]. The most common genetic variant of the gene is the atypical (A). Patients with one atypical gene are heterozygous atypical (UA), seen in 1 in 480 patients [4,10]. Patients with 2 atypical genes are homozygous atypical (AA), seen in 1 in 3200 patients [10]. The rest have normal genes and are denoted by UU.

Patients with PChED experience prolonged paralysis from SCh because of slower SCh degradation rate in the plasma. The functionality of the PChE enzyme determines the duration of action of SCh by influencing the rate of SCh hydrolysis and, thus, how much drug reaches the NMJ [10]. Since the enzyme has a diminished ability to hydrolyze ester bonds in medications such as SCh and mivacurium, significantly more of these molecules reach the NMJ, causing prolonged neuromuscular paralysis. When a patient experiences prolonged paralysis following SCh or mivacurium administration PChED should be suspected, and the dibucaine inhibition test should be ordered to confirm the diagnosis. Dibucaine is an amide local anesthetic that inhibits normal plasma cholinesterase activity by 80%. During the test, benzoylcholine and dibucaine are added to the blood [10-12]. Dibucaine decreases the breakdown of benzoylcholine by normal plasma cholinesterase (UU) by 80%, giving the patient a dibucaine number of 80, by heterozygous atypical (UA) by 40-60%, giving the patient a dibucaine number of 40-60, and by homozygous atypical (AA) by 20%, giving the patient a dibucaine number of 20 [10-12]. SCh usually causes 5-10 minutes of paralysis in normal UU patients, 20-30 minutes in heterozygous atypical UA patients, and 1-8 hours in homozygous atypical AA patients [4,6]. When drawing blood for a dibucaine inhibition test, blood should be collected after 48 hours have passed from the SCh administration time, to prevent interference with the integrity of the test [11,13]. If the blood sample is taken too soon, the muscle relaxant in the blood may interfere with the hydrolysis of the test substrate, resulting in competitive inhibition; this could result in an artificially decreased PChE activity [11]. The dibucaine inhibition test does not identify genotypic and phenotypic differences; molecular genetic techniques can identify specific PChE variants at the DNA level, although these tests are primarily used for research [6,14].

Liver and kidney disease, malignancies, major burns, malnutrition, pregnancy, and certain drugs, such as neostigmine and esmolol, may decrease the plasma cholinesterase enzyme concentration, but lower levels of normal PChE prolongs SCh's paralysis only modestly [9]. Hypothermia may also cause abnormal metabolism of SCh. In general, the effects of various diseases, medications, and hypothermia on SCh-induced paralysis are insignificant compared to the substantial prolongation of paralysis caused by genetic variants. Severe liver disease may decrease the synthesis of PChE with a clinically significant prolongation of SCh-induced paralysis, but to cause a 20-second prolongation of SCh-induced paralysis, the quantity of PChE in the plasma must decrease by 70%. Decreases in PChE concentration due to liver cirrhosis or other causes are associated with a normal dibucaine number, since despite lower levels, the enzyme has normal function [15].

When ACh is released from the Presynaptic Motor Neuron (PSMN) into the synapse, AChE rapidly metabolizes 50% of it. The remaining ACh mostly binds to the postsynaptic nicotinic ACh (nACh) receptors and, to a smaller extent, to the presynaptic nACh receptors, providing positive feedback to replenish the PSMN ACh reserves [16]. The binding of ACh to the postsynaptic nACh receptors is soon followed by dissociation from the receptors, driven by the large concentration gradient between the receptor area and the synapse, and is then immediately broken down by AChE, into acetic acid and choline, limiting the duration of action of ACh to 5-15 milliseconds (msec) [6]. Choline is then reabsorbed by the PSMN and used to synthesize more ACh, while acetate diffuses into the surrounding area.

Even though SCh is composed of 2 ACh molecules, it is not metabolized by AChE at the synapse but rather by PChE in the plasma, and this difference causes the duration of action of SCh to be 5-10 minutes, which is significantly longer than that of ACh's. The duration of action of SCh also depends on its initial plasma concentration and its elimination rate by PChE. Prolonged paralysis caused by PChED is treated by continuing mechanical ventilation and providing comfort measures to the patient, such as sedation [1,6,7]. Neostigmine is not recommended for neuromuscular blockade reversal, as this will inhibit plasma cholinesterase and prolong paralysis. Neuromuscular monitoring during surgery should be utilized any time any neuromuscular blocker is adminstered, even SCh, as this will help detect PChED early. Healthcare providers should be aware of this condition and consider alternative neuromuscular blocking agents instead of SCh when indicated, to avoid prolonged paralysis [6]. Patients with a known PChED should wear medic-alert bracelets to notify healthcare providers of their condition [6].

It is interesting that there might be an evolutionary advantage to having an abnormal allele of the BCHE gene, which is responsible for PChED. It is known that individuals who carry one copy of the sickle cell allele (heterozygous) have some level of protection against malaria. Similarly, individuals with an abnormal pseudocholinesterase allele may also have a heterozygote advantage. Some publications suggest that having an abnormal BCHE allele may protect against cardiovascular disease [6].

Our patient's dibucaine number was 45, which would classify him as having heterozygous atypical PChED, and a 20–30-minute neuromuscular blockade should have been expected. However, our patient experienced a 218-minute paralysis (3 hours 38 minutes). The cause of his prolonged paralysis could have been multifactorial, such as the presence of heterozygous atypical plasma cholinesterase, low plasma cholinesterase levels at 637 U/L (normal levels: 903-2964 U/L), his cancer, and the beta blockers he was on. In addition, we cannot discount the possibility that the lab miscalculated the dibucaine number, and it may be lower, since the lab already made a mistake initially, reporting the dibucaine number at 637. Despite the dibucaine number indicating that the patient had heterozygous atypical plasma cholinesterase, his clinical presentation was that of a homozygous atypical plasma cholinesterase genetic variant. This was communicated clearly with the patient and his family, and a medic-alert bracelet was prescribed for homozygous atypical plasma cholinesterase (AA) and PChED, as this is the most common term utilized. The diagnosis of PChED was also added to the patient's chart.

Conclusion

This case underscores the importance of considering rare enzymatic deficiencies such as PChED in patients with unexplained delayed recovery from neuromuscular blockade after general anesthesia. A high index of suspicion and prompt recognition are vital for appropriate management and prevention of potential complications associated with prolonged muscle weakness.

Author Statements

Consent

Informed consent was obtained from the patient to publish this case report, ensuring patient confidentiality.

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