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Case Report

Unexpected Persistent Paralysis Due to Rare Reduced Pseudocholinesterase Activity in Post-Partum Obstetric Hemorrhage Surgery: A Case Report

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Abstract:

Background

Due to increasing use of non-depolarizing muscle agents (NMBA) and decreased use of depolarizing muscle relaxants as suxamethonium, encountering an unknown genetic predisposition of pseudocholinesterase deficiency in clinical practice may become more exceptional. With a constant prevalence of genetic variants leading to either less active or inactive pseudocholinesterase, continuously raising awareness of this less frequent diagnosis is of considerable importance to avoid misjudgment and to prevent somatic and psychological harm to patients.

Case Report

Our 35-year-old woman of Turkish descent with no known family history of anesthesia-related adverse events, was presented from the maternity ward with excessive blood loss after surgical assisted vaginal birth. Considered general anesthesia was induced, including suxamethonium and a retained placenta was surgically removed. Upon ceasing sevoflurane, the patient did not show any clinical signs of recovery from paralysis which was confirmed with Train of Four (TOF) monitoring. After four hours of monitored continued mechanical ventilation and hypnosis, the patient spontaneously recovered from paralysis and could be extubated. On follow-up, the patient was diagnosed with a heterozygous genetic predisposition for pseudocholinesterase deficiency which, in combination with several different risk factors for delayed metabolization, including pregnancy, sevoflurane and significant blood loss is believed to have led to this clinical presentation.

Conclusions

Heterozygous predisposition for pseudocholinesterase deficiency alone is not explanatory for delayed paralysis induced by depolarizing muscle relaxants for over one hour but in combination with several known risk-factors can certainly lead to significant clinically relevant paralysis.

Key words: pseudocholinesterase deficiency; butyrylcholinesterase deficiency; neuromuscular blocker; suxamethonium, pharmacogenetics; obstetric anesthesia

Introduction

Pharmacogenetic predisposition regarding genetic diversity in metabolizing commonly used anesthetics is more common than often realized, affecting around 30% of all drugs and accounting for up to 95% of inter individual variability in drug effects [1]. The vast majority of anesthetic agents, 70-80%, are metabolized in the liver by cytochromes P450 [2]. Although, this rarely leads to unexpected adverse events, it is

reported to contribute up to 79.7% of anesthesiologic associated deaths after adverse events of anesthetics in therapeutic dose [3, 4]. In addition, anesthesiologic misjudgment or decision making can lead to unnecessary physical and emotional injury to individual patients. For instance, higher levels of pain and distress as well as developing post-traumatic stress disorder (PTSS) or anxiety disorders [5].

Pseudocholinesterase, also referred to as butyrylcholinesterase (BChE), is a plasma enzyme responsible for hydrolyzing choline esters including commonly used neuromuscular blocking agents, either non-depolarizing as mivacurium or depolarizing such as suxamethonium but also local anesthetics, e.g., tetracaine, cocaine, and procaine [6]. Pseudocholinesterase deficiency results in a distinct prolonged paralysis up to six hours after administration.

The subsequent case describes an unexpected case of an unexpected pseudocholinesterase deficiency in a 34-year-old postpartum woman (following CARE Guidelines [7] and uniform requirements for manuscripts [8]). The aim of this case report focusses on the unexpected presentation of heterozygous pseudocholinesterase deficiency, the direct clinical consequences in order to elaborate on the direct clinical management and patient follow-up, emphasizing early recognition within a simple decision-making tool. With the steep rise of the usage of sugammadex, clinical properties of non-depolarizing neuromuscular blocking agents (NMBA's), especially rocuronium widened, making it very suitable for rapid-sequence induction. Therefore, the administration of either suxamethonium or mivacurium is significantly reduced, most certainly considering the significantly reduced costs of sugammadex in recent years. As the prevalence of the genetic disorder is unchanged within the population, the reduced use of suxamethonium will make this specific finding much rarer including the awareness.

Case Report

A 35-year-old woman (G3P1) of Turkish descent with BMI of 27 was announced from our maternity ward with excessive postpartum blood loss estimated at 1300mL due to a retained placenta. Her first pregnancy ended in miscarriage and consecutively this second pregnancy resulted in a vaginal birth, requiring vacuum extraction but no other maternal complications requiring any surgical nor radiological intervention. Epidural anesthesia was performed successfully to relieve pain during labor and birth, with the catheter still in place upon presentation. Due to hypotonic labor, the spontaneous started labor needed additional stimulation using intravenous oxytocin to a maximum of 4,5mL/h of a 0.4IU/mL solution. Giving birth was complicated by maternal exhaustion and fetal distress, as derived by maternal irritability, and measured with an abnormal cardiotocography (consisting of an increased base heartrate of 160bpm with decreased variability) and with pre-acidotic blood gas results using micro blood sampling technology (pH 7.21). Vacuum extraction was performed which was then complicated by shoulder dystocia. A full-term baby girl was born with a normal weight of approximately 3550 grams but in need of respiratory support for which immediate care was provided by the pediatrician. Meconium in the amniotic fluid confirmed the fetal distress, which had resulted in meconium aspiration leading to respiratory failure. The attending pediatrician was able to stabilize the newborn utilizing positive airway pressure.

Patient's condition was considered hemodynamically stable when arriving at the operating complex, having a stable sinus tachycardia of 130 beats/minute and consequent mean arterial pressure well above 70mmHg. Her medical history only included limited excision of a pilonidal sinus under spinal anesthesia and today's mentioned vaginal birth. When conducting a limited preoperative assessment, patient reported no allergies, no medication, nor any anesthesia-related complications or known familial genetic disorders. Laboratory results at admission showed a Hemoglobin level of 7.0 mmol/L (11.3 g/dL), no irregular antibodies and a normal renal function. In the operating room, after standard protocol time-out procedure, confirming a free flow of NaCl 0,9% IV, general anesthesia was induced using 160mg of propofol, 100mcg of fentanyl and 100mg of suxamethonium. Intubation conditions were optimized putting patient in sniffing position and successful first-time endotracheal intubation was obtained utilizing a video laryngoscope. Anesthesia was maintained with 3% in sevoflurane (O2/air mixture of 40%).

After a 14-minute obstetric procedure, a small retained placental part was manually removed and total blood loss was estimated just above 2000mL, including the preoperative loss. During wash-out of sevoflurane to approximately end-tidal concentration below ETsev of 0.5%, the patient remained unresponsive and without any clinical sign of paralytic recovery. A neuromuscular transmission monitor (NMT) was then applied on the m. adductor pollicis on the right wrist, stimulating the ulnar nerve, which did not show any muscle contractions. Post-tetanic count (PTC) was not measured. In absence of other obvious explanations, a prolonged neuromuscular blockade due to a hydrolyzation deficiency of the administered choline ester molecules was expected. Patient was informed of prolonged paralysis and reassured while sevoflurane was restarted. Persistent patient paralysis was confirmed by a negative NMT on the contralateral side and verifying there were no instrumental or technical defects.

After consulting a colleague, anesthesia maintenance was exchanged for propofol and Bispectral index (BIS) monitoring was then applied, measuring a BIS of 46. The patient was transferred to the Intensive Care Unit for ventilation support. Three and a half hours after induction she first displayed return of spontaneous breathing. Propofol was stopped, and after careful evaluation, patient was extubated without any respiratory complications. Although, a period of approximately four and half minutes of solely light sedation during paralysis, she did not have any awareness with recall.

Hours after recovery, patient called her parents to ask if there have been apparent incidents with general anesthesia running in the family. She reported that it took her mother hours before she 'woke up' from general anesthesia and only after transfusion of 'fresh blood'. No additional diagnostics were performed at that time due to a lack of resources in this particular rural area in Turkey.

The following morning, we assessed the possibility of presence of awareness utilizing the modified version of the Brice questionnaire [9] (Table 1). She did not meet any of the criteria and thus did not have any awareness with recall. Patient was particularly satisfied with the extensive explanation and thorough information she and her husband were presented with. She emphasized, having had a very emotional, exhausting labor and fearing a bad outcome of her newborn, a third hit by experiencing paralysis while being awake would have devastated her.

Table 1. Brice Questionnaire [8]

1. What is the last thing you remember before going to sleep?
2. What is the first thing you remember after waking up?
3. Do you remember anything between going to sleep and waking?
4. Did you dream during your procedure?
5. What was the worst thing about your operation?

Patient was referred to a nearby university hospital for extensive genetic and neurological analysis. Thorough anamnesis and neurological examination showed no indications for a possible underlying neurological condition. Based on BChE genotyping on a EDTA plasma sample, patient appeared heterozygous for the abnormal genetic inactive haplotype AK "atypical" and "Kalow" (A 209A>G; rs1799807 and K 1615G>A; rs1803274), in combination with a normal and active "usual variant" U. This makes our patient a carrier of pseudocholinesterase deficiency. This genetic variant could account for approximately a 50% up to a 100% prolongation of paralysis due to reduction of pseudocholinesterase activity, but never more than one hour [10]. In this case, there must be a combination of non-genetic factors contributing to a more severe clinical

presentation. Given the fact that the complete DNA sequence and amino acid structure of the normal pseudocholinesterase protein, as well as most common abnormal variants are known, and the availability of genetic analysis, running once every week, other diagnostic methods such as dibucaine and fluoride numbers, as well as the more simplified screening Acholest test, were not reported [11].

Discussion

This case presents an unexpected finding in a young, Turkish woman after a complicated delivery who experienced a persistent paralysis after administration of a normal dosage of suxamethonium for general anesthesia for manual removal of a retained placenta. She was mechanically ventilated for 4 hours until she recovered from paralysis and could be extubated. Genetic analysis demonstrated that our patient appeared to be heterozygous (intermediate) for pseudocholinesterase deficiency. Although this would not fully account for the described clinical course, a total sum of additional risk factors is believed to be enough explanation to suffice for an exceptionally long recovery from paralysis induced by this depolarizing neuromuscular blocking agent. (Table 2)

Metabolic factors	Liver failure Renal failure Major Burns Advanced age *Pregnancy/ postpartum state*
Decrease in pseudocholinesterase activity	Oral contraceptive pill Cholinesterase inhibitors (neostigmine, pyrodostigmine) Cyclophosfamide Echothiopate iodide for ophthalmic solution
Potentiating agents	Antibiotics (clindamycin, tetracyclin) Antiarrhythmic drugs (procainamide, calcium channel blockers and magnesium sulphate) *Local anesthetics* Diuretics (furosemide) *Inhalational anesthetics* Lithium
Substantial increase in sensitivity	Myasthenia syndrome Autoimmune disorders (systemic lupus erythematosis)

Table 2: Synopsis of the most significant risk factors which may contribute to clinically relevant prolongation of depolarizing muscle relaxant induced paralysis. Factors present in the patient described are highlighted (Italic).

Pharmacodynamics	*Genetic variations/disorders*	Pseudocholinesterase deficiency
	Hypothermia *Drug interaction*	Impaired metabolism
Pharmacokinetics	(relative) overdose *Altered distribution* *Impaired metabolism* Impaired elimination Duration of surgery Drug interaction	Dilution errors/ narcotic overdose Large fluid shift surgery Liver failure/ Hypothyroidism Renal failure Stacking liposoluble anesthetics
Neurological	Hypoperfusion/ischemia Intracranial hemorrhage Thrombosis Central anticholinergic syndrome	Post-anoxic state
Metabolic	Hypoglycemia Hyperglycemia Hyponatremia *Hypernatremia* Acidosis	
Psychiatric	Conversion disorder	

Table 3: Causes of delayed emergence from anesthesia [15]

Dilution errors/ narcotic overdose of muscle relaxant	
Cholinergic crisis	
Myasthenic syndrome	
Electrolyte disturbances	Hypermagnesemia
	Hypophosphatemia
	Hypokalemia

Table 4: Causes of delayed recovery from paralysis [11]

General synopsis of factors contributing to delayed emergence from general anesthesia. Factors present in the patient described are highlighted (Italic).

Pseudocholinesterase, synonymous with serum cholinesterase, plasma cholinesterase, nonspecific cholinesterase, butyrylcholinesterase or S-type cholinesterase, is a complex molecule made up of four identical subunits each weighing 85kD and synthesized in the liver [12]. Deficiency may be inherited as an autosomal recessive condition with prevalence varying from 1:3200 to 1:5000 people. Male-to-female incidence ratio approximately 2:1 and prevalence is higher in Caucasian males, Alaska Natives and the Persian community [6,10-13]. The accountable gene is known and located on the long arm (E1 locus) of chromosome 3 (3q26.1-q26.2). Just over 96% of the total population are homozygous for a normal gene type and 3.9% is heterozygous for an atypical allele. Practically this will, depending on the variant, cause a 5 minute to a maximum of 1 hour prolongation of paralysis, whilst in a homozygous individual this could stretch up to 6 hours.

Remarkably, there is one very rare variant allele known that results in a significantly higher enzyme activity, making these individuals relatively resistant to the paralytic effects of suxamethonium. Approximately half

to 80% of patients with a (partly) deficient pseudocholinesterase, a homozygote mutation of the BChE gene is found [14,15]. When encountering a case of suspected persistent paralysis, we can revert to a concise and structured differential diagnosis, also accounting for possible contributing factors [10] (Tables 3 and 4).

There is no specific treatment for pseudocholinesterase deficient patients, and the most safe and acceptable management is to continue sedation and ventilator support until passive diffusion of succinylcholine away from the neuromuscular junction and respiratory muscle paralysis spontaneously resolves [16]. If more rapid recovery is necessary, for example if neurological assessment is required, it may be considered to administer donor plasma, as this contains small variable amounts of pseudocholinesterase, in concentrates of fresh frozen plasma (FFP), omniplasma (OP) or enzyme concentrate. Several cases report that one to two units of FFP would be sufficient to recover a paralyzed patient within minutes [18].

In this particular case the patient had a sufficiently working epidural catheter. In addition to birthweight, maternal diabetes, excessive maternal weight or weight gain, operative vaginal delivery, oxytocin use, multiparity and prior occurrence, epidural anesthesia is also a purported risk factor for shoulder dystocia. Recently this became more questionable considering a persistent increase in the rate of epidural use for pain relief in labor in the United States with an essentially constant rate of shoulder dystocia, occurring in around 1% of all deliveries [19]. Utilizing this for epidural anesthesia during the surgical procedure was considered and, in retrospect, would have prevented this clinical outcome. Considering the ongoing blood loss, the amount of extra time until surgical block would be sufficient after administering extra epidural local anesthetic and the impending hemodynamic instability, we opted for general anesthesia, despite a possibly more challenging airway management and possible respiratory complications.

Soliday et al. and Andersson et al. demonstrated that, next to genetic predisposition, many different metabolic factors, enzyme-inhibiting agents, depolarizing muscle relaxant potentiating drugs and disorders influence the clinical outcome when administering depolarizing muscle relaxants. In this case the combination of heterozygous pseudocholinesterase deficiency, postpartum state, administration of inhalational anesthetics, possible impaired metabolism/elimination and altered distribution due to large fluid shifts and dilution during acute major blood loss, caused a significant prolongation of drug induced paralysis of 4 hours [6, 20].

Conclusion

Heterozygous pseudocholinesterase deficiency has a constant prevalence but will be encountered less frequent with the increasing use of other neuromuscular blocking agents, e.g., rocuronium which after the introduction of sugammadex has become more popular taking into account the added value of being able to antagonize quickly in the context of patient safety, efficacy and efficiency. In addition to other risk factors, heterozygous pseudocholinesterase deficiency may lead to a significant prolonged paralysis when using depolarizing muscle relaxants, inducing the possible risk of a potential traumatic awareness for the patient when prolonged paralysis is not noticed in time. To prevent this, timely recognition should lead to (re-)start of mechanical ventilation, open communication and reassuring the patient followed by restart of sedation. The prolonged paralysis caused by pseudocholinesterase deficiency is safely managed by continued mechanical ventilation and in some cases may be treated with plasma transfusion but should never be counteracted with neostigmine.

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Not applicable

Abbreviations

NMBA's: non-depolarizing neuromuscular blocking agents; TOF: Train of Four; BChE: butyrylcholinesterase; PTSS: post-traumatic stress disorder; BMI: body-mass index; ETsev: end-tidal sevoflurane; NMT: neuromuscular transmission monitoring; PTC: post-tetanic count; BIS: Bispectral Index; FFP: fresh frozen plasma; OP: omniplasma

Conflict of interests

The authors declare that they have no competing interests.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Authors' contributions

RV: Writing, editing. PB: editing, revision. Both authors read and approved the final manuscript.

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